

Point-of-care ultrasound-guided conservative fluid therapy improved the outcome of critically ill patients: a before-and-after study

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Research

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Abstract

Background

The danger of volume overload was not yet well understood and appreciated. Point-of-care ultrasound assessment of blood volume was not widely practiced.

Methods

Critically ill patients managed with point-of-care ultrasound were compared with those managed without, in an intensive care unit (ICU) for medical and surgical cases. Distended internal jugular veins and inferior vena cava with reduced collapsibility were taken as signs of hypervolemia and negative fluid balance became a goal.

Results

Compared with critically ill patients admitted before application of point-of-care ultrasound assessment (from March, 2019 through October, 2019; 291 cases), cases admitted after (from November, 2019 through June, 2020; 285 cases) had significantly lower in-ICU mortality (34.7% vs 26.7%, $p=0.038$; Fisher's exact test), together with a dramatic change from overall positive fluid balance to negative one. Multiple logistic regression showed that cumulative fluid balance during ICU stay, Acute Physiology and Chronic Health Evaluation (APACHE) II score and Sequential Organ Failure Assessment (SOFA) scores on admission were independent risk factors for in-ICU mortality ($p<0.001$, $p<0.001$ and $p=0.043$ respectively). After controlling for APACHE II and SOFA scores on admission, Cox hazard ratio of cases with a negative cumulative fluid balance during ICU stay was 0.683 (95% confidence interval 0.475-0.981; $p=0.0039$).

Conclusions

Point-of-care ultrasound examination of internal jugular veins and inferior vena cava directed fluid therapy to conservative strategy, and negative cumulative fluid balance during ICU stay was associated with a reduced in-ICU mortality.

Background

Fluid therapy was of paramount importance in the management of critically ill patients. Fluids in excessive amounts could have deleterious effects on several organ functions, including acute kidney injury and worsening respiratory function[1]. The danger of volume overload had been noted in some critically ill patients, namely sepsis/septic shock patients[2–4]. However, the focus of intensivists was usually limited to resuscitation phase immediately after hospitalization of critically ill patients; intensivists paid little attention to fluid balance after initial hemodynamic stabilization. Fluid removal or de-resuscitation after hemodynamic stabilization was seldom put into practice[4, 5]. And too often, fluid balance of critically ill patients other than sepsis/septic shock cases was not the concern of intensivists. Up to date, the danger of volume overload was not well understood and appreciated.

In previous studies, internal jugular vein was found to be a good surrogate of central venous pressure (CVP)[6–11]. Distention of internal jugular veins had the same implications as distention of superficial neck veins, and the only difference was that ultrasound could probe deeper. Although visual inspection of jugular veins as an estimate of CVP had been an integral part of physical examination, its major limitation was that jugular veins were not always observable, especially in obese patients[12]. Although the disagreement persisted as to the interpretation of size and collapsibility of inferior vena cava[13–16], distension and reduced collapsibility of inferior vena cava pointed to normo-/ hyper-volemia and were proved to be very beneficial in guiding fluid therapy[17]. The present study was carried out to compare the outcome of critically ill patients before and after the implementation of point-of-care ultrasound examination of both internal jugular veins and inferior vena cava.

Methods

We conducted this study in Intensive Care Unit (ICU) of Jinniu Hospital affiliated to Sichuan Provincial Hospital. This ICU was a 24-bed setting for medical and surgical patients. The ethical committee at Jinniu Hospital approved the study protocol. The informed consents were obtained from the patients or their close relatives. The study was conducted in accordance with the Declaration of Helsinki.

From March, 2019 on, senior physicians from Emergency Intensive Care Unit (EICU) of Sichuan Provincial Hospital were sent to preside over daily works of this ICU, first by Dr Deng for 8 months, then by Dr Chen (the corresponding author) for another 8 months. During the first 8 months, point-of-care ultrasound was seldom used. Point-of-care ultrasound was widely used during the late 8 months. Distended internal jugular veins and inferior vena cava were viewed as signs of hypervolemia, together with raised CVP or brain natriuretic peptide (BNP) or radiological/clinical findings of pulmonary edema.

Cross-sectional area of internal jugular vein and diameter of inferior vena cava were measured with Mindray M9 (Shenzhen Mindray Bio-medical Electronics Co., Ltd., Shenzhen, Guangdong Province, China). Internal jugular vein was measured at cricoid level. Inferior vena cava was measured just below the xyphoid process, and within 2 cm from right atrium. They were both measured at end-expiration. To measure internal jugular vein, the probe was gently placed on the skin; internal jugular vein was readily deformed by any pressure applied to it. Cross-sectional areas of internal jugular veins were measured because many of them were in irregular shapes, and only a small number of them were rounded. Whenever distended internal jugular vein with a collapsibility index (cross-sectional area) > 50% and/or inferior vena cava diameter > 15 mm with a collapsibility index(diameter) > 50% were detected, negative fluid balance became a goal. Loop diuretics were frequently used to achieve a negative fluid balance, together with fluid restriction.

Inclusion criteria: a successive cohort of patients admitted to ICU were included.

Exclusion criteria: patients died or discharged against medical advice within 10 hrs after admission or referral to ICU; surgical patients, either emergent or elective, referred to EICU for anesthesia recovery, experiencing an uneventful recovery, and with an ICU stay shorter than 3 days.

Outcome measures: The primary endpoint was in-ICU mortality. The survivors were referred to medical or surgical ward. Non-survivors included patients discharged against medical advice, either dying or withdrawal of life support due to economic reason. They died on the way home or back home. It was stipulated by local authority that patients died in hospitals had to be cremated. These patients chose to be discharged against medical advice because they wanted to be buried, not cremated. Non-survivors also included patients referred to Sichuan Provincial Hospital and died within 72 hrs after referral. The secondary endpoints were length of ICU stay (LOS), length of ventilator support (invasive and/or non-invasive).

APACHE (Acute Physiology and Chronic Health Evaluation) II and SOFA (Sequential Organ Failure Assessment) scores were calculated by the corresponding author (YC) alone, using data of the first 24 hrs after admission to EICU. For patients died within 24 hrs after admission, data at least 30 min prior to death were taken into consideration.

Gastrointestinal loss and third space loss which was drawn with a needle and syringe or percutaneously drained were counted as output. Insensible losses were not counted.

Statistical analysis

These data were analyzed with IBM SPSS Statistics 20. APACHE II and SOFA scores of different groups were compared with Student's *t*-test. In-ICU mortalities of different groups were compared with chi-square test and Fisher's exact test. Fluid balances of cases enrolled before application of point-of-care ultrasound were compared with that of cases enrolled after application of ultrasound using Student's *t*-test. Amounts of intravenously-administered furosemide before application of point-of-care ultrasound were compared with that after application of ultrasound using Mann-Whitney U test. Logistic regression analysis was conducted to find out the risk factors of in-ICU mortality among APACHE II score, SOFA score, day 1 fluid balance, day 2 cumulative fluid balance, day 3 cumulative fluid balance and cumulative fluid balance during ICU stay. Logistic regression analysis did not report odds ratio and confidence interval when fluid balances were in ml. Then logistic regression analysis was done after fluid balances were transformed into –Ls (liters). Survival curve (Cox regression model) and ROC (receiver operating characteristic) curve were plotted with IBM SPSS Statistics 20. Length of ventilator support and LOS of cases before application of ultrasound were compared with that of cases after application of ultrasound using Mann-Whitney U test.

Results

From March, 2019 through June, 2020, 576 cases were enrolled. Cases enrolled before application of point-of-care ultrasound were not significantly different from those enrolled after application of ultrasound, in respect to age, principal diagnoses, and APACHE II and SOFA scores on admission (Table 1).

Table 1 Demographic characteristics of subjects

	Before application of ultrasound	After application of ultrasound	Sig.
No. of cases	291	285	
Age (years old)	65.5± 17.4(14-97)	65.9±17(15-96)	p=0.395
Sex (male:female)	189:102	169:116	
Principal diagnosis			
Sepsis/septic shock	129	119	p=0.556
Cardiac arrest/arrhythmia/acute coronary syndrome/heart failure	38	36	p=0.901
Intracranial hemorrhage/cerebral infarction	36	43	p=0.397
Traumatic brain injury	35	24	p=0.17
Multiple trauma	17	18	p=0.863
APACHE II score on admission	21.2±9.4	21.6±9.2	p=0.368
SOFA score on admission	7.5±4.1	6.9±4.2	p=0.502

Age, APACHE II score and SOFA score were compared with Student's *t*-test; principal diagnoses were compared with Pearson chi-square test.

Cumulative fluid balance during ICU stay for cases enrolled before application of ultrasound was significantly more than that for cases enrolled after application of ultrasound; there was a dramatic change from overall positive fluid balance to negative one (Fig. 1). After application of point-of-care ultrasound, intravenously-administered furosemide was markedly increased (Fig. 2). In-ICU mortality of cases enrolled before application of ultrasound was significantly higher than that of cases enrolled after application of ultrasound (34.7% vs 26.7%, $p = 0.038$; Fisher's exact test) (Fig. 3).

Figure 1 Fluid balances of the first three days and cumulative fluid balance during ICU stay. *Using Student's *t*-test.

Figure 2 Amounts of furosemide intravenously administered. *Compared with Mann-Whitney U test.

Figure 3 In-ICU mortalities. * Compared with chi-square test ($p = 0.036$) and Fisher's exact test ($p = 0.038$). For cases with positive vs. negative cumulative fluid balance during ICU stay, $p < 0.001$ by both chi-square test and Fisher's exact test.

After controlling for APACHE II and SOFA scores on admission, Cox hazard ratio of cases with a negative cumulative fluid balance during ICU stay was 0.683 (Fig. 4). Multiple logistic regression showed that cumulative fluid balance during ICU stay, APACHE II score and SOFA scores on admission were

independent risk factors for in-ICU mortality (Fig. 5). APACHE II and SOFA scores on admission, cumulative fluid balance during ICU stay, day 2 and day 3 cumulative fluid balances all could predict in-ICU mortality; AUCs(95% confidence intervals) were 0.82(0.784–0.857), 0.785(0.745–0.825), 0.714(0.667–0.76), 0.618(0.567–0.669) and 0.635(0.584–0.686) respectively, all < p0.001 (Fig. 6).

Figure 4 Survival curve by Cox regression model. *After correcting for APACHE II and SOFA scores on admission.

Figure 5 Multiple logistic regression

Figure 6 Receiver operating characteristic curve

Compared with cases before application of point-of-care ultrasound, cases after application of ultrasound had significantly shorter length of ventilator support, 4.7 ± 0.7 days vs. 2.8 ± 0.2 days ($Z = 2.465$, $p = 0.014$; Mann-Whitney U test). Their LOSs were not significantly different, 8.4 ± 0.8 days vs. 6.5 ± 0.3 days ($Z = 0.195$, $p = 0.845$; Mann-Whitney U test).

Conclusions

Volume overload might become increasingly evident in the course of illness. If not curbed, volume overload would minimize the chance of survival of critically ill patients. Overgenerous fluid administration should be avoided, and fluid balance should be meticulously managed during the whole ICU stay. More studies are needed to address the importance of fluid management during the whole ICU stay.

Abbreviations

ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; CVP, central venous pressure; LOS, length of ICU stay; ROC, receiver operating characteristic; AUC, area under curve.

Discussion

In the present study, two senior physicians of the same ICU, with similar background, were sent to preside over ICU daily works of Jinniu Hospital affiliated to Sichuan Provincial Hospital. And the patients enrolled before application of point-of-care ultrasound were not significantly different from those enrolled after, in respect to principal diagnoses, disease severity on admission and age. These patients were comparable, except for the application of point-of-care ultrasound.

The present study showed that cumulative fluid balance during ICU stay was an independent risk factor of in-ICU mortality. After application of point-of care ultrasound, a dramatic change from positive fluid balance to negative one occurred. And the change in fluid balance was associated with a significant reduction in in-ICU mortality.

It was reasonable to direct fluid therapy with point-of-care ultrasound examination of internal jugular veins and inferior vena cava. Point-of-care ultrasound examination of internal jugular veins should not be viewed as a brand-new concept; distention of internal jugular veins had the same implications as distention of superficial neck veins. Point-of-care ultrasound examination of internal jugular veins was better than visual inspection of superficial neck veins, in that it could probe deeper. One major limitation of visual inspection was that jugular veins were not always observable, especially in obese patients[12]. Distension and reduced collapsibility of inferior vena cava pointed to normo-/ hyper-volemia and were proved to be very beneficial in guiding fluid therapy[17].

Why cumulative fluid balance during ICU stay notably affected the outcome of critically ill patients? There were two reasons worth mentioning. First, some critically ill patients were hypervolemic from the very beginning of their hospitalization. Second, catabolism and disuse.

Previous studies showed that many critically ill patients were essentially hypervolemic. For example, in critically ill anemic patients, hypervolemia was common[18]. "Plasma volume excess", in addition to "hemoglobin deficiency", often characterized anemia when plasma volume was measured[19]. Plasma volume could increase by 70% in chronic severe anemia[20]. In heart failure with preserved ejection fraction, expanded total blood volume together with true anemia was common[21, 22]. In volume overload decompensated chronic heart failure, plasma volume expansion dilution-related "anemia" predominated[23]. Dilution in consequence of sodium and water retention was an important reason for development of anemia in chronic heart failure[24]. In patients with chronic kidney disease, anemia was often complicated with fluid retention and overhydration, resulting in increased risk of cardiovascular morbidity and mortality and chronic kidney disease progression[25]. Expansion of plasma volume and hemodilution were important features of anemia due to hemopoietic diseases, such as leukemia[26].

Most critically ill patients experienced a catabolic course which was not easily reversed by medication or nutritional support. Critically ill patients developed muscle atrophy rapidly[27], as a result of both anabolic resistance (reduced stimulation of muscle protein synthesis to a given dose of protein/amino acids) and enhanced skeletal muscle breakdown[28], or as a result of iatrogenic protein undernutrition[29], and preferentially affecting the lower limbs[30]. Both catabolism and disuse in bedridden cases resulted in breakdown of proteins and reduction of dry body weight, leading to production of "endogenous water" and release of water from degraded proteins and fats. Fluid derived from catabolism and disuse should be removed to avoid volume overload and tissue edema.

In critically ill postoperative patients and patients with severe nutritional depletion, a dramatic change in body composition was observed. Reduction of body weight was accompanied by a marked increase in extracellular water (by 4.0-5.1 liters in 31–34 days) [31]. Rapid and massive total protein loss was accompanied by retention of large amounts of fluids in critically ill patients with major traumatic injury or severe sepsis. Trauma patients had retained > 6L and sepsis patients > 12L of fluids, mainly in the extracellular compartment, by the time they were hemodynamically stable. And in elderly patients (>

60 years) the period of extracellular water expansion was markedly prolonged compared to younger patients (< 40 years)[32].

Fluids in excessive amounts could have deleterious effects on several organ functions, including acute kidney injury and worsening respiratory function[1]. The danger of volume overload was already noted in some critically ill patients, namely sepsis/septic shock patients[2–4]. The present study was in line with these studies, suggesting that conservative fluid strategy was superior to liberal one, and that fluid removal or de-resuscitation after hemodynamic stabilization should be put into practice.

The negative impact of positive cumulative fluid balance could not be overestimated. Many hypervolemic patients died when given diuretics. If fluid management could be improved, these cases would add to the difference in survival between cases enrolled before application of point-of-care ultrasound and those enrolled after. The diuresis of these deceased patients was not well titrated, in respect of timing and dosing of diuretic administration. Admittedly, the fluid balance was difficult to maintain in these critically ill patients. Studies conducted by nephrologists showed that shift of fluid between intravascular and extravascular compartments could be surprisingly rapid; plasma refill rate reached up to 20.1 ± 4.0 ml/min during hemodialysis[33–35]. When re-absorption far exceeded the rate of volume removal, a “well-controlled” pace of negative fluid balance would result in hemodynamic instability.

One main problem was that physicians had difficulty adapting to such a paradigm shift; fluid challenge and positive fluid balance were still the only solution when facing shock and lactic acidosis. The improvement in outcome would be greater if all physicians had abandoned fluid preference.

Another limitation of the present study was that 28-day or 90-day mortality was not recorded. However, the contribution of post-ICU treatment to 28-day or 90-day mortality was difficult to estimate, and physicians’ and surgeons’ fluid preferences would have major impact on these outcome measures.

Declarations

Ethics approval and consent to participate

The ethical committee at Jinniu Hospital approved the study protocol. The informed consents were obtained from the patients or their close relatives.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Availability of data and material

The datasets during and/or analyzed during the current study are available from the corresponding author on request.

Authors' contributions

HH and DL took part in data collection and analysis. ZM conducted ultrasound examination. CJ took part in data collection. CY took part in data collection and analysis, and wrote the manuscript. All authors read and approved the final manuscript.

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Figures

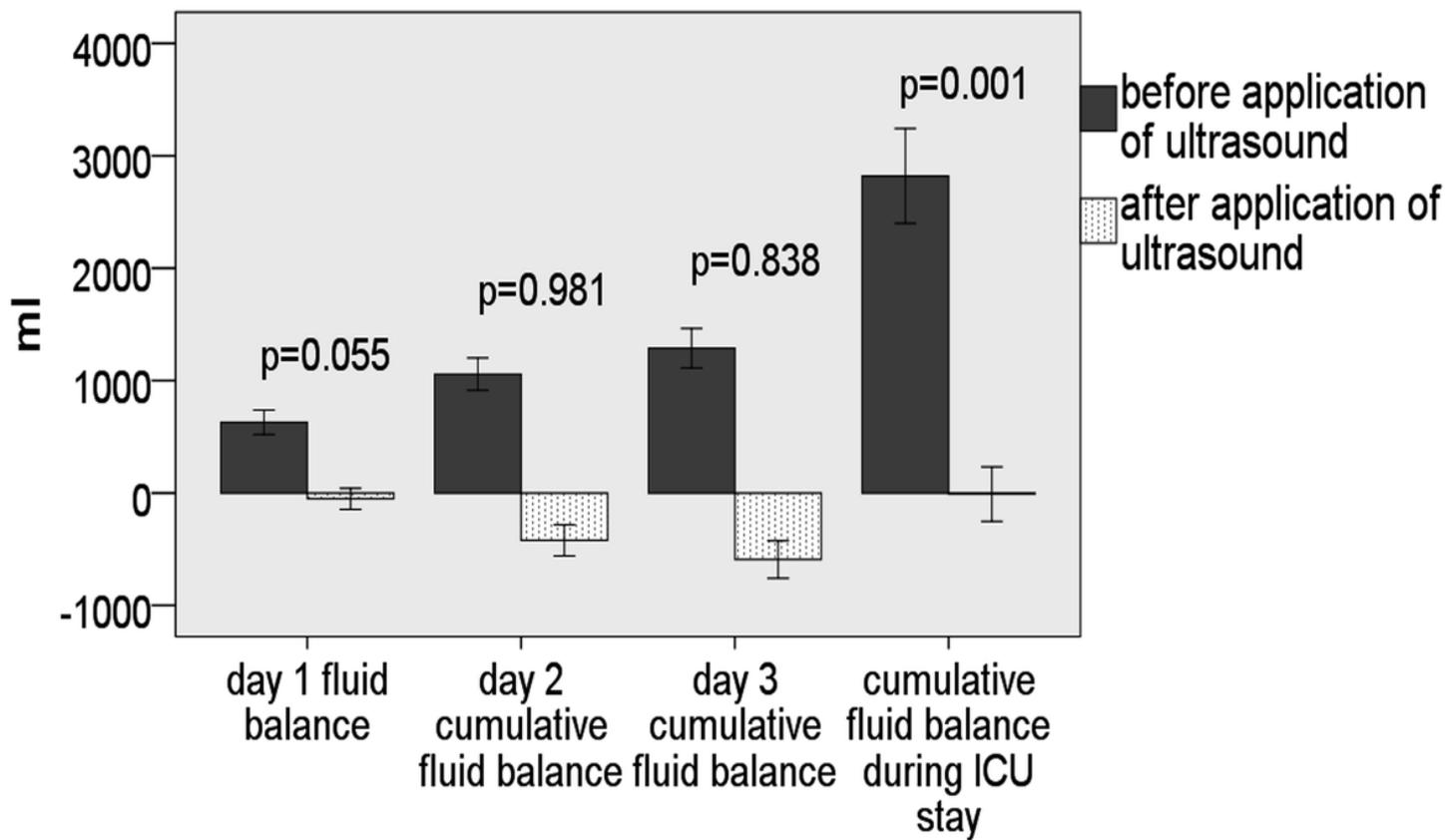


Figure 1

Fluid balances of the first three days and cumulative fluid balance during ICU stay. *Using Student's t-test.

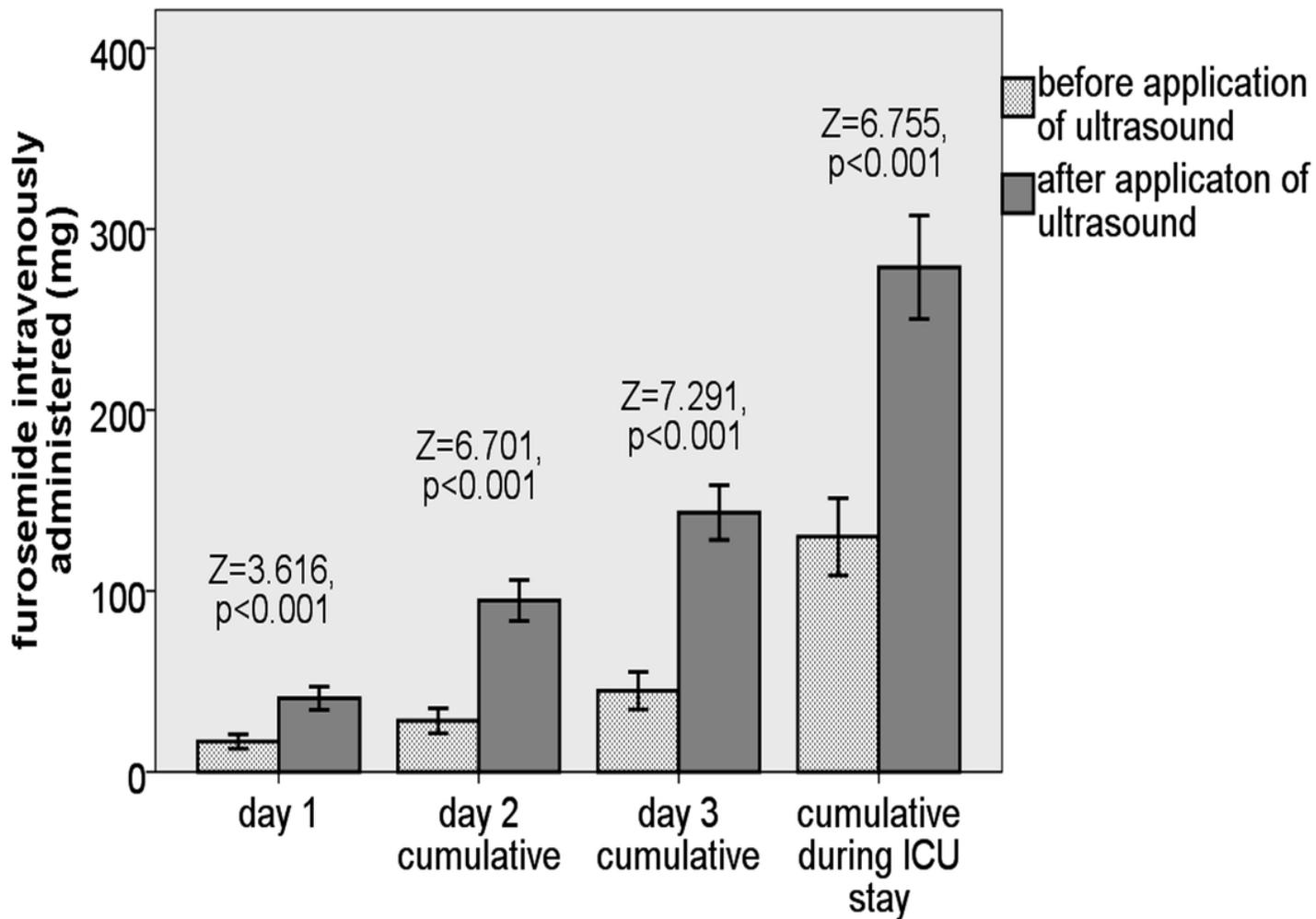


Figure 2

Amounts of furosemide intravenously administered. *Compared with Mann-Whitney U test.

in-ICU mortalities

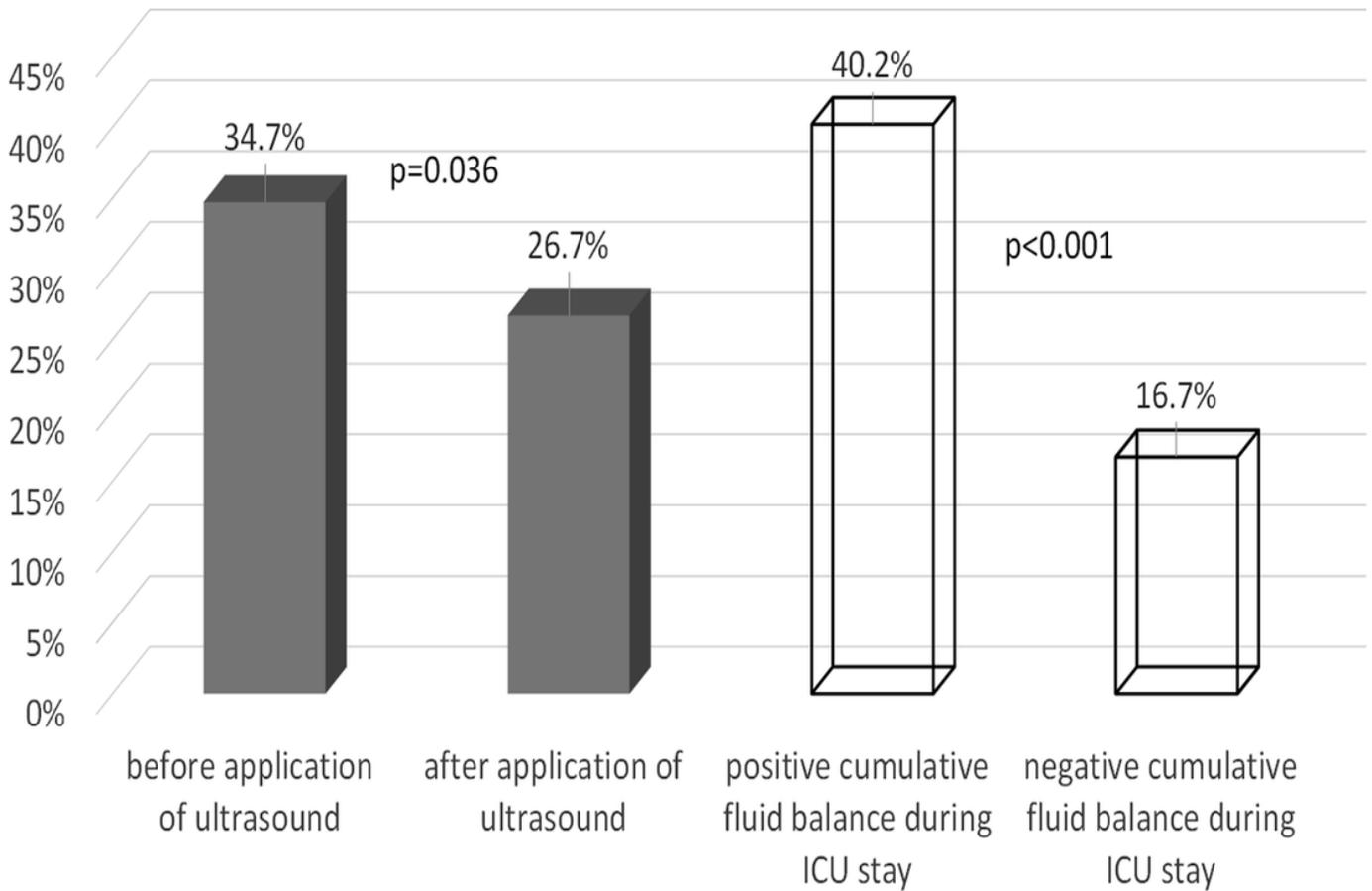


Figure 3

In-ICU mortalities. * Compared with chi-square test ($p=0.036$) and Fisher's exact test ($p=0.038$). For cases with positive vs. negative cumulative fluid balance during ICU stay, $p<0.001$ by both chi-square test and Fisher's exact test.

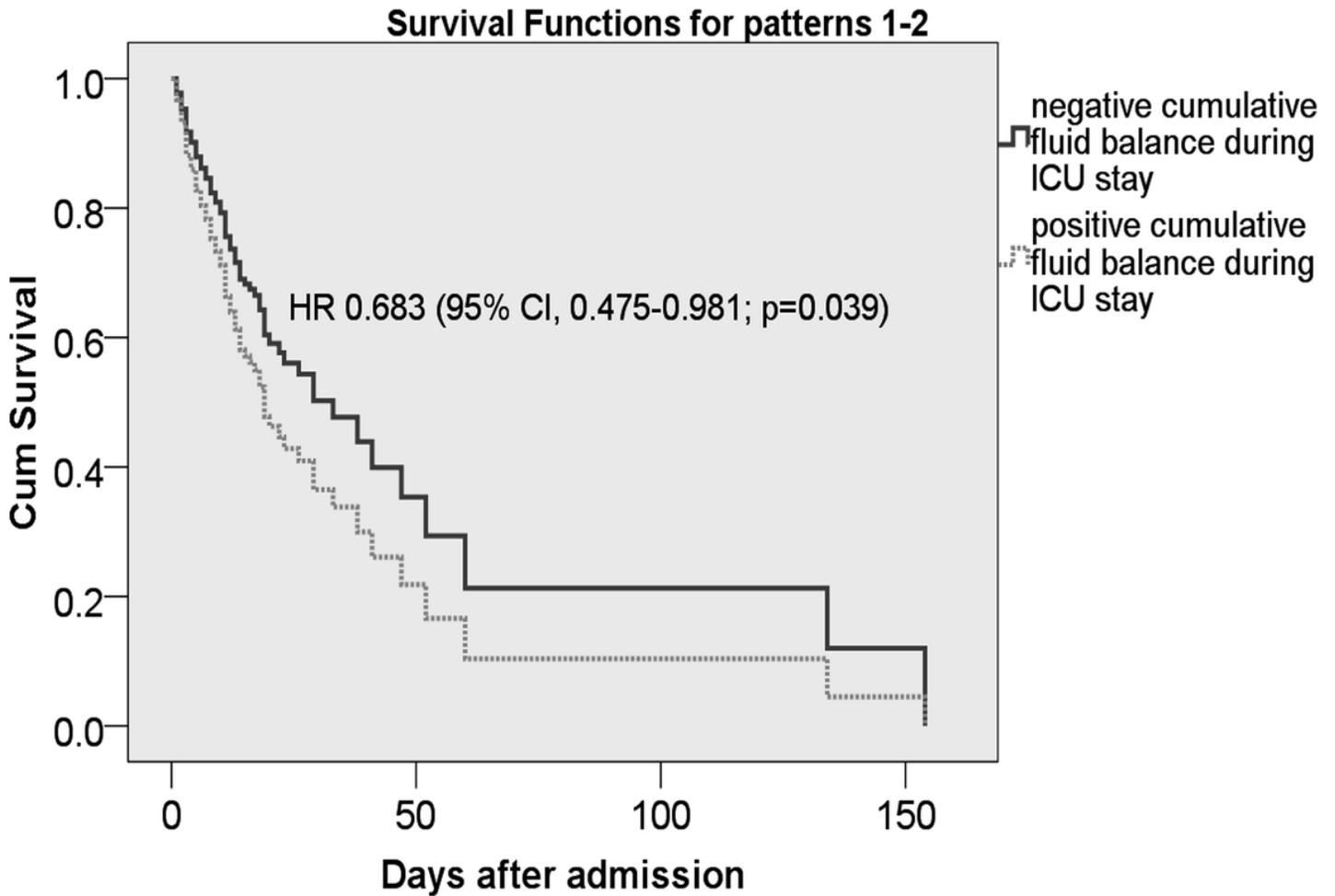


Figure 4

Survival curve by Cox regression model. *After correcting for APACHE II and SOFA scores on admission.

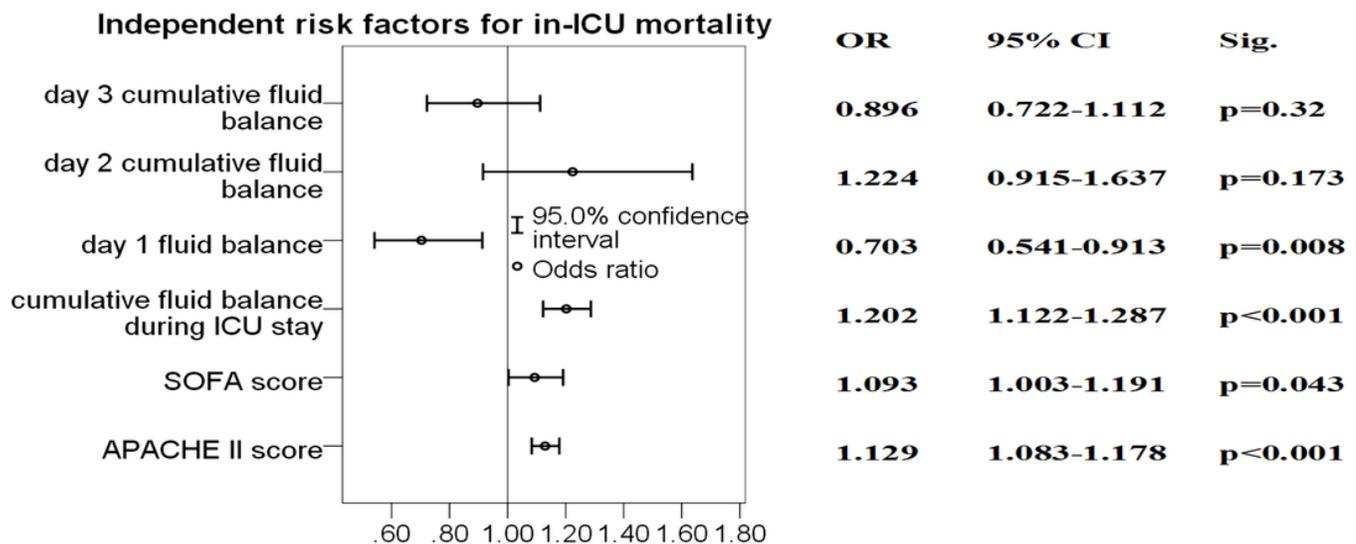


Figure 5

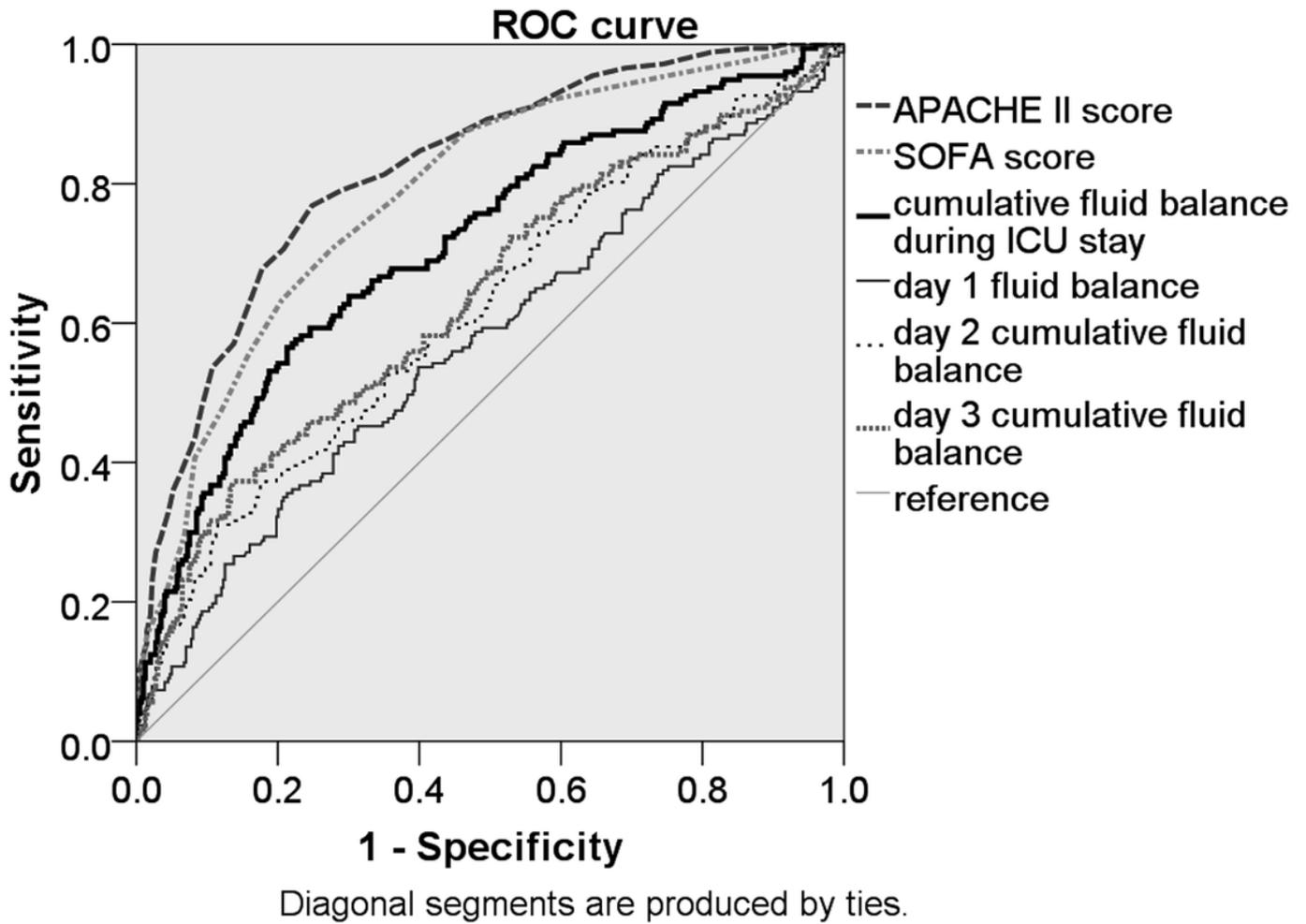


Figure 6

Receiver operating characteristic curve