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Original Article

Correlational Analysis of Vitamin B12 as an Inflammatory Marker in Patients with Sepsis

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ABSTRACT

Objective: To investigate the correlation between serum Vitamin B12 levels and inflammatory markers in patients with sepsis.
Study Design: Cross-Sectional Study.
Place and Duration of Study: Department of General Medicine, Pakistan Emirates Military Hospital, Rawalpindi, Pakistan, from Sep 2024 to Jan 2025.
Methodology: Patients of both genders between 18 and 65 years of age who were admitted with sepsis or septic shock were included. Blood samples were drawn on the first and third days of admission for lactate, C-reactive protein, and vitamin B12 levels. The comparison was made between first day and third-day biochemical markers. The patients were labelled as survivors and non-survivors.
Results: This study included three hundred and fifteen patients (n=315) with male predominance 184(58.41%). Most patients had gastrointestinal tract infections 120(38.10%) as a source of sepsis, followed by respiratory tract infections 95(30.16%). There were 273(86.67%) survivors and 42(13.33%) non-survivors. There was a statistically substantial (p<0.001) difference between median serum vitamin B12 levels in survivors 892.00 (973.50-823.50) pg/ml and non-survivors 1035.50 (1157.25-926.25) pg/ml, highlighting the raised levels in the non-survivors group. The mortality rate was found to be positively correlated with Vitamin B12 (r=0.293), serum lactate (r=0.128), and CRP levels (r=0.157), highlighting the significant role of these markers in sepsis.
Conclusion: Higher vitamin B12 levels are linked to increased mortality in sepsis. Additionally, plasma lactate and C-reactive protein are also significant predictors of outcomes.

Keywords: Cobalamin, C-reactive protein, Lactate, Mortality, Sepsis.

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INTRODUCTION

Sepsis, often referred to as "septicaemia", stands as one of foremost contributors to illness and death globally. In 2017 alone, an alarming 48.9 million cases of sepsis were reported around the world, underscoring its widespread impact. Tragically, this severe condition claimed lives of 11 million individuals that year, accounting for staggering 20% of all recorded deaths.[1] In critical care settings, Sepsis is leading cause of mortality worldwide.[2,3] In sepsis, the host's immune response is dysregulated against different inciting agents, which can cause an array of manifestations from simple organ dysfunction to multiple organ failure and ultimately lead to death.[1,2] In pathophysiology of sepsis, inflammatory cytokines such as TNF-alpha, Interleukins, and interferons are released, resulting in activation of complement and coagulation cascades, leading to cytokine storm.[4,5]

Vitamins are essential nutrients that significantly influence pathophysiology of sepsis due to their antioxidant and anti-inflammatory properties. Vitamin B12 (Cobalamin), primarily found in animal proteins, is a key micronutrient.[6,7] It exhibits antioxidant effects through a "glutathione-sparing effect," enhances "methionine synthase activity," and reacts with free radicals.[8] Additionally, it selectively inhibits nitric oxide via NOS pathway activation, promotes acetylcholine synthesis, stimulates cholinergic anti-inflammatory pathway, and has bacteriostatic effects.[9]

The increased levels of Vitamin B12 (Cobalamin) in sepsis patients have been correlated with increased inflammatory markers, higher mortality rates, and severe organ dysfunction.[6,7] However, providing sepsis patients with high doses of Vitamin B12 during sepsis has not been associated with profound outcomes.[10]

In this study, we investigated role of Vitamin B12 (Cobalamin) in relation to various markers of sepsis as predictors of mortality and morbidity in sepsis patients. The role of Vitamin B12 in sepsis progression will help to establish a better understanding and explore utilisation of Vitamin B12 in clinical settings to predict better or worse outcomes in patients. It will

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also help to lessen financial burden in this resource-constrained community.

METHODOLOGY

This cross-sectional study was conducted after approval of the research protocol from the institutional ethical review board vide certificate number A/28/ERC/26/2025. This study was carried out on admitted patients at the Department of Medicine, Pak Emirates Military Hospital, Rawalpindi, Pakistan, from Sep 2024 to Jan 2025. The sample size was calculated using the OpenEpi sample size calculator with a confidence interval of 95%, a margin of error of 5%, and 28.8% of patients having elevated vitamin B12 levels.[11] The sample size came out to be 315 patients. A convenient consecutive sampling technique was used, and informed written consent was obtained from all the participants.

Inclusion Criteria: Patients of either gender between 18 and 65 years admitted with sepsis or septic shock as per "The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).[12]

Exclusion Criteria: Patients who were unwilling to participate, received vitamin B-12 supplementation, required blood transfusion, or had intrinsic factor deficiency were excluded from the study. Patients with malignancies and pregnant females were also excluded.

After explaining the purpose and procedure of the study, the demographic and disease-related details, including age, gender, comorbid conditions, physical examination, and clinical source of sepsis, were documented. "The Acute Physiology and Chronic Health Evaluation II (APACHE-II) score" was calculated. The blood samples were drawn for complete blood counts, serum electrolytes, vitamin B12 levels, CRP, plasma lactate, and renal function tests. An arterial blood gas analysis was also performed. The laboratory tests were obtained by trained nursing staff and were processed as per the hospital's standing operating procedures for blood samples. The samples for vitamin B12 levels, CRP, and lactate were repeated on the third day of admission. The comparison was made between first day and third day biochemical markers. The patients were labelled as survivors (who got better and were discharged from the hospital) and non-survivors (who died during the hospital stay).

The Statistical Package for Social Sciences Version 25.0 was utilized for data entry and statistical analysis. Median and interquartile ranges (IQR) were employed for age, haemoglobin, procalcitonin, plasma lactate, total leukocyte count, serum vitamin B12 levels, CRP, and serum creatinine. At the same time, frequency and percentages were used for gender, smoking, comorbid conditions, and source of sepsis. The Shapiro-Wilk test was conducted to evaluate the normality of the data. The Chi-square test was used for gender, smoking, comorbid conditions, and source of sepsis to assess any baseline differences, and Mann-Whitney U test was performed to determine statistical differences in age, haemoglobin, procalcitonin, plasma lactate, total leukocyte count, serum vitamin B12 levels, CRP, and serum creatinine at the time of admission. The Spearman correlation test was applied to establish a correlation between CRP, plasma lactate, and vitamin B12. A p-value of ≤0.05 was considered significant.

RESULTS

This study included three hundred and fifteen patients (n=315). The sample population was male predominant, 184(58.41%). Diabetes Mellitus (DM) was the most common comorbid condition, 114(36.19%). Most patients had gut 120(38.10%) as a source of sepsis, followed by respiratory tract infections 95(30.16%). There were 273(86.67%) survivors and 42(13.33%) non-survivors. DM was the most common comorbid condition 15(35.71%), and the chest was the most common source of infection 16(38.0%) in non-survivors. The total population and group-wise details are shown in Table-I.

Note: Mann-Whitney U Test (*) was used for non-normal continuous variables, and Chi-square test ($) for categorical variables to calculate p-values.

There was a statistically substantial (p<0.001) difference between median serum vitamin B12 levels in survivors 892.00(973.50-823.50) pg/ml and non-survivors 1035.50 (1157.25-926.25) pg/ml, highlighting the raised levels in the non-survivors group. The serum CRP (p=0.006) and plasma lactate (p=0.050) were statistically different not only at the time but on the third day of admission as well, p=0.022 and p=0.005, respectively. The differences are shown in Table-II.

The correlation analysis revealed a positive correlation between mortality and Vitamin B12 (r=0.293), serum lactate (r=0.128), and CRP levels (r=0.157), indicating a strong association with sepsis, as shown in Table-II

and plasma lactate (p=0.050) were statistically different not only at the time but on the third day of admission as well. This highlights the crucial role of serum CRP and plasma lactate in the prognosis and mortality associated with sepsis.

Table-I: Baseline Characteristics (n=315)

Characteristics	Total Population (n=315)	Groups		*p*-value
		Survivors (n=273)	Non-Survivors (n=42)	
Median Age, years	58.00 (62.00-51.00)	58.00 (62.00-52.00)	56.00 (62.25-47.00)	0.422*
Gender				
Male	184 (58.41%)	161 (58.97%)	23 (53.76%)	0.606$
Female	131 (41.59%)	112 (41.03%)	19 (45.24%)	
Comorbid Conditions				
Hypertension	52 (16.51%)	47 (17.22%)	5(11.90%)	0.388$
Diabetes Mellitus	114 (36.19%)	99 (36.26%)	15(35.71%)	0.945$
IHD	35 (11.11%)	33 (12.09%)	2(4.76%)	0.160$
COAD	50 (15.87%)	42(15.38%)	8(19.05%)	0.545$
Smoking	68 (21.59%)	63 (23.08%)	5 (11.90%)	0.101$
Sepsis Source				
Abdomen	120 (38.10%)	107 (39.19%)	13 (30.95%)	
Chest	95 (30.16%)	79 (28.94%)	16 (38.10%)	
CNS	44 (13.97%)	35 (12.82%)	9 (21.43%)	0.210$
Genito-urinary	48 (15.24%)	44 (16.12%)	4 (9.52%)	
CVS	8 (2.54%)	8 (2.93%)	-	
Median Hb, g/dL	12.40 (13.95-10.21)	12.30 (13.79-10.11)	12.96 (14.27-11.47)	0.064*
Median TLC, 109/L	14.39 (19.02-9.94)	14.39 (18.82-10.08)	13.92 (19.68-9.08)	0.876*
Median Procalcitonin, µg/l	41.80 (59.15-27.36)	41.86 (59.24-27.54)	41.46 (55.64-25.77)	0.672*
Median Serum Creatinine, µmol/L	231.12 (296.57-149.41)	234.06 (297.09-149.60)	211.41 (301.31-144.69)	0.629*
Median Plasma Lactate, mmol/L	4.09 (5.05-2.98)	4.26 (5.07-3.01)	3.41 (4.76-2.75)	0.050*
Median APACHE-II Score	26.00 (32.00-20.00)	26.00 (32.00-20.00)	24.00 (30.00-19.75)	0.087*
Median CRP at admission, mg/dL	56.27 (78.97-30.60)	58.29 (80.47-33.17)	37.97 (71.46-20.14)	0.006*
Median Vitamin B12 at admission, pg/ml	801.00 (890.00-646.00)	805.00 (891.00-650.50)	789.50 (867.50-581.50)	0.437*

IHD: Ischaemic heart disease; Hb: Haemoglobin; CNS: central nervous system; TLC: Total leukocyte count; CVS: Cardio-vascular system; APACHE-II: Acute Physiology and Chronic Health Evaluation II; COAD: Chronic obstructive airway disease; CRP: C-reactive protein

Table-II: Comparison of lab Parameters Between Survivors and Non-survivors on the Third day (n=315)

Characteristics	Groups		*p*-value
	Survivors (n=273)	Non-Survivors (n=42)	
Median Plasma Lactate, mmol/L	3.10 (2.50-3.58)	3.51 (2.81-3.79)	0.022*
Median CRP, mg/dL	40.91 (26.20-54.33)	52.12 (33.06-67.49)	0.005*
Median Vitamin B12, pg/ml	892.00 (823.50-973.50)	1035.50 (926.25-1157.25)	<0.001*

CRP: C-reactive protein

Table-III: Correlation Between Mortality and Different Laboratory Markers in Patients with sepsis (n=315)

Variable	Mortality	
	Correlation Coefficient (r)	*p*-value
CRP Levels, mg/dL	0.158	0.005
Plasma Lactate, mmol/L	0.129	0.022
Vitamin B12 Levels, pg/ml	0.293	<0.001

CRP: C-reactive protein

DISCUSSION

This research evaluated vitamin B12 levels and their correlation with septic markers. In this study, 315 patients diagnosed with sepsis were enrolled, with male predominance 184(58.41%) and slightly older age individuals, 58 years (62.00-51.00). Out of these 315 patients, 42(13.33%) died of respiratory system infections, with 16(38.10%) as the leading cause. There was a statistically significant difference between serum vitamin B12 levels in survivors and non-survivors, highlighting the raised levels in the non-survivors' group (p<0.001). The serum CRP (p=0.006)

Sepsis is a serious medical condition characterized by a dangerous response to infection that can lead to systemic inflammation and organ dysfunction.[13] This severe condition is linked to significantly elevated rates of both mortality and morbidity. Chaftari *et al.*, indicated that the mortality rate for sepsis can reach alarming levels, ranging from 40% to 50%, particularly among patients who experience complications or are treated in resource-limited settings. These statistics underscore the critical nature of timely diagnosis and intervention in the management of sepsis.[14] Serum CRP, serum lactate,

and serum albumin levels are already established markers that provide significant insight as diagnostic and prognostic markers in predicting sepsis-related deaths, as reported by Gamarra-Morales *et al*.[15] There was a positive correlation between outcome and septic markers, including vitamin B12, in this study.

A review by Pregernig et al., highlighted that the higher cobalamin levels were linked with augmented inflammatory markers and mortality in sepsis.[16] On the contrary, Patel *et al*., found no association between vitamin B12 levels and their metabolite with the development of sepsis in bacterial infections.[17] Simonetti *et al*., found the beneficial role of intravenous therapy in septic/vasodilatory shock.[18] In the present research, the raised vitamin B12 levels were associated with increased mortality in sepsis patients. Though the antioxidant properties of vitamin B12 are known, this difference in results can be explained by different inclusion and exclusion criteria, ethnicity, and other clinical parameters.

In coherence with the findings of our research, research conducted in the Netherlands by Flores-Guerrero *et al*., showed that elevated levels of serum vitamin B12 were linked to increased mortality rates, even among the general population. However, a meta-analysis found no mortality benefit with vitamin B12 supplementation/ levels. Serum CRP and cobalamin were found to be elevated in infection, so they can be used as markers for infection and sepsis.[19] A distinct study by Zeitouni *et al*., revealed a concerning correlation between elevated serum vitamin B12 levels and increased mortality rates among critically ill patients. This finding suggests that higher concentrations of this vitamin in the blood may be associated with poorer outcomes for those facing severe health challenges.[20] In this study, too, the CRP and vitamin B12 levels were raised in our patients with sepsis, thus confirming the positive correlation of Vit B12 as an inflammatory marker in sepsis.

LIMITATIONS OF STUDY

This study has been conducted at a single center, and the limited number of participants involved may hinder the ability to generalize the findings to broader populations. Additionally, because the research is cross-sectional in nature, it does not allow for the determination of causal relationships between the variables studied. To gain a more comprehensive understanding of the relationships in question, future research that incorporates multiple centers and a larger cohort of participants will be essential. Such studies could provide deeper insights into the correlation and help to validate the findings presented here.

CONCLUSION

In this study, the elevated vitamin B12 and CRP levels in septic patients showed significant associations with mortality, highlighting their potential role as supplementary prognostic markers in sepsis.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

MSS & SS: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

MFS & MEW: Data acquisition, data analysis, approval of the final version to be published.

HS: Critical review, concept, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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