ORIGINAL ARTICLE

Impact of Iron Profile and Vitamin D Levels on Clinical Outcomes in Patients with Sepsis and Septic Shock: A Cross-sectional Analysis at a Tertiary Care Center

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Abstract

Aim and background: Sepsis is a major global health affecting millions worldwide, hence understanding its contributing factors becomes paramount. This cross-sectional study at a tertiary care center explores the relationship between iron profile, vitamin D levels, and outcomes in sepsis and septic shock patients. The primary objective was to explore the prevalence of iron profile and vitamin D parameters during early intensive care unit (ICU) admission and their association with 28-day mortality.

Materials and methods: Spanning 18 months, the study enrolled adult patients meeting sepsis or septic shock criteria at the ICU. Data collection included demographic information, clinical characteristics, and blood samples for iron profile and vitamin D levels at admission. Disease severity was assessed using sequential organ failure assessment (SOFA) and acute physiology and chronic health evaluation II (APACHE II) scores, and treatment was administered as per surviving sepsis-3 guidelines.

Results: The research involved 142 participants, uncovering prevalent organisms such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*. Noteworthy connections to mortality were identified for factors including vasopressor support, ICU stay duration, SOFA score, and APACHE-II score. Interestingly, age, gender, and vitamin D levels showed no significant associations. However, the study did reveal a significant association between iron, ferritin, and transferrin saturation levels with increased 28-day mortality.

Conclusion: Our study concluded that low Iron, elevated ferritin, and decreased transferrin saturation levels maintained associations with the outcome of interest. While no such relationship was established with vitamin D levels. These results suggest potential implications for patient management and prognosis, warranting further exploration in future research.

Keywords: Acute physiology and chronic health evaluation II, Ferritin, Iron profile, Mortality, Sepsis, Septic shock, SOFA score, Transferrin saturation, Vitamin D levels.

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Highlights

- Novel insights into sepsis mortality factors: This study insights into the factors influencing mortality in patients with sepsis and septic shock. The study goes beyond the traditional markers by exploring the micronutrients like iron, ferritin, transferrin saturation, and vitamin d levels on clinical outcomes.
- Cross-sectional study of 142 patients conducted in patients with sepsis and septic shock admitted to the intensive care unit (ICU) revealed a significant association between low iron, elevated ferritin, and decreased transferrin saturation levels with 28-day mortality. However, demographics and vitamin D showed no significant association. These findings could serve as potential indicators of severity and mortality.
- Notable correlation to mortality were identified for factors including vasopressor support, ICU stay duration, sequential organ failure assessment (SOFA) score, and acute physiology and chronic health evaluation II (APACHE-II) score. This study lays the ground work for future studies.

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Introduction

Sepsis, a life-threatening condition, posed a significant global health challenge, claiming the highest mortality rate among critically ill patients. The World Health Organization's latest estimates from 2017 revealed alarming statistics: 48.9 million individuals worldwide suffered from sepsis, resulting in 11 million deaths, accounting for nearly 20% of global mortality. Low- and middle-income countries disproportionately bore this burden, constituting about 85% of sepsis cases and related deaths.[1]

Sepsis, as defined by the survival sepsis guidelines, was a life-threatening organ dysfunction resulting from a dysregulated host response to infection and stood as one of the predominant causes of ICU admissions worldwide. Within the spectrum of sepsis, septic shock represented a subset characterized by profound circulatory, cellular, and metabolic abnormalities, translating to a heightened risk of mortality compared to sepsis alone.[2]

Within the complex human body, trace elements abounded, with iron being one of the most prevalent. Numerous studies have explained the pivotal role of trace elements in the development of various diseases.[3] Iron, an important nutrient, plays a vital role in numerous physiological processes, including hemoglobin synthesis, oxygen transport, energy production, and immune function.[4] In the context of sepsis, the host's response to infection often triggered alterations in iron metabolism, resulting in heightened iron sequestration and diminished iron availability for critical functions, including erythropoiesis. This shift in iron metabolism was believed to serve as a host defense mechanism against pathogens, as iron constituted an essential nutrient for bacterial growth and proliferation. However, excessive iron sequestration in sepsis might have contributed to complications such as anemia, compromised immune function, and an increased vulnerability to secondary infections.[5]

Vitamin D, known as the sunshine vitamin, plays an important role in the body's immune response and bone health. Vitamin D deficiency was linked to impaired immunity, increasing the risk of sepsis in critically ill patients. While studies suggested a connection between vitamin D and sepsis severity, further research was needed to confirm this link.[6]

Investigating iron and vitamin D metabolism in sepsis was crucial for understanding their impact on infection risk and outcomes. It is important to unveil the potential of iron-related markers as early indicators of severity and mortality in sepsis and septic shock patients. We explored diverse iron-related markers and their correlation with patient outcomes, intending to enhance comprehension and potentially inform therapeutic strategies for this critical condition. The objectives of this study were to investigate the prevalence of iron and vitamin D-related parameters in patients with sepsis during the early stages of ICU admission and their association with 28-day mortality. Additionally, the study aimed to assess the utility of iron parameters and vitamin D as predictors of outcomes in ICU patients. Through these objectives, this research strived to contribute to a deeper understanding of the role of iron and vitamin D metabolism in sepsis, potentially paving the way for improved patient care and outcomes in this critical condition.

MATERIALS AND METHODS

Study Design, Patient Selection

In this cross-sectional study conducted in the Medical ICU of the Department of Internal Medicine at All India Institute of Medical Sciences (AIIMS), Rishikesh, a convenience sampling method was employed to investigate the relationship between iron profile and vitamin D Levels and the outcomes of patients diagnosed with sepsis and septic shock, following the guidelines of the Surviving Sepsis Campaign. The study spanned 18 months after receiving clearance from the Institutional Ethics Committee (IEC) with reference: AIIMS/IEC/22/192. The study population included consenting adult patients of both sexes aged 18 years or older who met the criteria for sepsis or septic shock. Exclusion criteria encompassed patients who had received blood transfusions or iron supplementation in the past 90 days, pregnant or lactating mothers, post-cardiopulmonary resuscitated patients, individuals taking multivitamin supplements containing Vitamin D, those with malabsorption syndromes, chronic diarrhea, or chronic kidney disease.

Data Collection Methods

Upon enrollment, demographic information such as age, sex, and comorbidities, along with admission diagnosis and clinical characteristics, were recorded. Blood samples collected at admission were used to measure serum iron, ferritin, transferrin saturation, and vitamin D levels through radioimmunoassay kits. Deficiency levels for these parameters were established. Additionally, disease severity was assessed using the sepsis-related organ failure assessment and APACHE-II scores at ICU admission, 24 hours post-admission, and subsequently at regular intervals up to 28 days or until mortality occurred.

Patients received standard treatment for sepsis and septic shock by the surviving sepsis-3 guidelines, with the investigator covering the cost of blood investigations for this study. Patient follow-up continued for up to 28 days or until death, and the recorded iron profile and Vitamin D levels were correlated with patient outcomes. These levels were also compared with prognostic scoring systems like APACHE II and SOFA scores.

Statistical Analysis

Statistical analysis included expressing categorical variables as percentages and continuous variables as mean $\pm$ standard deviation (SD). Categorical variables were compared using the Fisher exact test and Chi-square test when applicable, while continuous variables were analyzed using t-tests and ANOVA when appropriate. The significance level of $p < 0.05$ was considered statistically significant. Bivariate correlations were calculated using Pearson's correlation coefficient, and all statistical analyses were performed using SPSS version 25 software. Throughout the study, utmost confidentiality of patient data was maintained to ensure the protection of subject identities, and no conflicts of interest with any financial entities or organizations were involved in the research.

RESULTS

The study population consisted of 142 patients who were enrolled based on inclusion and exclusion criteria, the associations between all the variables and the outcome were explained using statistical tests and effect size measures, comparing survivors ($n = 60$) and non-survivors groups ($n = 82$), several key variables were examined to discern differences between the two groups (Table 1). First, there were no statistically significant distinctions in age (Survivors: 51.90 ± 18.48 years, non-survivors: 51.29 ± 18.31 years) or gender distribution (Survivors: 50% male, 50% female; non-survivors: 42% male, 40% female).

The source of sepsis varied among survivors and non-survivors, with respiratory infections being predominant in both groups (93.3% in survivors and 92.7% in non-survivors, $p = 1.0003$). Sepsis originates from the skin and soft tissue, with 16.7% of survivors and 8.5% of non-survivors having this source ($p = 0.1402$). Similarly, the genitourinary system as a source between survivors (13.3%) and non-survivors (18.3%, $p = 0.4282$), gastrointestinal system with 8.3% in survivors and 9.8% in non-survivors, ($p = 0.7722$), central nervous system comprised 8.3% in survivors and 13.4% in non-survivors,

Table 1: Comparison of demographic clinical and biochemical data between survivors and non-survivors

Parameters	Survivors (n = 60)	Non-survivors (n = 82)	p-value
Age (years) (mean ± SD)	51.90 ± 18.48	51.29 ± 18.31	0.8461
Gender			
Male	(50.0%)	42% (51.2%)	0.8862
Female	(50.0%)	40% (48.8%)	
Source			
Respiratory	56 (93.3%)	76 (92.7%)	1.0003
Skin and soft tissue	10 (16.7%)	7 (8.5%)	0.1402
Genitourinary	8 (13.3%)	15 (18.3%)	0.4282
Gastrointestinal	5 (8.3%)	8 (9.8%)	0.7722
Central nervous system	5 (8.3%)	11 (13.4%)	0.3442
CRBSI	3 (5.0%)	3 (3.7%)	0.6973
Organism			
Acinetobacter baumanni	27 (45.0%)	36 (43.9%)	0.8972
Klebsiella pneumoniae	21 (35.0%)	28 (34.1%)	0.9162
Pseudomonas aeruginosa	18 (30.0%)	12 (14.6%)	0.0272
MRSA	7 (11.7%)	11 (13.4%)	0.7572
Diabetes	25 (41.7%)	29 (35.4%)	0.4452
Hypertension	24 (40.0%)	22 (26.8%)	0.0982
Organ failure: Acute kidney injury	51 (85.0%)	76 (92.7%)	0.1412
Organ failure: Acute hepatitis	12 (20.0%)	24 (29.3%)	0.2102
Organ failure: ARDS	25 (41.7%)	35 (42.7%)	0.9042
Organ failure: Acute encephalopathy	11 (18.3%)	20 (24.4%)	0.3882
Vasopressor support	12 (52.2%)	64 (94.1%)	<0.0013
Duration of ICU stay (Days)	23.80 ± 17.29	13.11 ± 9.52	<0.0014
Iron (µg/L)	46.32 ± 33.50	47.94 ± 32.82	0.8154
Ferritin (ng/mL)	500.65 ± 491.55	1,395.01 ± 594.47	<0.0014
Vitamin D (ng/mL)	25.45 ± 14.96	20.59 ± 10.91	0.0264
Transferring saturation (%)	33.83 ± 5.76	21.31 ± 10.07	<0.0014
SOFA score	7.23 ± 2.55	13.05 ± 2.35	<0.0014
APACHE-II score	17.33 ± 7.55	34.15 ± 5.09	<0.0014

APACHE II, acute physiology and chronic health evaluation II; ARDS, acute respiratory distress syndrome; CRBSI, catheter-related bloodstream infections; MRSA, methicillin-resistant *staphylococcus aureus*; SD, standard deviation; SOFA, sequential organ failure assessment

with no statistically significant disparity (*p* = 0.3442). Regarding the identified organisms, *Acinetobacter baumannii* was prevalent in both groups (45.0% in survivors and 43.9% in non-survivors, *p* = 0.8972), as was *Klebsiella pneumoniae* (35.0% in survivors and 34.1% in non-survivors, *p* = 0.9162). However, a notable difference was observed in the occurrence of *Pseudomonas aeruginosa*, with survivors having a higher incidence (30.0%) compared to non-survivors (14.6%, *p* = 0.0272). These findings suggest that while the source of sepsis did not significantly impact survival, the specific organism involved, particularly *Pseudomonas aeruginosa*, may influence outcomes. The source of catheter-related bloodstream infections (CRBSI) accounted for 5.0% of survivors and 3.7% of non-survivors, with no significant difference noted (*p* = 0.6973). *Methicillin-resistant Staphylococcus aureus* (MRSA) between survivors (11.7%) and non-survivors (13.4%) (*p* = 0.7572).

The prevalence of diabetes and hypertension showed no significant difference between survivors (41.7%) and non-survivors (35.4%). Regarding organ failures, the study found no statistically significant differences in the prevalence of acute kidney injury (Survivors: 85.0%, non-survivors: 92.7%), acute hepatitis

(Survivors: 20.0%, non-survivors: 29.3%), acute respiratory distress syndrome (ARDS) (Survivors: 41.7%, Non-survivors: 42.7%), or acute encephalopathy (Survivors: 18.3%, Non-survivors: 24.4%).

However, notable distinctions emerged in other parameters. Non-survivors exhibited a significantly higher prevalence of vasopressor support (Survivors: 52.2%, non-survivors: 94.1%) and a considerably shorter duration of ICU stay (Survivors: 23.80 ± 17.29 days, non-survivors: 13.11 ± 9.52 days). Iron levels showed no significant difference between survivors (46.32 ± 33.50 µg/L) and non-survivors (47.94 ± 32.82 µg/L).

Crucially, significant differences were observed in ferritin levels (Survivors: 500.65 ± 491.55 ng/mL, non-survivors: 1,395.01 ± 594.47 ng/mL), vitamin D levels (Survivors: 25.45 ± 14.96 ng/mL, non-survivors: 20.59 ± 10.91 ng/mL), and transferrin saturation (Survivors: 33.83 ± 5.76%, non-survivors: 21.31 ± 10.07%). These variables demonstrated statistically significant distinctions between survivors and non-survivors.

Moreover, non-survivors presented with markedly higher SOFA scores (Survivors: 7.23 ± 2.55, non-survivors: 13.05 ± 2.35) and APACHE-II scores (Survivors: 17.33 ± 7.55, non-survivors:

Table 2: Regression analysis for the dependent variable using all the predictor variables together in one go

Variable	OR (univariable)	OR (multivariable)	p-value (multivariable)
Age (Mean ± SD)	1.00 (0.98–1.02)	1.02 (0.98–1.06)	0.334
Gender (Female vs Male)	0.95 (0.49–1.86)	0.48 (0.11–1.83)	0.298
Vasopressor support	9.71 (4.53–21.99)	3.54 (0.96–13.62)	0.058
Iron (µg/L)	1.00 (0.99–1.01)	1.02 (1.00–1.04)	0.046
Ferritin (ng/mL)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	<0.001
Transferring saturation (%)	0.79 (0.74–0.85)	0.82 (0.74–0.88)	<0.001
Vitamin D (ng/mL)	0.97 (0.94–1.00)	0.99 (0.94–1.04)	0.695

This table summarizes the odds ratios (OR) and *p*-values for each predictor variable in both univariable and multivariable analyses, along with their respective 95% confidence intervals. The *p*-value for the multivariable analysis indicates the significance of each variable while controlling for all other variables in the model. SD, standard deviation

Variable	N	Odds ratio		p
Age_Years	142		1.02 (0.98, 1.06)	0.33
Gender				
Male	72		Reference	
Female	70		0.48 (0.11, 1.83)	0.30
Diagnosis				
Sepsis	54		Reference	
Septic shock	88		3.54 (0.96, 13.62)	0.06
Iron_mg_L	142		1.02 (1.00, 1.04)	0.05
Ferritin ng mL	142		1.00 (1.00, 1.00)	<0.001
Transferring_Saturation_percent	142		0.82 (0.74, 0.88)	<0.001
Vitamin_D_ng_mL	142		0.99 (0.94, 1.04)	0.70

Fig. 1: Regression analysis for the dependent variables using all the predictor variables together in one go

34.15 ± 5.09). These findings underscore the critical impact of vasopressor support, ICU stay duration, ferritin levels, vitamin D levels, transferrin saturation, and organ failure scores in distinguishing outcomes between survivors and non-survivors in critical care settings.

The regression analysis aimed to assess the relationship between various predictor variables and the dependent variable "outcome," categorized as "survivors" and "non-survivors." Several variables were examined in this analysis (Table 2). Firstly, in terms of age (Years), the mean age in both the "Survivors" and "Non-survivors" groups appeared similar, with no notable difference in odds ratios between the two groups (OR = 1.02, p = 0.334). Similarly, when evaluating gender, there was a roughly equal distribution between males and females in both groups, and the odds ratios did not exhibit significant disparities (p = 0.886). Even after controlling for other variables, the gender-related odds ratios remained non-significant (p = 0.298). Moving on to the variables it was observed that the "Septic Shock" carried a substantially higher odds ratio for non-survivors in comparison to the reference category "Sepsis" (OR = 9.71, p < 0.001). However, this effect became somewhat attenuated when accounting for other variables (OR = 3.54, p = 0.058).

Assessing iron levels (µg/L), the univariable analysis did not reveal any significant differences in odds ratios between the two outcome groups (p = 0.772). Nonetheless, when incorporating other variables into the analysis, a noteworthy association with non-survivors emerged (OR = 1.02, p = 0.046). Likewise, ferritin levels (ng/mL) exhibited a substantial association with mortality in both the univariable (p < 0.001) and multivariable (p < 0.001) analyses. A similar pattern was observed for transferrin saturation (%), with significant associations with mortality evident in both univariable (p < 0.001) and multivariable (p < 0.001) analyses.

In contrast, vitamin D levels (ng/mL) displayed a significant association with mortality solely in the univariable analysis (p = 0.033). However, this association lost significance when considering other variables (p = 0.695).

In summary, the multivariable analysis unveiled that certain variable—specifically, the vasopressor support, ferritin levels, transferrin saturation levels, and iron levels—maintained associations with the outcome of interest. Notably, age, gender, and vitamin D levels did not exhibit significant associations with the outcome when other variables were accounted for in the analysis (Fig. 1).

DISCUSSION

We conducted this research to explore the relationship between the mortality rate within 28 days among patients diagnosed with sepsis and septic shock, and the levels of serum iron, transferrin saturation, ferritin, and vitamin D. Additionally, the study aimed to determine the correlation between these variables and SOFA and APACHE II scores.

The results of this study revealed a significant association between the variables ferritin, transferrin saturation, and vitamin D with mortality. In addition, variables like septic shock, vasopressor support, and duration of ICU stay (Days) were also significantly associated with mortality. Specifically, it was found that high levels of ferritin were linked to increased 28-day mortality, whereas low levels of transferrin saturation and vitamin D were associated with higher mortality rates. However, multivariable analysis revealed that certain variables—specifically, the vasopressor support, ferritin levels, transferrin saturation levels, and iron levels—maintained associations with the outcome of interest. Notably, age, gender, and vitamin D levels did not exhibit significant associations with the outcome. Moreover, significant correlations were observed between high SOFA and APACHE II scores and increased mortality.

Our study results strongly support our initial hypothesis. We anticipated a substantial link between 28-day mortality and the levels of serum iron, transferrin saturation, ferritin, and vitamin D in sepsis and septic shock patients. Our findings not only confirmed this relationship but also revealed compelling patterns that further reinforced our hypothesis. Our research aligns with previous studies that emphasized the significance of various biomarkers and clinical tools in predicting sepsis-related mortality. Prior studies have highlighted the importance of prognostic markers and clinical assessment tools in predicting mortality outcomes among patients with sepsis and septic shock. Our research contributes to this body of knowledge by further establishing the correlations between specific variables and mortality rates, thus reinforcing existing theories.[7–9]

Our hypothesis regarding higher Ferritin levels linked with elevated 28-day mortality was validated by our findings. The strong correlation between high ferritin levels and higher mortality rates provides evidence in favor of our hypothesis. These findings are consistent with earlier studies that also showed a similar connection between elevated Ferritin levels and mortality in various disease contexts.[10–12] However, it is worth noting that our findings contradict the results reported by Israel et al. who suggested that ferritin levels higher than 2,000 ng/mL are primarily associated with infectious and malignant diseases, but do not predict mortality.[13]

It is important to consider the differences in the study populations between our research and Israel et al.'s study. Our study focused specifically on patients with sepsis and septic shock, whereas their study encompassed all hospitalized patients with infectious, malignant, and autoimmune/rheumatological diseases. This distinction in patient populations could account for the contrasting findings. Secondly, we expected that lower levels of transferrin saturation would be linked to higher mortality, and our findings indeed confirmed this relationship. The significant associations revealed between decreased levels of transferrin saturation and increased mortality rates provide strong support for our hypothesis and these findings were consistent with previous studies.[14,15] Likewise, the observed relationship between lower levels of vitamin D with higher mortality rates is consistent with previous research that has emphasized the role of nutritional

deficiencies and impaired immune response in sepsis mortality.[16,17] Additionally, we have observed high scores on the SOFA and APACHE II assessment tools were significantly associated with higher mortality, and our results validated this expectation and aligned with previous research.[18–20]

These strong correlations reinforce the utility of these scoring systems as valuable tools for assessing disease severity and prognosis. Furthermore, we observed that both the survivor and non-survivor groups had low levels of iron, specifically below 50 µg/L, with percentages of 60 and 63.4% respectively. This finding is consistent with a previous study.[21] However, the multivariable analysis revealed a significant association of iron with outcome. Based on similar studies by Yanling Lv et al., a possible explanation could be that low iron levels are indeed associated with adverse outcomes.[22]

However, additional research is necessary to validate these findings and better understand the relationship between iron levels and mortality in this patient population. Our study also revealed significant associations between several variables such as vasopressor support, and duration of ICU stay (in days) were found to be significantly associated with mortality. These findings highlight the role of early recognition, targeted interventions, and comprehensive management strategies in improving outcomes for patients with sepsis and septic shock.

In summary, the results of this study not only met our initial expectations but also provided substantial support for our hypothesis. The strong correlations between iron, ferritin, transferrin saturation, SOFA, and APACHE II scores, and mortality rates observed in this research validate our assumptions and contribute significantly to our understanding of the prognostic factors in sepsis-related mortality.

CONCLUSION

In summary, our study highlighted significant associations between iron, ferritin, transferrin saturation levels, and 28-day mortality in sepsis and septic shock patients. Elevated ferritin, lower transferrin saturation, and iron levels were linked to higher mortality rates. However, we acknowledge the study limitations, including its cross-sectional nature and single-center setting, are crucial. Despite these limitations, our study contributes to our comprehension of iron profile, vitamin D, and mortality in sepsis, suggesting potential implications for patient management and prognosis, prompting further exploration.

Clinical Significance

By contextualizing our findings within the existing body of research and theoretical frameworks, our study supports and expands upon prior knowledge regarding the prognostic factors and markers associated with sepsis-related mortality. These findings could potentially inform clinical practice by facilitating earlier identification of high-risk patients and guiding appropriate interventions to improve patient outcomes.

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