

# Thiamine status and lactate concentration in sepsis

## A prospective observational study

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### Abstract

Thiamine is an essential co-factor for aerobic metabolism. Both thiamine deficiency and sepsis may be associated with hyperlactatemia and hypotension. We assessed the relationship between thiamine compounds, lactate concentrations and clinical outcomes in septic patients.

We undertook a prospective observational single-center study. Erythrocyte levels of total thiamine, free thiamine, thiamine mono, di and triphosphate (TMP, TDP, and TTP respectively), the erythrocyte transketolase activity (ETKA) and the effect of thiamine diphosphate on ETKA were measured in septic patients by high performance liquid chromatography and correlated with arterial lactate. Vital status at the end of intensive care unit stay was recorded.

Overall, 28 patients suffering from sepsis were included. Median (interquartile range [IQR]) age was 60 [44–77.3] years, 15 (53.6%) patients were male, median [IQR] simplified acute physiology score II was 40 [27–50]. There was no correlation between total thiamine and lactate levels ( $P = .33$ ). There was no correlation between free thiamine ( $P = .81$ ), TMP ( $P = .71$ ), TDP ( $P = .31$ ), TTP ( $P = .86$ ), and lactate levels in our population. There was no correlation between ETKA ( $P = .58$ ) or the effect of TDP on ETKA ( $P = .40$ ) and lactate concentration. Total thiamine and TDP concentration were significantly higher in intensive care unit (ICU) survivors than in nonsurvivors ( $P = .03$  and  $P = .03$ ). The effect of TDP on ETKA was significantly higher in nonsurvivors compared to survivors ( $P = .04$ ).

We found no correlation between thiamine compounds and lactate concentration in sepsis. Thiamine deficiency in sepsis may be associated with ICU-mortality.

**Abbreviations:** ETKA = erythrocyte transketolase activity, ICU = intensive care unit, TDP = thiamine diphosphate, TMP = thiamine monophosphate, TTP = thiamine triphosphate.

**Keywords:** hyperlactatemia, metabolism, septic shock, thiamine deficiency, vitamin B1

### 1. Introduction

Lactate plays a key role in cellular metabolism and energy production.<sup>[1]</sup> Hyperlactatemia related acidosis, resulting from the balance between lactate production and clearance occurs in a

series of conditions, including shock, trauma, vigorous muscular exercises, liver diseases, cancer, carbon monoxide or cyanide poisoning and after drug intake such as  $\beta_2$  agonists or metformin.<sup>[2]</sup> Sepsis, the inappropriate host response to an

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This monocentric observational study was an ancillary study of 2 trials (ClinicalTrials.gov NCT00318942 and NCT00167596). This study was conducted in accordance with the Declaration of Helsinki. The local ethics committee (Comité de Protection des Personnes de Saint-Germain-en-Laye) approved each independent trial (approval numbers 02027 and 05008, respectively). Informed consent to participate was obtained from participants or next of kin.

Consent for publication is not applicable.

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infection, is also associated with hyperlactatemia.<sup>[3,4]</sup> During sepsis, the pathogenesis of hyperlactatemia, although poorly understood is thought to be due to increased lactate production in response to the stress response, and impaired lactate clearance.<sup>[5,6]</sup> Hyperlactatemia related acidosis is associated with an increased risk of mortality and lactate normalization is a therapeutic target in sepsis-associated hypotension or septic shock.<sup>[7]</sup> Hyperlactatemia may be an adaptive response to stress, since lactate provides substrates for gluconeogenesis as well as optimizes tissue bioenergetics.<sup>[8]</sup> Thiamine deficiency is characterized by impaired cardiac performance, water and salt retention, vasodilatation and hyperlactatemia related acidosis, which are all hallmarks of sepsis.<sup>[9]</sup>

Thiamine, or vitamin B1, is implicated in cellular and mitochondrial energy production.<sup>[10]</sup> In the cytosol, thiamine is an obligatory cofactor for the transketolase enzyme, implicated in the pentose phosphate pathway.<sup>[11]</sup> Thiamine is a cofactor for the pyruvate dehydrogenase, enabling the entry of pyruvate into the mitochondria, and the subsequent entry of its metabolite, acetyl-CoA into the citric acid cycle.<sup>[11]</sup> Since excess pyruvate is subsequently converted into lactate, thiamine deficiency leads to hyperlactatemia.<sup>[12]</sup> Thiamine is also a cofactor for the  $\alpha$ -ketoglutarate dehydrogenase and branched-chain keto-acid dehydrogenase, implicated respectively in the citric acid cycle and in the metabolism of branched chain amino acids. The vitamin occurs as free thiamine and under various stages of phosphorylation, including thiamine monophosphate (TMP), thiamine diphosphate (TDP), and thiamine triphosphate (TTP), which can all be measured in red blood cells.<sup>[13]</sup> Thiamine content can be indirectly estimated by measuring the erythrocyte transketolase activity (ETKA). The recommended daily intake of thiamine is usually covered by a balanced diet. Risk factors for thiamine deficiency include improper vitamin intake and alcoholism.<sup>[9]</sup>

It has recently been proposed that a cocktail consisting of steroids, vitamin C, and thiamine could be associated with improved outcomes in severe sepsis and septic shock.<sup>[14,15]</sup> We sought in the current work to assess the thiamine status of septic patients, both directly, by measuring erythrocyte concentrations of thiamine compounds and indirectly by measuring the activity of thiamine dependent enzymes. We also assessed the interaction between thiamine compounds and lactate concentration. Finally, we sought to determine whether thiamine status affected outcomes in septic patients.

## 2. Material and methods

### 2.1. Study setting and patients

This monocentric observational study was an ancillary study of 2 trials (ClinicalTrials.gov NCT00318942 and NCT00167596). This study was conducted in accordance with the Declaration of Helsinki. The local ethics committee (Comité de Protection des Personnes de Saint-Germain-en-Laye) approved each independent trial (approval numbers 02027 and 05008, respectively), and written informed consent was obtained from all patients or their surrogate. Inclusion criteria were any adult patient with a diagnosis of sepsis.<sup>[16]</sup> We excluded from the current analysis any patient suffering from severe liver disease or treated by metformin, linezolid or thiamine. We obtained whole blood samples from subsequent patients included in the general intensive care unit of the Raymond Poincaré University hospital.

### 2.2. Blood samples

Initial blood samples were collected through venipuncture or a preexisting arterial line in heparin-containing tubes, on the day sepsis was diagnosed. Samples were centrifuged (3500g, 15 minutes, +4°C) and frozen at -80°C. Total thiamine and thiamine compound concentrations were determined in erythrocytes by high performance liquid chromatography.<sup>[13]</sup> Normal values in the local laboratory for erythrocyte thiamine is between 126 and 250 nmol/L. Normal values for thiamine compounds in erythrocytes are between 0 and 8 nmol/L for free thiamine, between 0 and 2 nmol/L for TMP, between 120 and 230 nmol/L for TDP and between 0 and 20 nmol/L for TTP. ETKA and the effect of TDP supplementation on ETKA were measured by the spectrophotometric determination of sedoheptulose 7-phosphate.<sup>[17]</sup> To measure the TDP effect, TDP was added to the assay reaction mixture to a final concentration of 500  $\mu$ mol/L. Normal values in the local laboratory for ETKA and TDP effect were 123 to 206 units/L and 0% to 20%, respectively.

### 2.3. Data collection

Collected data included, age, gender, a history of congestive heart disease, hypertension, chronic pulmonary disease or malignancy, McCabe class,<sup>[18]</sup> the source of sepsis as well as the severity thereof assessed through the simplified acute physiology score II<sup>[19]</sup> and the sequential organ failure assessment scores.<sup>[20]</sup> We also collected heart rate, temperature, systolic blood pressure, white blood cell count, hematocrit, creatinine, glucose, bilirubin, protein, PaO<sub>2</sub>, and lactate levels at the time of inclusion. Outcomes included length of vasopressor administration and intensive care unit (ICU)-mortality.

### 2.4. Statistical analysis

Quantitative variables were expressed as median (interquartile range) and categorical variables as number (percentage). Categorical variables were compared using the Fisher exact test and continuous variables using the Wilcoxon rank-sum test. The association between quantitative variables was assessed using the Spearman rank correlation. A univariate logistic regression model was used to predict the likelihood of death in septic patients. Statistical analyses were performed using SAS 9.3 (SAS Inc, Cary, NC) and R 2.13.0 (<http://www.R-project.org/>) software. Tests were 2 sided.  $P < .05$  was considered statistically significant.

## 3. Results

### 3.1. Descriptive analysis

Twenty-eight patients were prospectively recruited in the medical ICU of the Raymond Poincaré hospital. Baseline characteristics of the recruited patients are described in Table 1. Sepsis occurred within a median of 1 [0.75; 3.25] days following ICU admission. Ten out of 28 patients (36%) suffered from septic shock.<sup>[16]</sup>

### 3.2. Thiamine status and correlation with lactate levels.

Subjects exhibited median erythrocyte thiamine concentration of 195 [146; 276] nmol/L. Median erythrocyte free thiamine concentration was 7.5 [2.75; 11.25] nmol/L, TMP was 5.5 [4; 9] nmol/L, TDP was 180 [123; 250] nmol/L and TTP was 2

**Table 1**  
**Main characteristics at baseline.**

Variable	n=28
Age, median [IQR], yr	60 [44; 77]
Male sex, no. (%)	15 (53.6)
Congestive heart failure, no. (%)	4 (14.3)
Hypertension, no. (%)	9 (32.1)
Chronic pulmonary disease, no. (%)	9 (32.1)
History of malignancy, no. (%)	6 (21.4)
McCabe class, no. (%)	
No underlying disease or no fatal disease	17 (60.7)
Underlying ultimately fatal disease (>5 yr)	9 (32.1)
Underlying rapidly fatal disease (<1 yr)	2 (7.2)
Source of sepsis, no. (%)	
Lungs	14 (50)
Abdomen	6 (21.4)
Urinary tract	2 (7.1)
Soft tissue	5 (17.9)
Meningitis	1 (3.6)
Heart rate (bpm), median [IQR]	100 [92;116]
Systolic blood pressure (mmHg), median [IQR]	90 [80;106]
Administration of vasopressors, no. (%)	14 (50)
Norepinephrine, no. (%)	11 (39)
Dopamine, no. (%)	3 (11)
Temperature (°C), median [IQR]	38.5 [38;39]
White blood cell count ( $\times 10^9/L$ ), median [IQR]	13.6 [9.4;19.1]
Hematocrit (%), median [IQR]	34 [28;37]
Creatinine ( $\mu\text{mol/L}$ ), median [IQR]	85 [65;190]
Glucose (mmol/L), median [IQR]	7.8 [5.8;9.2]
Protein (g/L), median [IQR]	52 [47;60]
Bilirubin (mmol/L), median [IQR]	11 [6;17]
Lactate (mmol/L), median [IQR]	2.8 [1.4;6]
PaO <sub>2</sub> (kPa), median [IQR]	12 [8.75;15]
SAPS II, median [IQR], median [IQR]	40 [27;51]
SOFA, median [IQR], median [IQR]	6 [4;10]

IQR=interquartile range, SAPS II=simplified acute physiology score II, SOFA=sequential organ failure assessment.

[1; 6] nmol/L. Median ETKA was 174 [122; 203] units/L while the effect of TDP on ETKA was 15 [12; 23] %. Median lactate levels were 2.8 [1.4; 6] mmol/L. Eight patients (29%) exhibited subnormal levels of thiamine and of TDP and/or subnormal levels of ETK activity. There was no correlation between total thiamine

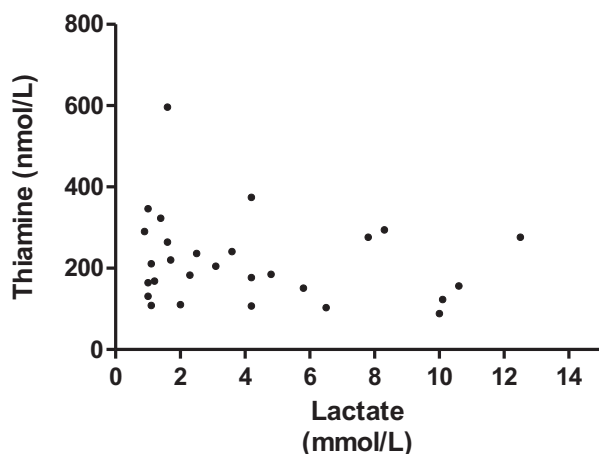


Figure 1. Relationship between total thiamine and lactate concentration.

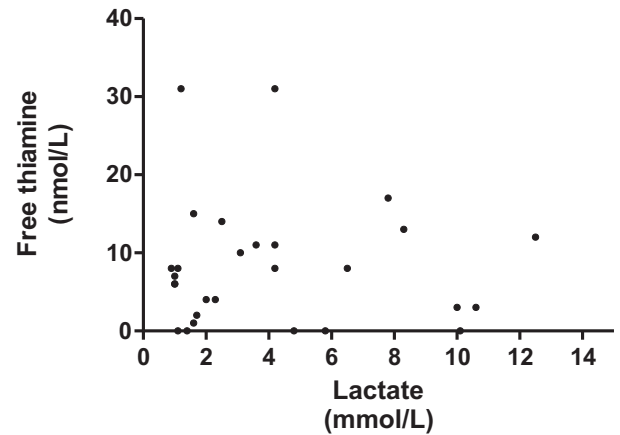


Figure 2. Relationship between free thiamine and lactate concentration.

and lactate concentration ( $P=.33$ ) (Fig. 1). There was no correlation between free thiamine and lactate concentration ( $P=.81$ ) (Fig. 2). There was no correlation between TMP and lactate concentration ( $P=.71$ ) (Fig. 3). There was no correlation between TDP and lactate concentration ( $P=.31$ ) (Fig. 4). There was no correlation between TTP and lactate concentration ( $P=.86$ ) (Fig. 5). There was no correlation between ETKA and lactate concentration ( $P=.58$ ) (Fig. 6). There was no correlation between the effect of TDP and lactate concentration ( $P=.40$ ) (Fig. 7). Variations of thiamine metabolites over time (including day 0, day 2, and day 7) are described in Table 2.

**3.3. Thiamine status and outcome**

Comparing non survivors to survivors, we found that thiamine and TDP levels were lower in nonsurvivors compared to survivors (respectively 110 [103; 123] vs 211 [166; 283] nmol/L;  $P=.03$ ; odds ratio [OR] (confidence interval [CI] 95%) for ICU mortality 0.98 [0.96–1.00]  $P=.07$  and 100 [91;110] vs 204 [150;261] nmol/L;  $P=.03$ ; OR [CI 95%] for ICU mortality 0.98 [0.96–1.00]  $P=.07$ ) (Supplemental Fig. 1, <http://links.lww.com/MD/D703>). Similarly, the effect of TDP was significantly higher in nonsurvivors compared to survivors (respectively 32 [22; 43]

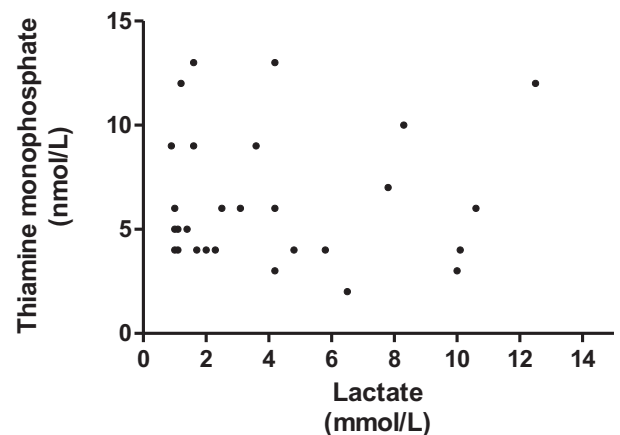


Figure 3. Relationship between thiamine monophosphate and lactate concentration.

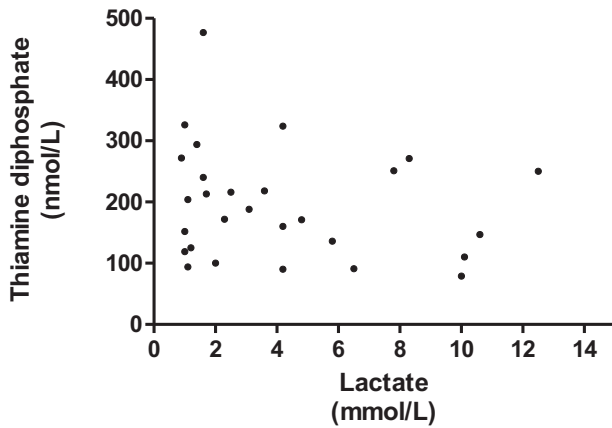


Figure 4. Relationship between thiamine diphosphate and lactate concentration.

vs 15 [11; 19] %;  $P = .04$ ; OR [CI 95%] for ICU mortality 1.14 [1.01–1.29]  $P = .03$  (Table 3). Median length of vasopressor administration was 4 [2; 5] days. Overall, 5 out of 28 patients (17.9%) died whilst in the ICU. Among the subgroup of patients identified as suffering from thiamine deficient, 3 deaths occurred in the ICU (37% mortality), while among the non-thiamine deficient group, 2 deaths occurred in the ICU (9.5% mortality). Lactate levels in ICU survivors and ICU nonsurvivors appear in Supplemental Figure 2, <http://links.lww.com/MD/D705>.

#### 4. Discussion

In this prospective monocentric study, we describe thiamine status in a cohort of septic patients. Thiamine deficiency occurred in 29% of our cohort. This figure does not depict the true prevalence of thiamine deficiency since our population was selected, excluding patients suffering from liver failure or those receiving thiamine supplementation. Previous studies reported that thiamine deficiency occurred in 20% to 40% of all the critically ill.<sup>[21,22]</sup> Prospective studies in the United States observed thiamine deficiency in 10 to 35% of cases of sepsis.<sup>[23,24]</sup> In Brazil, the prevalence of thiamine deficiency is reported to reach 71% in sepsis.<sup>[25]</sup> Contrary to previous prospective studies in sepsis, we assessed thiamine status by measuring erythrocyte and

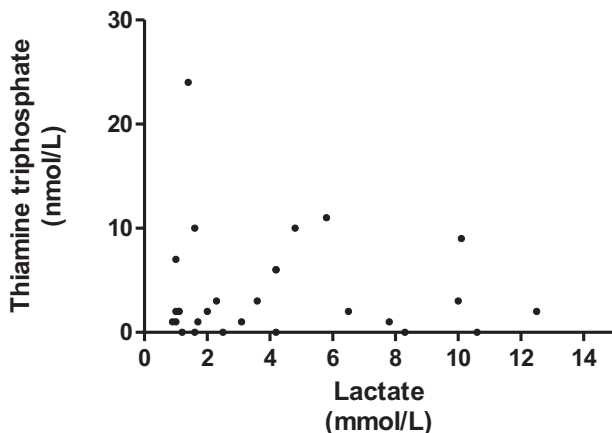


Figure 5. Relationship between thiamine triphosphate and lactate concentration.

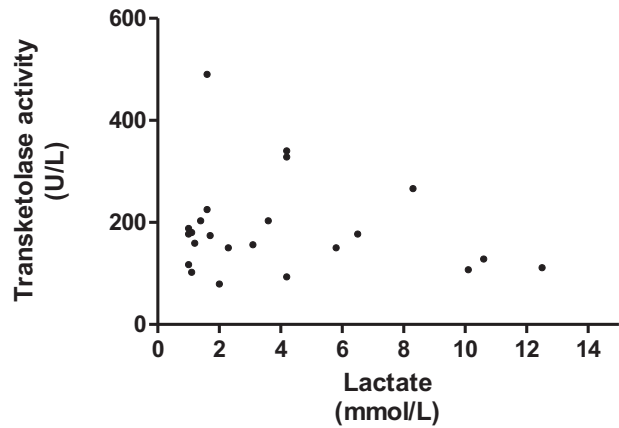


Figure 6. Relationship between erythrocyte transketolase activity and lactate concentration.

not serum levels of thiamine. We also measured the erythrocyte levels of thiamine esters. Indeed, among thiamine compounds, TDP is the biologically active form of the vitamin, acting as a coenzyme for the enzymes implicated in the metabolism of carbohydrates.<sup>[11]</sup> While the exact physiological function of TMP and TTP remains uncertain, these compounds may play non-coenzyme roles.<sup>[26,27]</sup> We also assessed thiamine status through indirect means, namely the ETKA and its increase in response to the *in vitro* addition of TDP. We; therefore, provide in the present study a uniquely detailed overview of thiamine status in septic patients.

We also sought to determine whether low thiamine levels were associated with hyperlactatemia related acidosis during sepsis. Metabolic acidosis due to thiamine deficiency is reported as reversible in several case reports.<sup>[28–31]</sup> However, in keeping with findings from previous studies, we did not observe any correlation between and thiamine or thiamine compounds and levels of lactate. A prospective study by Donnino et al did not find any correlation between plasma thiamine levels and lactate levels in patients suffering from sepsis.<sup>[23]</sup> Only in the subgroup of patients devoid of liver injuries was there evidence of correlation

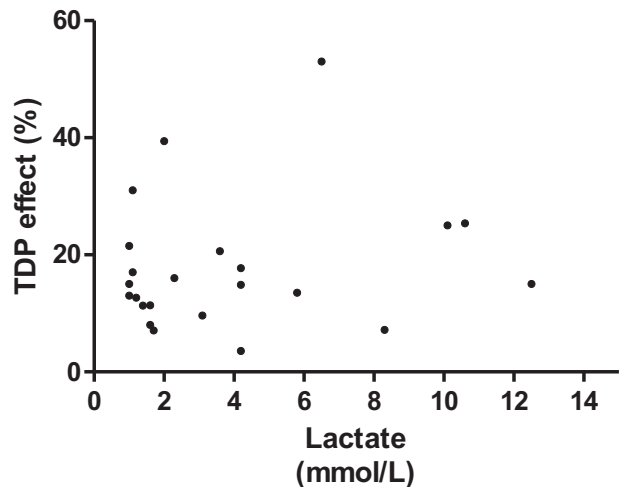


Figure 7. Relationship between the effect of thiamine diphosphate on erythrocyte transketolase activity and lactate concentration.

**Table 2**  
Serial measurements of thiamine metabolites.

Variable, median [IQR]	Day 0	Day 2	Day 7
Thiamine, nmol/L	195 [146; 276]	210 [170; 266]	174 [163; 253]
Free thiamine, nmol/L	7 [3; 11]	7 [4; 12]	7 [9; 15]
Thiamine monophosphate, nmol/L	5 [4; 9]	7 [4; 9]	5 [4; 7]
Thiamine diphosphate, nmol/L	180 [123; 250]	197 [163; 249]	160 [149; 221]
Thiamine triphosphate, nmol/L	2 [1; 6]	2 [0; 4]	1 [0; 3]

IQR = interquartile range.

between thiamine and lactate levels. In a randomized controlled trial of thiamine versus placebo in sepsis, the same team observed no differences in lactate levels between the thiamine treatment and control arms. However, the subgroup of patients with baseline thiamine deficiency exhibited a significant difference in lactate levels at 24 hours.<sup>[24]</sup>

Initial low thiamine levels were associated with ICU-mortality in our cohort of septic patients. We do not have sufficient evidence to demonstrate that increased lactate levels were mediated by low thiamine levels in septic patients. Thiamine deficiency may lead to poor outcomes through other functions of thiamine than those related to the Krebs cycle. Indeed, thiamine is an essential coenzyme in the pentose phosphate pathway, an alternative pathway to glycolysis, as measured in the present study using the ETK activity. Thiamine also regulates oxidation and the production of glucose-derived neurotransmitters.<sup>[32]</sup> Thiamine deficiency, by limiting the amount of energy available to the myocardium, is implicated in myocardial weakness and heart failure, which may lead to worse outcomes in sepsis.<sup>[33]</sup>

A retrospective study found thiamine deficiency to be common in the critically ill and to be associated with mortality.<sup>[21]</sup> Donnino et al, in a trial assessing thiamine supplementation in sepsis found no difference regarding severity of illness or mortality between the treatment and the control arms. Only in the subgroup of patients with baseline thiamine deficiency was there a significant difference regarding time to death.<sup>[24]</sup> Finally, Marik et al, proposed that a cocktail consisting of steroids, vitamin C and thiamine could be associated with improved outcomes in severe sepsis and septic shock.<sup>[14]</sup>

Our study has several limits namely a small size and a monocentric nature. Findings regarding outcome must; therefore, be regarded as exploratory and need to be confirmed in larger

**Table 3**  
Risk factors for ICU mortality by univariate analysis.

Variable	OR [95% CI]	P
Thiamine	0.98 [0.96; 1.00]	.07
Free thiamine	0.93 [0.78; 1.10]	.38
Thiamine monophosphate	0.80 [0.53; 1.22]	.30
Thiamine diphosphate	0.98 [0.96; 1.00]	.07
Thiamine triphosphate	0.98 [0.87; 1.10]	.69
ETKA	0.97 [0.94; 1.00]	.09
Effect of Thiamine diphosphate on ETKA	1.14 [1.01; 1.29]	.04
SAPS II	1.03 [0.99; 1.08]	.18
SOFA	1.30 [1.01; 1.67]	.04

CI = confidence interval, ETKA=erythrocyte transketolase activity, OR = odds ratio, SAPS II=simplified acute physiology score II, SOFA=sequential organ failure assessment.

studies. Additionally, thiamine measurements made in erythrocytes may not accurately reflect tissue concentration of TDP. Overall, we observed thiamine deficiency in 29% of our population. Thiamine status did not correlate with lactate levels in our cohort of septic patients. Thiamine deficiency in sepsis was associated with ICU mortality.

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