Brain natriuretic peptide (BNP) and cardiac troponin I(cTnI) for prediction of the prognosis in cancer patients with sepsis

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Research article

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Abstract

Background

This study aimed to study the value of brain natriuretic peptide (BNP) and cardiac troponin I(cTnI) for predicting the prognosis in cancer patients with sepsis.

Methods

A cohort of 233 cancer patients with sepsis admitted to our ICU from January 2017 to October 2020 was included in this retrospective study. BNP and cTnI on the first day (d1) and the third day(d3) after entering ICU, blood lactate (Lac), procalcitonin (PCT), Leucocyte, Sequential Organ failure assessment (SOFA) scores, the incidence of septic shock, acute kidney injury(AKI), acute respiratory failure (ARF) requiring mechanical ventilation(MV) and sepsis-induced myocardial dysfunction(SIMD) within 24 hours of entering ICU, fluid balance in 24hr and 72hr of entering ICU, time of MV, length of stay in ICU ,emergency surgery were collected. According to the 28-day mortality, these patients were divided into the survival group (190 cases) and the death group (43 cases). All the above variables were compared.

Results

The multiple COX regression analysis of these variables indicated that BNP on d1 and d3, SOFA scores ,72hr fluid balance were independent predictors of the mortality in these patients ($P < 0.05$); The area under the ROC curve was 0.91 ± 0.01($P < 0.05$) for BNP on d3. BNP on d3 at 681.5 pg/mL predicted the mortality with a sensitivity of 91.5% and a specificity of 88.7%. All patients were divided into two groups (BNP on d3 < 681.5 pg/ml or > 681.5 pg/ml), Kaplan-Meier analysis performed on the two groups showed a significant difference in the survival curve ($P < 0.05$) .There were also significant differences on the comorbidities including shock, AKI, ARF in both groups ($P < 0.05$). 126 out of 233 patients underwent random bedside echocardiography, and a total of 42 cases developed SIMD with an incidence rate of 33.3% (30.6% in the survival group and 40.9% in the death group). There was no significant difference in the incidence of SIMD between the survival group and the death group ($P = 0.23$). There was a significant difference between the non-SIMD and the SIMD group for BNP on d1 and d3($P < 0.05$).

Conclusions

BNP was a great predictor for the prognosis of cancer patients with sepsis, while cTnI was not.

Background

Sepsis is “a life-threatening condition that arises when the body’s response to infection injures its own tissues”[1]. Although more progress has been made in the treatment of sepsis, it is still one of the common

causes of death in critically ill patients worldwide[2]. Sepsis is prone to tissue hypoperfusion and develops into septic shock or even life-threatening multiple organ dysfunction [3]. Sepsis induced myocardial dysfunction(SIMD) is common, with an incidence of about 40%, which usually indicates a significant poor prognosis in sepsis[4]. Early warning and active intervention for sepsis can significantly reduce its mortality and improve its prognosis[5].The application of BNP and cTnI in congestive heart failure and acute coronary syndromes has been widely recognized and accepted[6,7].At present, the use of the two cardiac biomarkers to evaluate the prognosis of patients with sepsis has also become a hot spot in domestic and foreign research[7–9]. However, the value of BNP and cTnI for the prognosis of sepsis is still controversial. This retrospective study was also to verify whether there are differences in the prognosis of cancer patients with sepsis for BNP and cTnI.

Methods

Participants

A retrospective data of 233 cancer patients with sepsis admitted to ICU from January 2017 to October 2020 who met the inclusion criteria was collected after approved by the ethics committee of Peking University cancer hospital.

Inclusion criteria: Patient data were collected according to the 2016 European definition of sepsis 3.0 and septic shock[1]: Sepsis refers to the loss of control of the body's inflammatory response to infection leading to life-threatening organ dysfunction. Organ dysfunction is defined as an acute increase in the Sequential Organ Failure Assessment score (SOFA score ≥ 2 points) secondary to infection. Septic shock refers to refractory hypotension (patients still need vasopressor drugs to maintain mean arterial pressure ≥ 65 mmHg after adequate fluid resuscitation) and blood lactate ≥ 2 mmol/l; Patients with sepsis were treated with active cluster treatment according to the sepsis treatment guidelines of Surviving sepsis campaign[5].

Exclusion criteria: life expectancy is less than 24 h, acute coronary syndrome, chronic heart disease (such as severe hypertension, heart valve disease or arrhythmia, etc.), chronic liver and kidney insufficiency, cardiogenic or hemorrhagic shock.

Both clinical and biological data were collected in the following period.

The clinical data included age, gender, Infection category, comorbidities including the incidence of septic shock, acute kidney injury(AKI), acute respiratory failure (ARF) requiring mechanical ventilation(MV), sepsis-induced myocardial dysfunction (SIMD) within 24 hours of entering ICU, time of MV, length of stay in ICU ,24hr and 72hr fluid balance in ICU, and emergency surgery conditions.

The biological data included lactate, leucocyte and PCT obtained from the blood gas, blood routine, and procalcitonin test when patients entered ICU. BNP and cTnI on the first day(d1) and the third day (d3)

after entering ICU were collected. The normal value was less than or equal to 100 pg/ml for BNP, less than or equal to 0.05 ng/mL for cTnI.

SOFA scores were recorded to assess the severity of all the patients' condition.

SIMD: SIMD is defined as left ventricular ejection fraction (LVEF) less than 50%. The bedside echocardiogram results were collected within 24 hours of entering ICU.

AKI: AKI is defined as any of the following: Increase in serum creatinine(SCr)by 0.3 mg/dL(26.5 μmol/L) within 48 hours; Increase in SCr to 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; Urine volume□0.5 mL/kg/h for 6 hours[10].

ARF: ARF is defined as acute severe dysfunction of lung ventilation caused by various reasons; Arterial blood oxygen partial pressure (PaO2) is lower than 8 kPa (60 mmHg), or accompanied by carbon dioxide partial pressure (PaCO2) higher than 6.65 kPa (50 mmHg)

Statistical Analysis

SPSS software version 26.0 (SPSS Inc, Chicago, IL) was used for statistical analysis. Data were analyzed as the mean ± standard deviation, number(percentage) or median (25th /75th percentile). Unpaired t test and Mann-Whitney U test were used to compare continuous variables and skewed distribution. X^2 test was used to compare categorical variables. Significantly different variables in univariate analysis were put into COX regression analysis to select the independent risk factors of sepsis. Receiver operating characteristic curve (ROC curve) was used to predict the value of all the independent risk factors for the mortality of cancer patients with sepsis. The cut-off value of BNP or cTnI were obtained by Youden index in ROC curve. The patients were divided into the new two groups according to the cut-off value, and the difference in survival curve between the new two groups was compared with the Kaplan-Meier method. $P < 0.05$ was considered statistically significant.

Results

1. According to the 28-day mortality rate, all cancer patients with sepsis were divided into the survival group and the death group. The baseline data of the two groups were as follows (**Table 1**). The incidence of septic shock, AKI and ARF; the time of MV, 72h fluid balance, lactate, BNP or cTnI on d1 and d3, SOFA scores in the survival group were significantly different from those in the death group by univariate analysis (P<0.05).
2. The variables with significant differences in Table 1 were put into the Cox regression analysis. It can be seen that BNP on d1 and d3, SOFA score, and 72hr fluid balance were independent risk factors for the mortality of patients (**Table 2**).
3. ROC curve was used to evaluate the predicating ability of the independent risk factors including BNP on d1 and d3, SOFA score, and 72hr fluid balance from Table 2. The area under the ROC curve was 0.63 ± 0.04 (P<0.05) for BNP on d1, 0.91 ± 0.01 (P<0.01) for BNP on d3, 0.86 ± 0.03(P<0.01) for

SOFA score, 0.84 ±0.04 (*P*<0.01) for 72h fluid balance (**Figure 1**). BNP on d1 at 784.5 pg/mL predicted mortality with a sensitivity of 49% and a specificity of 75%，BNP on d3 at 681.5 pg/mL predicted mortality with a sensitivity of 91% and a specificity of 89%, SOFA score at 7 predicted mortality with a sensitivity of 79% and a specificity of 81%, 72h fluid balance at 75.9ml/kg predicted mortality with a sensitivity of 81% and a specificity 77%.It can be seen that BNP on d3 had the largest area of ROC curve, and it also had the best sensitivity and specificity.

4. According to the cut-off value of BNP on d3(681.5 pg/ml), all patients were divided into two groups (BNP on d3<681.5pg/ml or BNP on d3>681.5pg/ml), Kaplan-Meier analysis performed on the two groups of patients showed a significant difference in the survival curve (P<0.05) which means that the greater the BNP on d3 above the cut-off value, the higher the 28-day mortality rate of the patients. (**Figure 2**)
5. There were also significant differences in the comorbidities (shock, AKI, ARF) with 24 hours of entering ICU occurred in the two groups of patients (BNP on d3<681.5pg/ml or BNP on d3>681.5pg/ml) (P<0.05), which indicated that the higher the BNP of the patients, the more likely to merge with shock, AKI or ARF. (**Table 3**)
6. The correlation between BNP on d3 and 72h fluid balance were compared. Both of them had a positive correlation (P<0.05), but the correlation was extremely weak (r= 0.286) (**Figure 3**)
7. Among the 233 patients with sepsis, 126 underwent random bedside echocardiography (the remaining were not available). A total of 42 cases developed SIMD, with an incidence rate of 33.3% (30.6% in the survival group and 40.9% in the death group). There was no significant difference in the incidence of SIMD between the two groups (P=0.26) (**Table 4**). However, there was a significant difference between the non-SIMD and SIMD groups for BNP on d1 and d3 (P<0.05), while cTnI was the opposite (**Table 5**).

Discussion

BNP is a classic marker in patients with congestive heart failure. BNP released into the blood when the ventricular wall tension increased[11]. The main mechanism of SIMD is that the heart's variable myocardial contractility would increase the tension of the ventricular wall and cause ventricular dilatation, which leads to a significant increase in the secretion of BNP[12]. Patients with septic shock often have acute renal injury in the early stage, and the metabolism of BNP produced in plasma is slowed down[13]. These two factors are the main reason causing the increase of BNP in patients with sepsis. The main finding of this study was to understand that BNP is an independent risk factor for the prognosis of cancer patients with sepsis, especially the BNP on d3 after entering the ICU at 681.5 pg/ml had high diagnostic power and great sensitivity and specificity for the mortality of these patients. The higher the BNP level larger than 681.5 pg/ml, the higher the 28-day mortality rate, and the greater the possibility of sepsis combined with septic shock, AKI and ARF at the same time. This result is consistent with some domestic and foreign studies [14,15]. From the results of random bedside cardiac ultrasound examination with 126 patients, it was found that BNP on d1 and d3 of the SIMD group were significantly higher than those of the non-

SIMD group($P < 0.05$). This was similar to the findings of Post, and there would be a correlation between BNP and SIMD [16].

This study also found that SOFA score and 72 h fluid balance were independent risk factors for the mortality in these patients. SOFA score is a reliable indicator to assess the severity of critical ill patients[17,18]. Its predictive value for the mortality of patients with sepsis has been confirmed by a large number of studies and would not be discussed further here[19,20]. 72 h fluid balance was also one of the independent risk factors[21]. The area under the ROC curve was 0.84 ± 0.04 ($P < 0.01$) for 72 h fluid balance. 72 h fluid balance at 75.9 ml/kg predicted mortality with a sensitivity of 81% and a specificity 77%. It can be seen that 72 h fluid balance has good predictive value for the mortality of cancer patients with sepsis. In the early treatment of sepsis, in order to optimize organ perfusion, fluid shock therapy should be performed in time. But the continuous positive fluid balance in patients with sepsis in the following periods may indicate a poor prognosis. The European SOAP study in 2006 showed that the cumulative fluid balance within 72 hours is the strongest predictor of the mortality of sepsis patients in the ICU, which means that fluid balance is the only changeable risk factor identified in their study [22]. Boyd reported a retrospective study of VASST, which also confirmed the relationship between the cumulative fluid balance after 4 days and the mortality of patients with sepsis [23]. The correlation analysis between BNP on d3 and 72 h fluid balance showed that the two were positively correlated (P□0.05), but the correlation was extremely weak ($r = 0.286$). BNP didn't appear to be a reliable marker of fluid status in septic patients. Similar studies had also shown that BNP was not significantly associated with fluid volume and fluid responsiveness in patients with sepsis[24,25].

cTnI is the most sensitive and specific marker of myocardial injury. Cardiac hypoperfusion and the application of a large number of vasoactive drugs in patients with sepsis both may cause myocardial injury[26]. The degree of elevated cTnI was significantly related to the severity and mortality of patients with sepsis[27]. However, Studies had shown that SIMD has no obvious relationship with cTnI[28,29]. Røsjø found that the increase of cTnI in patients with sepsis only reflected the damage state of myocardial cells and cannot accurately predict the risk of SIMD or increased the mortality of sepsis[30]. This study also found that cTnI was significantly different between the survival group and the death group ($P < 0.05$), but cTnI was not an independent risk factor predicting the mortality in patients with sepsis. There were no significant differences in cTnI on d1 and d3 between the SIMD and non-SIMD groups. Combining the above multiple studies, It can be seen that the value of cTnI for the prognosis of patients with sepsis is still controversial.

Limitations:

This study refered to the latest definition of sepsis 3.0. The enrollment and grouping of sepsis patients had new standards, and the conclusions were different from previous studies. For BNP, cTnI and fluid balance, dynamic observation data were obtained, which increased the accuracy of the results. This study still had certain limitations: First, The enrolled patients had a short hospital stay in ICU, so most of

the BNP and cTnI data were within 3 days of entering ICU. The dynamic observation data were relatively limited, which may affect the judgment of the results to a certain extent. Secondly, Not all the patients had undergone bedside echocardiography, so the sample size was reduced. Because of the limited technology of bedside echocardiography, patients diagnosed with SIMD were actually based on left ventricular systolic dysfunction, which would lose some patients with left ventricular diastolic dysfunction or right heart dysfunction. The incidence of SIMD may be smaller. The difference of BNP and cTnI with SIMD, and the mortality between SIMD and non-SIMD groups may be biased ultimately. In future, more sample size and more cardiac ultrasound parameters should be added. Prospective studies would be carried out to improve the rigor of the research.

Conclusions

For cancer patients with sepsis, early warning and effective intervention to reduce the mortality are still the difficulties in ICU. BNP is a great predictor for evaluating the prognosis of patients with sepsis, while cTnI is not.

Declarations

Data Sharing Statement:

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

Ethics Approval and Consent to Participate:

The study was in line with the Helsinki Declaration and approved by the Peking University Cancer Hospital Ethics Committee. Written informed consent was obtained from the patients for their anonymized information to be published in this study.

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Disclosure

The authors declare that they have no competing interests, and all authors should confirm its accuracy.

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Tables

Table1 Baseline data for the survival and death groups of cancer patients with sepsis

	Total(n=233)	Survival(n=190)	death(n=43)	P
Sex,male	169(72.5%)	139(73.2%)	30(69.8%)	0.65
Age(year)	63.7±9.9	63.5±9.9	64.9±10.1	0.4
Infection category				
Respiratory	79(33.9%)	66(34.7%)	13(30.2%)	0.21
Gastrointestinal	17(7.3%)	11(7.9%)	4(9.3%)	0.32
Abdominal cavity	99(42.3%)	80(42.1%)	18(41.9%)	0.54
Thoracic cavity	27(11.6%)	23(12.1%)	7(16.2%)	0.14
CLABSI	3(1.3%)	3(1.6%)	0	0.13
Genitourinary	5(2.1%)	5(2.1%)	0	0.21
Others	3(1.3%)	2(1.1%)	1(2.3%)	0.16
Septic shock	94(40.3%)	60(31.6%)	34(79.1%)	0.001
AKI	40(17.2%)	14(7.4%)	26(60.5%)	0.001
ARF to MV	137(58.8%)	102(53.7%)	35(81.4%)	0.001
Total MV time(day)	3.6±5.9	2.7±4.7	7.5±8.7	0.001
ICU stay time(day)	7.8±5.9	7.7±5.3	8.6±7.7	0.46
Fluid-balance（ml/kg）				
24hr	49.4±35.8	46.1±33.1	53.9±43.3	0.083
72hr	63.1±54.9	50.5±45.8	118.5±58.2	0.002
Emergency surgery	62(26.7%)	51(26.8%)	11(25.6%)	0.26
Lactatemia(mmol/l)	2.9±2.2	2.6±1.6	4.6±3.5	0.001
Leucocyte (10^9/l)	13.3±8.3	13.2±8.4	13.7±8.3	0.73
PCT (ng/ml)	17.6±45.2	15.7±43.6	25.4±51.5	0.21
Cardiac biomarkers				
BNP (pg/ml)				
d1	673.6±786.6	618.1±724.7	919.0±989.6	0.01
d3	656.6±912.4	370.2±456.9	1922.1±1284.1	0.000
cTnI(ng/ml)				
d1	0.04(0.02/0.17)	0.03(0.01/0.16)	0.08(0.03/0.23)	0.04

d3	0.03(0.01/0.12)	0.02(0.01/0.05)	0.21(0.11/1.11)	0.02
SOFA Score	5(4/10)	4(3/7)	9(4/12)	0.000

Data were expressed as mean± standard deviation, number (percentage), or median (25th/75th percentile). AKI: acute kidney injury; ARF: acute respiratory failure; CRRT: continuous renal replacement therapy; MV: mechanical ventilation; ICU: intensive care unit; PCT: Procalcitonin; BNP: brain natriuretic peptide; cTnI: cardiac troponin I; SOFA: Sequential Organ failure assessment.

Table 2 Cox regression analysis for cancer patients with sepsis

Variables	B	Wald	P-value	OR	95%CI
BNP on d1	-0.002	7.639	0.007	0.998	0.997-0.999
BNP on d3	0.003	23.609	0.000	1.003	1.002-1.005
SOFA score	0.128	12.133	0.000	1.136	1.057-1.221
72hr Fluid balance	0.012	4.514	0.034	1.012	1.001-1.023

BNP: brain natriuretic peptide; d1: the first day in ICU; d3: the third day in ICU; SOFA: Sequential Organ failure assessment; 72hr: In 72 hours after entering ICU

Table 3 Comparison of comorbidities between the new groups of patients grouped by the cutoff value

BNP on d3 (pg/ml)	<681.5(n=172)	>681.5(n=61)	P
Shock			0.000
yes	53(30.8%)	41(67.2%)	
no	119(69.2%)	20(32.8%)	
AKI			0.001
yes	10(5.8%)	30(49.2%)	
no	162(94.2%)	31(50.8%)	
ARF			0.025
yes	83(48.3%)	40(65.6%)	
no	89(51.7%)	21(34.4%)	

BNP: brain natriuretic peptide; d3: the third day in ICU; AKI: acute kidney injury; ARF: acute respiratory failure;

Table 4 Occurrence of SIMD between the survival group and the death group

	Total(n=126)	The survival(n=98)	The death(n=28)	P
SIMD				0.26
Yes	42(33.3%)	30(30.6%)	12(42.9%)	
No	84(66.7%)	68(69.4%)	16(57.1%)	

SIMD: sepsis-induced myocardial dysfunction

Table 5 Comparison of BNP and cTnI between the non-SIMD group and the SIMD group

	Non-SIMD(n=84)	SIMD(n=42)	P
BNP on d1	753.0±779.8	1191.2±978.1	0.008
BNP on d3	748.7±1004.6	1076.2±1175.6	0.03
cTnI on d1	0.03(0.01/0.23)	0.04(0.02/0.31)	0.28
cTnI on d3	0.02(0.01/0.10)	0.06(0.04/0.29)	0.43

BNP: brain natriuretic peptide; cTnI: cardiac troponin I; d1: the first day in ICU; d3: the third day in ICU; SIMD: sepsis-induced myocardial dysfunction

Figures

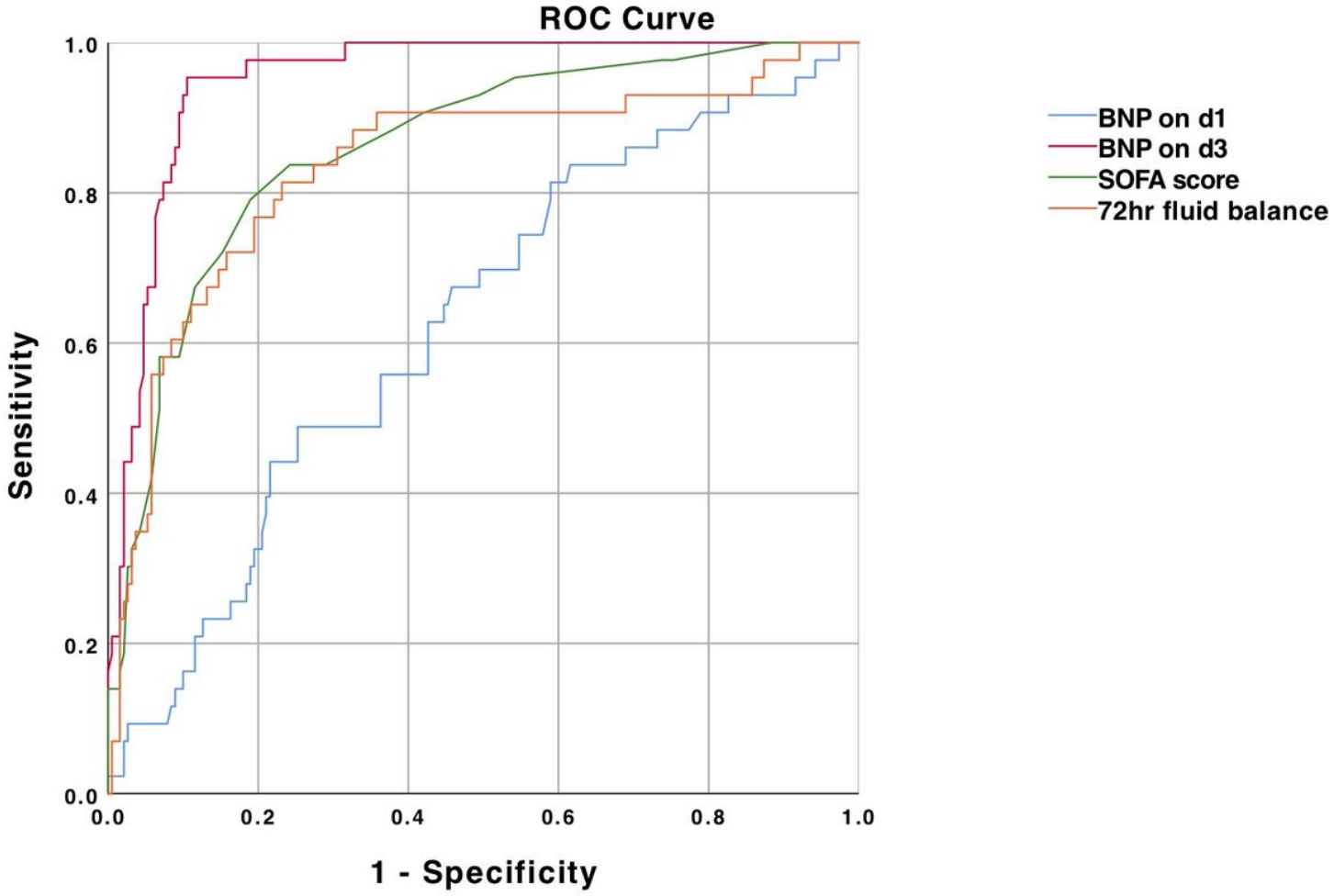

Figure 1

ROC curves of BNP on d1, BNP on d3, SOFA score and 72hr fluid balance for predicting the mortality of cancer patients with sepsis. The AUC of BNP on d3 was significantly larger than others (P□0.05)

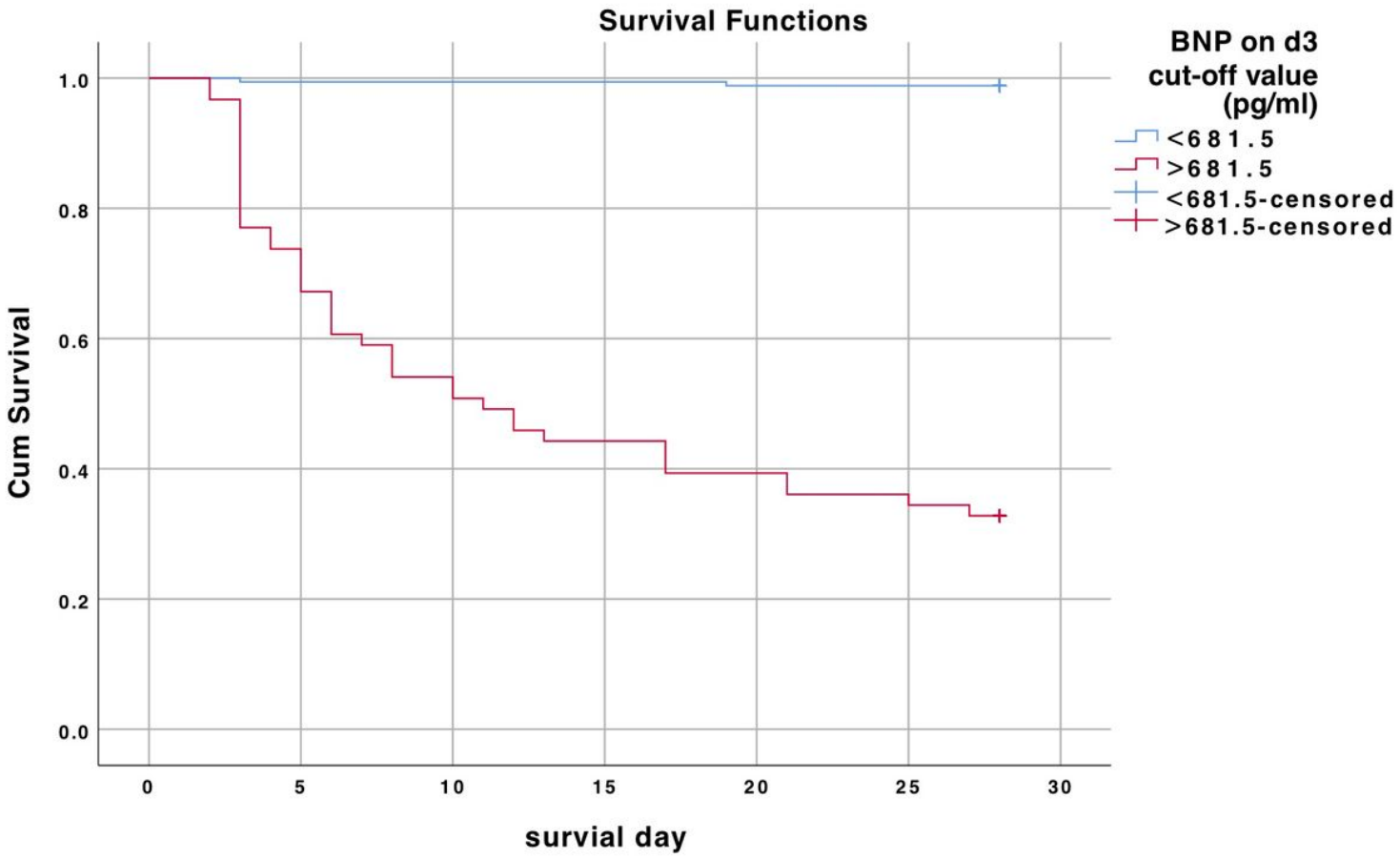

Figure 2

The new two groups (BNP on d3<681.5pg/ml and BNP on d3>681.5pg/ml) had a significant difference in the survival curve (P<0.05)

Correlations

		BNP on d3	72hr fluid balance
BNP on d3	Pearson Correlation	1	.286**
	Sig. (2-tailed)		.000
	N	233	233
72hr fluid balance	Pearson Correlation	.286**	1
	Sig. (2-tailed)	.000	
	N	233	233

**. Correlation is significant at the 0.01 level (2-tailed).

Figure 3

BNP on d3 and 72hr fluid balance had a positive correlation (P<0.05), but the correlation was extremely weak (r= 0.286)