Significance of lactate clearance in septic shock patients with high bilirubin levels.

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Abstract

Background

Although lactate clearance is affected by hepatic function, it is unclear whether the hepatic dysfunction is associated with lactate clearance as a prognostic marker of clinical outcomes in septic shock. We aimed to evaluate association between the lactate clearance and mortality divided by hepatic dysfunction based on total bilirubin level using two cohort of septic shock patients.

Methods

Lactate clearance, delta base excess and delta anion gap in 24 hours from septic shock onset were analyzed using two cohorts of septic shock patients (derivation cohort, n = 230; validation cohort, n = 396) categorized into two groups by total bilirubin levels (TBIL) < 2 mg/dL and ≥ 2 mg/dL on day 1. The primary analysis was association between lactate clearance and 28-day mortality by total bilirubin category.

Results

In derivation cohort, lactate clearance was lower in non-survivors compared to survivors in the patients with TBIL ≥ 2 mg/dL (P = 0.0035), while there was a no significant difference in those with TBIL < 2 mg/dL. There were no significant differences in delta base excess and delta anion gap between non-survivors and survivors both in the patients with TBIL ≥ 2 mg/dL and < 2 mg/dL. In the multivariate logistic regression analysis, increased lactate clearance was significantly associated with decreased 28-day mortality in TBIL ≥ 2 mg/d group (10% lactate clearance, adjusted odds ratio 0.88, 95%CI; 0.80−0.97, P = 0.0075), whereas there was no significant association in TBIL < 2 mg/d group. We next tested for lactate clearance in TBIL ≥ 2 mg/dL using the validation cohort; lactate clearance was lower in non-survivors compared to survivors in the TBIL ≥ 2 mg/dL group (P = 0.0006), while no significant difference was observed in TBIL < 2 mg/dL. Increased lactate clearance was significantly associated with decreased 28-day mortality in the TBIL ≥ 2 mg/dL group (10% lactate clearance, adjusted odds ratio 0.89, 95%CI; 0.83−0.96, P = 0.0038); while no significant difference was observed in TBIL < 2 mg/dL in the validation cohort.

Conclusions

Patients with increased lactate clearance had decreased 28-day mortality when patients had hepatic dysfunction (TBIL ≥ 2 mg/dL) in septic shock.

Background

Blood lactate levels potentially reflect the imbalance between oxygen delivery and consumption under the global tissue hypoxia, which reduces the availability of pyruvate into TCA cycle and accelerates an aerobic glycolysis caused by excess beta-adrenergic stimulation [1, 2]. Blood lactate level is a corner stone of diagnosis and management in patients with septic shock [3–6]. Patients with increased blood lactate levels have worse clinical outcome in septic shock; Persistent lactate elevation, in other words decreased lactate clearance may be a signal of danger in management of septic shock [7–10].

Lactate clearance consists of the balance of the generation and elimination [11, 12]. Hepatic function is key to eliminate lactate; hepatic dysfunction potentially decreases lactate clearance [13, 14]. Lactate clearance has been substantially investigated in septic shock [7–9, 15, 16]; However, it was rarely tested whether the association between lactate clearance and clinical outcomes is different among patients with and without hepatic dysfunction.

Thus, we hypothesized that hepatic function provides a difference in relationship between lactate clearance and mortality in septic shock. We tested for association between the lactate clearance and 28-day mortality in two groups divided by hepatic dysfunction based on total bilirubin value using two cohorts of septic shock patients. The change of anion gap and base excess were also examined, since these directly reflect the nonvolatile acid which is generated by tissue hypoxia and may be affected by hepatic function.

Materials And Methods

Study design, definition and patients

This observational study was retrospectively conducted. Septic shock was defined by the presence of systemic inflammatory response syndrome criteria caused by infection [17], at least one new organ dysfunction by the Brussels criteria, and hypotension despite adequate fluid resuscitation [18]. According to these criteria, hepatic dysfunction was defined by blood levels of total bilirubin (TBIL) $\geq$2 mg/dL [19].

Derivation cohort: CHIBA cohort

Patients admitted to the ICU at Chiba university hospital (CHIBA) in Chiba, Japan between October 2012 and September 2018 were screened (n=9290). Of these, 230 patients met the definition of septic shock on ICU admission and had blood lactate clearance, delta anion gap and delta base excess data available, who were included in the analyses. This study was approved by the Institutional Review Board of Chiba University Graduate School of Medicine.

Validation cohort: VASST cohort

VASST (Vasopressin and Septic Shock Trial) was a multicenter (ICUs, n=27, Canada, Australia, and the United States), randomized, double-blind trial conducted between July 2001 and April 2006 [18]. Of 6229 patients screened, 396 patients screened with septic shock were included in the analyses. The

Institutional Review Board at St. Paul's Hospital and the University of British Columbia (UBC) approved the study.

Measurements and clearance

Blood levels of lactate and base excess and anion gap were examined at the presentation of septic shock (day 1) and 24 hours later (day 2). Blood lactate clearance (percent) was defined as the following formula:

Lactate clearance (percent) = $(Lactate^{Day1} - Lactate^{Day2}) / Lactate^{Day1} *100$

($Lactate^{Day1}$, Lactate level at recognition of septic shock; $Lactate^{Day2}$, Lactate level 24 hours after septic shock recognition)

Anion gap, which was calculated using sodium, chloride ion and bicarbonate, was only available in the derivation cohort. Delta base excess and anion gap were calculated by subtracting day 2 values from day 1 values.

Statistical analysis

The primary outcome variable was lactate clearance. Secondary outcome variables were delta base excess and delta anion gap. Patients were categorized into two groups by TBIL levels<2mg/dL and ≥2mg/dL on day 1.

The primary analysis used logistic regression to test association between lactate clearance and 28-day mortality by TBIL category (< and ≥2mg/dL). We chose this multivariate analysis approach to adjust for potential baseline imbalances (age, sex and APACHE II score). The correlation between lactate clearance and delta anion gap was analyzed using a Pearson correlation coefficient test.

Univariate analysis was performed using a Mann-Whitney U test. Differences were considered significant using a two-tailed value of $P<0.05$. Data were presented as means with standard deviations. Analyses were performed using R$^®$ version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria, http://www.R-roject.org/) and PRISM$^®$ version 8 (GraphPad Software, Inc. California, USA).

Results

Of 230 patients, 153 patients were TBIL < 2 mg/dL and 77 patients of TBIL ≥ 2 mg/dL in the derivation cohort (Table 1). In baseline characteristics, there was no significant difference in between patients with TBIL ≥ 2 mg/dL and < 2 mg/dL except for higher levels of lactate on day 1 in the patients with TBIL ≥ 2 mg/dL compared to TBIL < 2 mg/dL.

Table 1
Baseline characteristics, vital signs, blood gas analysis and laboratory data in the derivation cohort (CHIBA cohort, n = 230)

	TBIL < 2 mg/dL (n = 153)	TBIL ≥ 2 mg/dL (n = 77)	P value
Age, yr	69 (59, 76)	66 (56, 74)	0.19
Male sex, n (%)	91 (59.5)	50 (64.9)	0.51
APACHE II score [1]	31 (26, 36)	34 (24, 40)	0.20
Comorbidity, n (%)			
Congestive heart failure	15 (9.8)	12 (15.6)	0.29
Chronic pulmonary disease	7 (4.6)	2 (2.6)	0.71
End stage renal failure	11 (7.2)	9 (11.7)	0.37
Hepatic cirrhosis	7 (4.6)	9 (11.7)	0.084
Steroid use (> 7 days)	25 (16.3)	8 (10.4)	0.31
Vital signs on Day1			
Body temperature, °C	37.0 (36.5, 38.2)	37.4 (36.6, 38.3)	0.68
Heart rate, beats/min	108 (94, 124)	114 (98, 129)	0.11
Mean arterial pressure, mmHg	63 (55, 77)	66 (56, 80)	0.50
Blood gas analysis on Day1			
pH	7.36 (7.28, 7.44)	7.36 (7.29, 7.45)	0.50
$PaCO_2$, mmHg	35 (29, 44)	35 (29, 41)	0.41
PaO_2, mmHg	99 (73, 147)	97 (74, 154)	0.85
Base excess, mmol/L	-4.6 (-8.2, 0.3)	-3.8 (-9.0, -0.2)	0.99
Median (inter quartile range)			
P values were calculated using Pearson's chi-square test and Mann-Whitney U test.			
1) APACHE, acute physiology and chronic health evaluation			
2) Delta lactate was calculated by subtracting lactate level on day2 from day1			
3) Lactate clearance was calculated by delta lactate divided by day1 value			
4) Delta base excess was calculated by subtracting base excess on day1 from day2			
5) Delta anion gap was calculated by subtracting anion gap on day1 from day2			

	TBIL < 2 mg/dL (n = 153)	TBIL ≥ 2 mg/dL (n = 77)	P value
Anion gap, mEq/L	14.5 (11.8, 19.0)	18.0 (12.0, 23.5)	0.21
Lactate, mmol/L	2.8 (1.5, 4.9)	3.6 (1.9, 7.0)	0.031
Laboratory data on Day1			
WBC, $*10^3/mm^3$	108 (34, 171)	111 (62, 166)	0.52
Platelet, $*10^5/mm^3$	13.2 (6.9, 23.1)	7.7 (3.6, 12.7)	< 0.0001
Total bilirubin, mg/dL	0.9 (0.6, 1.1)	3.6 (2.7, 6.1)	< 0.0001
Creatinine, mg/dL	1.67 (1.04, 2.57)	1.81 (1.14, 3.03)	0.28
Lactate level on Day2, mmol/L	1.7 (1.2, 2.6)	2.2 (1.5, 3.6)	0.0023
Delta lactate Day1-2, mmol/L[2]	0.8 (0.0, 2.7)	0.7 (0.0, 2.8)	0.74
Lactate clearance Day1-2[3]	34.7 (0.0, 61.9)	35.3 (0.0, 53.9)	0.51
Delta base excess Day1-2[4]	-3.8 (-8.2, -0.7)	-3.7 (-9.5, -0.9)	0.97
Delta anion gap Day1-2[5]	-4 (-8, -3)	-4 (-8, 3)	0.43
28 Days survival, n (%)	125 (81.7)	60 (77.9)	0.61
Median (inter quartile range)			
P values were calculated using Pearson's chi-square test and Mann-Whitney U test.			
1) APACHE, acute physiology and chronic health evaluation			
2) Delta lactate was calculated by subtracting lactate level on day2 from day1			
3) Lactate clearance was calculated by delta lactate divided by day1 value			
4) Delta base excess was calculated by subtracting base excess on day1 from day2			
5) Delta anion gap was calculated by subtracting anion gap on day1 from day2			

In the patients with TBIL ≥ 2 mg/dL, non-survivors had significantly lower lactate clearance compared to survivors ($P = 0.0035$), while in those with TBIL < 2 mg/dL, there was a no significant difference in lactate clearance between survivors and non-survivors ($P = 0.88$) (Fig. 1A). Lactate clearance was not significantly correlated to TBIL (TBIL ≥ 2 mg/dL group, $P = 0.82$; TBIL < 2 mg/dL group, $P = 0.35$, total, $P = 0.80$). There were no significant differences in delta base excess between non-survivors and survivors both in the patients with TBIL ≥ 2 mg/dL ($P = 0.74$) and < 2 mg/dL ($P = 0.64$). No significant differences in delta anion gaps were observed between non-survivors and survivors in the patients with TBIL < 2 mg/dL

(*P* = 0.70), while there is a non-significant trend of decreased delta anion gap in survivors compared to non-survivors TBIL ≥ 2 mg/dL (*P* = 0.13) (Fig. 1B and 1C). Lactate clearance was significantly correlated to delta anion gap in the derivation cohort (all, R = 0.54, *P* < 0.0001; TBIL < 2 mg/dL, R = 0.56, *P* = 0.00017; TBIL ≥ 2 mg/dL, R = 0.57, *P* < 0.0001) (Fig. 2).

In the primary analysis using a multivariate logistic regression analysis with adjustments of baseline imbalances, patients with increased lactate clearance had significantly decreased 28-day mortality in TBIL ≥ 2 mg/d group (10% lactate clearance, adjusted odds ratio [OR] 0.88, 95%CI; 0.80−0.97, *P* = 0.0075); however, in TBIL < 2 mg/d group, lactate clearance was not significantly associated with altered 28-day mortality in the derivation cohort (10% lactate clearance, adjusted OR 0.99, 95%CI; 0.93−1.05, *P* = 0.69) (**Table 3A**). In accord with lactate clearance, patients with increased delta anion gap had significantly decreased 28-day mortality in TBIL ≥ 2 mg/d group (adjusted OR 1.09, 95%CI; 1.00-1.19, *P* = 0.045); however, in TBIL < 2 mg/d group, delta anion gap was not significantly associated with altered 28-day mortality (delta anion gap, adjusted OR 0.96, 95%CI; 0.83−1.11, *P* = 0.58) (**Table 3B**). Delta base excess was not significantly associated with altered 28-day mortality in the multivariate logistic regression analysis with the same adjustments of baseline imbalances (delta base excess, TBIL < 2 mg/dL, *P* = 0.65, TBIL ≥ 2 mg/dL, *P* = 0.74).

We next tested for the significant findings of lactate clearance in TBIL ≥ 2 mg/dL using the validation cohort (Table 2). In baseline characteristics, patients with TBIL ≥ 2 mg/dL were younger and had an increased probability of chronic hepatic failure compared to TBIL < 2 mg/dL. In accord with the derivation cohort, non-survivors had significantly lower lactate clearance compared to survivors in the TBIL ≥ 2 mg/dL group (*P* = 0.0006), while no significant difference in lactate clearance was observed in TBIL < 2 mg/dL (*P* = 0.46) (Fig. 3). Furthermore, patients with increased lactate clearance had significantly decreased 28-day mortality in the TBIL ≥ 2 mg/dL group (10% lactate clearance, adjusted odds ratio 0.89, 95%CI; 0.83−0.96, *P* = 0.0038); however, in the TBIL < 2 mg/dL group, lactate clearance was not significantly associated with altered 28-day mortality in the validation cohort (**Table 3C**).

Table 2
Baseline characteristics, vital signs, blood gas analysis and laboratory data in the derivation cohort (VASST cohort, n = 396)

	TBIL < 2 mg/dL (n = 280)	TBIL ≥ 2 mg/dL (n = 116)	P value
Age, yr	65 (51, 74)	57 (45, 66)	< 0.00001
Male sex, n (%)	161 (57.5)	63 (54.3)	0.64
APACHE II score	26 (22, 32)	28 (23, 33)	0.094
Comorbidity, n (%)			
Chronic heart failure	18 (6.4)	10 (8.6)	0.58
Chronic pulmonary disease	52 (18.5)	8 (6.9)	0.0052
Chronic hepatic failure	16 (5.7)	36 (31.0)	< 0.00001
End stage renal failure	34 (12.1)	13 (11.2)	0.93
Chronic steroid use	62 (22.1)	29 (25.0)	0.63
Vital signs on Day1			
Body temperature, °C [1]	38.6 (37.7, 39.3)	38.4 (37.6, 39.2)	0.37
Heart rate, beats/min [2]	125 (108, 140)	130 (118, 140)	0.20
Mean arterial pressure, mmHg [3]	54 (50, 60)	55 (49, 61)	0.61
Laboratory data on Day1			
WBC, $*10^3/mm^3$	14.2 (9.2, 21.5)	13.6 (7.5, 18.7)	0.076
Platelet, $*10^5/mm^3$	164 (92, 262)	92 (45, 149)	< 0.00001
Total bilirubin, mg/dL	0.8 (0.5, 1.3)	3.8 (2.6, 6.8)	< 0.00001
Creatinine, mg/dL	1.70 (1.06, 2.91)	2.18 (1.36, 3.31)	0.030
Lactate level on Day1, mmol/L	2.2 (1.3, 3.8)	3.5 (1.9, 6.5)	< 0.00001

Median (inter quartile range)
P values were calculated using Pearson's chi-square test and Mann-Whitney U test.
1) Most abnormal degree on Day1
2) Highest rate on Day1
3) Lowest pressure on Day1

	TBIL < 2 mg/dL (n = 280)	TBIL ≥ 2 mg/dL (n = 116)	P value
Lactate level on Day2, mmol/L	1.9 (1.3, 3.0)	3.2 (1.8, 5.6)	< 0.00001
Delta lactate Day1-2, mmol/L	0.1 (-0.5, 0.7)	0.2 (-0.8, 1.4)	0.56
Lactate clearance Day1-2	0.8 (-28.6, 29.7)	6.2 (-27.1, 33.0)	0.62
28 Days survival, n (%)	184 (65.7)	69 (59.4)	0.29
Median (inter quartile range)			
P values were calculated using Pearson's chi-square test and Mann-Whitney U test.			
1) Most abnormal degree on Day1			
2) Highest rate on Day1			
3) Lowest pressure on Day1			

Table 3. Multivariate logistic regression analysis for 28 days mortality

A. Derivation cohort, lactate clearance

	TBIL<2mg/dL		TBIL≥2mg/dL	
	Odd ratio (95%CI)	P value	Odd ratio (95%CI)	P value
Age -per year	0.98 (0.95-1.01)	0.17	1.03 (0.95-1.11)	0.45
Male sex	0.78 (0.31-1.91)	0.58	1.26 (0.30-5.22)	0.76
APACHE II score	1.13 (1.06-1.22)	0.00043	1.03 (0.95-1.11)	0.45
Lactate clearance -per 10%	0.99 (0.93-1.05)	0.69	0.88 (0.80-0.97)	0.0075

B. Derivation cohort, delta anion gap

	TBIL<2mg/dL		TBIL≥2mg/dL	
	Odd ratio (95%CI)	P value	Odd ratio (95%CI)	P value
Age -per year	0.97 (0.90-1.04)	0.38	1.05 (0.99-1.12)	0.13
Male sex	0.32 (0.037-2.75)	0.30	2.15 (0.41-11.2)	0.37
APACHE II score	1.11 (0.96-1.28)	0.15	1.11 (1.00-1.24)	0.05
Delta anion gap	0.96 (0.83-1.11)	0.58	1.09 (1.00-1.19)	0.045

C. Validation cohort

	TBIL<2mg/dL		TBIL≥2mg/dL	
	Odd ratio (95%CI)	P value	Odd ratio (95%CI)	P value
Age -per year	1.01 (0.99-1.02)	0.57	1.02 (0.99-1.05)	0.12
Male sex	0.97 (0.57-1.65)	0.91	1.03 (0.44-2.38)	0.95
APACHE II score	1.12 (1.08-1.17)	<0.0001	1.09 (1.03-1.16)	0.0043
Lactate clearance -per 10%	1.01 (0.99-1.03)	0.48	0.89 (0.83-0.96)	0.0038

APACHE, acute physiology and chronic health evaluation

Discussion

In the present study of lactate clearance in septic shock patients, stratified by hepatic dysfunction, increased lactate clearance in the initial 24 hours was significantly associated with decreased mortality in patients with TBIL ≥ 2 mg/dL. In contrast, lactate clearance was not associated with altered mortality in patients with TBIL < 2 mg/dL

Lactate clearance has been substantially studied as a prognostic marker in sepsis/septic shock [7, 9, 15, 20]. However, increased lactate clearance has not always been observed to be associated with decreased mortality in sepsis/septic shock. In the present study of two septic shock cohorts, the association between increased lactate clearance and decreased 28-day mortality was significant only in TBIL ≥ 2 mg/dL group, but not in TBIL < 2 mg/dL, which may explain why the previous reports obtained inconsistent conclusions in mixed patient populations with hepatic dysfunction and no hepatic dysfunction. The present study may highlight the importance of the hepatic dysfunction when considering lactate clearance as a prognostic marker.

Lactate kinetics has been investigated [21–25]. An investigation using intravenous infusion of sodium lactate revealed that clearance of lactate from blood in normal postprandial subjects was 17.9 mL/kg/min [21]; it decreased 14.5 mL/kg/min in patients with hepatic dysfunction [22]. Additionally, a significant prolongation in lactate half-life was observed in the patients with liver cirrhosis due to impaired hepatic lactate uptake (18.8 min compared to 14.7 min) [23]. Similarly, in severe sepsis/septic shock, hepatic dysfunction was significantly associated with impaired lactate clearance and normalization during the early phase of quantitative resuscitations [13]. Thus, hepatic dysfunction decreased lactate elimination. In the condition of insufficient elimination, lactate generation has a large effect on lactate clearance, which is a potential explanation for the significance of lactate clearance in hepatic dysfunction.

In this study, delta base excess, which reflect the bicarbonate at the end of lactate metabolism, was not associated with 28-day mortality in both TBIL ≥ 2 mg/dL and TBIL < 2 mg/dL group. Base excess reflects increased non-volatile acid including lactate in sepsis [26], and low base excess predicted increased lactate levels [27, 28]. However, base excess is affected by other abnormalities such as a metabolic acidosis (ketoacidosis, renal tubular acidosis and uremia), acute respiratory acidosis or hemoglobin level change, which are sometimes observed in critically ill patients [29]. The change of base excess as a prognostic marker of septic shock may be affected by these complex acidosis mechanisms.

Conversely, delta anion gap was significantly associated with altered mortality and had a good correlation with lactate clearance. Anion gap directly reflect the nonvolatile acid compared to base excess calculated using pH and bicarbonate; anion gap simply shows the ion balance [30, 31]. In accord with this, lactate clearance was significantly correlated to delta anion gap. The significant association of delta anion gap with altered 28-day mortality is a supportive evidence on the significant finding in lactate clearance in the present study.

Our study has several limitations. First, it is a retrospective study, although we found the same effect of hepatic dysfunction in both cohorts of septic shock patients. Second, we defined hepatic dysfunction as TBIL ≥ 2 mg/dL based on Brussels criteria; however, there are different criteria or cut-off values of hepatic dysfunction.

Conclusions

In septic shock, patients with increased lactate clearance had decreased 28-day mortality when patients had hepatic dysfunction (TBIL ≥ 2 mg/dL). These highlighted the importance of hepatic dysfunction when considering the lactate clearance as a clinical parameter.

Abbreviations

TBIL, total bilirubin; CHIBA, Chiba university hospital; VASST, Vasopressin and Septic Shock Trial

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Chiba University Graduate School of Medicine, the Institutional Review Board at St. Paul's Hospital and the University of British Columbia. Written informed consent was waived because of the study design.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

N.T. and T.N. contributed to the study's conceptualization and design, the acquisition of data, analysis, and interpretation of data, statistical analysis, and drafting and critical revision of the manuscript for intellectual content. K.W. and J.R. contributed to the acquisition of data, interpretation of data, and critical revision of the manuscript for intellectual content. All authors read and approved the manuscript.

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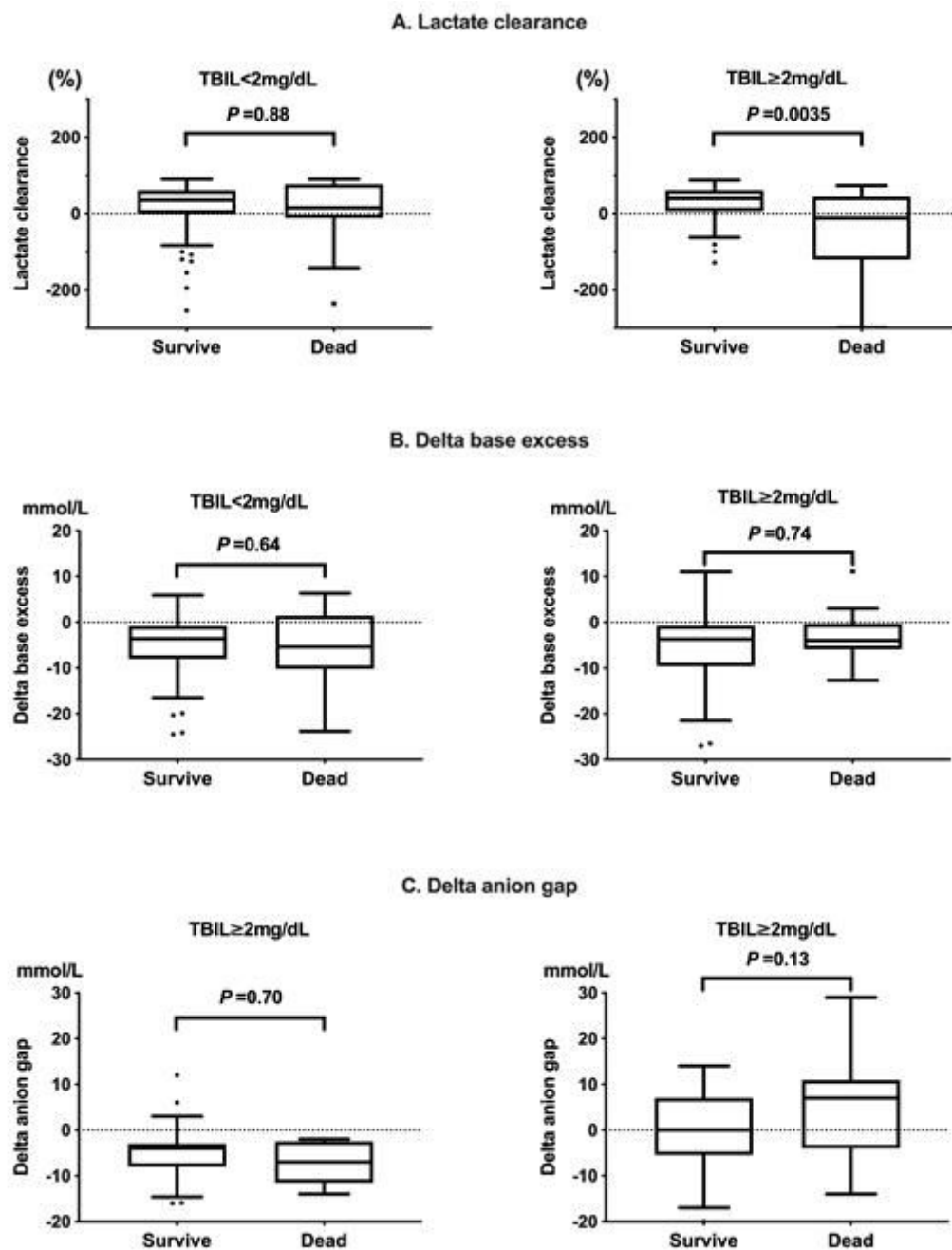
Figures

Figure 1

Lactate clearance, delta value of base excess and anion gap between survivors and non-survivors in the derivation cohort Panel A. Lactate clearance, Panel B. Delta base excess, Panel C. Delta anion gap
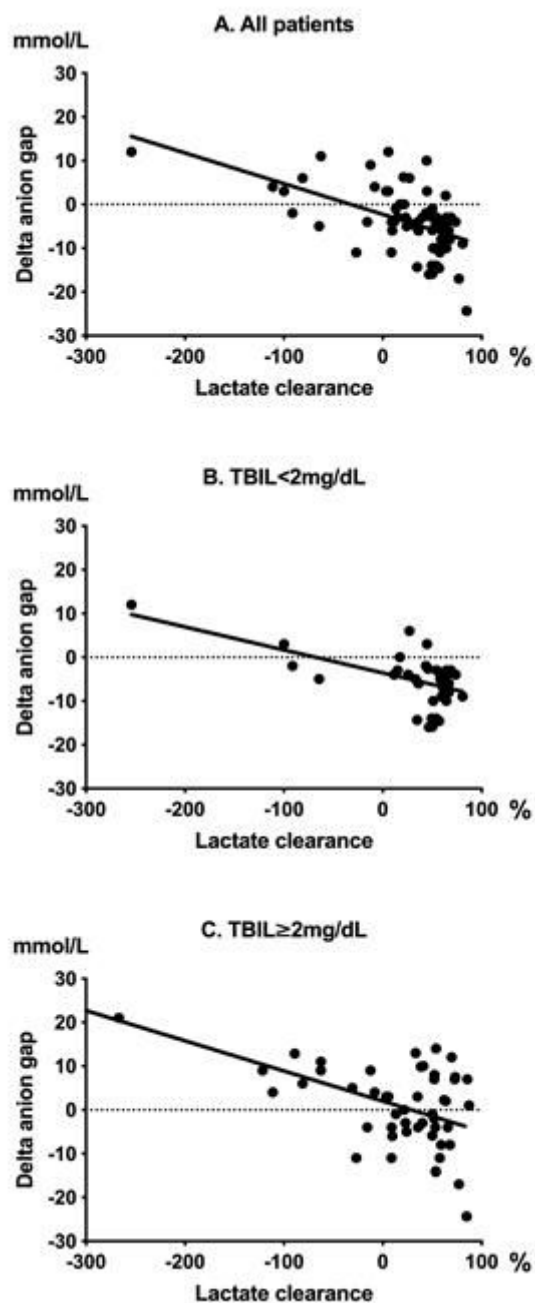
Figure 2

The correlation between lactate clearance and delta anion gap Panel A. All patients, Panel B. TBIL<2mg/dL, Panel C. TBIL≥2mg/dL
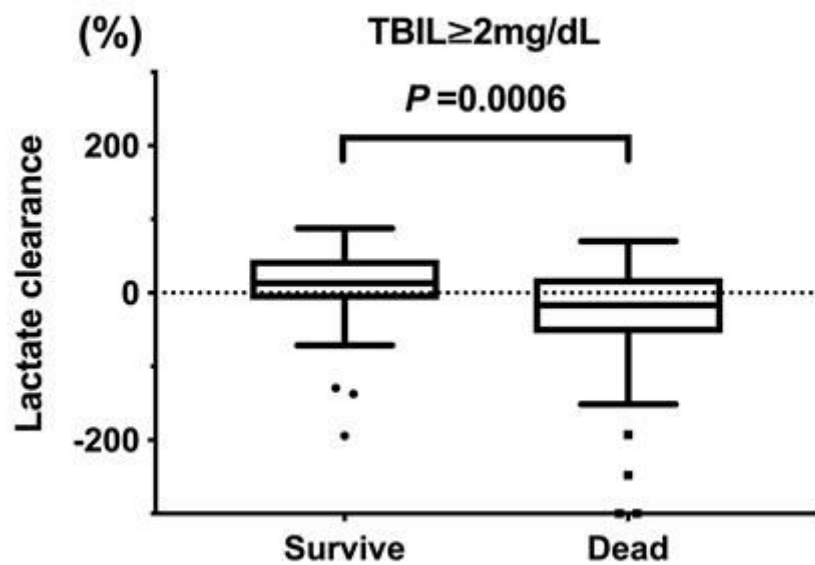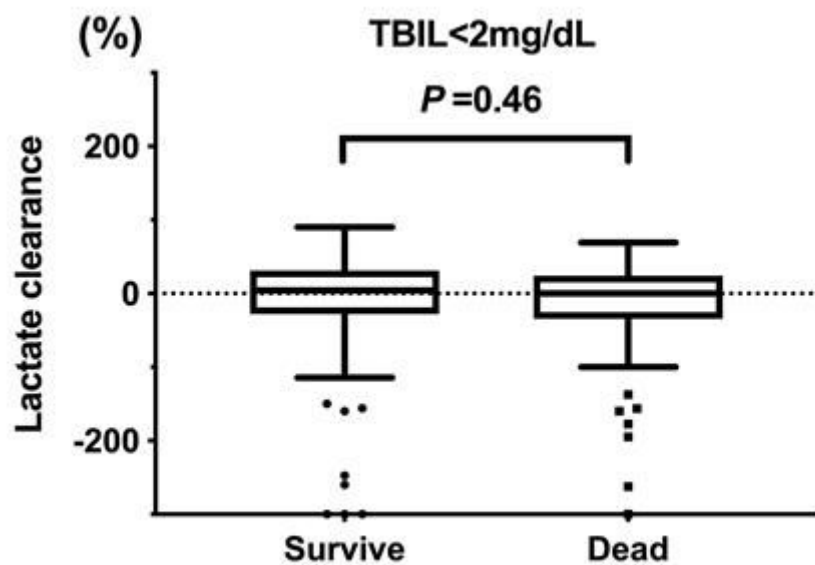
Figure 3

Lactate clearance between survivors and non-survivors in the validation cohort