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Adjunctive Micronutrient Therapy in Sepsis: Associations with Inflammation and Organ Dysfunction

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ABSTRACT

Introduction: Despite advances in supportive care, sepsis remains a major cause of morbidity and mortality among critically ill patients. Adjunctive therapies targeting inflammation and endothelial dysfunction, such as thiamine and ascorbic acid, have gained increasing attention in recent years. Matrix metalloproteinase-9 (MMP-9) and its inhibitor TIMP-1 are key biomarkers involved in inflammatory dysregulation and organ dysfunction in sepsis.

Methods: This retrospective cohort study was conducted over 12 months at Haji Adam Malik General Hospital. A total of 147 adult patients with sepsis were initially enrolled and categorized into four groups: normal saline (control), thiamine, ascorbic acid, and thiamine–ascorbic acid combination therapy. Propensity score matching was applied to achieve comparable baseline characteristics, resulting in 25 patients in each group. Serum MMP-9 and TIMP-1 levels were measured at the Integrated Laboratory, Faculty of Medicine, Universitas Sumatera Utara. The clinical outcomes included incidence rates, MMP-9/TIMP-1 ratios, and Sequential Organ Failure Assessment (SOFA) scores.

Results: Combination therapy did not significantly reduce the incidence rate (OR 1.19; 95% CI 0.37–3.80) or MMP-9/TIMP-1 ratio (OR 0.34; 95% CI 0.09–1.30) compared to the control. In contrast, a single administration of ascorbic acid and thiamine significantly reduced the incidence rates and improved the MMP-9/TIMP-1 balance. Combination therapy was not associated with improved SOFA scores (OR 2.66; 95% CI 0.85–8.36).

Conclusion: Combined thiamine and ascorbic acid therapies did not confer any superior clinical or biomarker benefits. Single-agent thiamine or ascorbic acid therapy demonstrated favorable effects on the incidence rate, MMP-9/TIMP-1 ratio, and organ dysfunction in patients with sepsis.

Keywords

Sepsis, Thiamine, Ascorbic Acid, MMP-9/TIMP-1 Ratio, SOFA Score

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INTRODUCTION

The global burden of sepsis continues to rise, placing substantial demands on healthcare systems to improve early recognition, accelerate timely management, and optimize the implementation of sepsis bundles in critically ill patients to reduce the incidence and adverse outcomes [1]. Despite extensive research efforts over the past three decades, including multiple phase II and III clinical trials evaluating novel pharmacological agents and therapeutic strategies, no new targeted therapy has consistently demonstrated a significant survival benefit in patients with severe sepsis or septic shock. Consequently, current management remains largely supportive, emphasizing early resuscitation, antimicrobial therapy, and organ support.

This persistent lack of effective pharmacological innovation underscores the urgent need for alternative adjunctive therapies that are effective, affordable, safe, and widely accessible to improve sepsis outcomes

across diverse healthcare settings [1]. Several adjunctive therapeutic agents, including vitamin C, vitamin B1 (thiamine), vitamin B12, and vitamin D, have been explored for the management of sepsis to modulate inflammatory responses and improve cellular metabolism [2,3]. Among these, ascorbic acid and thiamine have received particular attention because of their pleiotropic biological effects and favorable safety profile. Ascorbic acid plays a critical role in endothelial function, oxidative stress regulation, and immune modulation, all of which are profoundly disrupted in sepsis. Thiamine, an essential cofactor in cellular energy metabolism, influences the enzymatic pathways involved in mitochondrial function and vascular tone, thereby contributing to the maintenance of hemodynamic stability in critically ill patients. Previous studies have suggested that thiamine deficiency is common in sepsis and may exacerbate metabolic dysregulation and organ dysfunction, supporting its potential role as an adjunctive therapy in septic states [4-7].

The combined administration of thiamine and ascorbic acid in sepsis has been evaluated in several clinical studies, most notably within the framework of hydrocortisone–ascorbic acid–thiamine (HAT) therapy. Iglesias et al. reported that HAT therapy was safe and associated with reduced shock duration and vasopressor requirements in patients with sepsis; however, no significant reductions in mortality or length of ICU stay were observed [8,9]. In that study, patients receiving HAT demonstrated a numerically higher mortality rate than those in the placebo group. Conversely, a smaller study reported lower mortality rates and improved SOFA scores among patients treated with HAT, suggesting a potential benefit in preventing the progression of organ dysfunction [10]. Notably, these studies incorporated concomitant glucocorticoid therapy, which may confound the independent effects of thiamine and ascorbic acid in septic shock.

Further evidence from the VITAMINS randomized clinical trial, involving 216 patients with septic shock, demonstrated that HAT therapy did not improve survival or increase vasopressor-free days during the first seven days of ICU treatment compared to hydrocortisone alone [11]. These findings challenge earlier reports suggesting the organ-protective and hemodynamic benefits of combination therapy and indicate that intravenous ascorbic acid and thiamine, when administered alongside hydrocortisone, may not accelerate recovery from septic shock beyond the effects of corticosteroid therapy alone [11]. Lubis et al. conducted a one-year observational study in the ICU of Haji Adam Malik General Hospital, Medan, involving septic patients evaluated using MMP-9 and TIMP-1 biomarkers [12]. In that study, patients received intravenous thiamine (200 mg), ascorbic acid (50 mg/kg), or a combination of both, administered every 12 h for three days. The findings demonstrated that thiamine monotherapy was associated with more favorable modulation of MMP-9 and TIMP-1 levels than ascorbic acid alone or combination therapy, resulting in a more balanced MMP-9/TIMP-1 ratio [12]. Despite these improvements in biomarker levels, the overall mortality rate in this cohort remained high (approximately 36 %). Importantly, mortality outcomes were not specifically analyzed in relation to thiamine, ascorbic acid, or their combination, in contrast to prior studies reported by Marik, Iglesias, and Fujii [9–11]. Based on these observations and the existing gaps in the literature, the present study aimed to evaluate the association between intravenous thiamine and ascorbic acid administration, either as monotherapy or in combination, and clinical outcomes in patients with sepsis. The outcomes of interest included mortality-related incidence, survival duration, MMP-9/TIMP-1 ratio, and SOFA score among patients treated in the ICU.

METHOD

This retrospective cohort analytic investigation evaluated the association between intravenous adjunctive therapies (thiamine, ascorbic acid, and their combination) and clinical outcomes in patients with sepsis treated in the intensive care unit (ICU). The study was conducted in the ICU of Haji Adam Malik General Hospital in Medan, Indonesia. Clinical and laboratory data were collected from medical records over a 12-month period from January to December 2020. Adult patients aged ≥18 years who were diagnosed with sepsis and admitted to the ICU during the study period were screened for eligibility. Patients were included if they received intravenous thiamine, ascorbic acid, or a combination of both as part of their treatment regimen. The exclusion criteria were incomplete MMP-9 or TIMP-1 laboratory data and patients who discontinued treatment or were

discharged against medical advice during intensive care unit (ICU) care. Patients who died during the treatment period were included in the analysis.

Patients received intravenous thiamine (200 mg every 12 h for three consecutive days), intravenous ascorbic acid (50 mg/kg every 12 h for three consecutive days), or a combination of both. Treatment allocation was based on routine clinical practices documented in the patients' medical records. The primary outcomes assessed were incidence-related outcomes, modulation of the MMP-9/TIMP-1 ratio, and changes in organ dysfunction, as evaluated using the Sequential Organ Failure Assessment (SOFA) score. Serum MMP-9 and TIMP-1 levels were measured at the Integrated Laboratory, Faculty of Medicine, Universitas Sumatera Utara. The MMP-9/TIMP-1 ratio was calculated to reflect the balance between inflammation and inhibition of inflammation. SOFA scores were derived from clinical and laboratory parameters recorded in the patients' medical charts.

Propensity score matching was used to minimize baseline differences between the treatment groups. After the initial screening of 186 patients, 147 patients met the eligibility criteria. Following specimen quality assessment and matching procedures, 25 patients were included in each treatment group for the final analyses.

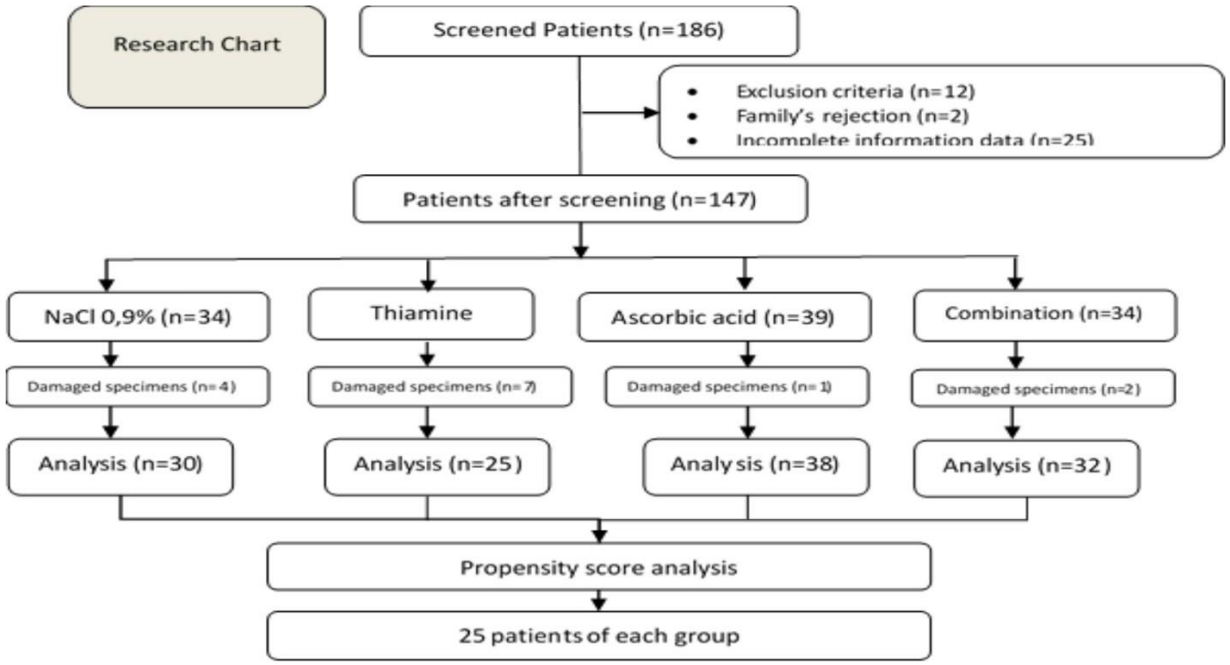

Figure 1. Flow diagram of patients with sepsis admitted to the ICU receiving thiamine, ascorbic acid, or combination therapy, including screening, exclusion, and propensity score matching.

Data were analyzed using SPSS version 25.0. Normally distributed numerical variables are presented as mean ± standard deviation, whereas non-normally distributed variables are expressed as medians (minimum–maximum). Categorical variables are reported as frequencies and percentages. Data normality was assessed using the Kolmogorov–Smirnov test. Comparisons among the four groups were performed using one-way analysis of variance (ANOVA) for normally distributed data and the Kruskal–Wallis test for non-normally distributed data. Pearson's correlation analysis was used to assess the relationships between continuous variables. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to evaluate the association between exposure to thiamine, ascorbic acid, and combination therapy with incidence-related outcomes, the MMP-9/TIMP-1 ratio, and the SOFA score.

This study was conducted in accordance with the ethical principles of medical research involving human participants. Ethical approval was obtained from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara, and Haji Adam Malik General Hospital (approval no. 40/KEPK/USU/2022). Permission to access the medical records and laboratory data was granted prior to data collection.

RESULTS

This study used a retrospective cohort design. Data were obtained from patients with sepsis treated in the intensive care unit (ICU) of Haji Adam Malik General Hospital between April 2020 and April 2021, after approval from the Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara/Haji Adam Malik Hospital, Medan, Indonesia. A total of 186 patients were screened for inclusion in the study. After applying the inclusion and exclusion criteria, 147 patients were eligible for analysis. Propensity score matching was performed to minimize selection bias, resulting in 25 patients in each group. Baseline demographic and clinical characteristics were recorded using standardized observation. The variables included age, sex, mean arterial pressure (MAP), serum lactate level, Sequential Organ Failure Assessment (SOFA) score, and neutrophil-to-lymphocyte ratio (NLR). After matching, 100 patients were included in the final analysis of the study. The baseline characteristics were comparable across the groups and are summarized in Table 1.

Table 1. Baseline Characteristics of Study Participants

Variable	NaCl (n=25)	Thiamine (n=25)	Ascorbic Acid (n=25)	Combination (n=25)
Age, Years (Mean ± SD)	48.8 ± 18.4	52.3 ± 16.8	53.3 ± 11.7	50.7 ± 11.1
Male Sex, n (%)	10 (38.5)	12 (50.0)	11 (50.0)	20 (68.8)
MAP, mmHg (Mean ± SD)	94.8 ± 17.0	97.6 ± 25.4	91.4 ± 16.0	92.4 ± 16.0
Serum Lactate, mmol/L (Median, Range)	2.0 (1.0–10.0)	1.3 (1.0–5.5)	1.0 (1.0–10.0)	2.0 (1.0–4.0)
NLR (Median, Range)	10.6 (2.5–30.3)	14.4 (0.2–86.8)	13.9 (1.6–69.3)	10.7 (1.4–64.6)

Forest plot analysis demonstrated that the combination of ascorbic acid and thiamine was associated with an odds ratio of 1.19 (95% CI: 0.37–3.80) for incidence-related outcomes compared with that of the control group. In contrast, single administration of ascorbic acid yielded an odds ratio of 0.40, whereas thiamine monotherapy showed an odds ratio of 0.67 compared with the control group (Figure 2).

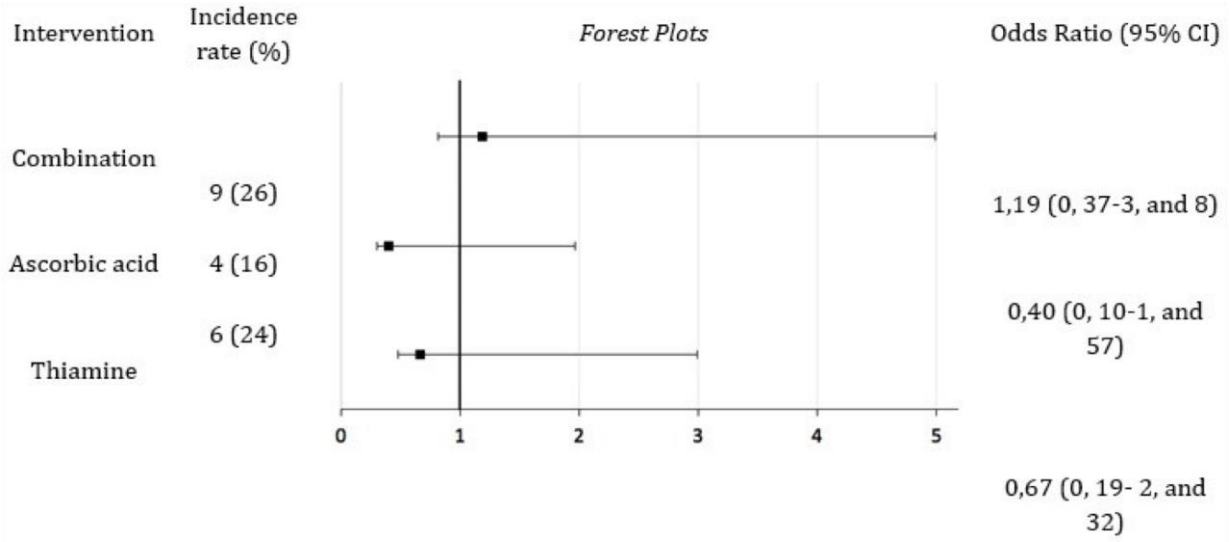

Figure 2. Forest plots of thiamine, ascorbic acid, and a combination of both on incidence rates during the intervention

Analysis of the MMP-9/TIMP-1 ratio revealed that combination therapy was associated with an odds ratio of 0.34 (95% CI: 0.09–1.30). A single administration of ascorbic acid and thiamine resulted in odds ratios of 0.77 and 0.78, respectively, indicating lower MMP-9/TIMP-1 ratios than those in the control group (Figure 3).

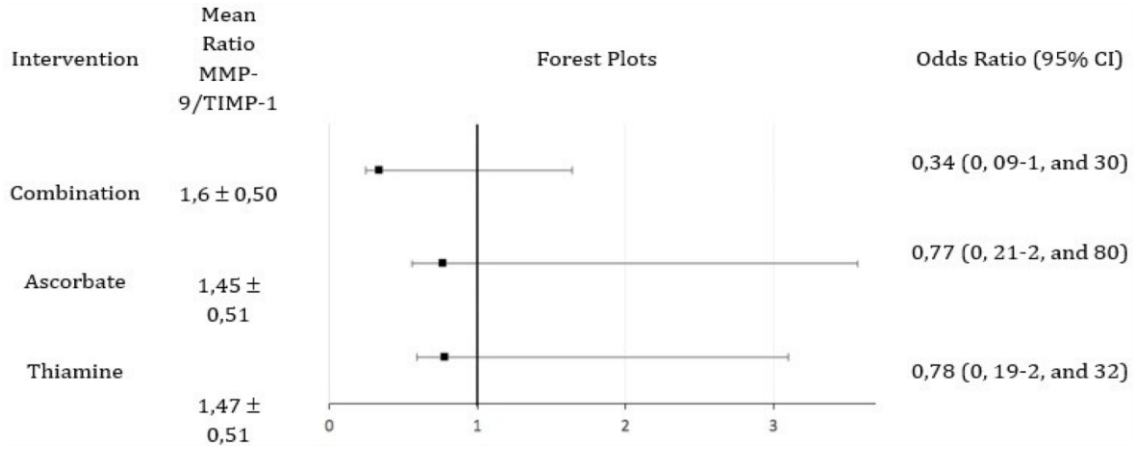

Figure 3. Forest plots of thiamine, ascorbate, and combination on the ratio of MMP-9/TIMP-1 level during the intervention

Among patients who died during the observation period, correlation analysis demonstrated a moderate and significant positive correlation between MMP-9 and TIMP-1 levels ($r = 0.746$, $p < 0.001$) (Figure 4).

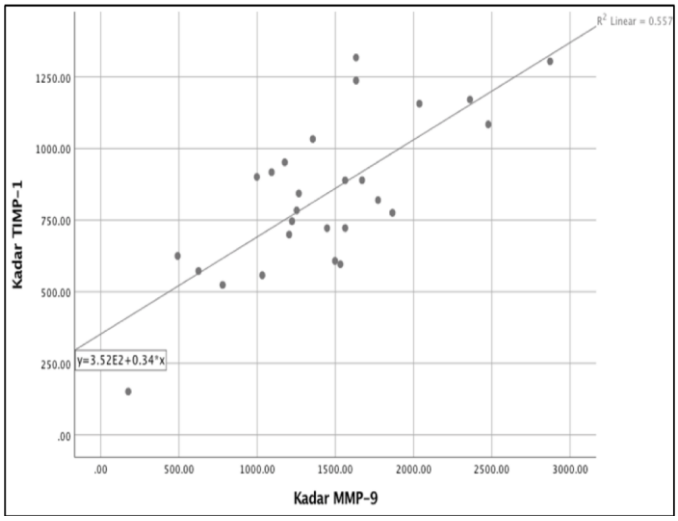

Figure 4. Scatterplot graph of MMP-9 enzyme level with TIMP-1 enzyme level in septic patients who passed away during observation

Linear regression analysis showed a strong positive association between MMP-9 levels and the MMP-9/TIMP-1 ratio ($R^2 = 0.445$, $p < 0.001$; $r = 0.667$). In contrast, TIMP-1 levels showed no significant association with the MMP-9/TIMP-1 ratio ($R^2 = 0.002$, $p = 0.809$, $r = 0.049$) (Figure 5).

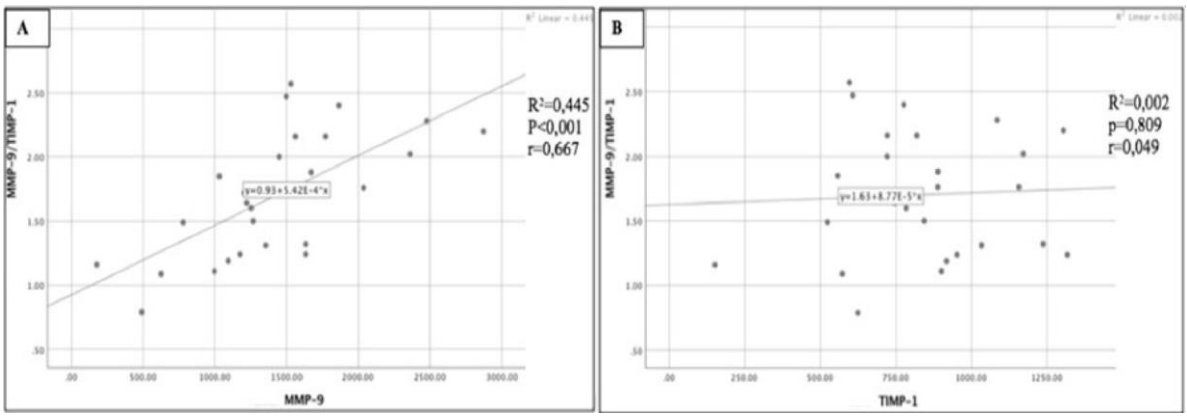

Figure 5: Scatterplot graph of MMP-9 enzyme level and MMP-9/TIMP-1 ratio (A), and TIMP-1 enzyme level and MMP-9/TIMP-1 ratio (B) in sepsis patients who have passed away during observation

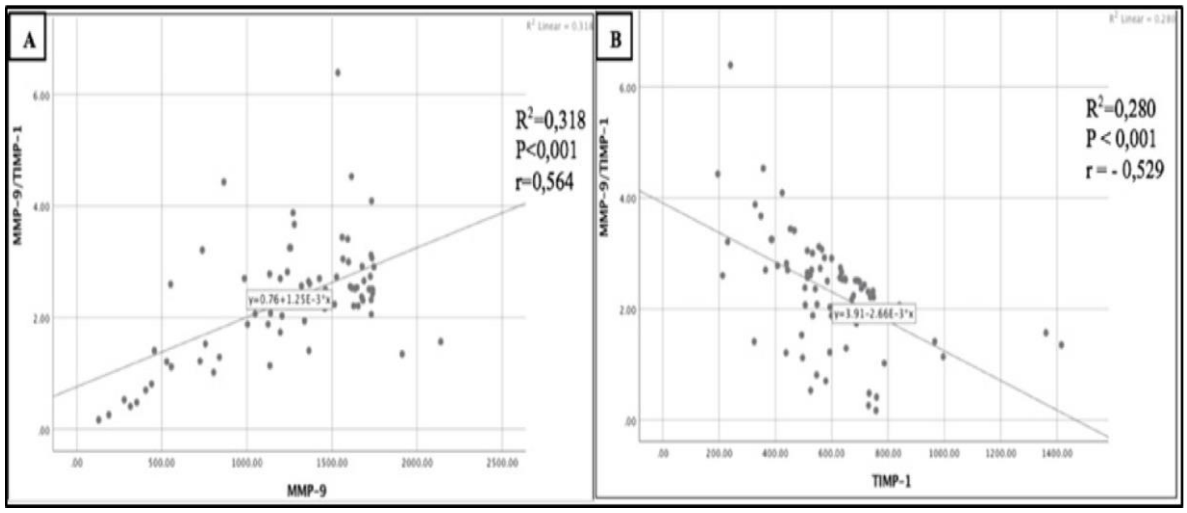

Figure 6: Scatterplot graph of MMP-9 enzyme level and MMP-9/TIMP-1 ratio (A), and TIMP-1 enzyme level and MMP-9/TIMP-1 ratio (B) in survive sepsis patients during observation

Forest plot analysis showed that the combination of ascorbic acid and thiamine was associated with an odds ratio of 2.66 (95% CI: 0.85–8.36) for an increased SOFA score. Ascorbic acid and thiamine monotherapies yielded odds ratios of 1.38 and 1.17, respectively, compared with the control group (Figure 7).

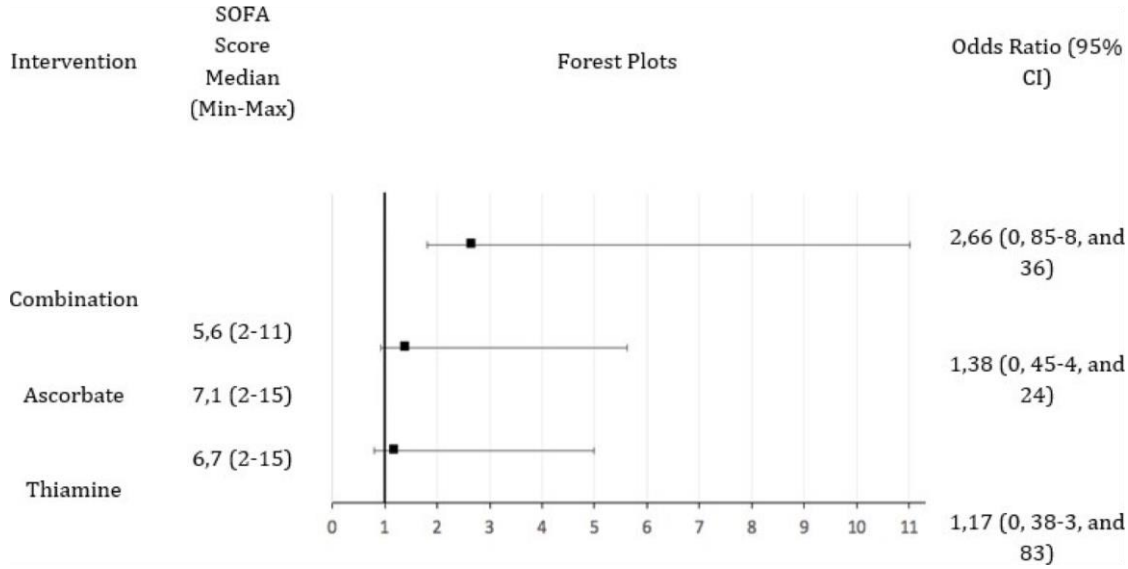

Figure 7: Forest plots of thiamine, ascorbate, and combination of both on SOFA scores during intervention

DISCUSSION

In this study, the overall mortality rate was 27%, which is consistent with previously reported mortality rates in patients with sepsis. Earlier studies have documented mortality rates of approximately 26% in sepsis and as high as 30–80% in patients with septic shock [1,2]. In addition, SOFA scores ranging from 6 to 7 have been associated with an estimated mortality risk of 10–20%. In contrast, studies conducted in Belgium have reported substantially higher mortality rates when SOFA scores fail to improve during therapy, highlighting the prognostic importance of the dynamic assessment of organ dysfunction [13]. Baseline characteristics, including age, sex, mean arterial pressure, SOFA score, serum lactate level, and neutrophil-to-lymphocyte ratio, were evenly distributed across the treatment groups. This finding suggests that these variables did not significantly influence the outcome differences observed in the present study and supports the validity of the comparisons among the treatment groups following propensity score matching.

Among patients who died within 72 h of observation, a significant positive correlation was found between MMP-9 and TIMP-1 levels. This finding supports the established role of MMP-9 and TIMP-1 in the inflammatory cascade and pathophysiology of sepsis [14-18]. Although both enzymes are upregulated during severe systemic inflammation, the balance between MMP-9 and TIMP-1 appears to be a critical determinant of cellular survival, tissue integrity, and organ dysfunction progression. The present findings indicate that non-surviving patients exhibited an imbalance in the MMP-9/TIMP-1 ratio, characterized by a dominant influence of MMP-9 without adequate counter-regulation by TIMP-1. MMP-9 plays a key role in cytokine storm amplification, immune cell migration, endothelial barrier disruption, and vascular leakage in patients with severe sepsis [19-21]. Previous studies have demonstrated that MMP-9 levels increase during the early phase of systemic inflammation and correlate with the severity of organ injury and adverse clinical outcomes [22,23]. Currently, few studies have specifically evaluated the effects of thiamine and ascorbic acid on MMP-9, TIMP-1, and their ratios in patients with septic shock. Most available evidence has focused on the clinical outcomes associated with hydrocortisone–ascorbic acid–thiamine (HAT) therapy. Several studies have reported reductions in shock duration and vasopressor requirements without significant improvements in mortality, whereas other studies have reported conflicting results [9,10]. The VITAMINS randomized clinical trial further showed no superiority of HAT therapy over hydrocortisone alone in improving survival or vasopressor-free days in patients with septic shock [11].

In contrast to combination therapy, the present study suggests that single administration of thiamine or ascorbic acid may better preserve the balance of the MMP-9/TIMP-1 ratio in surviving patients than combination therapy. This effect was accompanied by lower incidence-related outcomes and mortality rates than those of the combination therapies. These findings indicate that monotherapy with thiamine or ascorbic acid may confer biological advantages through the modulation of inflammatory biomarkers rather than through combined administration, supporting a more targeted adjunctive approach to sepsis management [24].

CONCLUSION

In this retrospective cohort study, the combined administration of ascorbic acid and thiamine did not demonstrate superior clinical or biomarker-related outcomes in critically ill patients with sepsis. In contrast, monotherapy with thiamine or ascorbic acid was associated with more favorable effects on incidence-related outcomes, preservation of the MMP-9/TIMP-1 balance, and organ dysfunction, as assessed using SOFA scores. These findings suggest that single-agent adjunctive therapy may offer biological and clinical advantages over combination therapy in the management of sepsis. Further prospective studies are warranted to clarify the underlying mechanisms and determine the optimal role of targeted vitamin supplementation in critically ill patients with sepsis.

DECLARATIONS

This study was conducted in accordance with the ethical standards of the institutional and national research committees and the Declaration of Helsinki. Ethical approval was obtained from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara, and Haji Adam Malik General Hospital (approval no. 40/KEPK/USU/2022). Owing to the retrospective nature of the study, the requirement for informed consent was waived by the Institutional Ethics Committee.

CONSENT FOR PUBLICATION

The Authors agree to the publication in the Journal of Society Medicine.

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None

COMPETING INTERESTS

The authors declare that there is no conflict of interest in this report.

AUTHORS' CONTRIBUTIONS

conceived and designed the study, contributed to the clinical concept, supervised data interpretation, and critically revised the manuscript for important, intellectual content. AP and BL were involved in data acquisition, literature review, data analysis, and drafting the initial manuscript. Both authors participated in the interpretation of the results, approved the final version of the manuscript, and agreed to be accountable for all aspects of the work, ensuring the accuracy and integrity of the study.

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