Effect of A Positive Cumulative Fluid Balance On The Prognosis of Patients With Sepsis In The Xining Area

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Research Article

Keywords: Sepsis, positive fluid balance, risk factors, Xining, prognosis

Posted Date: November 19th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1035959/v1

Abstract

Background: The aim of this work is to analyze the effect of a positive cumulative fluid balance and relative clinical indicators on the prognosis of patients with sepsis in the Xining area, China.

Methods: The clinical data of 480 sepsis patients (313 males and 167 females, aged 52–77 (65) years) admitted between January 2017 and December 2019 were retrospectively analyzed. The APACHE II score, SOFA score, SIRS score and clinical laboratory test indicators of the patients were collected. Receiver operating characteristic (ROC) curves were used to analyze the sensitivity and specificity of each indicator in predicting the poor prognosis of patients with sepsis, and the maximum Youden index was used to determine threshold values. Cox regression analysis was performed to assess patient prognosis using data from patients with different fluid balances.

Results: The following clinical indicators were significantly different between the 2 groups ($P<0.05$): APACHE II score, SOFA score, SIRS score, PCT, IL-6, BNP, CRP, PLT, BUN, CREA, Lac and total fluid balance from days 1 to 5. The area under the ROC curve (AUC) for total fluid balance from days 1 to 5 was 0.558, the cut-off value was 2120.5 mL, the sensitivity was 54.0%, and the specificity was 58.1%. The survival rates were different between the 2 groups (60.9% vs 48.9%, $P<0.05$). Total fluid balance was significantly higher in patients with septic shock and with Lac>2.0 mmol/L ($P<0.05$). Cox regression analysis indicated that APACHE II score, SOFA score, PLT score, Lac, and total fluid balance from days 1 to 5 were independent risk factors for poor prognosis.

Conclusion: A positive fluid balance from days 1 to 5 after ICU admission was associated with poor patient outcomes and was an independent risk factor for poor patient prognosis.

Background

Early and adequate fluid resuscitation is the cornerstone of sepsis and septic shock treatment [1, 2]. However, recommended fluid resuscitation regimens may present risks of fluid overload (FO) in some patients with stable blood pressure. In a recent study, it was found that during early fluid resuscitation in patients with sepsis, the first consideration for clinicians is hemodynamic stability, that is, blood pressure stability, rather than changes in organ function. An increasing number of studies have shown that FO can affect the organ function and prognosis of patients with sepsis [3−5]. The altitude of the Xining area of China is 2260 m, the atmospheric pressure is 585 mmHg, the atmospheric oxygen partial pressure is 121 mmHg, and the average human arterial oxygen partial pressure is 75 mmHg. Humans in this location are in a chronic hypoxic environment; however, the human body adapts through compensatory physiological changes. For example, pulmonary arterial pressure gradually increases, and microcirculation hyperplasia occurs. Due to these physiological changes, the cumulative amount of fluid resuscitation will impact the prognosis of patients with sepsis and septic shock. In this study, we retrospectively analyzed the clinical data of sepsis patients admitted to our hospital to observe whether the changes in positive fluid balance in sepsis patients are related to adverse patient outcomes and to explore the possible mechanisms.

Methods

Study population

The medical records of 480 sepsis patients admitted to the intensive care unit (ICU) of Qinghai Provincial People's Hospital from January 1, 2017, to December 31, 2019, were collected. The inclusion criteria were as follows: admitted patients who met the diagnostic criteria of Sepsis 3.0 [6]; and patients older than 18 years. The exclusion criteria were patients with severe hematological diseases; patients with severe malignant tumors; patients with long-term use of hormones; patients with diabetic ketoacidosis and diabetic hyperosmolar coma; patients who were pregnant; and patients with incomplete clinical data. All patients were performed in accordance with Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016.The informed consent was obtained from all subjects and/or their legal guardian(s).

Data collection

The following clinical data of patients at the time of admission to the ICU were collected: nationality, sex, source, diagnosis, acute physiology and chronic health evaluation II (APACHE II) score, sequential organ failure assessment (SOFA) score, systemic inflammatory response syndrome (SIRS) score, Glasgow coma scale (GCS) score, procalcitonin (PCT) concentration, interleukin-6 (IL-6) concentration, brain natriuretic peptide (BNP) concentration, C-reactive protein (CRP) concentration, white blood cell (WBC) count, platelet (PLT) count, blood urea nitrogen (BUN) concentration, creatinine (CREA) concentration, and fluid from days 1 to 5 after ICU admission. The number of days of hospitalization in the ICU and the prognosis at the time of discharge from the ICU were recorded. PCT concentration was determined using a Cobas 8000 (Roche, Germany). BNP concentration was determined using a DXi 800 (Beckman Coulter, USA). Routine blood analyses were performed using an XN9000 (Sysmex Corporation, Japan). Biochemical indicators were analyzed using a Siemens ADVIA®2400 automatic biochemical analyzer. Supporting reagents were supplied by the manufacturers.

Outcomes

Hospital mortality was the endpoint, which was defined as the status of patient survival before ICU discharge.

Statistical analysis

SPSS 22.0 was used for data processing. The 1-sample KS test (two-sided test) was used to determine whether the measurement data conformed to a normal distribution. Abnormally distributed measurement data are presented as $M\,(Q_1, Q_3)$, and the Mann–Whitney U test was used for comparisons between the 2 groups. Count data were analyzed using the four-grid table or row × column table X^2 test. Receiver operating characteristic (ROC) curves were used to determine the sensitivity, specificity, and maximum Youden index of each included indicator. The prognosis of patients with different fluid balances was compared using Cox regression analysis. $\alpha < 0.05$ indicated that a difference was statistically significant.

This clinical trial is registered by Chinese Clinical Trial Registry. The number is ChiCTR1900028628. This work has been approved by Ethnic Committee of Qinghai Provincial People's Hospital.

Results

Clinical data between survival group and deceased group

Patients were divided into a survival group and a deceased group based on their status at the time of leaving the ICU. The clinical data of the 2 groups were compared: there was no significant difference between the 2 groups in nationality, sex, etiological composition, or age (P>0.05). Patient source was statistically significant (P <0.05), and the mortality rate for patients from wards (51.2%) was significantly higher than that for patients from the emergency department and from other hospitals (38.8% and 37.4%, respectively). The primary infection was not significantly different between groups (P>0.05). APACHE II score, SOFA score, SIRS score, PCT, IL-6, BNP, CRP, PLT, BUN, CREA, Lac, and total fluid balance from days 1 to 5 were significantly different between the 2 groups (P<0.05) (Table 1).

Table 1

Comparison of clinical data between the survival group and the deceased group [M (Q 1, Q 3)]

Indicator		**Overall**	**Survival group**	**Deceased group**	**Statistics**	***P***
Number of cases		480(100.0%)	265(55.2%)	215(44.8%)		
Nationality	Han	360(75.0%)	206(42.9%)	154(32.1%)	X^2=5.371	0.147
	Tibetan	48(10.0%)	19(4.0%)	29(6.0%)		
	Hui	57(11.9%)	32(6.7%)	25(5.2%)		
Salar + Shui + Tu		15(3.1%)	8(1.7%)	7(1.4%)		
Sex	Male	313(65.2%)	165(34.4%)	148(30.8%)	X^2=2.260	0.133
	Female	167(34.8%)	100(20.8%)	67(14.0%)		
Age	Years old	66(52, 77)	65(50, 76)	67(54, 78)	Z=-1.850	0.064
Source	Emergency department	147(30.6%)	90(18.8%)	57(11.8%)	X^2=8.251	0.016
	Ward	242(50.4%)	118(24.6%)	124(25.8%)		
	Other hospital	91(19.0%)	57(11.9%)	34(7.1%)		
Primary infection	Chest	384(80.0%)	209(43.5%)	175(36.5%)	X^2=0.483	0.785
	Abdominal cavity	82(17.1%)	48(10.0%)	34(7.1%)		
	Head and neck	14(2.9%)	8(1.7%)	6(1.2%)		
Shock		178(37.1%)	71(14.8)	107(22.3%)	X^2=26.854	0.001
APACHE II	Score	18(13, 21)	16(12, 20)	21(16, 28)	Z=-7.899	0.001
SOFA	Score	7(5, 10)	6(4, 8)	9(6, 12)	Z=-7.563	0.001
SIRS	Score	2(2, 3)	2(2, 3)	2(2, 3)	Z=-2.862	0.004
PCT	ng/mL	2.29(0.58, 10.32)	1.36(0.36, 7.04)	2.94(1.25, 15.28)	Z=-4.374	0.001

Note: APACHE II: acute physiology and chronic health evaluation II; SOFA: sequential organ failure assessment; SIRS: systemic inflammatory response syndrome; PCT: procalcitonin; IL-6: interleukin-6; BNP: brain natriuresis peptide; CRP: C-reactive protein; WBC: white blood cell count; PLT: platelet count; BUN: blood urea nitrogen; CREA: creatinine; Lac: lactate.

This table mainly reflects the baseline data of the two groups with different final outcomes.

Indicator		Overall	Survival group	Deceased group	Statistics	*P*
IL-6	pg/ml	355(106, 1104)	236(77, 866)	520(165, 1447)	*Z*=-4.457	0.001
BNP	pg/ml	674(281, 1451)	504(231, 1155)	875(380, 1783)	*Z*=-4.233	0.001
CRP	mg/dl	10.14(3.77, 21.36)	7.97(3.03, 18.28)	13.26(4.74, 24.33)	*Z*=-0.357	0.001
WBC	$\times 10^9$/L	10.59(6.91, 15.37)	10.60(7.26, 15.22)	10.57(6.63, 15.60)	*Z*=-0.489	0.625
PLT	$\times 10^9$/L	127(81, 187)	135(82, 197)	121(78, 170)	*Z*=-2.340	0.019
BUN	mmol/L	9.44(6.72, 15.43)	8.61(6.33, 13.42)	11.06(7.24, 19.07)	*Z*=-4.218	0.001
CREA	μmol/L	87(59, 159)	80(58, 126)	97(61, 188)	*Z*=-2.711	0.007
ICU stay	Days	5(2, 10)	7(4, 11)	3(1, 9)	*Z*=-6.801	0.001
Lac	mmol/L	2.1(1.3, 4.0)	1.7(1.2, 3.0)	2.9(1.6, 5.7)	*Z*=-6.711	0.001
Total fluid balance from days 1 to 5	mL	1962(494, 3582)	1788(311, 3410)	2399(650, 3967)	*Z*=-2.157	0.031
Note: APACHE II: acute physiology and chronic health evaluation II; SOFA: sequential organ failure assessment; SIRS: systemic inflammatory response syndrome; PCT: procalcitonin; IL-6: interleukin-6; BNP: brain natriuresis peptide; CRP: C-reactive protein; WBC: white blood cell count; PLT: platelet count; BUN: blood urea nitrogen; CREA: creatinine; Lac: lactate.						
This table mainly reflects the baseline data of the two groups with different final outcomes.						

Ability of the clinical indicators to predict death from sepsis

The value of the significant indicators in the above table (APACHE II score, SOFA score, SIRS score, PCT, IL-6, BNP, CRP, PLT, BUN, CREA, Lac, and total fluid balance from days 1 to 5) in predicting the poor prognosis of patients with sepsis was analyzed using ROC curves. The sensitivity, specificity, and maximum Youden index cut-off value are shown in Table 2 and Figure 1.

Table 2
ROC curve results for each indicator

Indicator	AUC	*P*	Sensitivity	Specificity	Maximum Youden index cut-off value
APACHE II	0.711	0.001	0.556	0.766	20.5
SOFA	0.699	0.001	0.516	0.800	8.5
PCT	0.616	0.001	0.837	0.442	0.945 ng/mL
IL-6	0.617	0.001	0.814	0.392	123.65 pg/ml
BNP	0.612	0.001	0.544	0.653	806.5 pg/ml
CRP	0.594	0.001	0.523	0.653	12.51 mg/dl
PLT	0.562	0.019	0.744	0.370	163×10^9/L
BUN	0.612	0.001	0.395	0.785	14.08 mmol/L
CREA	0.572	0.007	0.553	0.600	90.50 μmol/L
Lac	0.678	0.001	0.586	0.706	2.45 mmol/L
Total fluid balance from days 1 to 5	0.558	0.030	0.540	0.581	2120.5 ml

This table mainly shows the cut-off value, sensitivity and specificity of the maximum Youden index for each index in predicting the prognosis of the patient.

Comparison of fluid balance based on different clinical factors

There was no significant difference in the total fluid balance from days 1 to 5 between sexes and among different nationalities and different sources (P>0.05). However, the total fluid balance of septic shock patients and patients with Lac>2.0 mmol/L was significantly increased (P<0.05) (Table 3).

Table 3
Comparison of fluid balance based on different clinical factors

Clinical factors		Number of cases	Total fluid balance from days 1 to 5	Statistics	*P*
Sex	Male	313	1968(369, 3664)	Z=-0.238	0.812
	Female	167	1947(780, 3459)		
Nationality	Han	360	1981(488, 3454)	Z=-0.013	0.989
	Ethnic minorities (Tibetan + Hui + Salar + Shui + Tu)	120	1877(541, 3925)		
Source	Emergency department	147	1810(486, 3459)	X^2=0.721[a]	0.697
	Ward	242	1992(436, 3626)	X^2=1.730[b]	0.421
	Other hospitals	91	2241(595, 3637)		
Shock	None	302	1662(350, 3348)	Z=-2.670	0.008
	Yes	178	2150(888, 4012)		
Lac	≤2.0 mmol/L	233	1526(284, 3332)	Z=-2.913	0.004
	>2.0 mmol/L	247	2340(712, 3978)		

Note a: The Kruskal–Wallis test was used to examine whether the distributions of the 2 groups were the same and b: to examine whether the medians of the 2 groups were the same.

This table mainly shows the comparison of fluid balance between 1 to 5 days in different clinical factors

Cox regression analysis

Using 2120.5 ml as the cut-off point for total fluid balance from days 1 to 5, the survival rates for patients with different total fluid balances from days 1 to 5 was statistic difference (60.9% vs. 48.9%, P<0.05). The independent risk factors for poor prognosis included APACHE II score, SOFA score, SIRS score, PCT, IL-6, BNP, CRP, PLT, BUN, CREA, and Lac, and total fluid balance from days 1 to 5 by Cox regression analysis (Table 4, Figure 2).

Table 4
Cox regression analysis results

Indicator	B	SE	Wald	P	Exp(B)	Exp(B) 95%CI	
						Lower limit	Upper limit
APACHE II	0.029	0.010	9.263	0.002	1.030	1.010	1.049
SOFA	0.066	0.022	9.249	0.002	1.038	1.024	0.114
PLT	-0.002	0.001	3.972	0.046	0.998	1.045	1.131
Lac	0.084	0.020	16.974	0.001	1.087	0.996	1.000
Total fluid balance from days 1 to 5	0.001	0.001	12.313	0.001	1.001	1.000	1.002

This table mainly shows the results of cox regression, in which the fluid balance of 1 to 5 days is an independent risk factor for death.

Discussion

Fluid resuscitation is the basis for maintaining hemodynamic stability and organ and tissue perfusion and for increasing oxygen delivery during the rescue phase of septic shock [7]. Studies have shown that early resuscitation can reduce the mortality of patients with sepsis and septic shock [8–10]. However, excessive fluid resuscitation may be harmful to patients. Many studies have shown that a positive fluid balance or FO is closely associated with the occurrence of acute kidney injury (AKI) and poor patient prognosis [11–16]. Chao et al. [17] found that a negative cumulative body fluid balance from days 1 to 4 reduced the mortality of patients with severe influenza. Judith et al. [18] found that cumulative FO during the first 5 days of pediatric ICU (PICU) admission was an independent risk factor for poor prognosis in children with septic shock. A recent prospective study also showed that in patients who underwent cardiac or aortic surgery, continuous positive fluid balance was associated with AKI and hemodialysis and that the risk of AKI in patients with a continuous positive fluid balance increased by 7.1 times [19]. Our study found that the total fluid balance from days 1 to 5 for patients in the deceased group was significantly higher than that for patients in the survival group, suggesting that total fluid balance from days 1 to 5 may be associated with poor patient prognosis. Furthermore, Cox regression analysis indicated that the total fluid balance from days 1 to 5 was an independent risk factor for poor patient prognosis; the risk of death increased by 0.1% for every 1 ml increase. However, a previous study [20] has shown that after adjusting for disease severity and the lactate clearance rate, cumulative fluid balance was not associated with increased mortality. The reason for this result may be related to the retrospective nature of the analysis. The results of our study showed that there was no significant difference in the mortality rate between sexes, among different nationality groups, and among different ages (P>0.05); however, the mortality rate was significantly different among different sources (P<0.05), with the mortality rate for sepsis patients from wards being the highest. One explanation for this result may be that ICU physicians paid more attention to sepsis than general ward physicians or that patients in wards received more fluid therapy. This is just speculation, as relevant data were not collected to address that issue. The comparison of clinical factors showed that there was no difference in fluid balance between sexes, among different nationality groups, and among different sources (P >0.05), indicating that these clinical factors had no effect on fluid balance. However, the fluid balance for patients with shock was significantly higher than that for patients with stable hemodynamics at the time of ICU admission, and the mortality rate for patients with septic shock was significantly higher (49.85% vs. 27.7%), a finding that is consistent with the clinical situation. However, it is not clear whether the poor prognosis of patients is due to septic shock or due to a positive fluid balance. More fluid therapy or a more positive fluid balance may be related to severe vascular leakage and third space leakage, but whether it is a direct cause of increased mortality remains unclear. Because this was a retrospective study, it can only be concluded that a more positive fluid balance may be associated with poor patient prognosis. Cox regression analysis showed that APACHE II score, SOFA score, PLT, and Lac were associated with poor patient prognosis. Studies have confirmed that APACHE II and SOFA scores are associated with poor patient prognosis [21]. Regarding the prediction of poor patient prognosis, the ROC curve results indicated a sensitivity of 55.6% and specificity of 76.6% for APACHE II > 20 points and a sensitivity of 51.6% and specificity of 80.0% for SOFA > 8 points. The decrease in PLT may be related to the progression of sepsis and dilution caused by the increased body volume resulting from a positive fluid balance. Regression analysis indicated that for every unit increase in PLT, the risk of death decreased by 0.2%. Elevated Lac represents oxygen utilization disorder in the body, which may be caused by oxygen uptake, and oxygen utilization disorder in the tissues, which may be due to the widening of the capillary space after fluid treatment. Among the clinical factors, fluid balance was significantly increased when Lac>2.0 mmol/L. Lac and fluid balance may have a causal relationship. Unfortunately, this study could not determine cause and effect as it was a retrospective analysis. BUN and CREA in the deceased group were significantly increased at the time of ICU admission; these findings may explain the excessive total fluid load from days 1 to 5 in the deceased group.

Based on the above research results, we need more rigorous studies to re-examine fluid resuscitation therapy for sepsis [22]. Degradation or damage to the glycocalyx layer of the vascular endothelial cell membrane can occur in the early stage of sepsis, and fluid resuscitation therapy may further damage the glycocalyx layer, especially during rapid infusions and transfusions that result in hypervolemia [23, 24]. The destruction of the glycocalyx layer of vascular endothelial cells may cause capillary leakage, local tissue edema, and oxygen utilization disorder, which may be side effects of fluid resuscitation treatment, thereby affecting the prognosis of patients. The use of hypertonic fluid for small volume resuscitation in patients with sepsis also requires further study.

Conclusions

This study reviewed the effect of fluid balance on the prognosis of sepsis patients in Chengdong District of Xining City, Qinghai Province. We found that the cumulative fluid balance from days 1 to 5 after admission to the ICU was associated with poor patient prognosis. The risk of death gradually increased when the cumulative fluid balance was greater than +2120.5 ml (60.9% vs. 48.9%, $P<0.05$). In view of the above results, fluid management, i.e., cumulative fluid balance, during the treatment of patients with sepsis and septic shock in the Xining area must receive attention from clinicians. Clinicians should focus on a positive fluid balance earlier (within 5 days) and optimize volume management early to achieve a negative cumulative fluid balance.

This study has limitations. First, this was a retrospective study conducted in a hospital in an urban area; therefore, the results may not completely represent the clinical reality at moderate altitudes. Second, because this was a retrospective study, the causal relationship between fluid balance and prognosis cannot be determined. Third, although possible confounding factors, such as sex, nationality, and origin, were compared, all confounding factors could not completely be eliminated. Fourth, the fluid balance before the ICU stay was not considered. Fifth, the use of diuretics was not recorded, and their use may have affected fluid management and the results. The results of this study should be further verified through a study with a larger sample size, and the resulting data should be paired and compared with data from low-altitude areas.

Abbreviations

APACHE II: acute physiology and chronic health evaluation II; SOFA: sequential organ failure assessment; SIRS: systemic inflammatory response syndrome; PCT: procalcitonin; IL-6: interleukin-6; BNP: brain natriuresis peptide; CRP: C-reactive protein; WBC: white blood cell count; PLT: platelet count; BUN: blood urea nitrogen; CREA: creatinine; Lac: lactate; FO: fluid overload; ICU: intensive care unit; GCS: Glasgow coma scale; AKI: acute kidney injury.

Declarations

Acknowledgments

Not applicable.

Authors’ contributions

SQM and HW conceived and designed the review. HW and YW drafted the manuscript and prepared figures and tables. SQM, BS, XXX and HW undertook the initial research and discussed the manuscript. SQM, YZY, JML and HW reviewed and revised the manuscript. All authors read and approved the final manuscript.

Funding

This work was supported by Key Research & Development and Transformation Program of Qinghai Province Science and Technology Department (2019-SF-132); Qinghai scientific and technological Basic research project (2019-ZJ-7080) and Guidance Program of Qinghai Province Health and Family Planning System (2018-wjzdx-07).

Availability of data and materials

The datasets generated and or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

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Figures

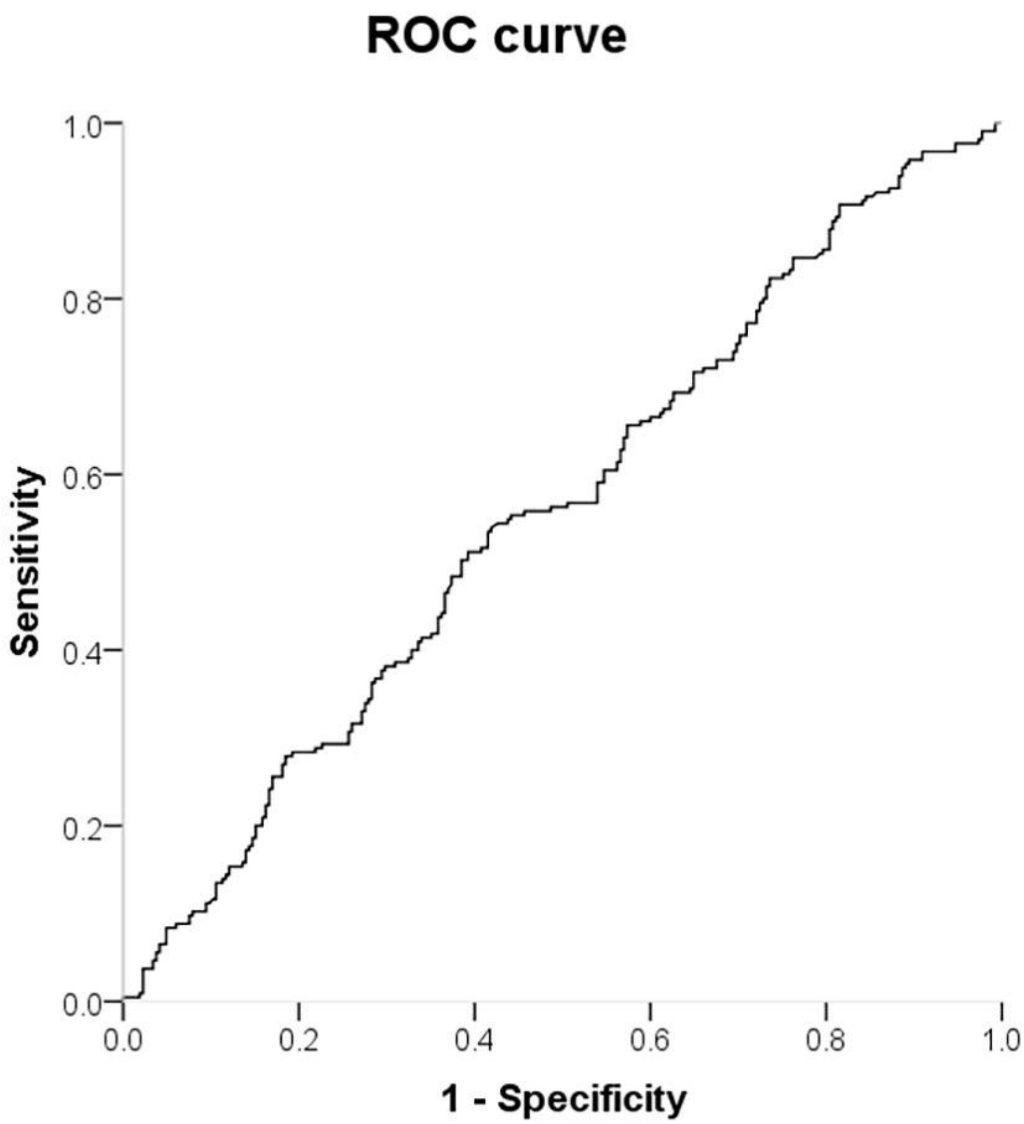

Figure 1

ROC curve for total fluid balance from days 1 to 5, The AUC of total fluid balance from days 1 to 5 was 0.558. The cut-off value, sensitivity and specificity of the maximum Youden index for total fluid balance was 2120.5 ml, 54.0% and 58.1%.

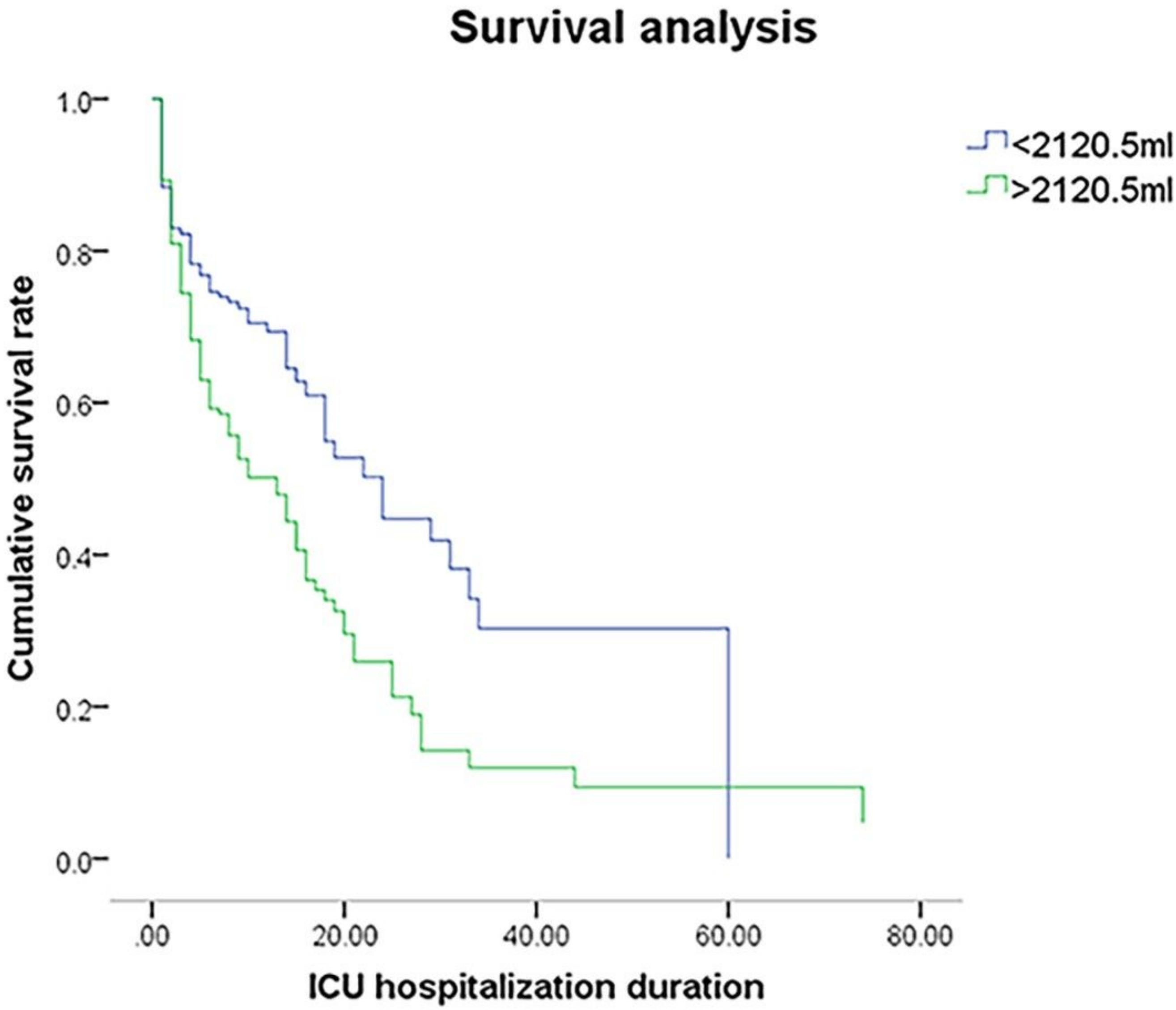

Figure 2

Survival analysis based on different total fluid balances from days 1 to 5, Kaplan-Meier survival plots for patients with different fluid balance. P > 0.05 [Log-rank (Mantel-Cox) test]. But the survival rates for patients with different total fluid balances from days 1 to 5 was statistic difference (60.9% vs. 48.9%, P <0.05).