Thiamine supplementation may be associated with improved prognosis in patients with sepsis

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Abstract  
Sepsis is a clinical syndrome characterised by a severe disorder of pathophysiology caused by infection of pathogenic micro-organisms. The addition of antioxidant micronutrient therapies such as thiamine to sepsis treatment remains controversial. This study explored the effect of thiamine on the prognosis of patients with sepsis. This study was a retrospective study involving patients with sepsis from the Medical Information Mart for Intensive Care IV. Patients were divided into two groups, the thiamine received group (TR) and the thiamine unreceived group (TUR), according to whether they were supplemented with thiamin via intravenous while in the intensive care unit (ICU). The primary outcome was ICU mortality. The association between thiamine and outcome was analysed using the Cox proportional hazards regression model, propensity score matching (PSM), generalised boosted model-based inverse probability of treatment weighting (IPTW) and doubly robust estimation. A total of 11 553 sepsis patients were enrolled in this study. After controlling for potential confounders using Cox regression models, the TR group had a statistically significantly lower ICU mortality risk than the TUR group. The hazard ratio of ICU mortality for the TR group was 0.80 (95 % CI 0.70–0.90). We obtained the same results after using PSM, IPTW and doubly robust estimation. Supplementation with thiamine has a beneficial effect on the prognosis of patients with sepsis. More randomised controlled trials are needed to confirm the effectiveness of thiamine supplementation in the treatment of sepsis.

Key words: Thiamine: Sepsis: Generalised boosted model: Inverse probability of treatment weighting: Doubly robust estimation

Sepsis is a clinical syndrome characterised by a severe disorder of pathophysiology caused by infection of pathogenic micro-organisms. To facilitate early identification of this disease, Sepsis-3 defines it as life-threatening organ dysfunction resulting from a dys-regulated host response to infection. This means that the diagnosis is considered to be met when the patient has a suspected or confirmed infection combined with the Sequential Organ Failure Assessment ≥2(1). Despite the lack of global epidemiological data on sepsis(2), current studies estimate that it affects more than 30 million people annually and may cause 6 million deaths(3), making it a major worldwide public health problem(4). Currently, various antibiotics and organ support therapies are widely used in the clinical treatment of sepsis, but the mortality rate remains high(5). The mechanism of sepsis is very complex, and further research is needed.

The primary causative factors of sepsis or the alterations in the internal environment and haemodynamics that occur during disease progression can lead to massive cytokine release, oxidative stress imbalance and mitochondrial dysfunction in the organism. When antioxidant defences are overwhelmed, reactive oxygen species cause cellular damage, leading to organ dysfunction and tissues becoming hypoxic; along with an increase in free radical production and oxidative stress. Mitochondria are both sites of reactive oxygen species production and targets of reactive oxygen species-mediated damage, therefore playing a prominent role in the pathogenesis of sepsis(6,7). For example, it was found that mitochondrial dysfunction plays a potential role in sepsis-induced acute kidney injury (AKI)(8). Linear spectroscopic dysfunction and biological failure are also important causes of cardiac insufficiency in patients with sepsis(9). The

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restoration of mitochondrial function, also known as metabolic resuscitation, may help relieve organ dysfunction in septic patients and improve their prognosis. Thiamine (vitamin B₁) is a water-soluble vitamin that plays an essential role in mitochondrial energy metabolism and is involved in multiple cellular metabolic processes in mitochondria and peroxisomes in the body. Moreover, it provides a certain resistance to oxidative stress of cells. Thiamine deficiency occurs in most acute and critically ill patients and may be related to the accumulation of lactate. A retrospective study revealed that in the early stages of sepsis, intravenous vitamin C along with corticosteroids and thiamine can reduce patient mortality and prevent organ failure. A randomised, double-blind, controlled study showed that intravenous thiamine administration reduces lactate production in a thiamine-deficient subgroup of patients with septic shock. Thiamine supplementation has also been shown to reduce the risk of sepsis-related kidney injury.

Mitochondrial dysfunction is commonly observed in critically ill patients, especially in those experiencing sepsis. The addition of antioxidant micronutrient therapies such as ascorbic acid and thiamine to sepsis treatment remains controversial. Here, we conducted a retrospective cohort study based on the Medical Information Mart for Intensive Care IV, a sizeable critical disease database, to investigate the effect of thiamine on the prognosis of patients with sepsis.

Methods

Data source

The Medical Information Mart for Intensive Care (MIMIC) IV is a free open-access database containing comprehensive information on tens of thousands of critically ill patients from 2008 to 2019, including comprehensive information on the patient’s hospital period, laboratory tests, medication and vital signs. The data used in this study were from MIMIC-IV version 0.4. The database was approved by the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center, and consent was obtained for the original data collection. Researchers need to complete the corresponding courses and obtain certificates before they can access and carry out data extraction (Record ID: 38601114). Considering that the database hides information about the identity of the patient, informed consent is not required.

Population

Patients who met the diagnosis of Sepsis-3 in the Medical Information Mart for Intensive Care IV database were included, whereas patients who died within 24 h after admission to the intensive care unit (ICU) and patients younger than 18 years were excluded.

Data extraction

Structured query language was used to extract data from the database. The data collected included age, sex, weight, ethnicity, first care unit, the severity of the disease (assessed using Sequential Organ Failure Assessment and Acute Physiological Score III), ventilator use, vasopressor use, continuous renal replacement therapy use, Charlson co-morbidity index and co-morbidities including myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, mild liver disease, severe liver disease, diabetes uncomplicated, diabetes complicated, paraplegia, renal disease, malignant cancer, metastatic solid tumour and AIDS. Results of the first laboratory examination after admission to the ICU included leucocyte count, Hb, platelet count, lactate, creatinine, urea nitrogen, glucose, PaCO₂, pH and PaO₂. The mean values of vital signs within 24 h of ICU admission include heart rate, mean arterial pressure, respiratory rate, temperature, pulse oximetry-derived oxygen saturation (SpO₂) and total urine output in the first 24 h.

The primary outcome included ICU mortality, while the secondary outcomes included 28-d mortality, ventilation-free days in 28 d, vasopressor-free days in 28 d and incidence of AKI within 7 d after diagnosis of sepsis.

Statistical analyses

The study population was divided into two groups, the thiamine received group (TR) and the thiamine unreceived group (TUR), based on whether thiamine was supplemented intravenously while in the ICU.

Missing data in public databases is a common phenomenon. In this study, we only included variables with missing rates less than 20 %, and the missing parts were filled using multiple imputation. This function can be implemented by the ‘mice’ package of the R programme. Data for continuous variables were expressed as median (interquartile range), and categorical data were presented as frequency. Mann–Whitney U test was used for continuous variables, and the χ² test or Fisher’s exact test was used for categorical variables. The relationship between thiamine and ICU mortality was measured using Cox proportional risk models, with estimated hazard ratios (HR) and 95 % CI. The effects of thiamine on the ventilation-free days and vasopressor-free days in 28 d were analysed by linear regression, expressed as regression coefficients (Coef) with 95 % CI. The association of thiamine with the occurrence of AKI after sepsis diagnosis was performed by logistic regression analysis and rendered as OR with 95 % CI. Multivariate analysis was used to control for confounders. Confounders included age, sex, weight, ethnicity, first care unit, Sequential Organ Failure Assessment, Acute Physiological Score III, ventilator use, vasopressor use, continuous renal replacement therapy use, Charlson co-morbidity index, myocardial infarct, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, mild liver disease, severe liver disease, diabetes uncomplicated, diabetes complicated, paraplegia, renal disease, malignant cancer, metastatic solid tumour, AIDS, leucocyte, Hb, platelet, lactate, creatinine, urea nitrogen, glucose, PaCO₂, pH, PaO₂, heart rate, mean arterial pressure, respiratory rate, temperature, SpO₂ and urine output.

Propensity score matching (PSM) and inverse probability of treatment weighting methods were conducted to balance the
baseline characteristics of the two groups of patients. Standard mean differences are commonly used to make quantitative comparisons between the mean (continuous covariate) or rate (categorical covariate) of covariates dealing with groups. Some researchers suggest that the baseline covariate is considered to have reached an acceptable equilibrium level when the normalisation difference is less than $0.2^{19,20}$. In this study, PSM applied one-to-one matching of the nearest neighbours, while inverse probability of treatment weighting used the generalised boosted model$^{21}$ to estimate the necessary tendency of the weighted score. The generalised boosted model estimation method estimates the use of a flexible dual propensity score for the treatment of indicators. It involves an iterative process with multiple regression trees to capture the treatment allocation and complex nonlinear relationship between pretreatment covariates without excessive fitting data. Studies have shown that among various propensity score estimation methods, generalised boosted model provides the estimated weight, which achieves the best balance among processing variables$^{22}$. When imbalance still exists after weighting, the doubly robust estimation combines the multivariate regression model with the IPTW model, which can be used to eliminate residual confounding factors$^{23}$. This results in more accurate estimates of therapeutic effects$^{24}$.

A two-sided $P < 0.05$ was considered statistically significant. R (version 4.0.3) was used for all statistical analyses.

Results

Subject characteristics

A total of 11,553 patients meeting the selection criteria were included in this study (Fig. 1). The patients with sepsis were divided into two groups according to whether they received intravenous thiamine or not. The TUR group included 10,017 patients and the TR group included 1,536 patients. Table 1 summarises the characteristics of the patients, including general conditions, degree of illness, co-morbidities and laboratory parameters. In the original population, the age of the TR group was 59 (49, 68), which is lower than that of the TUR group 68 (56, 79). The Acute Physiological Score III (65 (49, 89)) and Sequential Organ Failure Assessment score (3 (2, 5)) in the TR group were higher than those in the TUR group (54 (41, 72) and 3 (2, 4), respectively). The length of ICU stay in the TR group was longer than that in the TUR group (8·48 (3·76, 15·88) vs. 4·15 (2·02, 9·61)).

Cox proportional hazards regression model

After adjusting for confounders, the TR group showed a reduced risk of all-cause sepsis mortality rates. In comparison with the TUR group, the TR group had a statistically significantly lower risk of ICU mortality. The HR of ICU mortality for the TR group was 0·80 (95 CI 0·70, 0·93), indicating that, compared with the TUR group, the TR group had 0·80 times the risk for ICU mortality (Table 2).

Propensity score matching and inverse probability of treatment weighting

To reduce confounding bias, we performed PSM based on whether thiamine was used. A total of 1,563 pairs were successfully matched (online Supplementary Fig. S1). After matching, the imbalance was controlled based on a comparison of the patients’ clinical data (standard mean difference < 0·2, Table 1, online Supplementary Fig. S2). After inverse probability of treatment weighting, the standard mean difference and the baseline characteristics between the two groups of the virtual population can be seen in online Supplementary Table S1.

Although the baseline differences between the two groups were well controlled, there were still variables that were statistically different. We separately included variables with differences in the matched and weighted populations in the Cox regression models, yielding results with consistent trends in the original population. And by including all of the above variables in the multivariate Cox regression models, the results remained stable (Table 2).

Secondary outcome studies with the whole population

Based on the original population, we conducted a series of secondary outcome analyses to confirm the benefits of thiamine on the prognosis of patients. Multivariate Cox regression showed

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Fig. 1. Flow chart of study cohort selection.
Table 1. Baseline characteristics of the study population
(median (interquartile range [IQR]); numbers and percentages)

| Characteristic            | Original population | Matched population | P  |
|---------------------------|---------------------|--------------------|----|
|                           | TUR                | TR                 |    |
|                           | median  | IQR   | median  | IQR   |    |
| n                         | 10,017             | 1,536             | 1,536 | 1,536 | <0.001 |
| Age (year)                | 68·00              | 56·00, 79·00       | 59·00 | 49·00, 68·00 | <0.001 |
| Sex                       | n                  | %                 | n     | %     |    |
| Male                      | 5139               | 51.3              | 901   | 58.7  | <0.001 |
| Female                    | 4878               | 48.7              | 635   | 41.3  |    |
| Weight (kg)               | 77·50              | 65·00, 94·30       | 78·90 | 65·50, 96·30 | 0.103 |
| Ethnicity                 | n                  | %                 | n     | %     |    |
| White                     | 6801               | 67.9              | 949   | 61.8  | <0.001 |
| Black                     | 1134               | 11.3              | 175   | 11.4  |    |
| Others                    | 2082               | 20.8              | 412   | 26.8  |    |
| First care unit           | n                  | %                 | n     | %     |    |
| MICU/SICU/TSICU           | 7753               | 77.4              | 1322  | 86.1  | <0.001 |
| CCU                       | 1934               | 19.3              | 156   | 10.2  |    |
| Others                    | 330                | 3.3               | 58    | 3.8   |    |
| Severe score              | OR                 | 95 % CI           | OR    | 95 % CI | <0.001 |
| SOFA                      | 3.00               | 2.00, 4.00        | 3.00  | 2.00, 5.00 | <0.001 |
| APS III                   | 54.00              | 41.00, 72.00      | 65.00 | 49.00, 89.00 | <0.001 |
| Ventilator                | n                  | %                 | n     | %     |    |
| No                        | 3448               | 34.4              | 311   | 20.2  | <0.001 |
| Yes                       | 6569               | 65.6              | 1225  | 79.8  |    |
| Vasopressor               | OR                 | 95 % CI           | OR    | 95 % CI | <0.001 |
| No                        | 5833               | 58.2              | 645   | 42.0  |    |
| Yes                       | 4184               | 41.8              | 891   | 58.0  |    |
| CRRT                      | OR                 | 95 % CI           | OR    | 95 % CI | 0.357 |
| No                        | 9336               | 93.2              | 1303  | 84.8  |    |
| Yes                       | 681                | 6.8               | 233   | 15.2  |    |
| Charlson co-morbidity     | OR                 | 95 % CI           | OR    | 95 % CI | 0.486 |
| Myocardial infarct        | n                  | %                 | n     | %     |    |
| No                        | 8420               | 84.1              | 1315  | 85.6  |    |
| Yes                       | 1597               | 15.9              | 221   | 14.4  |    |
| Characteristic                           | Original population | Matched population |   |
|-----------------------------------------|---------------------|-------------------|---|
|                                        | TUR     | TR    |   | TUR     | TR    |   | P |
|                                        | median  | IQR  |   | median  | IQR  |   |   |
| Congestive heart failure                |         |      |   |         |      |   |   |
| No                                     | 6732    | 67.2 | 1165 | 75.8 | <0.001 | 1.000 |
| Yes                                    | 3285    | 32.8 | 371  | 24.2 |           |     |
| Peripheral vascular disease            |         |      |   |         |      |   |   |
| No                                     | 8834    | 88.2 | 1410 | 91.8 | <0.001 | 0.502 |
| Yes                                    | 1183    | 11.8 | 126  | 8.2  |           |     |
| Cerebrovascular disease                 |         |      |   |         |      |   |   |
| No                                     | 8538    | 85.2 | 1309 | 85.2 | 1.000   | 0.650 |
| Yes                                    | 1479    | 14.8 | 227  | 14.8 |           |     |
| Dementia                               |         |      |   |         |      |   |   |
| No                                     | 9455    | 94.4 | 1477 | 96.2 | 0.005   | 0.524 |
| Yes                                    | 562     | 5.6  | 59   | 3.8  |           |     |
| Chronic pulmonary disease               |         |      |   |         |      |   |   |
| No                                     | 7396    | 73.8 | 1163 | 75.7 | 0.125   | 0.672 |
| Yes                                    | 2621    | 26.2 | 373  | 24.3 |           |     |
| Rheumatic disease                      |         |      |   |         |      |   |   |
| No                                     | 9638    | 96.2 | 1492 | 97.1 | 0.087   | 1.000 |
| Yes                                    | 379     | 3.8  | 44   | 2.9  |           |     |
| Peptic ulcer disease                   |         |      |   |         |      |   |   |
| No                                     | 9727    | 97.1 | 1452 | 94.5 | <0.001  | 0.366 |
| Yes                                    | 290     | 2.9  | 84   | 5.5  | <0.001  | 0.619 |
| Mild liver disease                     |         |      |   |         |      |   |   |
| No                                     | 8665    | 86.5 | 1017 | 66.2 | <0.001  | 0.432 |
| Yes                                    | 1352    | 13.5 | 519  | 33.8 | <0.001  | 1.000 |
| Severe liver disease                   |         |      |   |         |      |   |   |
| No                                     | 9341    | 93.3 | 1239 | 80.7 | <0.001  | 0.094 |
| Yes                                    | 676     | 6.7  | 297  | 19.3 |           |     |
| Diabetes uncomplicated                 |         |      |   |         |      |   |   |
| No                                     | 7471    | 74.1 | 1218 | 79.3 | <0.001  | 1.000 |
| Yes                                    | 2546    | 25.4 | 318  | 20.7 | <0.001  | 0.692 |
| Diabetes complicated                   |         |      |   |         |      |   |   |
| No                                     | 8816    | 88.0 | 1408 | 91.7 | <0.001  | 0.032 |
| Yes                                    | 1201    | 12.0 | 128  | 8.3  |           |     |
| Paraplegia                             |         |      |   |         |      |   |   |
| No                                     | 9426    | 94.1 | 1451 | 94.5 | <0.001  | 0.377 |
| Yes                                    | 591     | 5.9  | 85   | 5.5  | <0.001  | 0.517 |
| Renal disease                          |         |      |   |         |      |   |   |
| No                                     | 7235    | 72.2 | 1279 | 83.3 | 0.032   | 0.797 |
| Yes                                    | 2782    | 27.8 | 257  | 16.7 |           |     |
| Malignant cancer                       |         |      |   |         |      |   |   |
| No                                     | 8708    | 86.9 | 1366 | 88.9 | 0.094   | 0.253 |
| Yes                                    | 1309    | 13.1 | 170  | 11.1 |           |     |
| Metastatic solid tumour                |         |      |   |         |      |   |   |
| No                                     | 9459    | 94.4 | 1467 | 95.5 | 0.042   | 0.797 |
| Yes                                    | 558     | 5.6  | 69   | 4.5  |           |     |
| AIDS                                   |         |      |   |         |      |   |   |
| No                                     | 9926    | 99.1 | 1513 | 98.5 |           |     |

Table 1. (Continued)
| Characteristic                  | Original population | TR                  | Matched population |
|--------------------------------|---------------------|---------------------|--------------------|
|                                | median   | IQR     | median   | IQR     | OR       | 95% CI    | median   | IQR     | OR       | 95% CI    | P       |
| Laboratory tests               |          |         |          |         |          |           |          |         |          |           |         |
| Leucocytes (K/μl)              | 11.60    | 7.90, 16.60 | 11.50    | 7.20, 16.80 | 0.217   |          | 11.60    | 7.50, 16.70 | 0.643   |
| Hb (g/dl)                      | 10.00    | 8.70, 11.50 | 10.10    | 8.60, 11.90 | 0.020   |          | 10.20    | 8.70, 11.80 | 0.661   |
| Platelet (K/μl)                | 190.00   | 129.00, 266.00 | 164.00   | 96.50, 239.00 | <0.001 |          | 165.00   | 100.00, 238.25 | 0.550   |
| Lactate (mmol/l)               | 1.70     | 1.20, 2.60   | 2.10     | 1.30, 3.60   | <0.001  |          | 2.10     | 1.40, 3.50   | 0.447   |
| Creatinine (mg/dl)             | 1.20     | 0.80, 1.90   | 1.10     | 0.70, 2.00   | 0.061   |          | 1.10     | 0.80, 1.80   | 0.491   |
| Urea nitrogen (mg/dl)          | 25.00    | 16.00, 43.00 | 22.00    | 13.00, 39.75 | <0.001  |          | 23.00    | 15.00, 39.00 | 0.072   |
| Glucose (mg/dl)                | 130.00   | 104.00, 172.00 | 126.00   | 101.00, 170.00 | 0.007  |          | 128.00   | 102.00, 170.25 | 0.233   |
| PaCO₂ (mmHg)                   | 41.00    | 35.00, 48.00 | 39.00    | 33.00, 46.00 | <0.001  |          | 39.00    | 33.00, 45.00 | 0.546   |
| pH                             | 7.37     | 7.31, 7.43   | 7.36     | 7.28, 7.42   | <0.001  |          | 7.36     | 7.29, 7.42   | 0.486   |
| PaO₂ (mmHg)                    | 91.00    | 54.00, 167.00 | 83.00    | 49.25, 147.75 | <0.001  |          | 86.00    | 51.00, 147.00 | 0.221   |
| Vital signs                    |          |         |          |         |          |           |          |         |          |           |         |
| Heart rate (beats/min)         | 86.92    | 75.91, 98.96 | 93.11    | 81.11, 105.95 | <0.001  |          | 93.55    | 81.34, 106.45 | 0.651   |
| Mean arterial pressure (mmHg)  | 73.80    | 68.29, 80.90 | 75.55    | 69.62, 83.08 | <0.001  |          | 75.58    | 70.12, 83.62 | 0.408   |
| Respiratory rate (breaths/min) | 19.60    | 17.20, 22.50 | 20.29    | 17.50, 23.62 | <0.001  |          | 20.13    | 17.61, 23.57 | 0.715   |
| Temperature (°C)               | 36.87    | 36.59, 37.22 | 36.93    | 36.63, 37.37 | <0.001  |          | 36.94    | 36.63, 37.38 | 0.626   |
| SpO₂ (%)                       | 97.17    | 95.78, 98.50 | 97.24    | 95.76, 98.63 | <0.001  |          | 97.22    | 95.71, 98.60 | 0.813   |
| Urine output (ml)              | 1380.00  | 814.00, 2172.75 | 1300.00  | 695.00, 2200.00 | 0.002  |          | 1280.00  | 672.25, 2194.25 | 0.834   |

| Outcomes                      |          |         |          |         |          |           |          |         |          |           |         |
| n                              | %        | n       | %        | n       | %        |          | n       | %        |          | n       | %        |         |
| ICU mortality                  | <0.001   |          | 1.000    |          |         |           |          |         |          |         |
| No                             | 8788     | 87.7    | 1236     | 80.5    |          | 1237     | 80.5    | 1236     | 80.5    |          |         |
| Yes                            | 1229     | 12.3    | 300      | 19.5    |          | 299      | 19.5    | 300      | 19.5    |          |         |
| OR                             | 95% CI   | OR      | 95% CI   | OR      | 95% CI   | P        | OR      | 95% CI   | OR      | 95% CI   |         |
| Length of ICU stay (days)      | 4.15     | 2.02, 9.61 | 8.48     | 3.76, 15.88 | <0.001  |          | 6.56     | 2.85, 13.26 | 0.484   |

TR, thiamine received group; TUR, thiamine unreceived group; PSM, propensity score matching; MICU, medical intensive care unit; SICU, surgical intensive care unit; TSICU, trauma surgical intensive care unit; CCU, coronary care unit; SOFA, Sequential Organ Failure Assessment; APS III, acute physiological score III; CRRT, continuous renal replacement therapy; SpO₂, pulse oximetry-derived oxygen saturation.
that the 28-d mortality of the TR group was improved (HR: 0.82; 95% CI (0.71, 0.94)). The ventilation-free days in 28 d of the TR group were 1.09 d longer than those in the TUR group (Coef: 1.09; 95% CI (0.52, 1.67)), and vasopressor-free days in 28 d of the TR group were 1.61 d longer than those in the TUR group (Coef: 1.61; 95% CI (1.10, 2.12)). There was no significant difference in the probability of AKI after the diagnosis of sepsis between the two groups (Table 2).

Subgroup analyses

We performed a subgroup analysis of the primary outcomes by using clinically significant scores and several complications (Fig. 2, online Supplementary Table 52). A significant interaction was observed in MI complication. The HR of people without MI was 0.88 (95% CI 0.76, 1.01), and the HR of people with MI was 0.61 (95% CI 0.44, 0.87). The use of thiamine has a significant protective effect on patients with MI.

Discussion

In the present study, we investigated the link between thiamine supplementation and sepsis mortality. After controlling for potential confounders using Cox regression models, we found that the use of thiamine is associated with the improvement of ICU all-cause mortality in patients with sepsis. This observation was also supported by the double robustness validation on the...
the next 72 h(30). Thiamine deficiency is common in critically ill.

Sepsis was 10% upon initial admission, increasing to 20% within
study, the prevalence of thiamine deficiency in patients with
less ATP production and affecting energy metabolism(29). In one
sepsis inhibits the intestinal absorption of thiamine, resulting in
port and utilisation of thiamine, and operations such as haemo-
dialysis may also increase its excretion(28). Animal tests show that

bicarbonate, a major component of the cellular antioxidant system,
are positively correlated with the activity of glutathione peroxi-
dase, a major component of the cellular antioxidant system, which
is also critical in scavenging oxygen-free radicals(26).

* The biologically active form of thiamine, thiamine pyrophos-
phate, is an essential co-enzyme for glucose metabolism, which
provides energy through the regulation of mitochondrial pro-
duction of NADPH and ATP^25). Additionally, thiamine levels
are positively correlated with the activity of glutathione peroxi-
dase, a major component of the cellular antioxidant system, which
is also critical in scavenging oxygen-free radicals^26).

Thiamine’s important role in cellular energy metabolism, oxida-
tive stress and maintenance of mitochondrial function provides
the basis for its therapeutic application in sepsis. The human
body cannot synthesise thiamine by itself and has limited stor-
age, so it must rely on external sources to avoid deficiency.

Patients with sepsis have an increased need for thiamine due
to infection, but the accompanying decrease in nutritional intake

is associated with higher mortality(32), in agreement with
our results. As such, thiamine supplementation is of great interest
to improve the prognosis of patients. Although intravenous
thiamine supplementation showed no statistically significant
relationship with the occurrence of AKI after sepsis, it does reduce the time that patients are treated with a ventilator and
vasopressors, which improves cardiopulmonary function and
general condition. The effects of hypoxia, hormones and inflam-
atory mediators on mitochondria in critical conditions are
thought to be functional changes rather than structural changes
and may be reversible^33). Therefore, exogenous supplemen-
tion with thiamine could promote the recovery of mitochondrial
function, prevent progression of the disease and reduce the mor-
ality of patients with sepsis.

Subgroup analysis showed a beneficial effect of thiamine in
patients with MI, with an HR of 0.61 (95% CI 0.44, 0.87). The
cardiovascular system is essential for maintaining adequate
organ perfusion, and its failure to function can affect the progres-
sion of sepsis. Cardiac muscle is rich in mitochondria that enable
it to provide a large amount of energy for the systolic activity of
the heart^34). In patients with MI, the presence of necrotic and
apoptotic myocardial cells leads to a reduction in the number of
mitochondria, despite the ability of the rest of the healthy cells
to compensate for the energy needed for myocardial activity.
Sepsis under autonomic nervous system disorders, reduced
blood volume and the release of endogenous cytokines all dam-
gage cardiac muscle^35,36). In addition, the electron transport chain^37), abnormal oxidative phosphorylation and various
mechanisms mentioned above in sepsis can impair mitochon-
drial function^38). Thus, intravenous thiamine supplementation
may protect mitochondrial function in patients with MI, thereby
reducing their risk of death.

Strengths and limitations of the study

The advantage of this study is the use of the Medical Information
Mart for Intensive Care IV database, which has a large sample
size and contains relatively recent data, thus providing strong
evidence for our conclusion. For further verification, we
obtained the same results after adjusting for baseline levels by
using PSM and inverse probability of treatment weighting.
However, this study also has some limitations. First, this study
is a single-centre clinical study. Second, we included only
patients who received thiamine intravenously in consideration
of gastrointestinal dysfunction in critical conditions. The prog-
nostic impact of different routes of administration on patients
could be studied in the future. Third, we did not consider the
effects of specific injection doses and timing. Fourth, because
patients have a large number of missing values of lactate levels
24 h after the diagnosis of sepsis, we were unable to determine
whether thiamine improves the prognosis of patients by reduc-
ing the concentration of lactate. This can be verified in future
studies. One more point was the lack of test results for thiamine
levels in patients in the database, so we could not take it into
account in this study.

Conclusion

Supplementation with thiamine has a beneficial effect on the
prognosis of patients with sepsis. More randomised controlled

| Primary outcome | HR/95% CI | P |
|-----------------|-----------|---|
| ICU mortality   |           |   |
| Multivariate model | 0.80  | 0.70, 0.93 | 0.002 |
| PSM             | 0.82  | 0.70, 0.96 | 0.015 |
| IPTW            | 0.80  | 0.69, 0.94 | 0.005 |
| Doubly robust with unbalanced covariates§ | 0.80  | 0.69, 0.94 | 0.005 |
| Doubly robust with all covariates§ | 0.82  | 0.71, 0.96 | 0.013 |

Secondary outcomes

| 28-d mortality | HR/95% CI | P |
|----------------|-----------|---|
| Ventilation-free days in 28 d | 0.82  | 0.71, 0.94 | 0.004 |
| Vasopressor-free days in 28 d | 1.09  | 0.52, 1.67 | <0.001 |
| AKI after diagnosis of sepsis | 1.61  | 1.10, 2.12 | <0.001 |

* Cox proportional hazards regression models were used to calculate hazard ratios (HR) with 95% CI.
† Logistic regression models were used to calculate coefficients (Coefs) with 95% CI.
§ Confounders for the doubly robust with unbalanced covariates included age, sex, ventilator use, vasopressor use, CRRT use, first care unit, APS III, myocardial infarct, mild liver disease, severe liver disease, PaCO2, pH, glucose, platelet and SpO2. Confounders of other models are consistent with multivariate analysis.

PSM, propensity score matching; IPTW, inverse probability of treatment weighting.

**Table 2. Analysis of the associations between outcomes and thiamine received (Hazard ratios; odds ratios; 95% confidence intervals)**

| 28-d mortality | HR/95% CI | P |
|----------------|-----------|---|
| Ventilation-free days in 28 d | 0.82  | 0.71, 0.94 | 0.004 |
| Vasopressor-free days in 28 d | 1.09  | 0.52, 1.67 | <0.001 |
| AKI after diagnosis of sepsis | 1.61  | 1.10, 2.12 | <0.001 |
trials are needed to confirm the effectiveness of thiamine supplementation in the treatment of sepsis.

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L. Z. created the study protocol, performed the statistical analyses and wrote the first manuscript draft. F. Z. conceived the study and critically revised the manuscript. S. L. and F. X. assisted with the study design and performed data collection. X. Z. assisted with data collection and manuscript editing. T. H. assisted the analysis and explained statistical methods. J. L. assisted with manuscript revision and data confirmation. H. Y. contributed to data interpretation and manuscript revision. All authors read and approved the final manuscript.

The authors declare that they have no competing interests.

Supplementary material
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References
1. Singer M, Deutschman CS, Seymour CW, et al. (2016) The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 315, 801–810.
2. Finfer S & Machado FR (2016) The global epidemiology of sepsis. Does it matter that we know so little? Am J Respir Crit Care Med 193, 228–230.
3. Bauer M, Gerlach H, Vogelmann T, et al. (2020) Mortality in sepsis and septic shock in Europe, North America and Australia between 2009 and 2019 – results from a systematic review and meta-analysis. Crit Care 24, 239.
4. Cecconi M, Evans L, Levy M, et al. (2018) Sepsis and septic shock. Lancet 392, 75–87.
5. Font MD, Thyagarajan B & Khanna AK (2020) Sepsis and septic shock – basics of diagnosis, pathophysiology and clinical decision making. Med Clin North Am 104, 573–585.
6. Suliman HB, Welty-Wolf KE, Carraway M, et al. (2004) Lipopolysaccharide induces oxidative cardiac mitochondrial damage and biogenesis. Cardiovasc Res 64, 279–288.
7. Vanasco V, Camolai MC, Evelson P, et al. (2008) The oxidative stress and the mitochondrial dysfunction caused by endotoxemia are prevented by α-lipoic acid. Free Radic Res 42, 815–823.
8. Sun J, Zhang J, Tian J, et al. (2019) Mitochondria in sepsis-induced AKI. J Am Soc Nephrol 30, 1151–1161.
9. Stanzani G, Duchen MR & Singer M (2019) The role of mitochondria in sepsis-induced cardiomyopathy. Biochim Biophys Acta Mol Basis Dis 1865, 759–773.
10. Kartal B & Palabiyik B (2019) Thiamine leads to oxidative stress resistance via regulation of the glucose metabolism. Cell Mol Biol 65, 73–77.
11. Leite HP & de Lima LFP (2016) Metabolic resuscitation in sepsis: a necessary step beyond the hemodynamic? J Thorac Dis 8, E552–E557.
12. Marik PE, Khangoora V, Rivera R, et al. (2017) Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock: a retrospective before-after study. Chest 151, 1229–1238.
13. Domino MW, Andersen LW, Chase M, et al. (2016) Randomized, double-blind, placebo-controlled trial of thiamine as a metabolic resuscitator in septic shock: a pilot study. Crit Care Med 44, 360–367.
14. Moskowitz A, Andersen LW, Cocchi MN, et al. (2017) Thiamine as a renal protective agent in septic shock. A secondary analysis of a randomized, double-blind, placebo-controlled trial. Ann Am Thorac Soc 14, 757–741.
15. Berger MM (2020) Do micronutrient deficiencies contribute to mitochondrial failure in critical illness? Curr Opin Clin Nutr Metab Care 23, 102–110.
16. Belsky JB, Wira CR, Jacob V, et al. (2018) A review of micronutrients in sepsis: the role of thiamine, L-carnitine, vitamin C, selenium and vitamin D. Nutr Res Rev 31, 281–290.
17. Zhou S, Zeng Z, Wei H, et al. (2021) Early combination of albumin with crystalloids administration might be beneficial for the survival of septic patients: a retrospective analysis from MIMIC-IV database. Ann Intens Care 11, 42.
18. Johnson AE, Pollard TJ, Shen L, et al. (2016) MIMIC-III, a freely accessible critical care database. Sci Data 3, 160035.
19. Austin PC (2008) Goodness-of-fit diagnostics for the propensity score model when estimating treatment effects using covariate adjustment with the propensity score. Pharmacoepidemiol Drug Saf 17, 1202–1217.
20. Heinze G & Jun J (2011) An overview of the objectives of and the approaches to propensity score analyses. Eur Heart J 32, 1704–1708.
21. McCaffrey DF, Griffin BA, Almira D, et al. (2013) A tutorial on propensity score estimation for multiple treatments using generalized boosted models. Stat Med 32, 3388–3414.
22. Harder ST, Stuart EA & Anthony JC (2010) Propensity score techniques and the assessment of measured covariate balance to test causal associations in psychological research. Psychol Methods 15, 234–249.
23. Nguyen TL, Collins GS, Spence J, et al. (2017) Comparison of the ability of double-robust estimators to correct bias in propensity score matching analysis. A Monte Carlo simulation study. Pharmacoepidemiol Drug Saf 26, 1513–1519.
24. Cefalu M, Dominici F, Avoland N, et al. (2017) Model averaged double robust estimation. Biomometrics 73, 410–421.
25. Manzañares W & Hardy G (2011) Thiamine supplementation in the critically ill. Curr Opin Clin Nutr Metab Care 14, 610–617.
26. Costa NA, Gut AL, de Souza Dorna M, et al. (2014) Serum thiamine concentration and oxidative stress as predictors of mortality in patients with septic shock. J Crit Care 29, 249–252.
27. Sedlai YR, Shrestha DB, Buddhathoki P, et al. (2021) Effect of thiamine supplementation in critically ill patients: a systematic review and meta-analysis. J Crit Care 65, 104–115.
28. Polegato BF, Pereira AG, Azevedo PS, et al. (2019) Role of thiamine in health and disease. Nutr Clin Pract 34, 558–564.
29. Sassoon CS, Zhu E, Fang L, et al. (2016) Inhibition of intestinal thiamin transport in rat model of sepsis. Crit Care Med 44, e875–e881.
30. Donnino MW, Carney E, Cocchi MN, et al. (2010) Thiamine deficiency in critically ill patients with sepsis. J Crit Care 25, 576–581.
31. Raj KM, Baranwal AK, Attri SV, et al. (2021) Thiamine status in children with septic shock from a developing country: a prospective case-control study. J Trop Pediatr 67, fmaa107.
32. Cruickshank AM, Telfer AB & Shenkin A (1988) Thiamine deficiency in the critically ill. Intens Care Med 14, 384–387.
33. Singer M, De Santis V, Vitale D, et al. (2004) Multiorgan failure is an adaptive, endocrine-mediated, metabolic response to overwhelming systemic inflammation. Lancet 364, 545–548.
34. Barth E, Stämmier G, Speiser B, et al. (1992) Ultrastructural quantitation of mitochondria and myofilaments in cardiac muscle from 10 different animal species including man. J Mol Cell Cardiol 24, 669–681.
35. Snow TR, Dickey DT, Tapp T, et al. (1990) Early myocardial dysfunction induced with endotoxin in rhesus monkeys. Can J Cardiol 6, 130–136.
36. Dhainaut JF, Huyghebaert MF, Monsallier JF, et al. (1987) Coronary hemodynamics and myocardial metabolism of lactate, free fatty acids, glucose, and ketones in patients with septic shock. Circulation 75, 533–541.
37. Lee I & Huttemann M (2014) Energy crisis: the role of oxidative phosphorylation in acute inflammation and sepsis. Biochim Biophys Acta 1842, 1579–1586.
38. Arulkumaran N, Deutschman CS, Pinsky MR, et al. (2016) Mitochondrial function in sepsis. Shock 45, 271–281.