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Association of Thiamine Supplementation With 30-Day Mortality Among ICU Patients With Sepsis-Associated Delirium

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ABSTRACT

Background: Sepsis-associated delirium (SAD) is a common and severe complication in critically ill patients and is associated with increased mortality. Thiamine is an essential coenzyme in mitochondrial energy metabolism, and deficiency is frequent in critical illness. However, the association between thiamine supplementation and survival in ICU patients with SAD remains unclear.

Method: We conducted a retrospective cohort study using the MIMIC-IV (v3.1) database. Adult ICU patients meeting Sepsis-3 criteria and diagnosed with delirium during ICU stay were included. Patients were categorized according to thiamine supplementation during ICU admission. Propensity score–based methods, including matching, adjustment, and multiple weighting approaches, were applied to balance baseline covariates. The primary outcome was 30-day all-cause mortality. We performed survival, subgroup, and sensitivity analyses. We also conducted duration–response and dose–response analyses to evaluate whether thiamine treatment duration and average daily dose were associated with prognosis.

Result: In the MIMIC-IV cohort, 332 ICU patients with sepsis-associated delirium received thiamine supplementation, while 956 did not. Thirty-day mortality was significantly lower in the thiamine group compared with the non-thiamine group (P<0.001). Thiamine use was associated with improved survival in crude analysis and remained significantly associated with lower 30-day mortality after multivariable adjustment (HR, 0.51; 95% CI, 0.33–0.79; P=0.002). Consistent associations were observed across propensity score analyses, including propensity score–adjusted analysis (HR, 0.59; 95% CI, 0.40–0.85; P=0.005), propensity score matching (HR, 0.59; 95% CI, 0.39–0.90; P=0.015), inverse probability of treatment weighting (HR, 0.54; 95% CI, 0.38–0.77; P=0.002), standardized mortality ratio weighting (HR, 0.68; 95% CI, 0.47–0.98; P=0.052), pairwise algorithmic weighting (HR, 0.63; 95% CI, 0.40–0.97; P=0.016), and overlap weight (HR, 0.60; 95% CI, 0.36–1.02; P=0.008). Weighted subgroup analyses demonstrated consistent associations across clinical strata, with a significant interaction by illness severity indicating a survival benefit of thiamine among patients with SOFA scores<4. Duration-response and dose-response analyses suggested greater benefit with longer treatment courses and lower daily dosing.

Conclusion: Thiamine supplementation was associated with reduced 30-day mortality in ICU patients with sepsis-associated delirium, with an observed interaction in the SOFA score subgroup, where a SOFA score below 4 was associated with survival benefit. Duration–response and dose–response analyses suggested greater benefit with longer treatment courses and lower daily dosing.

Keywords:Sepsis-associated delirium;Thiamine;Critical care;Mortality;Propensity score matching;MIMIC-IV database

INTRODUCTION

Delirium is characterized by an acute disturbance in attention, awareness, and cognition. It often fluctuates in severity and is frequently observed in critically ill patients[1]. Delirium affects a large proportion of intensive care unit (ICU) patients. It is associated with prolonged mechanical ventilation and longer ICU stays. Delirium also predicts worse short-term and long-term outcomes, including increased mortality[2, 3] and cognitive impairment[4, 5]. Current prevention and treatment strategies rely mainly on nonpharmacologic measures[6, 7] and attention to precipitating causes. Pharmacologic options remain of unproven benefit[8–10].

Sepsis is a major precipitant of delirium in critically ill patients. In a prospective ICU cohort, patients with severe sepsis or septic shock had significantly higher delirium incidence[11]. Large observational studies report delirium in 19% of septic ICU patients[12, 13]. Rates may be 10-fold more prevalent in older adults with sepsis[13, 14]. Delirium is a frequent neurologic manifestation of sepsis. The odds are substantially higher among septic ICU patients[15]. Mechanistically, systemic inflammation leads to endothelial dysfunction and blood–brain barrier disruption. Microcirculatory impairment with cerebral hypoperfusion and mitochondrial or metabolic derangements also contribute. These processes converge to produce sepsis-associated delirium (SAD)[16–18]. This underscores delirium as a clinically important phenotype[19] that requires active management in sepsis patients[20, 21].

Thiamine (Vitamin B_1) is an essential water-soluble vitamin that cannot be synthesized endogenously. In humans, it exists as thiamine monophosphate, thiamine pyrophosphate (TPP), and thiamine triphosphate. TPP is the major bioactive form and a reliable marker of thiamine status. TPP functions as a coenzyme for pyruvate and α-ketoglutarate dehydrogenase complexes. These enzymes are essential for mitochondrial oxidative decarboxylation and ATP production[22]. It also supports cellular redox balance through the pentose phosphate pathway, contributing to NADPH and glutathione synthesis[23]. Beyond enzymatic activity, thiamine derivatives regulate gene expression, stress response, and neuronal signaling[24]. Thiamine deficiency disrupts mitochondrial metabolism and reduces ATP production. It promotes oxidative injury and cell death, particularly in energy-demanding tissues such as nerves, brain, heart, and muscle[25]. Clinical studies report that thiamine depletion in critically ill patients is associated with up to a 50% increase in mortality, highlighting its potential prognostic and therapeutic relevance[26].

Several studies have evaluated the potential role of thiamine supplementation in critically ill patients. In a double-blind randomized controlled trial, thiamine significantly reduced serum lactate levels within 24 hours[27]. Among patients with baseline thiamine deficiency and septic shock, it also improved survival[27]. Other investigations reported that thiamine enhanced lactate clearance and reduced 28-day mortality in patients with septic shock[28]. Moreover, combined therapy with thiamine, hydrocortisone, and ascorbic acid (so-called HAT therapy) has been shown to improve organ function and lower mortality. For example, Iglesias et al. demonstrated that patients with sepsis receiving HAT therapy experienced a shorter duration of shock compared with those not receiving HAT[29]. Mechanistically, thiamine deficiency leads to lactate accumulation, reduced peripheral resistance, and increased cardiac preload, thereby contributing to cardiac dysfunction. Current evidence suggests that intravenous thiamine may correct lactic acidosis, improve cardiac function, and reduce mortality in critically ill populations[30].

Whether thiamine supplementation is associated with improved survival specifically among SAD patients is unknown. We therefore used the MIMIC-IV database to evaluate the association between thiamine supplementation and 30-day mortality in SAD patients, applying propensity score methods to address confounding and subgroup analyses to explore heterogeneity.

MATERIALS AND METHODS

We used the Intensive Care Medicine Information Marketplace (MIMIC-IV version 3.1[31]) to enroll SAD patients. MIMIC-IV is a real-world open clinical database. We leveraged Structured Query Language (SQL) with PostgreSQL to extract relevant data from the MIMIC-IV database. Access to MIMIC-IV was granted after the principal investigator completed the required training on the National Institutes of Health platform. The training included the courses "Study Data or Specimens Only" and "Conflict of Interest". The certification numbers were 59979404 and 59979406. Our

study findings were reported using the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (**Supplementary Table 1**)[32].

Exposure

Thiamine supplementation was defined as the record of thiamine use in the "ICU unit medication" in MIMIC-IV.

Outcome

The primary outcome was 30-day all-cause mortality, defined as death occurring within 30 days after ICU admission.

Study population and patient selection

A total of 28,087 adult ICU patients (aged≥18 years) who met the Sepsis-3 diagnostic criteria[33] were initially identified from the database. Patients with a negative Confusion Assessment Method for the ICU (CAM-ICU) evaluation were first excluded (n=18,036), leaving 10,051 patients eligible for further screening[34]. Among these, 8,489 patients without delirium-related diagnostic codes were excluded, resulting in a delirium cohort of 1,562 patients. To reduce clinical heterogeneity and minimize potential confounding, patients with pre-existing liver disease were excluded (n=212). Liver disease was defined according to the Charlson Comorbidity Index, including both mild and severe liver disease, and was identified using ICD-9 and ICD-10 diagnosis codes. The complete list of corresponding liver disease ICD codes is provided in **Supplementary Table 2**. We excluded patients with liver disease for two reasons. First, liver disease may alter thiamine storage and metabolism. This metabolic profile differs from that of patients without liver disease[35]. Moreover, patients with liver disease have a high short-term mortality risk, and the disease population confused the relationship between thiamine and prognosis[36]. In addition, patients with missing baseline covariates were excluded (n=62). The excluded variables included anion gap, blood urea nitrogen, chloride, diastolic blood pressure, glucose, hematocrit, hemoglobin, platelet count, potassium, respiratory rate, systolic blood pressure, sodium, and body temperature. The final analytic cohort therefore consisted of 1,288 patients. The SQL queries used for cohort identification are detailed in **Supplementary Table 3**.

Delirium was identified using ICD-9 and ICD-10 diagnosis codes recorded during the ICU stay. ICD-9 codes included 293.0 and 293.1. ICD-10 codes included F05, F10.231, F10.221, F10.121, F10.931, F10.131, F19.921, F19.931, F19.221, F19.231, F13.231, F13.221, F13.921, F13.931, F13.131, F11.121, F11.221, F12.121, F16.121, F16.921, F14.221, F14.921, F14.931, F15.121, F15.221, F15.921, F15.931, F11.921, F11.931, F12.921, F12.931, F29.041, and F29.03. However, previous studies have shown that reliance on ICD diagnostic codes alone has limited sensitivity. This approach may underidentify true delirium cases[37]. Meta-analytic evidence indicates that the Confusion Assessment Method for the ICU (CAM-ICU) has high diagnostic accuracy in critically ill patients[38]. The pooled sensitivity is approximately 81% (95%CI: 57-93%). The pooled specificity is approximately 98% (95%CI: 86-100%)[38]. Therefore, we defined delirium as requiring both a positive CAM-ICU assessment and a corresponding ICD diagnosis. This combined definition aimed to balance case identification sensitivity with coding consistency. It also reduced misclassification bias associated with single-method definitions. Overall, this approach improved the accuracy and reliability of delirium ascertainment in our retrospective cohort.

Statistical analysis

To minimize confounding due to baseline differences between patients who did and did not receive thiamine, propensity scores method (PSM) were estimated using a multivariable logistic regression model[39]. We used propensity score matching (1:1 nearest neighbor matching with a caliper of 0.2 of the logit of the PS) to balance baseline covariates between thiamine users and non-users. The standardized mean difference (SMD) is used to assess the degree of PSM. A threshold below 0.1 is considered acceptable. Distribution of propensity scores before and after matching is presented in **Figure 2a**, demonstrating adequate overlap. Balance in baseline covariates was assessed using SMD (**Figure 2b**), with SMD <0.1 indicating acceptable balance. The propensity score model included demographics, severity indices, vital signs, and laboratory measurements. Demographics included age at ICU admission, sex, and ICU-free days at day 28. Severity indices included SOFA and APACHE scores. Vital signs included systolic, diastolic, and mean arter

ial pressure. We also included heart rate, respiratory rate, temperature, and peripheral oxygen saturation. Laboratory v ariables included glucose, hemoglobin, hematocrit, and platelet count. We also included anion gap, sodium, potassium, chloride, and blood urea nitrogen. We additionally adjusted for pre-existing comorbidities. These included myocardial infarction, congestive heart failure, and cerebrovascular disease. We also included chronic pulmonary disease and mal ignant cancer. Metastatic solid tumor, paraplegia, and diabetes with complications were included. Acute kidney injury status and AKI stage were also included. ICU-related therapies reflecting baseline treatment were further considered, i ncluding corticosteroid use (dexamethasone and hydrocortisone); vasopressor therapy (norepinephrine, vasopressin, or is oprenaline); inotropic agents (dobutamine or milrinone); mechanical ventilation; renal replacement therapy; and exposur e to commonly used sedative agents (midazolam and dexmedetomidine) and analgesic agents (hydromorphone)[40–43].

Then we applied a series of complementary analytical strategies to evaluate the association between thiamine use and clinical outcomes. These included conventional regression-based analyses (unadjusted, multivariable-adjusted, and prop ensity score-adjusted models), as well as propensity score-based design and weighting approaches, including propensity score matching[44], inverse probability of treatment weighting (IPTW)[45], standardized mortality ratio weighting (S MRW)[46], pairwise algorithmic (PA) weighting[47], and overlap weight (OW)[48]. The use of multiple analytic appr oaches was intended to mitigate confounding[49] and selection bias[50] inherent to observational study and to examin e the robustness of the estimated associations across different modeling assumptions[51].

To evaluate the association between thiamine use and time-to-event outcomes, survival analyses were conducted using weighted Kaplan-Meier (KM) methods based on the pairwise algorithmic weighting scheme[52]. The advantage of th e weighted survival analysis is that it significantly reduces the confounding bias and improves the accuracy of the st atistical analysis[44].

Sensitive analysis

To assess the robustness of our findings to the choice of matching strategy, we conducted several additional sensitivit y analyses using the entire cohort. Specifically, after incorporating thiamine exposure and applying pairwise algorithmi c (PA) weighting, multivariable Cox proportional hazards regression models were fitted to evaluate the independent as sociation between thiamine use and the outcomes. Subgroup analyses were conducted to assess the consistency of the association between thiamine use and outcomes across strata, including age (65 versus ⩾65 years), gender (female versus male), comorbidities (chronic pulmonary disease, renal disease, cerebrovascular disease), illness severity (SOFA score <4 versus ⩾4 [53, 54]), and key ICU interventions (mechanical ventilation, hydromorphone, midazolam, and d exmedetomidine exposure). All subgroup analyses were conducted within the PA-weighted analysis. Forest plots were generated to display subgroup-specific effect estimates derived from the weighted analyses.

Duration-response and dose-response analyses

To further characterize exposure intensity, we conducted duration-response and dose-response analyses among sepsis-as sociated delirium patients. Thiamine exposure was summarized as (1) duration of administration (days) and (2) averag e daily dose (mg/day). Duration was categorized as <3 days, 3-5 days, and >5 days[55, 56]. Average daily dose was categorized as <100mg/day, 100-300mg/day, and >300 mg/day[55, 57, 58]. These cut points were selected a priori b ased on clinical guidance and expert recommendations for ICU thiamine supplementation[58, 59].

For each category, we estimated hazard ratios using Cox proportional hazards models. Models were fitted in weighte populations (IPTW, SMRW, PA, and OW). Non-use of thiamine served as the reference group. Non-use of thiamin e served as the reference group. The duration-response and dose-response trend tests were evaluated by fitting orde red categorical variables as continuous variables into the Cox proportional hazards model.

RESULTS

Population

A total of 28087 ICU patients aged 18 years or older who met the Sepsis-3 diagnostic criteria were initially screene d. We first excluded 18,036 patients with a negative CAM-ICU assessment, leaving 10,051 individuals eligible for fur

ther evaluation. Subsequently, 8489 patients without delirium-related diagnostic codes were excluded, resulting in 1562 patients in the delirium-suspected cohort. Figure 1 shows a flowchart of the study patients.

Visual inspection of propensity score distributions showed limited overlap in the unadjusted cohort. After applying pro pensity score‐based methods, overlap improved substantially. This improvement was most evident with pairwise algor ithmic weighting. Standardized mean differences were markedly reduced after adjustment. Nearly all baseline covariate s achieved values below 0.10. (**Figure 2a, Figure 2b**).

Baseline characteristics before and after propensity score adjustment

A total of 1,288 ICU patients with sepsis-associated delirium were included, of whom 332 (25.8%) received thiamine (Table 1). Before weighting, clinically relevant imbalances were observed between treatment groups, particularly in a ge, comorbidities, illness severity, and exposure to sedatives and vasoactive agents. After pairwise algorithmic propens ity score weighting, balance of measured baseline covariates improved substantially, with small standardized mean diff erences (all SMD <0.1).

Association Between ICU Admission Thiamine Usage and 30-Day Mortality

During the 30-day follow-up, mortality occurred in 182 of 956 patients (19.0%) in the non-thiamine group. Mortality occurred in 36 of 332 patients (10.8%) in the thiamine group (Table 2). In crude analysis, thiamine use was associa ted with a lower risk of 30-day mortality. The hazard ratio was 0.38 (95% CI, 0.27–0.55; P<0.001). This association remained significant after multivariable adjustment. The adjusted hazard ratio was 0.51 (95% CI, 0.33–0.79; P=0.00 2). We also estimated hazard ratios using multiple propensity score methods. These included propensity score adjustm ent (HR, 0.59; 95% CI, 0.40–0.85; P=0.005) and propensity score matching (HR, 0.59; 95% CI, 0.39–0.90; P=0.015). They also included inverse probability of treatment weighting (HR, 0.54; 95% CI, 0.38–0.77; P=0.002) and pairwise algorithmic weighting (HR, 0.63; 95% CI, 0.40–0.97; P=0.016). Additional methods were standardized mortality ratio weighting (HR, 0.68; 95% CI, 0.47–0.98; P=0.052) and overlap weighting (HR, 0.60; 95% CI, 0.36–1.02; P=0.008). Thiamine-treated patients consistently demonstrated higher survival probabilities across the observation period (**Figure 3**).

Sensitive Analysis

In weighted subgroup analyses using the pairwise algorithmic approach, the association between thiamine supplementat ion and 30-day mortality was generally consistent across most prespecified subgroups (**Table 3 and Figure 4**). No si gnificant effect modification was observed for age (<65 vs ≥65years; P for interaction=0.88), gender (P for interaction =0.77), chronic pulmonary disease (P for interaction = 0.64), renal disease (P for interaction=0.49), cerebrovascular di sease (P for interaction=0.95), use of sedative or analgesic agents, or mechanical ventilation (P for interaction>0.05 fo r all). A significant interaction was observed according to disease severity as assessed by the SOFA score (P for inte raction=0.002). Among patients with a SOFA score<4, thiamine use was associated with a lower risk of 30-day morta lity (HR, 0.09; 95% CI, 0.01–0.70).

Duration-response and dose-response relationships between thiamine use and outcomes

In the duration–response analysis (**Supplementary Table 4**), 30-day mortality was 179/954 (18.8%) among non-users. Thiamine administration for >5 days was consistently associated with lower 30-day mortality across models. The asso ciation was observed in the crude model (HR, 0.24; 95% CI, 0.14–0.41; P<0.001). It remained significant in the IPT W-weighted model (HR, 0.38; 95% CI, 0.23–0.63; P=0.001). Similar results were seen in the SMRW-weighted model (HR, 0.47; 95% CI, 0.29–0.78; P=0.008). It was also significant in the PA-weighted model (HR, 0.40; 95% CI, 0.2 2–0.72; P=0.001). The OW-weighted model showed the same direction (HR, 0.37; 95% CI, 0.18–0.76; P<0.001). By contrast, short-duration exposure (<3 days) showed heterogeneous estimates across methods. Associations were non-sig nificant in the crude model (HR, 1.20; 95% CI, 0.61–2.34; P=0.599). They were also non-significant in the IPTW-we ighted model (HR, 1.37; 95% CI, 0.73–2.57; P=0.312). Results were similar in the OW-weighted model (HR, 1.79; 9 5% CI, 0.72–4.44; P=0.083). However, increased risk estimates were observed in the SMRW-weighted model (HR, 2.

31; 95% CI, 1.23–4.33; P=0.009). A similar increase was seen in the PA-weighted model (HR, 2.02; 95% CI, 0.95–4.30; P=0.039). Trend testing across ordered duration categories suggested decreasing risk with longer duration in each model (crude: HR, 0.67; 95% CI, 0.58 – 0.78; P<0.001; IPTW: HR, 0.76; 95% CI, 0.66 – 0.88; P<0.001; SMRW: HR, 0.84; 95% CI, 0.73 – 0.96; P=0.018; PA: HR, 0.77; 95% CI, 0.65 – 0.92; P<0.001; OW: HR, 0.76; 95% CI, 0.61 – 0.93; P<0.001).

In the dose–response analysis (**Supplementary Table 4**), thiamine at <100 mg/day was associated with lower 30-day mortality in the crude model (HR, 0.39; 95% CI, 0.27–0.57; P<0.001) and remained significant in the IPTW-weighted model (HR, 0.53; 95% CI, 0.36–0.78; P=0.001), PA-weighted model (HR, 0.58; 95% CI, 0.36–0.94; P=0.009), and OW-weighted model (HR, 0.55; 95% CI, 0.31–0.96; P=0.003), but not in the SMRW-weighted model (HR, 0.73; 95% CI, 0.50–1.05; P=0.129). The 100-300 mg/day category showed no significant association across models (crude: HR, 0.33; 95% CI, 0.10–1.03; P=0.055; IPTW: HR, 0.32; 95% CI, 0.10–1.10; P=0.080; SMRW: HR, 0.59; 95% CI, 0.19–1.84; P=0.359; PA: HR, 0.58; 95% CI, 0.17–1.94; P=0.353; OW: HR, 0.50; 95% CI, 0.11–2.15; P=0.243), whereas > 300 mg/day was consistently associated with higher 30-day mortality (crude: HR, 2.87; 95% CI, 1.06–7.78; P=0.038; IPTW: HR, 3.09; 95% CI, 1.31–7.29; P<0.001; SMRW: HR, 5.38; 95% CI, 1.87–15.43; P<0.001; PA: HR, 4.78; 95% CI, 1.49–15.32; P=0.001; OW: HR, 4.20; 95% CI, 1.09–16.14; P=0.001). Dose-category trend testing was significant only in the crude model (HR, 0.56; 95% CI, 0.42 – 0.75; P<0.001), but not in weighted models (IPTW: HR, 0.75; 95% CI, 0.57–0.98; P=0.146; SMRW: HR, 0.91; 95% CI, 0.69–1.21; P=0.599; PA: HR, 0.84; 95% CI, 0.58–1.22; P=0.412; OW: HR, 0.80; 95% CI, 0.52–1.24; P=0.281).

Discussions

In this retrospective cohort of critically ill patients with sepsis associated delirium, ICU thiamine supplementation was consistently associated with a significantly lower risk of 30-day mortality. This association remained robust across multivariable adjustment and multiple propensity score–based approaches, including matching and several weighting strategies. Subgroup analyses indicated an interaction effect according to SOFA score, with thiamine use conferring a survival benefit among patients with SOFA scores<4. Duration – response and dose – response analyses suggested that longer courses and lower average daily dosing were more consistently associated with improved survival. Beyond the binary exposure definition, we observed exposure-intensity patterns. In the duration-response analyses, the association with lower mortality was most consistent among patients treated for more than 5 days. In the dose-response analyses, lower average daily doses tended to align with better outcomes. These findings suggest that the effectiveness of thiamine may depend on how it is administered, not simply whether it is given. Moreover, these exposure-intensity patterns are supported by prior literature. A propensity score – matched MIMIC-IV study in critically ill patients with cerebrovascular disease reported that longer courses (5 days) and lower daily dosing (100 mg/day) were most consistently associated with improved short-term outcomes[55]. In septic shock, a randomized evidence also frames thiamine as a multi-day metabolic support intervention; Donnino et al. administered thiamine over several days and observed improved lactate clearance, particularly among patients with baseline thiamine deficiency[60]. Therefore, our findings, together with prior evidence, highlight the importance of considering both treatment duration and dosing strategy when evaluating thiamine therapy in SAD, while underscoring the need for prospective studies to define the optimal regimen.

Several mechanisms may explain the protective effect of thiamine in SAD. Thiamine is an essential coenzyme for key metabolic enzymes. These include pyruvate dehydrogenase, α-ketoglutarate dehydrogenase, and transketolase. This supports its role in metabolic resuscitation and redox regulation. It also supports antioxidant and anti-inflammatory processes. In the setting of thiamine deficiency, the conversion of pyruvate to acetyl-CoA is impaired, resulting in lactate accumulation and decreased ATP production[61], which may trigger neuronal energy crisis and acute brain dysfunction such as delirium. Thiamine supplementation has been shown to reverse lactate accumulation and restore mitochondrial function[62–64]. In addition, thiamine contributes to neuronal repair and neurotransmission[65], and has been demonstrated to lower the concentration of reactive nitrogen species (RNS) within neurons under neurotoxic conditions[65–

67], exerting neuroprotective effects. Furthermore, thiamine deficiency has been associated with glutamate accumulation and excitotoxicity[68–70]. It has also been linked to disrupted transmembrane osmotic gradients and blood‑brain barrier integrity[68–70]. These changes may ultimately lead to neuronal injury and cell death[71, 72]. Collectively, these mechanisms provide a biological rationale for the neuroprotective role of thiamine and highlight the importance of considering thiamine in the context of neuronal protection.

A substantial body of evidence indicates that thiamine deficiency occurs in up to 20% of critically ill patients during hospitalization. This may result from metabolic stress, inadequate nutritional intake, and multiple comorbidities[73, 74]. Malnutrition, which is common in this population, may further exacerbate insufficient thiamine intake. Clinical diagnosis of thiamine deficiency is challenging in the ICU setting. Symptoms have low sensitivity and specificity. Thiamine deficiency has been linked to peripheral neuropathy[75] and congestive heart failure[76]. It has also been associated with gastrointestinal beriberi[77], Korsakoff syndrome, and Wernicke encephalopathy[78]. It may accelerate complications such as altered mental status and unexplained lactic acidosis[30,78]. Gastrointestinal dysfunction has also been reported[30, 79]. The brain has a high demand for energy metabolism. Thiamine acts as a key coenzyme for pyruvate dehydrogenase and α-ketoglutarate dehydrogenase. These enzymes support aerobic respiration and the tricarboxylic acid cycle[22, 23]. Thiamine deficiency leads to mitochondrial dysfunction and impaired glutamate clearance, thereby precipitating neuronal energy crisis and excitotoxicity[68–70]. It has been closely associated with multiple neurological disorders, including Wernicke encephalopathy, Korsakoff syndrome, and peripheral neuropathy, as well as with altered mental status, delirium, and unexplained lactic acidosis[30, 75, 78, 79]. Moreover, persistent oxidative stress is a key mechanism in sepsis-associated delirium. Neuroinflammatory responses also contribute to SAD and other critical illness–related encephalopathies[80–82]. Thiamine deficiency may exacerbate oxidative stress and neuroinflammation, accelerate cerebrovascular dysfunction and cognitive impairment, and ultimately increase mortality risk among patients with SAD. Thus, thiamine supplementation may exert a potential neuroprotective effect in improving neurological outcomes in critically ill patients.

Thiamine is transported via the bloodstream to tissues with high metabolic demands, with neurons particularly reliant on glucose oxidation to sustain normal function. Consequently, thiamine deficiency precipitates neuronal bioenergetic failure. Impaired entry of pyruvate into the tricarboxylic acid cycle shifts metabolism toward lactate production. This leads to intracellular lactate accumulation and acidosis. These changes may disrupt neuronal membrane potentials and synaptic transmission[83, 84]. Emerging evidence suggests that thiamine supplementation may improve central nervous system function. A systematic review included 8 randomized controlled trials and 10 cohort studies. It reported that thiamine administration reduced ICU delirium incidence in critically ill patients overall[85]. In contrast, a retrospective cohort study from Korea found that early thiamine therapy did not prolong delirium-free days in patients with septic shock[86]. Taken together, direct evidence specifically targeting SAD remains limited and inconsistent. Negative findings are plausibly attributable to suboptimal dosing or treatment duration, lack of stratification by baseline deficiency status or metabolic phenotype, and confounding from sedation practices and illness severity[86]. Future research should prioritize randomized controlled trials with SAD as the primary endpoint. Trials should stratify by baseline thiamine status and metabolic phenotype. Examples include deficiency, functional deficiency, hyperlactatemia, and energy phenotype. They should also use adequate intravenous dosing and treatment duration. Standardized delirium assessments and sedative exposure should be accounted for. At present, thiamine remains an attractive candidate supportive therapy for high-risk patients with suspected deficiency, given its safety, low cost, and biologically plausible benefits across mitochondrial, endothelial, and neurotransmitter pathways[68–70, 75]. Its role in SAD management warrants further clinical investigation and thoughtful integration into critical care practice.

This study investigated the association between thiamine supplementation and prognosis in patients with SAD and has several strengths. First, our findings were validated using propensity score matching (PSM) and a series of models adjusted for various confounding factors, all of which yielded consistent results. Second, the large patient population in

cluded in the MIMIC-IV database provided a solid foundation for our analysis. Third, we extended the exposure definition beyond binary use by conducting prespecified duration–response and dose–response analyses. These analyses helped address concerns about regimen heterogeneity and provided clinically relevant insight into how treatment intensity may relate to outcomes. However, several limitations must be acknowledged. First, the number of patients receiving thiamine was relatively limited, raising concerns about potential selection bias and reduced statistical precision. Accordingly, we implemented multiple propensity score-based analytic strategies to mitigate this issue. By incorporating key baseline covariates into the propensity score model[40–43], baseline differences between treatment groups were substantially balanced[87, 88]. The consistency of effect estimates across matching, adjustment, and several weighting approaches supports the robustness of our findings[89–91]. Together, these methods approximate covariate balance typically achieved in randomized studies and strengthen causal inference in this observational cohort[49]. Second, we were unable to determine whether thiamine is beneficial for all patients with SAD or only for those with thiamine deficiency, as baseline thiamine levels were not available in MIMIC-IV. Third, dose and duration were derived from routine medication administration records and analyzed in categories; therefore, some exposure misclassification is possible. In addition, because thiamine administration may vary over the ICU course, residual confounding related to treatment timing cannot be completely excluded. Finally, as this was a single-center database study, the generalizability of our findings to other healthcare settings or populations requires further validation. Therefore, further well-designed clinical trials are warranted to explore the prognostic relationship between thiamine supplementation and SAD.

Conclusions

In ICU patients with sepsis-associated delirium, thiamine supplementation was associated with lower 30-day mortality and remained consistent across multiple propensity score-based analyses. Longer treatment duration and lower daily dosing appeared to be linked with greater benefit.

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Author contributions

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Co-First Authors (†):

Haibo Wang and Yaotang Wang contributed equally to core research execution (study design, data acquisition, analysis, and manuscript drafting).

Corresponding Author (*):

Caixia Li oversaw project coordination, critical revision of the manuscript, and acts as the primary contact for communication.

Ruimin Hu finished technical assistance, resources provision and data curation.

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Data availability

The datasets analyzed during this investigation are publicly accessible in the MIMIC-IV repository (v3.1) at: https://physionet.org/content/mimiciv/3.1/

Declarations

Ethics approval and consent to participate

MIMIC-IV is a de-identified, publicly available database approved by the institutional review boards of Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology. Given the de-identified nature of the data, the requirement for informed consent was waived. Co-first author Yaotang Wang obtained access to the MIMIC-IV database after completing the required training on the National Institutes of Health (NIH) platform, including the courses "Study data or Specimens only" and "Conflict of interest" (certification numbers: 59979404 and 59979406).

Consent for publication

All authors have approved the manuscript and have provided consent for submission to the journal.

Competing interests

The authors declare no competing interests.

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Table1 Baseline characteristics of participants.

Variables	Unmatched Patients	Pairwise algorithmic matched patients

	Level	All patients (n=1288)	No thiamine use (n=956)	Thiamine use (n=332)	SMD	All patients (n=624.97)	No thiamine (n=310.52)	Thiamine use (n=314.45)	SMD
Admission age (mean (SD))		69.91 (16.09)	71.98 (15.91)	63.95 (15.13)	0.517	64.52 (16.71)	64.20 (18.59)	64.84 (14.63)	0.039
Gender (%)	Female	485.0 (37.7)	391.0 (40.9)	94.0 (28.3)	0.267	182.7 (29.2)	89.8 (28.9)	92.9 (29.5)	0.013
	Male	803.0 (62.3)	565.0 (59.1)	238.0 (71.7)		442.3 (70.8)	220.7 (71.1)	221.6 (70.5)	
Heart rate (mean (SD))		87.00 (16.85)	86.24 (16.26)	89.18 (18.30)	0.177	88.76 (17.46)	88.83 (16.73)	88.69 (18.17)	0.008
sbp (mean (SD))		116.41 (15.06)	116.62 (14.97)	115.80 (15.35)	0.054	115.88 (15.20)	115.84 (15.06)	115.92 (15.36)	0.005
dbp (mean (SD))		63.03 (10.82)	62.43 (10.83)	64.74 (10.62)	0.216	64.51 (10.86)	64.43 (11.06)	64.58 (10.67)	0.013
mbp (mean (SD))		78.56 (10.30)	78.13 (10.28)	79.78 (10.26)	0.166	79.61 (10.60)	79.54 (10.87)	79.68 (10.34)	0.013
Respiratory rate (mean (SD))		20.31 (4.02)	20.21 (3.93)	20.60 (4.29)	0.093	20.49 (4.17)	20.44 (4.04)	20.54 (4.29)	0.024
Temperature (mean (SD))		36.98 (0.53)	36.97 (0.54)	37.04 (0.50)	0.131	37.03 (0.56)	37.03 (0.63)	37.03 (0.49)	0.005
SpO_2 (mean (SD))		96.81 (2.10)	96.76 (2.15)	96.96 (1.94)	0.098	96.96 (2.04)	96.99 (2.13)	96.94 (1.94)	0.022
Glucose (mean (SD))		257.19 (3979.86)	295.89 (4619.41)	145.75 (50.21)	0.046	146.19 (50.28)	146.25 (49.86)	146.14 (50.74)	0.002
Hematocrit (mean (SD))		31.11 (7.10)	30.78 (7.06)	32.07 (7.14)	0.183	32.03 (7.31)	32.01 (7.45)	32.05 (7.18)	0.006
Hemoglobin (mean (SD))		10.13 (2.37)	10.02 (2.34)	10.47 (2.42)	0.191	10.44 (2.44)	10.43 (2.44)	10.45 (2.44)	0.008
Platelets (mean (SD))		185.61 (98.91)	187.47 (100.12)	180.23 (95.29)	0.074	181.92 (95.75)	182.27 (95.71)	181.58 (95.92)	0.007
Anion gap (mean (SD))		16.69 (4.94)	16.55 (4.54)	17.08 (5.92)	0.106	16.87 (5.36)	16.84 (4.94)	16.90 (5.75)	0.012
Bun (mean (SD))		32.41 (24.87)	33.11 (23.89)	30.39 (27.43)	0.106	30.50 (25.07)	30.57 (22.43)	30.42 (27.46)	0.006
Chloride (mean (SD))		101.71 (6.31)	101.80 (6.12)	101.43 (6.83)	0.057	101.56 (6.55)	101.58 (6.24)	101.54 (6.84)	0.006
Sodium (mean (SD))		137.16 (5.58)	137.17 (5.60)	137.12 (5.56)	0.008	137.21 (5.55)	137.23 (5.51)	137.19 (5.60)	0.007
Potassium (mean (SD))		4.69 (0.85)	4.69 (0.83)	4.69 (0.90)	0.006	4.69 (0.85)	4.70 (0.80)	4.69 (0.89)	0.012
Myocardial infarction	No	1018.0	748.0	270.0	0.0	506.9	252.8	254.1	0.01

(%)		(79.0)	(78.2)	(81.3)	77	(81.1)	(81.4)	(80.8)	6
	Yes	270.0 (21.0)	208.0 (21.8)	62.0 (18.7)		118.1 (18.9)	57.7 (18.6)	60.4 (19.2)	
Congestive heart failure (%)	No	829.0 (64.4)	595.0 (62.2)	234.0 (70.5)	0.1 75	438.3 (70.1)	218.7 (70.4)	219.6 (69.8)	0.01 3
	Yes	459.0 (35.6)	361.0 (37.8)	98.0 (29.5)		186.7 (29.9)	91.8 (29.6)	94.9 (30.2)	
Cerebrovascular disease (%)	No	1044.0 (81.1)	776.0 (81.2)	268.0 (80.7)	0.0 11	505.3 (80.9)	251.2 (80.9)	254.1 (80.8)	0.00 2
	Yes	244.0 (18.9)	180.0 (18.8)	64.0 (19.3)		119.7 (19.1)	59.3 (19.1)	60.3 (19.2)	
Chronic pulmonary disease (%)	No	940.0 (73.0)	697.0 (72.9)	243.0 (73.2)	0.0 06	454.5 (72.7)	226.4 (72.9)	228.2 (72.6)	0.00 8
	Yes	348.0 (27.0)	259.0 (27.1)	89.0 (26.8)		170.5 (27.3)	84.2 (27.1)	86.3 (27.4)	
Malignant cancer (%)	No	1136.0 (88.2)	832.0 (87.0)	304.0 (91.6)	0.1 47	572.5 (91.6)	284.6 (91.6)	287.9 (91.5)	0.00 4
	Yes	152.0 (11.8)	124.0 (13.0)	28.0 (8.4)		52.5 (8.4)	25.9 (8.4)	26.6 (8.5)	
Metastatic solid tumor (%)	No	1209.0 (93.9)	886.0 (92.7)	323.0 (97.3)	0.2 12	607.6 (97.2)	302.2 (97.3)	305.5 (97.1)	0.01 1
	Yes	79.0 (6.1)	70.0 (7.3)	9.0 (2.7)		17.3 (2.8)	8.3 (2.7)	9.0 (2.9)	
Paraplegia (%)	No	1214.0 (94.3)	901.0 (94.2)	313.0 (94.3)	0.0 01	588.0 (94.1)	291.9 (94.0)	296.1 (94.2)	0.00 6
	Yes	74.0 (5.7)	55.0 (5.8)	19.0 (5.7)		37.0 (5.9)	18.6 (6.0)	18.4 (5.8)	
Diabetes with complications (%)	No	1105.0 (85.8)	807.0 (84.4)	298.0 (89.8)	0.1 6	559.1 (89.5)	277.9 (89.5)	281.2 (89.4)	0.00 3
	Yes	183.0 (14.2)	149.0 (15.6)	34.0 (10.2)		65.9 (10.5)	32.6 (10.5)	33.3 (10.6)	
APACHE score (mean (SD))		61.49 (23.34)	60.53 (22.16)	64.27 (26.27)	0.1 54	63.13 (24.39)	62.95 (23.31)	63.31 (25.44)	0.01 5
Sofa score(mean (SD))		5.96 (3.05)	5.95 (3.04)	5.98 (3.09)	0.0 12	5.99 (3.09)	5.99 (3.09)	5.99 (3.09)	0.00 2
Aki stage 2day (%)	0	278.0 (21.6)	193.0 (20.2)	85.0 (25.6)	0.1 41	157.6 (25.2)	77.9 (25.1)	79.6 (25.3)	0.02 5
	1	270.0 (21.0)	206.0 (21.5)	64.0 (19.3)		118.5 (19.0)	58.4 (18.8)	60.1 (19.1)	
	2	499.0 (38.7)	380.0 (39.7)	119.0 (35.8)		230.7 (36.9)	116.4 (37.5)	114.3 (36.3)	
	3	241.0 (18.7)	177.0 (18.5)	64.0 (19.3)		118.2 (18.9)	57.8 (18.6)	60.4 (19.2)	
Aki stage 7day (%)	0	145.0	107.0	38.0	0.0	72.0	35.6	36.4	0.01

		(11.3)	(11.2)	(11.4)	43	(11.5)	(11.5)	(11.6)	6
	1	201.0 (15.6)	153.0 (16.0)	48.0 (14.5)		89.5 (14.3)	43.9 (14.1)	45.6 (14.5)	
	2	565.0 (43.9)	418.0 (43.7)	147.0 (44.3)		278.0 (44.5)	139.3 (44.9)	138.7 (44.1)	
	3	377.0 (29.3)	278.0 (29.1)	99.0 (29.8)		185.4 (29.7)	91.7 (29.5)	93.7 (29.8)	
Dexamethasone (%)	No	1179.0 (91.5)	885.0 (92.6)	294.0 (88.6)	0.1 38	558.2 (89.3)	278.6 (89.7)	279.6 (88.9)	0.02 6
	Yes	109.0 (8.5)	71.0 (7.4)	38.0 (11.4)		66.7 (10.7)	31.9 (10.3)	34.9 (11.1)	
Hydrocortisone (%)	No	1202.0 (93.3)	901.0 (94.2)	301.0 (90.7)	0.1 36	564.8 (90.4)	279.2 (89.9)	285.6 (90.8)	0.03 1
	Yes	86.0 (6.7)	55.0 (5.8)	31.0 (9.3)		60.1 (9.6)	31.3 (10.1)	28.8 (9.2)	
Dexmedetomidine (%)	No	636.0 (49.4)	528.0 (55.2)	108.0 (32.5)	0.4 7	213.8 (34.2)	105.8 (34.1)	107.9 (34.3)	0.00 5
	Yes	652.0 (50.6)	428.0 (44.8)	224.0 (67.5)		411.2 (65.8)	204.7 (65.9)	206.5 (65.7)	
Hydromorphone (%)	No	763.0 (59.2)	582.0 (60.9)	181.0 (54.5)	0.1 29	343.1 (54.9)	168.2 (54.2)	175.0 (55.6)	0.03
	Yes	525.0 (40.8)	374.0 (39.1)	151.0 (45.5)		281.8 (45.1)	142.3 (45.8)	139.5 (44.4)	
Midazolam (%)	No	884.0 (68.6)	681.0 (71.2)	203.0 (61.1)	0.2 15	396.0 (63.4)	196.5 (63.3)	199.5 (63.5)	0.00 4
	Yes	404.0 (31.4)	275.0 (28.8)	129.0 (38.9)		228.9 (36.6)	114.0 (36.7)	114.9 (36.5)	
Vassopressor (%)	No	643.0 (49.9)	501.0 (52.4)	142.0 (42.8)	0.1 94	274.1 (43.9)	135.8 (43.7)	138.3 (44.0)	0.00 5
	Yes	645.0 (50.1)	455.0 (47.6)	190.0 (57.2)		350.9 (56.1)	174.7 (56.3)	176.2 (56.0)	
Cardiotonic (%)	No	1212.0 (94.1)	905.0 (94.7)	307.0 (92.5)	0.0 9	580.9 (93.0)	288.6 (92.9)	292.4 (93.0)	0.00 2
	Yes	76.0 (5.9)	51.0 (5.3)	25.0 (7.5)		44.0 (7.0)	22.0 (7.1)	22.1 (7.0)	
Machine ventilation (%)	No	1035.0 (80.4)	756.0 (79.1)	279.0 (84.0)	0.1 28	519.1 (83.1)	256.7 (82.7)	262.4 (83.4)	0.02 1
	Yes	253.0 (19.6)	200.0 (20.9)	53.0 (16.0)		105.9 (16.9)	53.8 (17.3)	52.1 (16.6)	
Hemodialysis (%)	No	1251.0 (97.1)	923.0 (96.5)	328.0 (98.8)	0.1 49	617.0 (98.7)	306.6 (98.7)	310.5 (98.7)	<0.0 01
	Yes	37.0 (2.9)	33.0 (3.5)	4.0 (1.2)		8.0 (1.3)	4.0 (1.3)	4.0 (1.3)	
Icu free 28day		15.85	16.21	14.81	0.1	15.14	15.17	15.10	0.0

(mean (SD))	(9.81)	(9.97)	(9.26)	45	(9.38)	(9.53)	(9.24)	08

Table2 Associations between thiamine use and the outcome in the crude analysis, multivariable analysis, and propensity-score analyses.

Analysis	30-day mortality (%)	P-value
No. of events/no. of patients at risk (%)		
No thiamine use	182/956 (19)	
Thiamine use	36/332(10.8)	
Crude analysis — hazard ratio (95% CI)	0.38 (0.27~0.55)	<0.001
Multivariable analysis — hazard ratio (95% CI)		
Multivariable.adjusted[a]	0.51 (0.33~0.79)	0.002
PropensityScore.adjusted[b]	0.59 (0.40~0.85)	0.005
PropensityScore.Matched[c]	0.59 (0.39~0.90)	0.015
Weighted.IPTW[d]	0.54 (0.38~0.77)	0.002
Weighted.SMRW[e]	0.68 (0.47~0.98)	0.052
Weighted.PA[f]	0.63 (0.40~0.97)	0.016
Weighted.OW[g]	0.6 (0.36~1.02)	0.008

[a] Shown is the hazard ratio from the multivariable Cox proportional hazards model, with adjusted for all covariates in Table 1.

[b] Shown is the hazard ratio from a multivariable Cox proportional-hazards model with the same strata and covariates with adjustment according to the propensity score.

[c] Shown is the hazard ratio from a multivariable Cox proportional-hazards model with the same strata and covariates with matching according to the propensity score.

[d] Shown is the primary analysis with a hazard ratio from the multivariable Cox proportional-hazards model with the same strata and covariates with inverse probability weighting according to the propensity score.

[e] Shown is the primary analysis with a hazard ratio from the multivariable Cox proportional-hazards model with the same strata and covariates with standardized mortality ratio weighting.

[f] Shown is the primary analysis with a hazard ratio from the multivariable Cox proportional-hazards model with the same strata and covariates with pairwise algorithmic.

[g] Shown is the primary analysis with a hazard ratio from the multivariable Cox proportional-hazards model with the same strata and covariates with overlap weight.

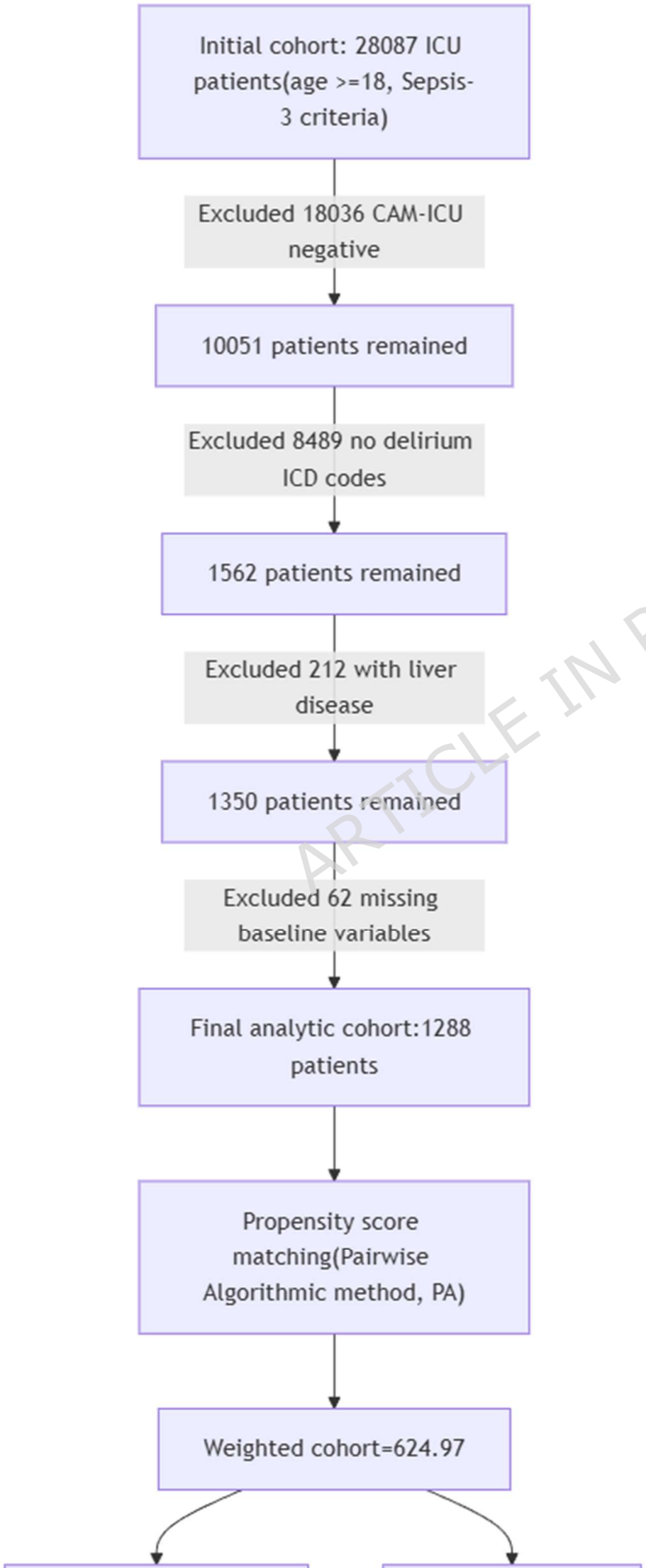
Table3 Subgroup analysis after PA weighted analysis

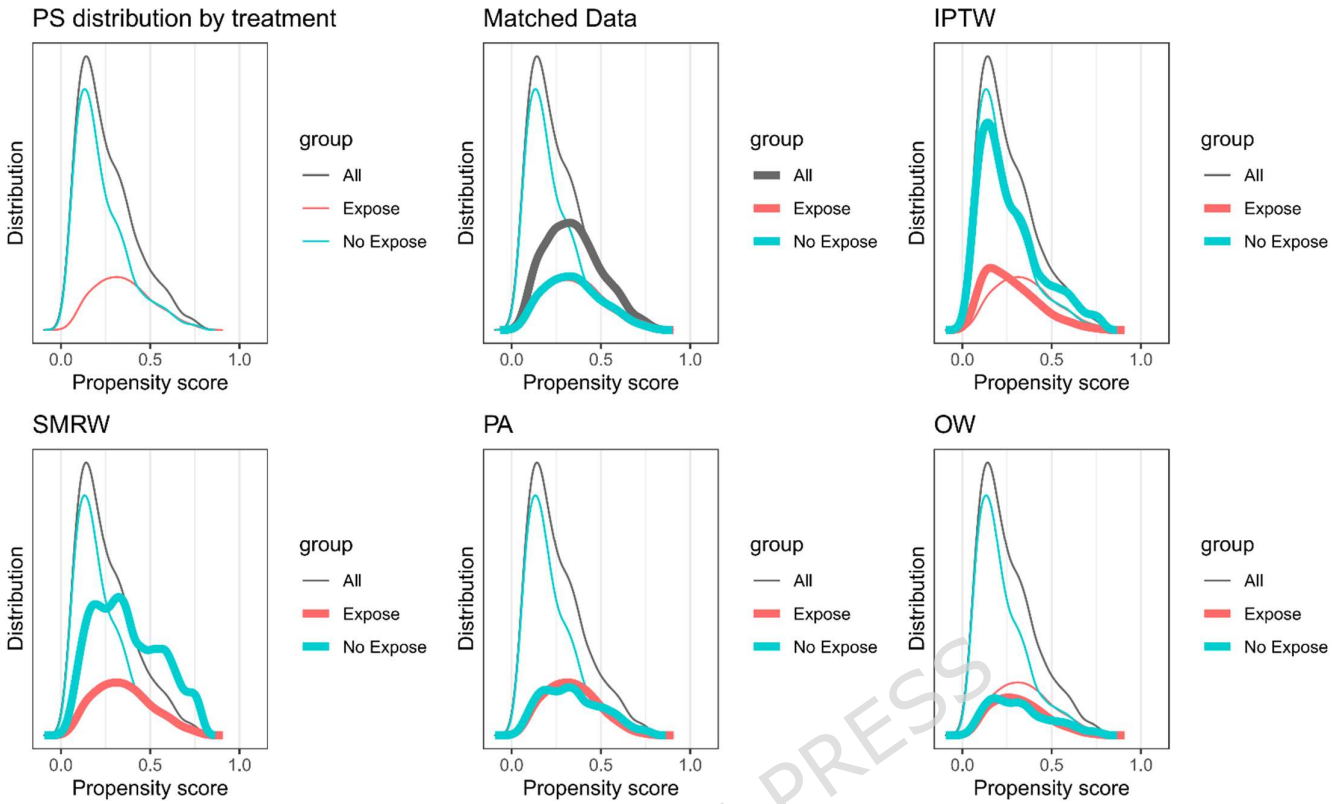
Subgroup	Variable	Total	Event (%)	HR (95%CI)	P for interaction	HR	HR.95CI.Low	HR.95CI.Up
Age								
<65					0.88			
	No_thiamine_use	251	18 (7.2)	1(Ref)		1	1	1
	Thiamine_use	163	7 (4.3)	0.77 (0.26~2.35)		0.77	0.26	2.35
>=65								
	No_thiamine	705	164	1(Ref)		1	1	1

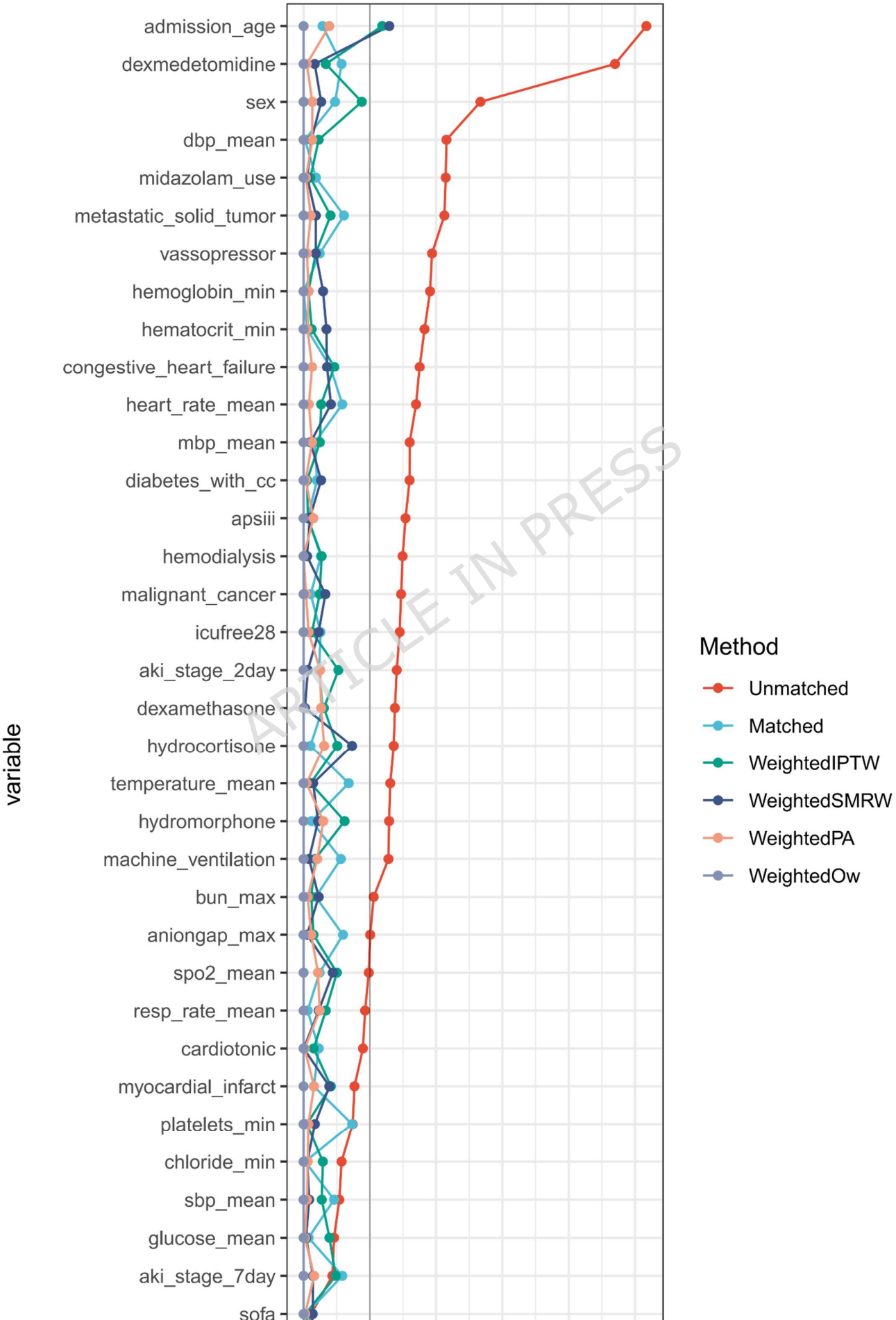
	_use		(23.3)					
	Thiamine_use	169	29 (17.2)	0.57 (0.35~0.92)		0.57	0.35	0.92
Gender								
Female					0.768			
	No_thiamine_use	391	82 (21)	1(Ref)		1	1	1
	Thiamine_use	94	14 (14.9)	0.51 (0.25~1.03)		0.51	0.25	1.03
Male								
	No_thiamine_use	565	100 (17.7)	1(Ref)		1	1	1
	Thiamine_use	238	22 (9.2)	0.65 (0.37~1.16)		0.65	0.37	1.16
Chronic_pulmonary_disease								
No					0.639			
	No_thiamine_use	697	121 (17.4)	1(Ref)		1	1	1
	Thiamine_use	243	25 (10.3)	0.74 (0.42~1.28)		0.74	0.42	1.28
Yes								
	No_thiamine_use	259	61 (23.6)	1(Ref)		1	1	1
	Thiamine_use	89	11 (12.4)	0.47 (0.22~0.98)		0.47	0.22	0.98
Renal disease								
No					0.494			
	No_thiamine_use	668	106 (15.9)	1(Ref)		1	1	1
	Thiamine_use	277	24 (8.7)	0.62 (0.36~1.08)		0.62	0.36	1.08
Yes								
	No_thiamine_use	288	76 (26.4)	1(Ref)		1	1	1
	Thiamine_use	55	12 (21.8)	0.58 (0.27~1.23)		0.58	0.27	1.23
Cerebrovascular disease								
No					0.954			
	No_thiamine_use	776	156 (20.1)	1(Ref)		1	1	1
	Thiamine_use	268	31 (11.6)	0.62 (0.38~1)		0.62	0.38	1

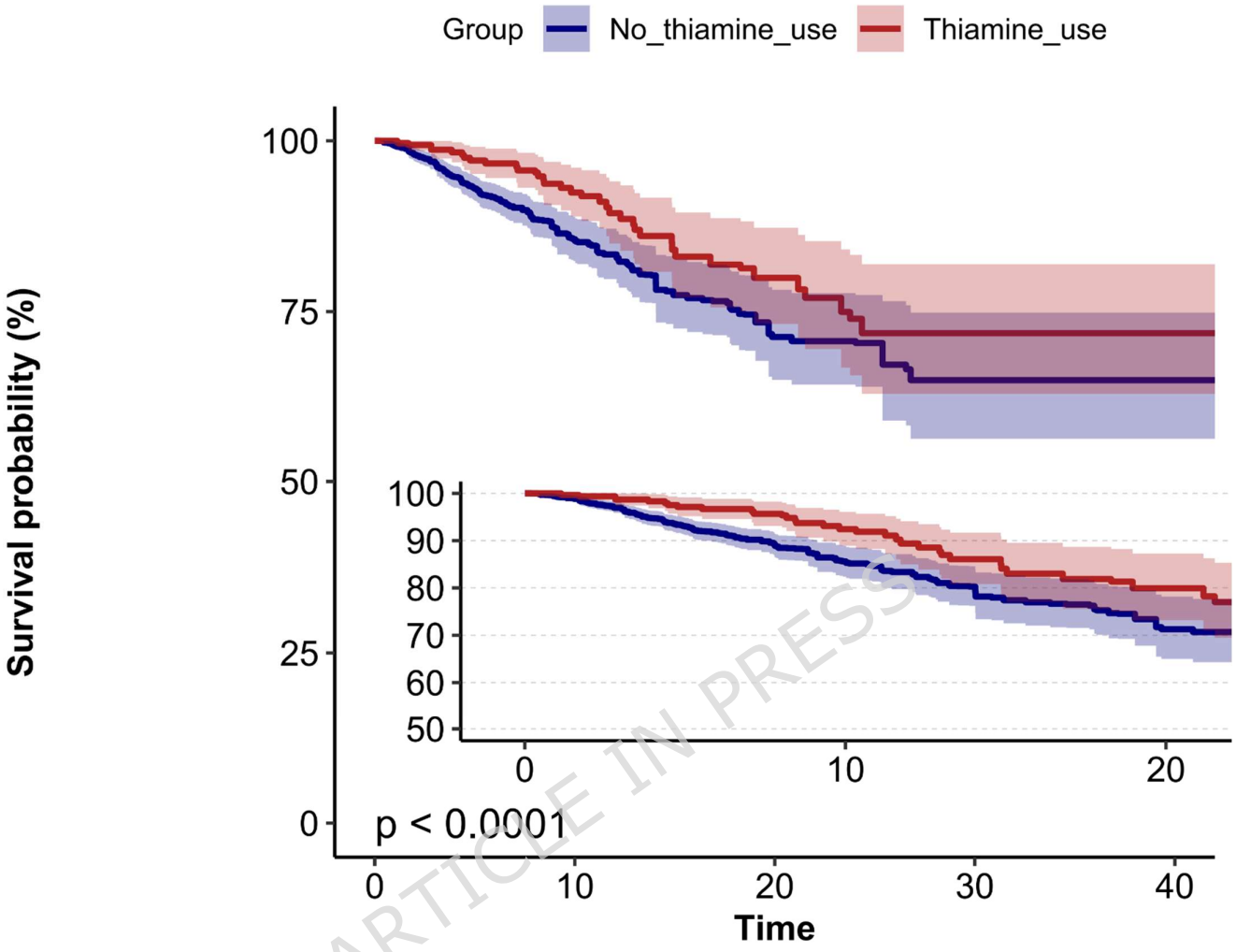
Yes								
	No_thiamine_use	180	26 (14.4)	1(Ref)		1	1	1
	Thiamine_use	64	5 (7.8)	0.65 (0.19~2.15)		0.65	0.19	2.15
Hydromorphone								
No					0.198			
	No_thiamine_use	582	111 (19.1)	1(Ref)		1	1	1
	Thiamine_use	181	24 (13.3)	0.65 (0.38~1.12)		0.65	0.38	1.12
Yes								
	No_thiamine_use	374	71 (19)	1(Ref)		1	1	1
	Thiamine_use	151	12 (7.9)	0.55 (0.26~1.17)		0.55	0.26	1.17
Midazolam								
No					0.971			
	No_thiamine_use	681	134 (19.7)	1(Ref)		1	1	1
	Thiamine_use	203	24 (11.8)	0.61 (0.36~1.05)		0.61	0.36	1.05
Yes								
	No_thiamine_use	275	48 (17.5)	1(Ref)		1	1	1
	Thiamine_use	129	12 (9.3)	0.65 (0.29~1.42)		0.65	0.29	1.42
Dexmedetomidine								
No					0.419			
	No_thiamine_use	528	117 (22.2)	1(Ref)		1	1	1
	Thiamine_use	108	11 (10.2)	0.53 (0.25~1.11)		0.53	0.25	1.11
Yes								
	No_thiamine_use	428	65 (15.2)	1(Ref)		1	1	1
	Thiamine_use	224	25 (11.2)	0.7 (0.4~1.23)		0.7	0.4	1.23
Machine ventilation								
No					0.489			
	No_thiamine_use	756	140 (18.5)	1(Ref)		1	1	1
	Thiamine_use	279	33 (11.8)	0.64 (0.4~1.03)		0.64	0.4	1.03

Yes								
	No_thiamine_use	200	42 (21)	1(Ref)		1	1	1
	Thiamine_use	53	3 (5.7)	0.51 (0.13~1.97)		0.51	0.13	1.97
SOFA_score								
<4					0.002			
	No_thiamine_use	224	44 (19.6)	1(Ref)		1	1	1
	Thiamine_use	68	1 (1.5)	0.09 (0.01~0.7)		0.09	0.01	0.7
>=4								
	No_thiamine_use	732	138 (18.9)	1(Ref)		1	1	1
	Thiamine_use	264	35 (13.3)	0.76 (0.47~1.23)		0.76	0.47	1.23









Number at risk

No_thiamine_use	311	117	38	16	7
Thiamine_use	314	137	53	19	7