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ASSOCIATION BETWEEN HYPOMAGNESEMIA AND COAGULOPATHY IN SEPSIS

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Abstract

Background: Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Magnesium reportedly has immunomodulatory effects and is associated with dysregulated host response to infection and the pathophysiology of sepsis. Previous studies reported that hypomagnesemia was associated with lactic acidosis in sepsis, increased incidence of sepsis or septic shock in critically ill patients, and increased mortality in sepsis. Thus, this study is being conducted to explore the association between serum magnesium levels and coagulopathy in sepsis, outcomes.

Materials: This cross-sectional study was performed on 40 Sepsis Cases Admitted in Intensive care Unit, Kempegowda institute of medical sciences during a 12-month period. SOFA score was calculated. Serum magnesium levels were estimated.

Sepsis cases were categorized based on serum magnesium levels as low, normal, high on the day of diagnosis of sepsis. ISTH criteria will be used for diagnosis of overt DIC/coagulopathy in sepsis cases during the course in the hospital. Serum magnesium levels was independently associated with both coagulopathy/DIC and clinical outcome of sepsis cases. The data was collected and compiled in MS Excel. Descriptive statistics has been used to present the data. To analyse the data SPSS (Version 26.0) was used. Significance level was fixed as 5% ($\alpha = 0.05$. Qualitative variables are expressed as frequency and percentages and Quantitative variables are expressed as Mean and Standard Deviation. To compare the association between numerical and categorical variables, student t test was used.

Observation: The mean age of the study participants was found to be 58.75 ± 17.299.

75% of the study participants were males. The mean serum magnesium levels were found to be 1.8798 ± 0.56902. 67.5% of the study participants had low grade DIC and 32.5% of the study participants had overt DIC. The mortality rate in the present study was found to be 35%. The mean Serum magnesium of the study participants with Overt DIC were found to be lower than low grade DIC study participants (1.37 ± 0.47vs2.12 ± 0.44; P value=0.000). The

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mean Serum magnesium of the study participants who died were found to be lower than that of study participants who were discharged (1.59±0.60vs2.03±0.49; P value=0.019).
Conclusion: Serum magnesium was found to be inversely related to DIC in sepsis patients and hypomagnesemia is associated with poor clinical outcome in sepsis patients. Consequently, treatment of hypomagnesemia may be a viable therapeutic approach for the prevention and management of coagulopathy in sepsis.
Keywords: Magnesium, Hypomagnesemia, Sepsis, Disseminated intravascular coagulation, Coagulopathy

Introduction

Life-threatening organ malfunction brought on by an abnormal host response to an infection is known as sepsis.[5] Sepsis continues to be a leading cause of morbidity and death in critically ill patients, despite notable advances in our understanding of the pathophysiology of this clinical illness, hemodynamic monitoring technologies, and resuscitation techniques.[2] A common feature of sepsis is coagulation abnormalities, which raises the possibility of bleeding and/or thrombotic events.[3] Significant cellular and metabolic abnormalities are hallmarks of sepsis.[4]

The human body needs magnesium as a cofactor for a number of vital enzymes. It is vital to the function of several organs, including the heart, brain, and skeletal muscles.[5] Magnesium is a common intracellular cation that is involved in several enzymatic reactions and important physiological processes, including immunological responses, oxidative metabolism, and the generation of proteins and nucleic acids.[15] Magnesium is necessary for various ATP-generating processes, including Na+/K+-ATPase and mitochondrial ATP synthase, and it is also necessary for regular mitochondrial activity.[6] The primary effects of magnesium imbalance are on the cardiovascular and neuromuscular systems. Due to neuromuscular hyperexcitability, magnesium shortage can produce seizures, muscle weakness, and respiratory depression.[7] Moreover, it has been linked to coronary artery disease, heart failure, cardiac arrhythmia, and can ultimately result in death.[8]

With an estimated prevalence of 20% to 65%, hypomagnesemia is one of the most prevalent but underdiagnosed electrolyte abnormalities in critically ill patients, including those with sepsis.[9-11] Additionally, a meta-analysis has demonstrated a strong correlation between hypomagnesemia in critically sick patients and longer hospitalizations in the intensive care unit (ICU), higher mortality, and the requirement for mechanical ventilation.[12-14] Thus, this study was conducted to evaluate the relationship between serum magnesium levels and coagulation status, clinical outcome in patients with sepsis.

OBJECTIVE OF THE STUDY:

- To investigate the relationship between different serum magnesium levels and coagulation status, and the association between hypomagnesemia and DIC in patients with sepsis.
- To evaluate and compare the association between serum magnesium levels and clinical outcome in sepsis cases.

METHODOLOGY

- **STUDY DESIGN:** Observational study
- **STUDY DURATION:** 12 months (April 2023 to March 2024)
- **STUDY AREA:** Kempegowda Institute of Medical Sciences, Bangalore.

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- **STUDY PARTICIPANTS:** Sepsis Cases Admitted in the Intensive care unit after obtaining consent from patient's legally acceptable representative.
- **INCLUSION CRITERIA**
  - Sepsis Cases Admitted in the Intensive care unit with age above 18 years after obtaining consent from patient's legally acceptable representative.
- **EXCLUSION CRITERIA**
  - Pregnancy / postpartum period (up to 8 weeks).

ESTIMATION OF SAMPLE SIZE:

Based on the probability, 12% was the prevalence of hypomagnesemia among the Sepsis patients & was associated with more frequent DIC as per the findings of previous literature by Tonai K *et al.* [15], The sample size was estimated using the formula

$N= (Z^2_{(1-\alpha)}X\ PQ) /d^2$

$Z\ (1-\alpha)=1.96$ (For 95% Confidence Interval)

$P=0.12$

$Q=1-P$

d^2(Margin of Error) =0.10

$N=40.56$, rounded off to 40

The total sample size for the present study included 40 Sepsis patients

Method of Collection of Data:

Sepsis Cases Admitted in the Intensive care unit of Kempegowda Institute of Medical Sciences, Bangalore were included in the study. Clearance from the institutional ethical committee was taken before starting the study. Study participants were included in the study by Purposive Sampling technique, till the sample size was reached. Written informed consent was taken from the study participants before collecting the data. A pre-tested, semi-structured questionnaire was used to collect information on socio-demographic variables and clinical history related to sepsis by interview method. Clinical examination including vitals, general physical examination and systemic examination were done. Complete Haemogram, Blood Sugar Level, Renal Function Test, Liver Function Test, urine routine, urine culture and sensitivity, Arterial Blood Gas, chest x-ray, USG abdomen and pelvis, 2D Echo, ECG, Serum magnesium, D-Dimer, prothrombin time, serum fibrinogen were done. SOFA score was calculated. ISTH criteria was used for diagnosis of overt DIC/coagulopathy in sepsis cases during the course in the hospital. Serum magnesium levels was independently associated with both coagulopathy/DIC and clinical outcome of sepsis cases.

Statistical Analysis

The data was collected and compiled in MS Excel. Descriptive statistics has been used to present the data. To analyse the data SPSS (Version 26.0) was used. Significance level was fixed as 5% ($\alpha = 0.05$. Qualitative variables are expressed as frequency and percentages and Quantitative variables are expressed as Mean and Standard Deviation. To compare the mean values between groups student t test was applied.

Results

The mean age of the study participants was found to be 58.75 ± 17.299 years. 75% of the study participants are males. 55% of the study participants had associated comorbidities. The diet was mixed in 85% of the study participants. 52.5% and 22.5% of the study participants had origin of sepsis in the lungs and genitourinary tract respectively. 32.5% of the study

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participants had overt DIC. The mean serum magnesium of the study participants was found to be 1.8798±0.56902. The incidence of mortality in the present study was found to be 35%.

The serum magnesium levels were found to be lower among study participants with overt DIC than low grade DIC (1.37±0.47vs2.12±0.44) and this association was found to be statistically significant. The serum magnesium levels were found to be lower among study participants with mortality than discharges study participants (2.03±0.49vs1.59±0.60) and this association was found to be statistically significant.

TABLE 1: PATIENT CHARACTERISTICS:

PATIENT CHARACTERISTICS		
AGE, MEAN±SD		58.75±17.299
GENDER, n (%)	MALE	30 (75%)
	FEMALE	10 (25%)
COMORBIDITIES, n (%)	YES	22(55%)
	NO	18(45%)
DIET, n (%)	MIXED	34(85%)
	VEGETARIAN	6(15%)
ORIGIN OF SEPSIS, n (%)	CNS	7(17.5%)
	GENITOURINARY	9(22.5%)
	GIT	3(7.5%)
	LUNGS	21(52.5%)
DIC, n (%)	LOW GRADE	27(67.5%)
	OVERT	13(32.5%)
SERUM MAGNESIUM, MEAN±SD		1.8798±0.56902
OUTCOME OF THE DISEASE, n (%)	DEATH	14(35%)
	DISCHARGED	26(65%)

TABLE 2: ASSOCIATION OF SERUM MAGNESIUM WITH DIC

DIC	**SERUM MAGNESIUM**		**P VALUE**
	Mean	**Std. Deviation**	
LOW GRADE	2.1215	0.44242	**0.000***
OVERT	1.3777	0.47292	

TABLE 3: ASSOCIATION OF SERUM MAGNESIUM WITH OUTCOME OF THE DISEASE

OUTCOME OF THE DISEASE	**SERUM MAGNESIUM**		**P VALUE**
	Mean	**Std. Deviation**	
DISCHARGED	2.0323	0.49457	0.000*
DEATH	1.5964	0.60660	

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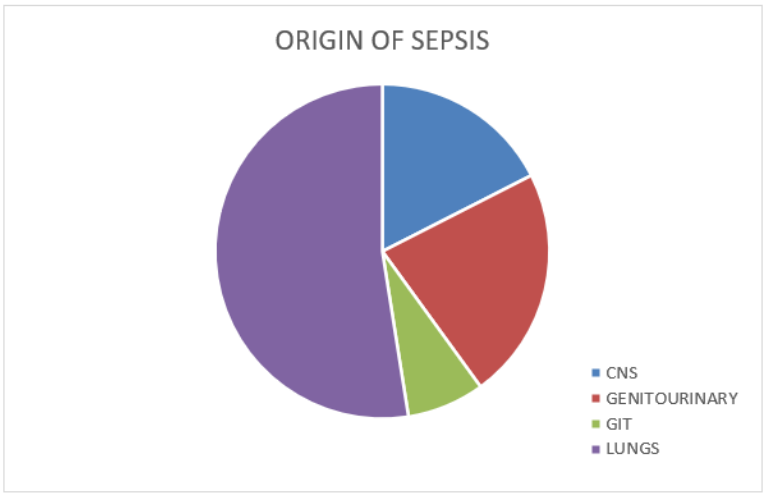

FIGURE 1

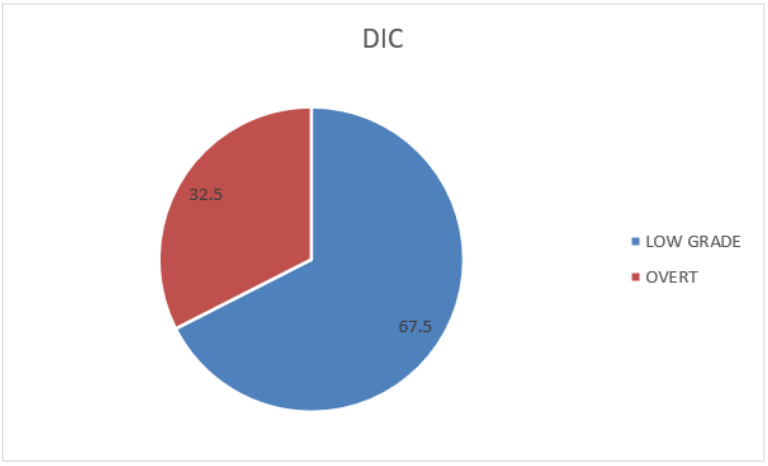

FIGURE 2

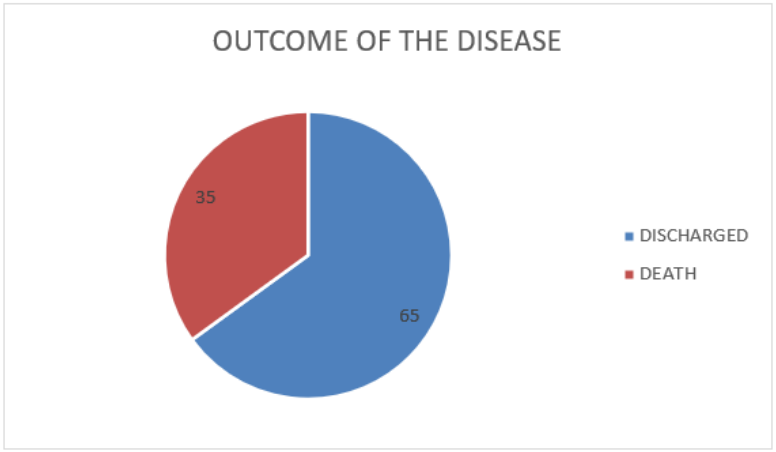

FIGURE 3

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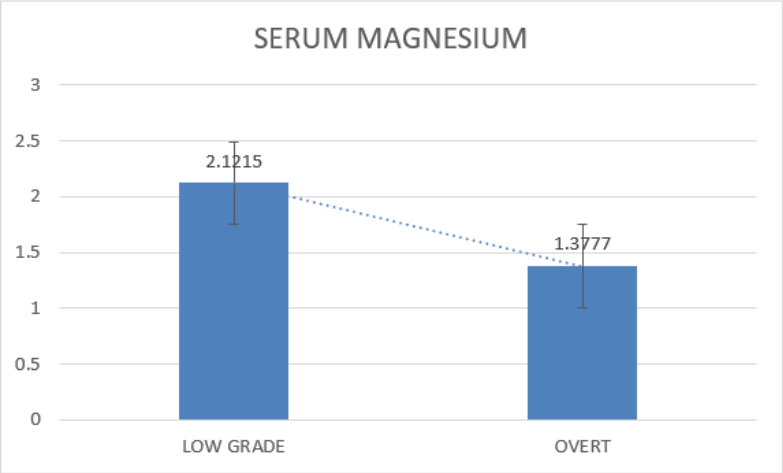

FIGURE 4

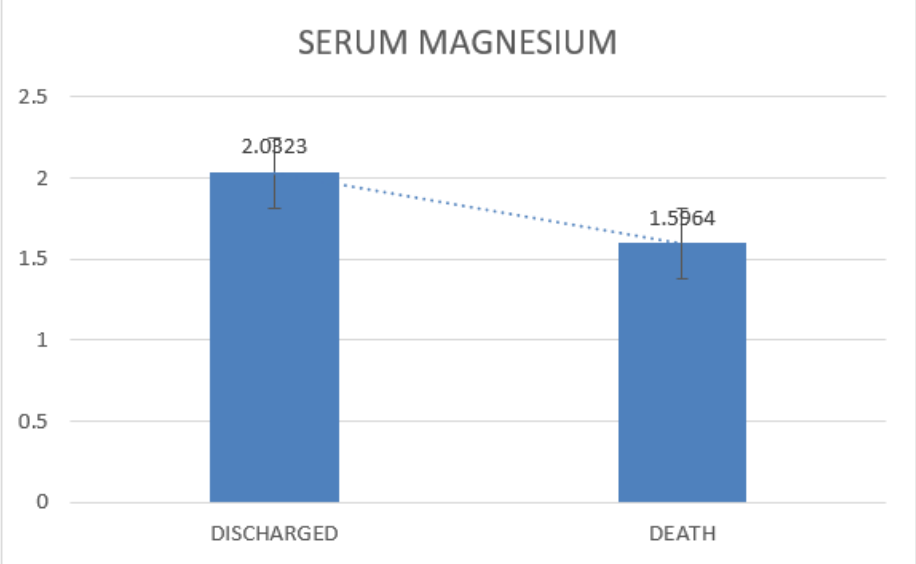

FIGURE 5

Discussion

Mg, a very important intracellular cation which activates enzyme systems involved in energy metabolism, is required for nucleic acid transcription, messenger RNA translation and protein synthesis, and is responsible for regulation of mitochondrial function. In addition, Mg ions have important role in immunological functions, including macrophage activation, adherence and bactericidal activity of granulocyte oxidative burst, lymphocyte proliferation and endotoxin binding to monocytes. In addition, increased cytokine concentration has been recorded in experimental Mg deficiency inflammatory models. Therefore, the critical role of Mg in sepsis could be attributed to its immune system effects, which are important in the pathogenesis of sepsis.[13]

The age, gender, comorbidity profile of the present study was found to be similar to the studies done by Tonai K *et al.*[15] and Chenwei L *et al.*[16] In the present study, 52.5% and 22.5% of the study participants had origin of sepsis in the lungs and genitourinary tract

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respectively. In a study done by Tonai K *et al.*,[15] 43.8% of the study participants had origin of sepsis in the abdomen and 22.9% in the thorax.

In the present study, the mean serum magnesium of the study participants was found to be 1.8798±0.56902. In a study done by Chenwei L *et al.*,[16] the median serum magnesium of the study participants was found to be 1.9. In a study done by Tonai K *et al.*,[15] the median serum magnesium of the study participants was found to be 1.8. In the present study, the incidence of mortality in the present study was found to be 35%. In a study done by Chenwei L *et al.* ,[16] incidence of mortality was found to be 27.44%.

In the present study, The serum magnesium levels were found to be lower among study participants with overt DIC than low grade DIC (1.37±0.47vs2.12±0.44) and this association was found to be statistically significant. In a study done by Tonai K *et al.*, [15] DIC was found to be associated with hypomagnesemia (odds ratio [OR], 2.77; P < 0.001).

In the present study, The serum magnesium levels were found to be lower among study participants with mortality than discharges study participants (2.03±0.49vs1.59±0.60) and this association was found to be statistically significant. In a study done by Tonai K *et al.*,[15] mortality rates were found to be higher among study participants with low and high magnesium levels. In a study done by Chenwei L *et al.*,[16] hypomagnesemia was found to significantly affect the ICU mortality.

Limaye CS *et al.* [9] in their study found that patients with hypomagnesemia had increased incidence of sepsis (38%vs19%, P < 0.05) and higher mortality (57.7%vs31.7%, P < 0.05) compared to patients with normal Mg levels. Soliman HM *et al.*[17] in their study found that hypomagnesemia had significantly higher prevalence of septic shock (57%vs11%, P < 0.01) and higher mortality (35%vs12%; P < 0.01). Kumar S *et al.*[18] in their study found that hypomagnesemia was associated with mortality (38.56% vs14.73%; P < 0.0001). Chen M *et al.*[19] in their study found that hypomagnesemia was associated with mortality (54.90%vs33.88%; P = 0.010). Safavi M *et al.* [20] in their study concluded that Monitoring of serum magnesium levels may have prognostic, and perhaps therapeutic, implications.

Uncertainty surrounds the relationship between serum magnesium levels and the pathogenesis of sepsis. According to research conducted on animals, hypomagnesemia is associated with higher TNF-α and IL-6 levels as well as more activated neutrophils, endothelial cells, and macrophages,[21,22] while magnesium supplementation prevents gasdermin-D N-terminal-induced pyroptosis in mice, protecting them against lipopolysaccharide-induced deadly septic shock.[23] Although studies on this subject are debatable, hypomagnesemia may potentially impair the synthesis of nitric oxide (NO), which raises the risk of recurrent infections because NO is essential in preventing infections in body cavities, including sinusitis, pneumonia, and mucositis.[24-26] Furthermore, magnesium is an important cofactor in the production of thiamine pyrophosphate, a coenzyme in a variety of enzymatic processes. Reduced gastric acid production can be caused by inadequate thiamine pyrophosphate levels, which raises the risk of gastrointestinal (GI) infections[24] The increased recurrence of bacterial infections, including sepsis, urinary tract infections, and bronchopneumonia, has been associated with hypomagnesemia; this association may be explained by the immunological regulatory actions of magnesium.[27]

Serum lactate is a significant marker of tissue hypoperfusion and a prognostic factor for the severity of sepsis. Magnesium and thiamine are essential Krebs cycle cofactors.[28-30] and can hinder the formation of adenosine triphosphate (ATP) when insufficient, which causes an increase in anaerobic metabolism and the onset of lactic acidosis. According to this

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biological process, magnesium may contribute to accelerating the rate of lactate clearance by either lowering the generation of lactate or improving its excretion.[31]

A critical component of sepsis is altered coagulation. As was previously mentioned, a shortage in magnesium causes the release of inflammatory cytokines, which in turn cause dysregulation of the immune system, induce tissue damage, and trigger coagulation.[32]

Conclusion

In conclusion, hypomagnesemia is associated with DIC in sepsis patients and is independently associated with worsened sepsis progression, and decreased survival rates. Preventive measures and therapeutic measure such as the use of magnesium supplementation, in conjunction with standard medical practices can be advised among patients with sepsis with respect to improved prognosis.

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