Evaluation of Thiamine as Adjunctive Therapy in COVID-19 Critically Ill Patients: A Multicenter Propensity Score Matched Study

Khalid Al Sulaiman (alsulaimankh@hotmail.com)
King Abdulaziz Medical City https://orcid.org/0000-0002-5547-2043

Ohoud Aljuhani
King Abdulaziz University

Maram Al Dossari
King Abdulaziz Medical City

Asma Alshahrani
King Khalid University

Aisha Alharbi
King Abdulaziz University Hospital

Rahmah Algarni
King Abdulaziz University Hospital

Majed Al Jeraisy
King Abdullah International Medical Research Center

Shmeylan Al Harbi
King Abdulaziz Medical City

Abdulmalik Al Katheri
King Saud bin Abdulaziz University for Health Sciences

Fahad Al Eidan
King Abdulaziz Medical City

Abdulkareem M. Al Bekairy
King Saud bin Abdulaziz University for Health Sciences

Nouf Al Qahtani
King Abdulaziz Medical City

Mashael Al Muqrin
King Abdulaziz Medical City

Ramesh Vishwakarma
King Abdullah International Medical Research Center

Ghassan Al Ghamdi
King Abdulaziz Medical City

Research

Keywords: COVID-19, SARS-CoV-2, Thiamine, Vitamin B1, Vitamins, Critically ill, Intensive Care Units (ICUs), 30-days ICU mortality

Posted Date: April 13th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-400565/v1

Abstract

Background: Thiamine is a precursor of the essential coenzyme thiamine pyrophosphate (TPP) required for glucose metabolism; it improves the immune system function and has been shown to reduce the risk of several diseases. The role of thiamine in COVID-19 critically ill patients is still unclear, however, its role in the critically ill septic patient has been addressed in multiple studies. The objective of this study was to evaluate the use of thiamine as adjunctive therapy on the mortality in COVID 19 critically ill patients.

Methods: This is a multicenter, non-interventional, retrospective cohort study for all critically ill patients admitted to intensive care units (ICUs) with a confirmed diagnosis of COVID19. All patients aged 18 years or older who were admitted to ICUs between March 1st to December 31st, 2020 with positive PCR COVID-19 were included in the study. We investigated the association between thiamine use as an adjunctive therapy and clinical outcomes in COVID -19 after propensity score matching using baseline severity scores, systemic use of corticosteroids and study centers.

Results: A total of 738 critically ill patients with COVID-19 who had been admitted in ICUs at the two governmental hospitals included in the study. Among 166 patients matched using propensity score, 83 had received thiamine as adjunctive therapy. There was significant association between thiamine use with in-hospital mortality (OR=0.49; 95% CI = 0.25- 0.97; *P*=0.04) as well with 30-day ICU mortality (OR=0.45; 95% CI = 0.215- 0.935; *P*=0.03). Moreover, patients who received thiamine as an adjunctive therapy were less likely to have thrombosis during ICU stay by 81 % (OR (95%CI): 0.19 (0.040,0.884), p-value=0.034).

Conclusion: Thiamine use as an adjunctive therapy may have potential survival benefits in critically ill patients with COVID-19.

Introduction

Thiamine is a precursor of the essential coenzyme thiamine pyrophosphate (TPP) required for glucose metabolism; it improves the immune system function and has been shown to reduce the risk of several diseases such as type-2 diabetes, cardiovascular, renal, mental, and neurodegenerative disorders. As antibodies, and importantly T-cells, are required to eliminate the SARS-CoV-2 virus, thiamine deficiency can potentially result in inadequate antibody responses and subsequently more severe symptoms[1]. Hence, adequate thiamine levels are likely to aid in the proper immune responses during SARS-CoV-2 infection. COVID-19 symptoms are very similar to altitude sickness and high-altitude pulmonary edema. In such cases, acetazolamide is commonly prescribed to inhibit the carbonic anhydrase isoenzymes and subsequently increases oxygen levels. Thiamine also functions as a carbonic anhydrase isoenzyme inhibitor; thus, high doses of thiamine given to people at the early stages of COVID-19 could potentially limit hypoxia and decrease hospitalization.[2]

The role of thiamine in COVID-19 critically ill patients is still unclear; however, its role in the critically ill septic patient has been addressed in multiple studies. A randomized controlled trial was conducted to

determine if intravenous thiamine would reduce lactate in patients with septic shock. Patients were randomized to thiamine 200 mg or placebo twice daily for seven days. In those with baseline thiamine deficiency, patients in the thiamine group had significantly lower lactate levels at 24 hours and a possible decrease in 30 days mortality[3]. In this trial's post hoc analysis, patients with septic shock who received thiamine had lower serum creatinine with a lower progression rate to renal replacement therapy than patients who received placebo[4]. Moreover, in a single-center retrospective cohort study (n = 123), thiamine administration to septic shock patients within 24 hours was associated with improved likelihood of lactic acid clearance and reduced 28-day mortality[5]. In a retrospective before-after trial in 47 septic shock patients, the combination of intravenous thiamine with corticosteroids and vitamin C was associated with a reduction of organ dysfunction, including acute kidney injury. However, the findings of this study are highly controversial and need validation[6].

The question remains about the thiamine role in COVID-19 critically ill patients. An in vitro study found that high-dose thiamine lowers the Th17 cell proinflammatory response believed to be associated with the COVID-19 cytokine storm. The modulation of Th17 proinflammatory response was investigated through a combination of both in vivo and in vitro experiments. The study demonstrates that thiamine interrupts the cycle of inflammation believed to play a role in the cytokine storm associated with COVID-19, leading to reduced levels of IL-17 proinflammatory cytokines and increased levels of the anti-inflammatory IL-22 cytokines. Notably, this study did not involve patients with COVID-19 but rather patients with alcohol use disorder, who also tend to experience a proinflammatory state characterized by elevated IL-17 levels. However, thiamine effectiveness in COVID-19 still needs to be tested in a clinical setting. This study is in the pre-print phase only and is currently under review by a peer-reviewed journal[7].

As of July 15th, 2020, over 300 COVID-19 patients were treated with a protocol named MATH + protocol which combines a range of substances: methylprednisolone, ascorbic acid, thiamine, heparin, and several additional components, including melatonin, zinc, vitamin D, atorvastatin, and famotidine. The efficacy of the proposed MATH + protocol against COVID-19 was measured in two hospitals in the United States based on patient registry information. The average hospital mortality of these two centers was 5.1 %, which represents more than a 75 % absolute risk reduction in mortality compared to the average published worldwide hospital mortality. However, this comparison is limited by the lack of data on the severity of illness and course of treatment[8–10].

There are no current studies specifically investigating thiamine's effect in COVID-19 patients to the best of our knowledge. Therefore, this study aims to determine the association of thiamine use as an adjunctive therapy on the outcomes in COVID 19 critically ill patients (i.e., ICU mortality, ICU Length of stay (LOS), and duration of mechanical ventilation).

Methods

Study design

This was a retrospective, multi-center, non-interventional study of critically ill patients admitted to intensive care units (ICUs) with a confirmed diagnosis of COVID19 in Saudi Arabia. The diagnosis of COVID19 was confirmed by Reverse Transcriptase – Polymerase Chain Reaction (RT-PCR) on nasopharyngeal and/or throat swabs. All the patients who met our inclusion criteria during the study period (01/03/2020 – 31/12/2020) were included. COVID19 critically ill patients have been divided into two groups based on thiamine use as adjunctive therapy during ICU stay. Patients were followed during their hospital stay until discharge or in-hospital death, whichever occurred first. The study was approved by the Ministry of National Guard Health Affairs Institutional Review Board, Riyadh, Saudi Arabia (Study Number: RC20/589/R).

Eligibility criteria

Patients were enrolled in the study if they were critically ill, aged 18 years or older, and admitted to ICU with positive PCR COVID-19. Patients were excluded if the ICU Length of stay (LOS) ≤1 day and/or labeled as "Do-Not-Resuscitate" status within 24 hours of ICU admission.

Setting

This study was conducted in two large, tertiary governmental hospitals; King Abdulaziz Medical City, Riyadh, and King Abdulaziz University Hospital, Jeddah. The ICUs admits medical, surgical, trauma, burn, and transplant patients and operates as a closed unit with 24/7 onsite coverage by critical care board-certified intensivists [8]. The distributions of total enrolled patients were 77 % and 23 % in KAMC-CR and KAUH, respectively. The primary site for this multicenter study was King Abdulaziz Medical City (Riyadh).

Data collection

We collected the following information, demographic data (See additional file 1), thiamine use, Acute Physiology And Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA) and Nutrition Risk in Critically ill (*NUTRIC*) scores, comorbidities, vital signs, laboratory tests, the needs for mechanical ventilation (MV) and MV parameters (e.g., PaO2/FiO2 ratio, FiO2 requirement) and inflammatory markers (CRP, procalcitonin) within 24 hours of ICU admission. ICU complication (s) during ICU stay (e.g., thrombosis, Acute Kidney Injury (AKI)) were recorded for eligible patients. Additionally, ICU length of stay (LOS), hospital LOS, mechanical ventilation (MV) duration, and ICU mortality were collected and followed. Patients were followed during ICU LOS until ICU discharge after improving, or in-hospital death, whichever occurred first.

Outcomes

The primary endpoints were to determine the association between using thiamine as adjunctive therapy with in-hospital mortality and 30-day ICU mortality in critically ill patients with COVID 19 (i.e., ICU mortality, ICU LOS). The secondary endpoints include MV duration, length of stay, evaluation of complication (s) during ICU stay (i.e., acute kidney injury (AKI), liver injury, thrombosis during ICU stay).

Definition (s)

- The acute kidney injury (AKI) was defined using AKIN definition [29].
- Thrombosis/infraction was defined using ICD10-CM code (i.e., Myocardial infarction (MI), ischemic stroke, pulmonary embolism, deep vein thrombosis) [30].
- Respiratory failure was defined as either hypoxemic respiratory failure (PaO_2 < 60 mm Hg with a normal or low arterial carbon dioxide tension ($PaCO_2$) or hypercapnic respiratory failure ($PaCO_2$> 50 mm Hg) that requires invasive mechanical ventilation.
- Liver injury, defined as alanine aminotransferase (ALT), exceeds three times the upper limit of normal or double in patients with elevated baseline ALT.

Data management and Statistical analysis

Categorical variables were reported using numbers and percentages, whereas continuous variables reported using mean with standard deviation (SD) or median with interquartile range (IQR) when appropriate. The normality assumptions were assessed for all numerical variables using a statistical test (i.e., Shapiro–Wilk test) and also using graphical representation (i.e., histograms and Q-Q plots). We compared categorical variables using the chi-square or Fisher exact test, normally distributed numerical variables with the t-test, and other quantitative variables with the Mann-Whitney U test. Baseline characteristics, baseline severity, and outcome variables were compared between the two treatment groups. Multivariate logistic regression and generalized linear regression were used to determine the relationship between thiamine use and different outcomes considered in this study.

On the other hand, we assessed model fit using the Hosmer-Lemeshow goodness-of-fit test. Generalized linear regression was also used to determine the relationship between study outcome and the different study parameters considered in this study. The odds ratios (OR) and estimates with the 95% confidence intervals (CI) were reported for the associations. No imputation was made for missing data as the cohort of patients in our study was not derived from random selection.

Propensity scores were used to match patients who received thiamine to patients receiving no thiamine using a Propensity score matching Procedure (Proc PS match) (SAS, Cary, NC). A greedy nearest neighbor matching method was used in which one non-thiamine (control) is matched with each patient in the thiamine (treated) group. This eventually produces the smallest within-pair difference among all available pairs with treated patients. These patients are matched only if the difference in the logits of the propensity scores for pairs of patients from the two groups is less than or equal to 0.5 times the pooled estimate of the standard deviation. We considered a P value of < 0.05 statistically significant and used SAS version 9.4 for all statistical analyses.

Results

A total of 738 critically ill patients with COVID-19 had been admitted to ICUs at the two governmental hospitals included in the study. Thiamine was given to 88 patients, whereas 650 patients didn't receive thiamine. A total of 166 patients were included after propensity score matching using baseline severity scores (i.e., APACHE II, SOFA score, NUTRIC scores), systemic use of corticosteroids, and study centers [22]. The median (Q1, Q3) dose of thiamine given per day was 100 mg (50, 200) with a median duration (days) of 7 (5, 12).

Demographic And Clinical Characteristics

Among critically ill patients admitted to ICUs, the patients' average age was 60 years (± 15). A total of 531 (72 %) patients were male (Table 1, Supplemental Digital Content 1). Diabetes mellitus (61 %) was the most common coexisting illness, followed by hypertension (56.8 %) and dyslipidemia (23.2 %). Coexisting illness between the two groups was not statistically significant (Table 2, Supplemental Digital Content 2).

Table 1
Regression analysis for the outcomes

Outcomes	Thiamine group n of outcomes/Total no-of patients			Odds Ratio (OR) (95%CI)	P-value
	NO	Yes	P-value		
ICU mortality within 30 days					
Analysis on all eligible patients	258/606 (42.6)	17/80 (21.25)	0.0003^^	0.28 (0.162 ,0.469)	< .0001*^
Propensity score matched	29/83 (38.7)	14/83 (18.4)	0.006^^	0.45 (0.215 ,0.935)	0.03$
In-hospital mortality, n(%)					
Analysis on all eligible patients	304/626 (48.6)	21/81 (23.4)	0.0001^^	0.36 (0.217 ,0.583)	< .0001*^
Propensity score matched	35 (43.8)	18 (23.4)	0.007^^	0.49 (0.25 ,0.97)	0.04$
				Beta coefficient (95%CI)	
MV duration during ICU, Median (Q1, Q3) &#					
Analysis on all eligible patients	10.0 (4.0, 17.0)	7.0 (3.0, 16.0)	0.17^	0.02 (-0.24, 0.30)	0.84*^
Propensity score matched	11.0 (5.0, 20.0)	7.0 (3.0, 20.0)	0.68^	-0.13 (-0.54, 0.27)	0.51$*
ICU Length of Stay (Days), Median (Q1, Q3) &					
Analysis on all eligible patients	8.0 (5.0, 14.0)	8.0 (5.0,13.0)	0.89^	0.07 (-0.12, 0.27)	0.49*^
Propensity score matched	8.0 (4.0, 12.0)	8.0 (5.0, 13.0)	0.78^	0.11 (-0.19, 0.39)	0.48$*
Hospital Length of Stay (Days), Median (Q1, Q3) &					
Analysis on all eligible patients	17.0 (11.0, 26.5)	15.0 (10.0, 24.5)	0.47^	0.04 (-0.12,0.21)	0.59*^
Propensity score matched	13.0 (11.0, 21.0)	15.0 (10.0, 25.0)	0.30^	0.08 (-0.17,0.33)	0.52$*

Outcomes	Thiamine group			Odds Ratio (OR) (95%CI)	P-value
	n of outcomes/Total no-of patients				
	NO	Yes	P-value		

-Denominator of the percentage is the total number of patients

*T -Test / ^ Wilcoxon rank sum test is used to calculate the P-value.

^^Chi-square test is used to calculate the P-value.

**Fisher Exact test is used to calculate the P-value.

$*propensity score adjusted Generalized linear model is used to calculate beta coefficient (estimates) and p-value.

$ propensity score adjusted Logistic regression is used to calculate Odds ratio and p-value.

*^Multivariate Logistic regression is used after adjusting for patient's baseline severity scores, systemic use of corticosteroids and hospital center to calculate Odds ratio and p-value.

& Denominator is patients who survived.

&# Denominator is patients who have respiratory failure requiring MV during ICU stay.

Table 2
Regression analysis for ICU complication (s) during ICU stay

Outcomes	Thiamine group n of outcomes/Total no-of patients		P-value	Estimates of effects OR (95%CI)	P-value$
	No	Yes			
Acute Kidney Injury (AKI), n(%)					
Analysis on all eligible patients	304/639 (47.6)	31/87 (35.6)	0.04^^	0.56 (0.360 ,0.864)	0.0090*^
Propensity score matched	21 (25.3)	15 (18.1)	0.26^^	0.91 (0.487 ,1.682)	0.7531$
Liver Injury, n(%)					
Analysis on all eligible patients	70/637(10.9)	7/87 (8.1)	0.40^^	0.09 (0.044 ,0.198)	< .0001*^
Propensity score matched	5 (6.1)	6 (7.2)	0.77^^	0.93 (0.302 ,2.872)	0.9017$
Respiratory Failure Required MV, n(%)$*					
Analysis on all eligible patients	67/197 (34.0)	16/42 (38)	0.61^^	1.05 (0.49, 2.22)	0.90
Propensity score matched	14/31 (45.1)	16/40 (40)	0.66^^	0.95 (0.35, 2.57)	0.92$
Thrombosis During ICU, n(%)					
Analysis on all eligible patients	71/632 (11.2)	2/87 (2.3)	0.01^^	0.03 (0.008 ,0.104)	< .0001*^
Propensity score matched	9 (11.1)	2 (2.4)	0.02^^	0.19 (0.040 ,0.884)	0.0343$

-Denominator of the percentage is the total number of patients.

OR: Odds Ratio

*T -Test / ^ Wilcoxon rank sum test is used to calculate the P-value.

^^Chi-square /**Fisher Exact test is used to calculate the P-value.

$ propensity score adjusted Logistic regression is used to calculate Odds ratio and p-value.

*^Multivariate Logistic regression is used after adjusting for patient's baseline severity scores, systemic use of corticosteroids and hospital center to calculate Odds ratio and p-value

$*Denominator of the percentage is non-mechanically ventilated patients with 24 hours of ICU admission.

The baseline severity scores (i.e., APACHE II, SOFA, and NUTRIC scores), mechanical ventilation (MV) needs within 24 hours of ICU admission, and laboratory tests (i.e., INR, Fibrinogen, CRP, Ferritin, HCT, pH) were significantly high among patients who did not receive thiamine during ICU stay. However, after propensity score matching for patient's baseline severity scores, systemic corticosteroids use, and hospital center, most of these baseline and demographic characteristics were similar between the two groups (Table 1, Supplemental Digital Content 1).

Study Outcomes

There were 14 patients (18.4%) who died during ICU stay among the thiamine group, compared with 29 patients (38.7%) in the other group. In other words, patients who used thiamine as adjunctive therapy during ICU stay had a lower 30-day ICU mortality by 55 % (OR (95%CI): 0.45 (0.22, 0.94), p-value = 0.03) (Table 1). Additionally, thiamine use was associated significantly with a lower in-hospital mortality by 51% (OR (95%CI): 0.49 (0.25 ,0.97), p-value = 0.04). The overall survival probabilities were higher during hospital stay among patients who received thiamine before and after propensity score-matched (Fig. 1a, 1b).

The duration of MV (Beta coefficient − 0.13 CI = -0.54, 0.27; p-value = 0.51), ICU length of stay (LOS) (Beta coefficient 0.11 CI = -0.19, 0.39; p-value = 0.48) and hospital LOS (Beta coefficient 0.08 CI = -0.17,0.33; p-value = 0.52) were statistically not significant in patients who received thiamine as adjunctive therapy compared to patients who did not (Table 1) .

Icu Complications During Icu Stay

Only 2 (2.4%) patients who received thiamine developed thrombosis during ICU stay, compared with 9 (11.1%) patients in the non-thiamine group. Patients who received thiamine as an adjunctive therapy were less likely to have thrombosis during ICU stay as compared to patients who did not (OR (95%CI): 0.19 (0.040 ,0.884), p-value = 0.03). (Table 2)

Critically ill patients with COVID19 who received thiamine an adjunctive therapy have lower incident acute kidney injury (AKI) (OR (95%CI): 0.91 (0.49,1.68)), and liver Injury (OR (95%CI): 0.93 (0.30 ,2.87)); however, it was not statistically significant (Table 2).

Discussion

With the rapid spread of the disease, as well as high mortality among critically ill patients, there are many studies with different methodology approaches conducted among COVID-19 patients to investigate the effectiveness of many medications (e.g., steroids, antivirals, immunomodulators) and respiratory support strategies (e.g., prone position, volume protected strategy)[8, 9, 11, 12]. Our study is a multicenter, non-interventional retrospective study of critically ill patients admitted to intensive care units (ICUs) with a

confirmed diagnosis of COVID-19 investigate the correlation between thiamine use as adjunctive therapy and ICU LOS, MV duration, and ICU mortality as a primary endpoint. Although we evaluate the occurrence of new-onset acute kidney injury (AKI), liver injury, and thrombosis during ICU stay.

In our study, the 30-day ICU mortality was significantly lower in the thiamine group with a p-value of (0.0323) after using propensity score matching. It is well known that critically ill patients, in general, predispose to thiamine deficiency, which leads to the inability to create adenosine triphosphate, inability to use oxygen, high-output cardiac failure, cardiovascular collapse, and death when untreated[13]. Unfortunately, there are no current trials directly investigating the effect of thiamine in critically ill COVID-19 patients. Our finding agrees with a substantial number of studies published over the past decades and reported an increment of lactate clearance resulted in mortality benefit with intravenous thiamine administration in critically ill patients. Woolum et al. proved the relation between early thiamine administration to critically ill patients with septic shock during the first 24 hours of admission with rapid lactate clearance and decreased 28-day mortality [4].

The ICU length of stay was not statistically significant between the groups (p-value = 0.48), with a median duration of eight days in both groups. The lack of difference in ICU LOS could be justified by the improved survival among the group but still requiring ICU care. There is a lack of studies that assess thiamine's role alone on ICU LOS in COVID 19 critically ill patients. Conversely, a retrospective study by Mitchell et al. investigates the benefit of administrating IV thiamine in combination with IV vitamin C and hydrocortisone to ICU patients with sepsis or septic shock14. This study illustrated a significant difference in ICU LOS in the intravenous thiamine, vitamin C, and hydrocortisone as a combination group14. In our study, we included corticosteroids in the model of propensity score matching since it showed mortality benefits in recovery trial [9]. Other therapies have not been assessed due to the lack of mortality benefits.

In our data, the incidence of AKI was not significant between the two groups. Acute kidney injury is one of the most frequent complications during critical illness. Impaired kidney function could contribute to a malnutrition state, especially in patients treated with renal replacement therapy (RRT); the unintentional loss of micronutrients during the dialysis can also contribute to poor nutrition state and impaired patients' immunity[15].A randomized, double-blind, placebo-controlled trial by Moskowitz et al. studied thiamine's effect as a kidney protective agent among ICU patients diagnosed with septic shock. This study found that serum creatinine level was lower in patients who received thiamine and were less likely to have kidney failure requiring RRT [4]. The lack of finding difference in AKI rate among our group could be justified by utilizing a lower dose than published studies for renal protective dosing, our median thiamine dose was 100 mg per day, however Moskowitz et al utilized a higher dose of 200 mg Twice daily[4].

Interestingly, thiamine use was found to be associated with a statistically significant reduction in thrombosis by 81 % compared to the control group (OR (95%CI): 0.19 (0.040,0.884), p-value = 0.03). The exact mechanism and explanation for thrombosis reduction observed in this cohort with thiamine supplementation are unknown. These findings worth further investigation and should trigger future

research to provide direct evidence on the precise impact of thiamine supplementation on the prevention of thrombosis in COVID-19 critically ill patients.

Our study's uniqueness is the lack of extensive well-conducted studies connecting thiamine administration's effect directly with a positive impact on mortality in COVID 19 critically ill patients. COVID-19 patients. We encountered many confounding factors that could affect the external validity and the interpretation of the mortality outcome. Therefore, we conducted several analyses to control these variables using multivariate regression adjustment after propensity score matching using baseline severity scores (i.e., APACHE II, SOFA, and NUTRIC scores), systemic use of corticosteroids, and study centers.

On the flip side, our study may have been affected by several limitations, including our design's observational nature and some residual confounding factors are still possible. Besides, the treatment decision based on the treating physician's bias toward using one treatment regimen versus another cannot be ruled out. Further interventional studies are required to confirm our finding.

Conclusions

Thiamine use as adjunctive therapy may have potential survival benefits in critically ill patients with COVID-19.

Abbreviations

Intensive care units (ICUs), Coronavirus disease (COVID-19), Mechanical ventilation (MV), Thiamine (Vitamin B1), LOS (Length of stay), Acute physiology and chronic health evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA), Nutrition Risk in the Critically Ill (NUTRIC)

Declarations

Acknowledgements

Not applicable.

Author contributions

All authors contributed to data collections, analysis, drafted, revised, and approved the final version of the manuscript.

Funding

None.

Ethical consideration

The study was approved on November 19th, 2020, by King Abdullah International Medical Research Center Institutional Review Board, Riyadh, Saudi Arabia (Study Number: RC20/589/R). Participants' confidentiality was strictly observed throughout the study using the anonymous unique serial number for each subject and restricting data only to the investigators. Informed consent was not required due to the research's method as per the governmental and local research center's policy.

Author contributions

All authors contributed to data collections, analysis, drafted, revised, and approved the manuscript's final version.

Compliance with Ethical standards

Funding: None

Disclosure: No author has a conflict of interest in this study.

Availability of data and material

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

Consent for publication

Not applicable.

Competing interests

No author has a conflict of interest in this study.

References

1. Amrein K, Oudemans-van Straaten HM, Berger MM. Vitamin therapy in critically ill patients: focus on Thiamine, vitamin C, and vitamin D. Intensive care medicine. 2018;44(11):1940–44.
2. Donnino MW, Andersen LW, Chase M, et al. Randomized, double-blind, placebo-controlled trial of Thiamine as a metabolic resuscitator in septic shock: a pilot study. Critical care medicine. 2016;44(2):360.
3. Moskowitz A, Andersen LW, Cocchi MN, et al. Thiamine as a renal protective agent in septic shock. A secondary analysis of a randomized, double-blind, placebo-controlled trial. Annals of the American Thoracic Society. 2017;14(5):737–41.
4. Woolum JA, Abner EL, Kelly A, et al. Effect of thiamine administration on lactate clearance and mortality in patients with septic shock. Critical care medicine. 2018;46(11):1747–52.

5. Marik PE, Khangoora V, Rivera R, et al. Hydrocortisone, vitamin C, and Thiamine for the treatment of severe sepsis and septic shock: a retrospective before-after study. Chest. 2017;151(6):1229–38.
6. Vatsalya V, Li F, Frimodig JC, et al. Therapeutic Prospects for Th-17 Cell Immune Storm Syndrome and Neurological Symptoms in COVID-19: Thiamine Efficacy and Safety, In-vitro Evidence and Pharmacokinetic Profile. *medRxiv* 2020.
7. Paul E, Marik P, Kory J, Varon JI. & G Umberto Meduri (2020) MATH + protocol for the treatment of SARS-CoV-2 infection: the scientific rationale, Expert Review of Anti-infective Therapy, DOI: 10.1080/14787210.2020.1808462.
8. Alattar R, Ibrahim TB, Shaar SH, et al. Tocilizumab for the Treatment of Severe COVID-19. *Journal of Medical Virology* 2020.
9. Group RC. Dexamethasone in hospitalized patients with Covid-19—preliminary report. *New England Journal of Medicine* 2020.
10. Slessarev M, Cheng J, Ondrejicka M, et al. Patient self-proning with high-flow nasal cannula improves oxygenation in COVID-19 pneumonia. *Canadian Journal of Anesthesia/Journal Canadien d'anesthésie* 2020:1–3.
11. Telias I, Katira BH, Brochard L. Is the prone position helpful during spontaneous breathing in patients with COVID-19? *Jama* 2020.
12. Jovic TH, Ali SR, Ibrahim N, et al. Could Vitamins Help in the Fight Against COVID-19? *Nutrients* 2020;12(9):2550. DOI: 10.3390/nu12092550.
13. Singer M. (2007). Mitochondrial function in sepsis: Acute phase versus multiple organ failure. *Critical Care Medicine, 35*(9 SUPPL.), S441-S448. doi:10.1097/01.CCM.0000278049.48333.78.
14. Mitchell AB, Ryan TE, Gillion AR, et al. Vitamin C and Thiamine for sepsis and septic shock. Am J Med. 2020;133(5):635–38.
15. Marlies O, Summers J, Lei K, et al. Micronutrients in critically ill patients with severe acute kidney injury–a prospective study. *Scientific Reports (Nature Publisher Group)* 2020;10(1).

Figures

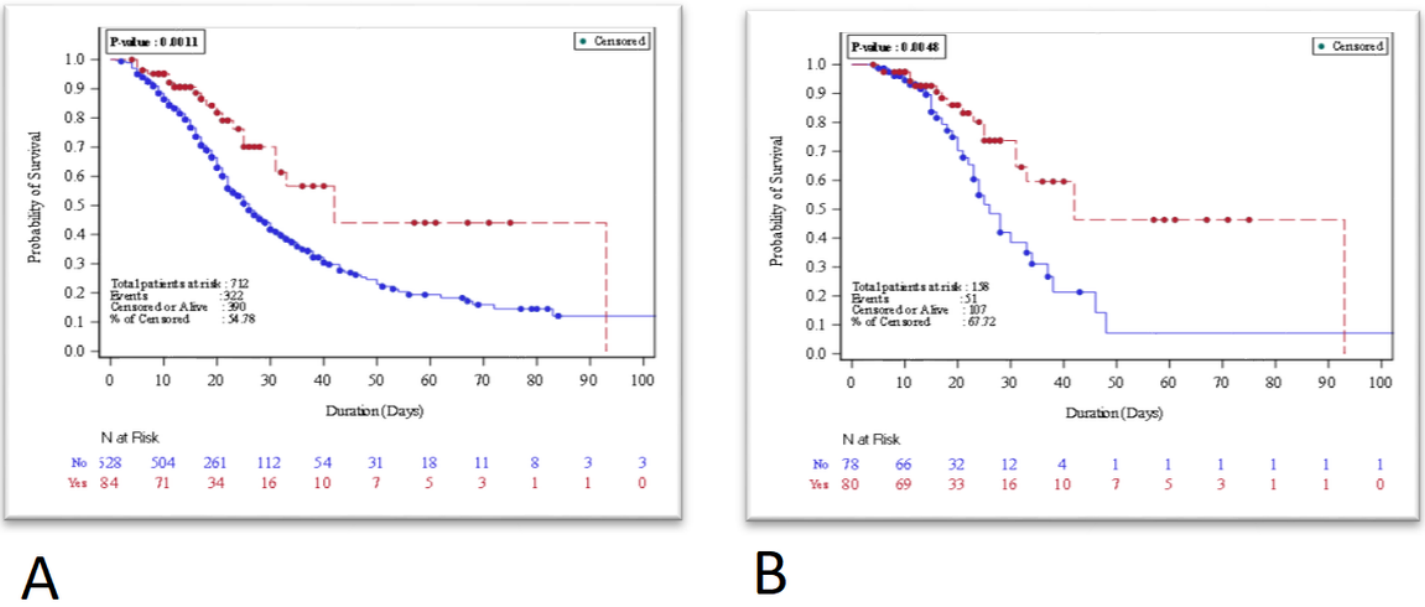

Figure 1

a: Overall survival plot during Hospital stay (Before Propensity score matching) b: Overall survival plot during Hospital stay (After Propensity score matching)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile1Table1.docx
- Additionalfile2Table2.docx