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Effectiveness of treatment based on PiCCO parameters in critically ill patients with septic shock and/or acute respiratory distress syndrome: a randomized controlled trial

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Trial registration: www.clinicaltrials.gov NCT01526382.

Take-home message: This randomized controlled trial provides no evidence that treatment based on the use of PiCCO will benefit critically ill patients with septic shock and/or ARDS.

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Abstract *Purpose:* To compare treatment based on either PiCCO-derived physiological values or central venous pressure (CVP) monitoring, we performed a prospective randomized controlled trial with group sequential analysis. *Methods:* Consecutive critically ill patients with septic shock and/or ARDS were included. The planned total sample size was 715. The primary outcome was 28-day mortality after randomization. Participants underwent stratified randomization according to the classification of ARDS and/or septic shock. Caregivers were not blinded to the intervention, but participants and outcome assessors were blinded to group assignment. *Results:* The study was stopped early because of futility after enrollment of 350 patients including 168 in the PiCCO group and 182 in the control group. There was no loss to follow-up and data from all enrolled participants were analyzed. The result showed that treatment based on PiCCO-derived physiological values was not able to reduce the 28-day mortality risk (odds ratio 1.00, 95 % CI 0.66–1.52; $p = 0.993$). There was no difference between the two groups in secondary outcomes such as 14-day mortality (40.5 vs. 41.2 %; $p = 0.889$), ICU length of stay (median 9 vs. 7.5 days; $p = 0.598$), days free of vasopressors (median 14.5 vs. 19 days; $p = 0.676$), and days free of mechanical ventilation (median 3 vs. 6 days; $p = 0.168$). No severe adverse event was reported in both groups. *Conclusion:* On the basis of our study, PICCO-based fluid management does not improve outcome when compared to CVP-based fluid management.

Keywords Septic shock · PiCCO · Intensive care unit · 28-day mortality · Acute respiratory distress syndrome · Randomized controlled trial

Introduction

Hemodynamic monitoring is of paramount importance for critically ill patients with circulatory failure. While inadequate intravascular fluid volume can result in circulatory shock and tissue hypoperfusion, fluid overload may result in cardiac failure and subsequent pulmonary edema and hypoxia [1–3]. Therefore, optimization of volume status is the cornerstone of the management of such patients. With optimized volume status, the use of vasopressors and inotropes may also require accurate hemodynamic monitoring. The last several decades have witnessed rapid advances in hemodynamic monitoring and quantification of extravascular lung water (EVLW) [4–7].

Transpulmonary thermodilution (TPTD) has been extensively studied and elevated EVLW measured by TPTD has been associated with increased risk of death in heterogeneous ICU patients [8]. During strenuous fluid resuscitation, EVLW monitoring may help to prevent fluid overload [9]. The PiCCO system incorporates techniques of TPTD and pulse contour analysis that allows for monitoring of numerous physiological variables reflecting the hemodynamic status of a patient. These variables include global end diastolic volume, intrathoracic blood volume (ITBV), and cardiac index (CI). However, the clinical efficacy of PiCCO has not been systematically explored. This study aimed to investigate the efficacy or futility of treatment based on PiCCO-derived physiological values on 28-day mortality. We hypothesized that treatment based on PiCCO-derived physiological values may provide a beneficial or neutral effect on clinical outcome. Group sequential analysis was employed to see whether the trial could be stopped early.

Methods

Trial design

A detailed study protocol has been published and we therefore describe it only briefly here [10]. Changes made to the original study protocol are displayed in supplemental Table 1. The study was a randomized controlled trial (RCT) with group sequential analysis using an interval of 50 patients. The study was approved by the ethics committees of the participating centers and informed consent was obtained from each participant (or next of kin).

Participants

Adult patients (at least 18 years old) who met the clinical criteria of septic shock and/or acute respiratory distress syndrome (ARDS) within 24 h after admission to ICU were enrolled after being screened for eligibility. Detailed inclusion/exclusion criteria were reported in the study protocol [10] and are summarized in supplemental Table 2.

The trial was conducted in two tertiary ICUs in Zhejiang province of mainland China.

Interventions

Because TPTD is incorporated into the PiCCO system (PULSION medical system) and the present study aims to investigate the efficacy of the PiCCO system in terms of clinical outcome, we refer to PiCCO instead of TPTD throughout the manuscript [11].

In the PiCCO group, fluid management aiming to optimize the effective circulatory volume and vasoactive agents were used to achieve a mean arterial blood pressure of at least 60 mmHg (supplemental Fig. 1). When the volume status (ITBVI greater than 850 ml m^{-2}) was optimized but with an EVLWI of at least 10 ml/kg, strategies such as diuretics and/or renal replacement therapy were instituted to achieve a negative fluid balance. If circulatory failure was thought to be the result of cardiac dysfunction (CI less than 2.5 L m^{-2} min^{-1}), dobutamine was started at the dose of 2.5 μg kg^{-1} min^{-1}.

In the control group, volume status was assessed by using central venous pressure (CVP), aiming to maintain a CVP between 8 and 12 mmHg [10]. Patients in the control arm did not receive PiCCO monitoring, but a central venous catheter was routinely inserted (supplemental Fig. 2). If the CVP was less than 8 mmHg, a 500-ml bolus of hydroxyethyl starch 130/0.4 (VoluvenW) was infused over 30 min aiming to achieve a CVP of 8–12 mmHg. The bolus could be repeated if the target was not reached. If CVP exceeds 12 mmHg, furosemide and/or nitroglycerin and/or dobutamine could be used at the discretion of the attending physician. If MAP was less than 60 mmHg, norepinephrine was started at 0.05 μg kg^{-1} min^{-1} with the option to increase at an increment of 0.05 μg kg^{-1} min^{-1}. If MAP exceeds 100 mmHg, nitroglycerin was given at the dose range of 0.5 to 3.0 μg kg^{-1} min^{-1}.

The treatment algorithm was not in a one-way flow direction, but it was a circle that could be repeated. In the absence of shock, strenuous fluid bolus was not given for volume expansion. There was no prespecified time interval for the measurement of hemodynamic parameters, which was at the discretion of the treating physician.

Outcomes

The primary endpoint was 28-day mortality (death from any cause before day 28).

Secondary study endpoints included ICU length of stay, days on mechanical ventilation, days on vasopressors and continuous renal replacement therapy (CRRT), and maximum sequential organ failure assessment (SOFA) score during the first 7 days. Days free of ventilator, vasopressors, and CRRT during 14- and 28-day periods were also reported.

Sample size

We assumed that the mortality rate in the control group was 40 %, and the intervention could reduce the mortality rate to 30 %. A total of 715 patients were required to provide a power of 80 % and a two-sided type I error of 0.05. The sample size was used as the total information

size for subsequent sequential analysis. Efficacy and futility analyses were performed. In the efficacy assessment, the O'Brien–Fleming method was used to identify decision boundaries that preserve the desired α error rate during interim monitoring [12]. The spending function provides the probability of making type I error up to a fraction during the trial [13]. In futility analysis, the β-spending function (O'Brien–Fleming spending function) was used to examine the futility of PiCCO monitoring in improving 28-day mortality risk. Futility and efficacy of treatment based on PiCCO monitoring were predefined as the stopping rule for the study. Group sequential analysis was performed at enrollment of every 50 subjects. These boundaries were constructed by using TSA software.

Randomization

Randomization sequence was generated using Stata 12.0 (StataCorp, College Station, TX) statistical software and was stratified by type of disease (e.g., ARDS, septic shock, or both) with a 1:1 allocation using simple randomization.

Blinding

We used the same electrocardiogram (ECG) monitor (Philips IntelliVue Patient Monitor with a PiCCO module) for both intervention and control arms. A sham procedure of injecting cold water was performed every 8 h for patients in the control arm. Cardiac output and lung water were measured every 8 h in the PiCCO group. Investigators who collected baseline characteristics and follow-up results were blinded to patient assignment.

Statistical analysis

Baseline characteristics were compared between treatment groups by using the one-sample t test or Mann–Whitney U test as appropriate. Normality was determined by examining the normal quantile plot. The primary outcome was compared by using Pearson's Chi square test. Secondary outcomes such as ICU length of stay, ventilator-free days, and days free of vasopressors were assumed to be skewed and comparisons were made by using the Mann–Whitney U test.

Multivariable logistic regression was employed to adjust for confounding variables. Variables that were statistically different between PiCCO and control groups in univariate analysis with $p < 0.05$ were entered into the multivariable model. Age was entered because a large body of evidence suggested that it was an independent predictor of mortality risk. The efficacy of treatment based on PiCCO monitoring was investigated in subgroups of ARDS and/or septic shock.

Results

The trial stopped early after enrollment of 350 participants because of futility of treatment based on PiCCO-derived physiological values (supplemental Fig. 3). The flow chart of subject enrollment is shown in Fig. 1.

The baseline characteristics are shown in Table 1. A total of 350 patients including 168 in PiCCO group and 182 in the control group were enrolled. The PiCCO group included more critically ill patients than the control group as reflected by the APACHE II score (median 29 vs. 24, $p = 0.0027$) and SOFA score (median 10 vs. 9, $p = 0.041$). Patients in the PiCCO group were more likely to be from floor wards (33.93 vs. 18.68 %, $p < 0.001$) but less likely to be from operating rooms (18.45 vs. 34.62 %, $p < 0.001$). The PiCCO group showed lower oxygenation index (median 180 vs 206 mmHg, $p = 0.041$) and Glasgow coma scale (median 10 vs. 12, $p = 0.031$). There was no difference between PiCCO and control groups in fluid balance from day 1 to day 6. On day 7 the PiCCO group received significantly less fluid volume than the control group (188 (−810, 1,059) vs. 644 (−211, 1,420) ml, $p = 0.028$).There was no difference in dobutamine use between PiCCO and control groups (41.07 vs 34.62 %, $p = 0.213$). The treatments given in the PiCCO and control groups are shown in supplemental Figs. 4–11.

There was no difference in 28-day mortality rate between the PiCCO and control groups (OR 1.00, 95 % CI 0.66–1.52; $p = 0.993$). There was no difference between PiCCO and control groups in secondary outcomes (Table 2). However, days free of CRRT in 14 days (median 11 vs. 14, $p = 0.0038$) and 28 days (median 15.5 vs. 21, $p = 0.048$) were significantly lower in the PiCCO group than in the control group. While the first 3 days showed significantly higher SOFA scores in the PiCCO group than in the control group, there was no difference between the two groups from day 4 throughout (supplemental Fig. 10).

A multivariable logistic regression model showed that the imbalance between treatment and control groups did not affect the estimated treatment effect too much (OR 1.23, 95 % CI 0.75–2.01; Table 3). In subgroup analysis, treatment based on PiCCO variables showed a marginal beneficial effect in patients with septic shock (RR 0.94, 95 % CI 0.72–1.25) and both (RR 0.82, 95 % CI 0.60–1.13). However, treatment based on PiCCO variables was harmful in ARDS patients (RR 4.43, 95 % CI 1.38–14.17, Fig. 2).

Complications associated with the placement of the femoral arterial catheter of the PiCCO system included 15

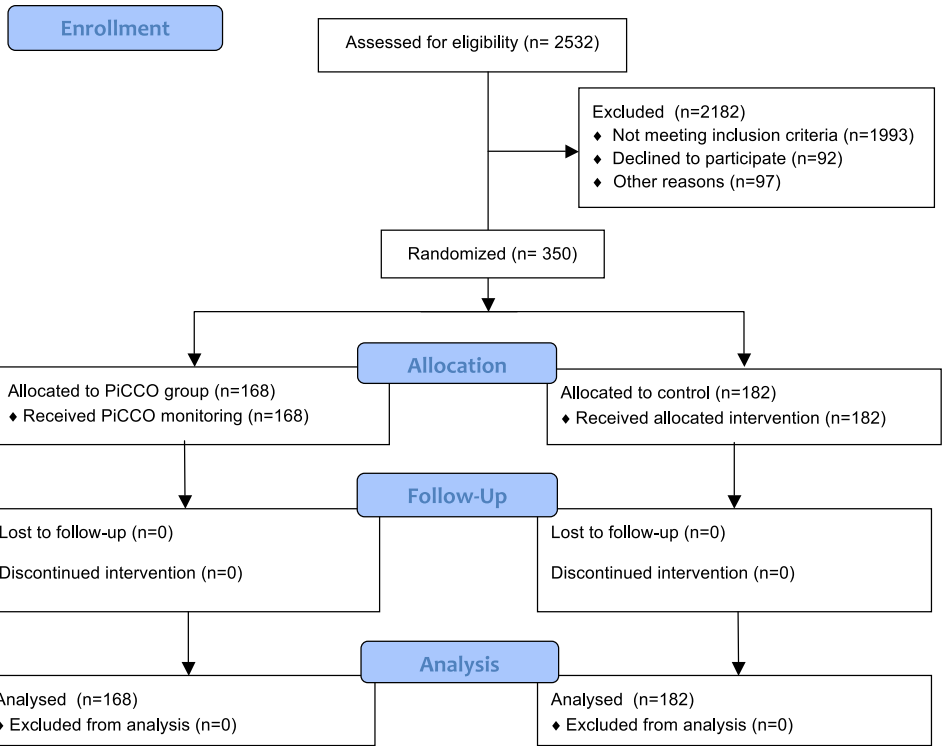

Fig. 1 Flow chart of subject enrollment. A total of 2,532 subjects were screened for eligibility during the study period. Finally a total of 350 subjects were enrolled into the study, including 168 in the PiCCO group and 182 in the control group

Table 1 Characteristics of patients at baseline

Characteristics	PiCCO group (n = 168)	Control group (n = 182)	P value
Male (n, %)	121 (72.0)	137 (75.3)	0.490
Age (years)	62.1 ± 15.7	64.7 ± 15.2	0.109
APACHE II (median IQR)	29 (21–35)	24 (17–31)	0.0027
SOFA (median IQR)	10 (8–12)	9 (7–12)	0.041
Site of infection (n, %)			0.251
Lung	71 (42.3)	71 (39.0)	
Urinary tract	9 (5.4)	3 (1.7)	
Abdomen	33 (19.6)	35 (19.2)	
Intestine	5 (3.0)	8 (4.4)	
Bloodstream	8 (4.8)	8 (4.4)	
Central nervous system	8 (4.8)	12 (6.6)	
Skin	5 (3.0)	15 (8.2)	
Others	29 (17.3)	30 (16.5)	
Type of patient (n, %)			0.790
ARDS	39 (23.2)	37 (20.3)	
Septic shock	79 (47.0)	87 (47.8)	
Both	50 (30.0)	58 (31.9)	
Sources (n, %)			<0.001
Emergency room	80 (47.6)	85 (46.7)	
Post-operation	31 (18.5)	63 (34.6)	
Floor ward	57 (33.9)	34 (18.7)	
Time from acute onset to ICU admission (h, median IQR)	13 (6–39)	11.5 (5–29)	0.256
Use of vasopressors (n, %)	119 (73.0)	127 (69.8)	0.508
Oxygenation index (mmHg)	180 (125–240)	206 (133–297)	0.041
Platelet count ($\times 10^9$)	133 (84–191)	136 (77.5–196)	0.845
Total bilirubin (mmol/l)	16.1 (9.4–30.5)	16.7 (9.8–31)	0.981
Glasgow coma scale	10 (6–15)	12 (8–15)	0.031
Serum creatinine (mmol/l)	156 (89.5–241.5)	133.5 (85.5–202.5)	0.148

ARDS acute respiratory distress syndrome, *ICU* intensive care unit, *IQR* interquartile range, *APACHE II* Acute Physiology and Chronic Health Evaluation II, *SOFA* sequential organ failure assessment

Table 2 Comparison of outcomes between PiCCO and control groups

Outcome variables	PiCCO group ($n = 168$)	Control group ($n = 182$)	P value
Primary outcome			
28-day mortality	83 (49.4)	90 (49.5)	0.993
Secondary outcomes			
Maximum SOFA	13 (10–15)	12 (9–14)	0.023
14-day mortality	68 (40.5)	75 (41.2)	0.889
Days on vasopressor	4 (2–6)	3 (2–6.5)	0.852
Days on MV	6 (3–12)	5.5 (3–12)	0.897
Days on CRRT	4 (3–7)	4.5 (3–7)	0.586
Length of stay in ICU	9 (5–13)	7.5 (4–15)	0.598
Days free of vasopressor in 14 days	10 (0–12)	9 (0–12)	0.562
Days free of MV in 14 days	1 (0–10)	4 (0–12)	0.127
Days free of CRRT in 14 days	11 (3–14)	14 (4–14)	0.0038
Days free of vasopressor in 28 days	14.5 (0–25)	19 (0–26)	0.676
Days free of MV in 28 days	3 (0–24)	6 (0–25)	0.168
Days free of CRRT in 28 days	15.5 (3–28)	21 (4–28)	0.048

Patients without use of MV, CRRT, or vasopressor were treated as missing variable, instead of zero
MV mechanical ventilation, *ICU* intensive care unit, *IQR* interquartile range, *CRRT* continuous renal replacement therapy

Table 3 Multivariable logistic regression model to adjust for unbalanced covariates between PiCCO and control groups

28-day mortality	Odds ratio	Lower limit of 95 % CI	Upper limit of 95 % CI	$P > z$
Group (control vs. PiCCO)	1.23	0.75	2.01	0.416
Gender (male as the reference)	1.04	0.61	1.78	0.874
Age (with 1 year increase)	1.01	0.99	1.02	0.488
Time from acute onset to ICU admission	0.99	0.99	1.00	0.038
Source (ER as reference)				
Operating room	0.72	0.40	1.29	0.265
Floor ward	1.17	0.65	2.11	0.590
Type of patient (ARDS as reference)				
Septic shock	3.26	1.62	6.54	0.001
Both	3.18	1.50	6.75	0.003
APACHE II	1.06	1.03	1.09	<0.001
SOFA D1	1.06	0.98	1.15	0.138

APACHE II Acute Physiology and Chronic Health Evaluation II, *SOFA* sequential organ failure assessment, *ER* emergency room, *OR* operating room

cases of venous puncture (8.9 %), 13 cases of hematoma (7.7 %), 4 cases of guide wire kinking (2.4 %), and 1 case of catheter malfunction (0.6 %).

Discussion

On the basis of our study, PiCCO-based fluid management did not improve outcome when compared to CVP-based fluid management. The SOFA scores during the first 3 days were significantly higher in the PiCCO group than in the control group, but thereafter the difference disappeared. The study included patients with both septic shock and ARDS, because treatment based on PiCCO monitoring might benefit both of them [8]. Furthermore, the two conditions usually coexist [14]; as shown in our study, approximately 30 % of participants had both ARDS and septic shock.

To the best of our knowledge, there are few RCTs exploring the effectiveness of treatment based on PiCCO-derived physiological values on mortality in patients with ARDS and/or septic shock [15]. In cardiac surgery patients, Goepfert and coworkers compared the effect of treatment based on PiCCO monitoring to the historical control and found that PiCCO-based fluid management was able to reduce the number of days on vasopressors and shorten the length of stay in ICU [16]. This study was limited by the small sample size and the use of historical controls. Another study compared the effectiveness of goal-directed therapy guided by either PAC or PiCCO on patients' outcome [17]. Similarly, the study did not have enough power and the population comprised those undergoing cardiopulmonary bypass surgery. The study found that PiCCO-based fluid management was able to improve hemodynamics and oxygen delivery and reduce the duration of postoperative respiratory support. Cardiac surgery patients usually have well-preserved pulmonary

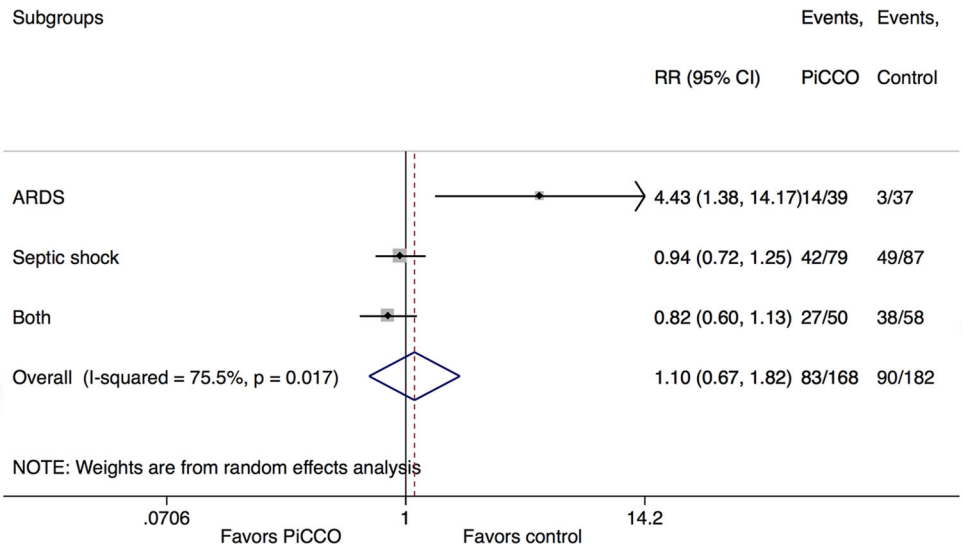

Fig. 2 Forest plot showing subgroup analysis by the type of patient. Treatment based on PiCCO variables showed a marginal beneficial effect in patients with septic shock (RR 0.94, 95 % CI 0.72–1.25) and both (RR 0.82, 95 % CI 0.60–1.13). However, treatment based on PiCCO variables was harmful in ARDS patients (RR 4.43, 95 % CI 1.38–14.17)

and circulatory function as compared to those with septic shock and/or ARDS, which could partly explain the difference between these studies. Consistent with our findings, Trof and coworkers showed that PiCCO-based fluid management failed to improve ventilator-free days, lengths of stay, and mortality of critically ill patients with shock [15].

EVLW measured by TPTD has long been known as a predictor of mortality [8], and negative fluid balance has also been associated with improved clinical outcomes [18–20]. However, there is no significant difference in daily fluid balance between PiCCO and control groups. Most probably, the notion that negative fluid balance benefits critically ill patients with ARDS has been widely accepted and practiced in routine clinical practice. If auscultation or chest X-ray suggests pulmonary edema that is consistent with ARDS, diuretics or CRRT with a higher fluid removal rate will be given. Despite unawareness of the exact quantity of EVLW by the treating physician, the control group may actually experience similar levels of negative fluid balance. Another reason for the neutral effect of PiCCO-based fluid management on fluid balance lies in the fact that a substantial proportion of patients (more than 70 %) had shock requiring vasopressor support on ICU admission for which the study protocol dictates positive fluid balance. At a later stage (day 7), treatment guided by PiCCO monitoring resulted in more negative fluid balance than the control group. As compared to the FACCT trial, our study showed much more negative fluid balance in both groups [18]. The plausible explanations could be (1) the FACCT trial was conducted 10 years ago when the beneficial effect of a restrictive strategy had not been established. Since there is now a large body of evidence suggesting the beneficial effect of negative fluid balance, higher doses of diuretics would be given at a certain EVLWI value. (2) The FACCT trial included ALI patients with less severe pulmonary edema, resulting in less negative fluid balance.

Several limitations of the study need to be acknowledged. First, the study was stopped prematurely because of futility of treatment based on PiCCO monitoring and some parameters were not balanced by randomization. We acknowledged that the randomization was not blocked in our design such that the stratification was ineffective in balancing groups. In order to adjust for the treatment effect, we used multivariable regression analysis. On the other hand, the imbalance could be introduced by the origin of patients, and that patients from floor wards were more severely ill than others. As a consequence, the APACHE II, SOFA, and Glasgow scores were higher. Second, the study employed futility, instead of over-mortality using PiCCO, as the stopping rule. Some may argue that recruiting more patients is not unethical. However, because PiCCO is very expensive and is not covered by medical insurance in China, it is unethical to use it from the perspective of cost-effectiveness. Third, the treatment algorithm based on hemodynamic monitoring is not evidence-based and primarily based on experience, thus we cannot exclude beneficial effects of other treatment algorithms guided by PiCCO monitoring. Hemodynamic monitoring is complex and controversial, and there are multiple factors that may influence the algorithm. For example, the parameters to predict fluid responsiveness are controversial. Dynamic parameters such as stroke volume variation (SVV) and pulse pressure variation (PPV) may be better, but they are only applicable to patients with controlled mechanical ventilation rather than spontaneously breathing patients [21, 22]. The passive leg raising test is usable even in arrhythmic patients and with protective ventilation, but its performance is complex. In real clinical settings, $ScVO_2$

can be normal in septic shock, low cardiac output can be related to preload deficit, and ITBV can be elevated in cases of hypervolemia without cardiac dysfunction. Therefore, the treatment algorithm in our study is a general guidance and clinicians still have room to make their own judgment. On the other hand, we have tried to keep the algorithm simple because if it becomes more complex the compliance by the treating physician will be significantly compromised. Furthermore, if the protocol is too complex, it may fail to reflect the situation in real-word settings. In other words, the result of the study may not be generalizable to real clinical settings (e.g., clinicians may not obey an algorithm that is deemed too complex). With respect to outcome variables, the study endpoint we chose was short-term mortality, and the impact of PiCCO-based fluid management on other endpoints such as 90-day mortality and quality of life after hospital discharge is largely unknown. Forth, specific values of hemodynamic variables were employed to trigger certain treatment (e.g., ITBVI less than 850 was used to trigger fluid bolus). It should be acknowledged that normal ranges of PiCCO-derived physiological values are not fixed but varied among subjects [23]. In some situations the algorithm should be modified to accommodate patients' clinical conditions. For example, in patients with high EVLWI we may give furosemide as per the protocol, but in reality some of the patients may still be in shock and in such cases it is inappropriate to administer furosemide. Excessive furosemide administration leads to hypovolemia and low cardiac output, which in turn will justify the use of dobutamine. These are shortcomings of treatment simply based on PiCCO variables. One alternative to the algorithm would be first to judge the shock status, and then to decide whether furosemide should be used or not. In real-world settings we propose that the clinical condition and clinicians' judgment should be considered rather than simply relying on PiCCO readings. Lastly, the mortality rate in our population is higher than expected, which may compromise the generalizability of the result. Most probably, the high mortality is due to limited ICU beds in China. Limited resources mean that only the most critically ill patients can be admitted to central ICUs and others were managed in floor wards. Another reason for the high mortality may be due to the treatment algorithm used in both arms [24]. For example, a substantial number of patients received furosemide as a result of PiCCO variables (e.g., someone with hypovolemia may have normal ITBVI and high EVLWI), which may lead to hypovolemia and tissue hypoperfusion.

In conclusion, on the basis of our study, PiCCO-based fluid management does not improve outcome when compared to CVP-based fluid management.

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Conflicts of interest There was no conflict of interest.

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