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RESEARCH ARTICLE

Correlation between serum zinc and mortality in septic patients.

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Abstract

Objective Activation of acute phase response occurs in initial stage of sepsis, with rapid decline in zinc blood levels for intracellular mobilization to synthesize acute phase proteins. Our study aim was to explore if there is a correlation between serum zinc levels and mortality in septic patients. **Design** A comparative prospective observational study. **Setting** Intensive Care Department of Alexandria University Hospitals. **Patients** 100 patients with proved sepsis according to the Surviving sepsis Campaign guidelines and in need for ICU admission. **Methods** Patients were followed up for 28 days. Acute Physiology and Chronic Health Evaluation II score and Sequential Organ Failure Assessment score were calculated in every patient using the data at enrollment. Venous blood samples were obtained on admission for determination of a panel of markers including serum lactate, C-reactive protein, procalcitonin level, and serum zinc levels. All parameters were correlated with mortality. **Results** APACHE II score, SOFA score, serum lactate, CRP, procalcitonin, and serum zinc could predict mortality without significant statistical difference in-between, ($p < 0.05$). There was an inverse statistical correlation between serum zinc levels and all other studied parameters **Conclusion** Low serum zinc levels may be one of the predictors of mortality in septic patients.

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Introduction:-

Mortality from sepsis often occurs when the host response to systemic infection becomes dys-regulated and over-amplified, resulting in septic shock, and multiple organ dysfunction. The pathophysiology of sepsis is complex, which has so far limited our capacity to develop effective drug therapies (Williams; 2012). Sepsis patients with a poor prognosis often exhibit over-activation of the initial innate immune response, which is accompanied by a markedly elevated cytokine response, also referred to as the cytokine storm (Rittirsch et al; 2008).

During the initial stage of sepsis, the rapid release of cytokines activates the acute phase response (APR) primarily in the liver leading to the production of acute phase proteins (APPs). The fundamental role of APPs in the setting of sepsis remains poorly defined in part because APPs exhibit both pro- and anti- inflammatory functions (Quinton et al; 2012).

Zinc (Zn) blood levels decline rapidly at the onset of the APR, which is referred to as hypozincemia, following its redistribution from the plasma into tissues (Moshage; 1997). The presumed beneficial role of hypozincemia is resulting in the strategic sequestration of bioavailable Zn from pathogenic microorganisms (Kehl-Fie and Skaar; 2010). Further, mobilization of Zn into the cellular compartment is required to facilitate gene transcription and protein production that includes the synthesis of APPs (Oteiza; 2012). Zn also assists in the regulation of intracellular redox balance thereby playing a direct role in cytoprotection during the host response (Knoell et al; 2009). Our study aim was to explore the correlation between serum zinc and mortality in septic patients.

Patients and methods:-

100 patients, according to sample size calculation, were presented to the Emergency Room of Alexandria University Hospitals with proved sepsis according to the Surviving sepsis Campaign guidelines (Dellinger et al; 2008) and in need for ICU admission were considered eligible for the study. Those under 18 years old, end-stage renal or liver disease, conditions influencing zinc level; (pregnancy, hypoalbuminemia, malignancy, burn patients, thyroid dysfunctions (hyper or hypothyroidism), and multivitamin supplements including zinc) were excluded from the study (Heyland et al; 2008).

Informed written consent was taken from all patients' next of kin according to the Helsinki declaration. The study was approved by the local ethical committee of Alexandria Faculty of Medicine. Patients enrolled into the study were subjected to collection of demographic data, associated co-morbidities, routine ICU investigations, culture from suspected sites of infection and/or automated blood culture. Acute Physiology and Chronic Health Evaluation (APACHE) II score and Sequential Organ Failure Assessment (SOFA) score were calculated in every patient using the data at enrollment.

Venous blood samples were obtained at the time of ICU admission for determination of a panel of markers including serum lactate, C-reactive protein, procalcitonin level, and admitting serum zinc levels. Serum zinc level was measured by direct atomic absorption spectroscopy (AAS) method (Diann et al; 1972). Patients were followed up for 28 days. Survival was recorded daily by in-hospital observation and later by phone call. Serum zinc levels were correlated with all other parameters and mortality.

Results:-

Age of the studied patients ranged between 55 & 71.7 years. 69 patients were males. Positive cultures were obtained in 90% of cases. The APACHE II score ranged between 13 & 20 while the range of SOFA score was between 4 & 10 on admission, (table 1). Admission levels of different serum biomarkers were presented in table 1. Serum zinc level on admission ranged between 43 & 62.7 $\mu\text{g/dl}$. The mortality rate in the present study was 32%.

Admission values of APACHE II score, SOFA score, serum lactate, CRP, procalcitonin, and serum zinc could predict mortality in the studied population without significant statistical difference in-between, ($p < 0.05$). Cut-off values, sensitivity, specificity, positive, and negative predictive values of previous parameters were presented in table 2. The ROC curves of these parameters were given in figures 1&2. Of notice was the inverse statistical correlation between serum zinc levels and all other studied parameters including mortality (figures 1 & 2).

Discussion:-

Growing evidence regarding the association between zinc deficiency and immune dysfunction in infection encouraged researchers to investigate the role of this trace element as a possible prognostic marker in sepsis (Kehl-Fie et al; 2010, Liuzzi and Cousins; 2004, Oteiza; 2012, and Knoell et al; 2009). It was reported that moderate zinc deficiency significantly increased mortality during the early stages of sepsis in a murine model of polymicrobial sepsis (Knoell et al; 2009). Therefore, it is possible that the alteration of zinc metabolism in critically ill septic patients may be an important determinant in predicting the host response and outcome.

According to the present study, low serum zinc levels at a cut-off value of 43.5 $\mu\text{g/dl}$ showed inverse statistical correlation with APACHE II score, SOFA score, serum lactate, CRP, and procalcitonin in predicting mortality. These results augment the possible prognostic role of hypozincemia in conjunction with different parameters to predict mortality in septic patients.

Guanghuan et al (2013) studied the prognostic value of serum zinc and other trace elements' levels in critically ill children with pediatric risk of mortality score III. They enrolled 31 pediatric patients; 24 of them showed overt signs of infection. They found that serum Zn concentrations were inversely correlated with mortality. They recommended that Zn supplements may be beneficial for critically ill children.

Besecker et al (2011) studied correlation between zinc metabolism and disease severity in critically ill infected and non-infected adults. 56 patients were evaluated; 22 of them were septic. They concluded that sepsis was associated with lower plasma zinc concentrations which correlated with an increased severity of illness, including cardiovascular dysfunction. However they did not investigate correlation between serum zinc levels and survival due to low mortality encountered in their study.

Liu et al (2014) studied the relation between zinc and acute phase response in an animal model of sepsis. They demonstrated that zinc deficiency enhances the acute phase response through up-regulation of a certain genetic pathway, thereby perpetuating increased inflammation that may lead to increased morbidity and mortality in response to sepsis.

Based on the theory obtained in previous researches concerning the deleterious effect of hypozincemia in septic patients and its relation to mortality, a randomized double-blind, placebo-controlled trial was done by Bhatnagar et al (2012). They used zinc as an adjunct therapy in neonates between 7 and 120 days with probable serious bacterial infection. They concluded that zinc could be given to reduce the risk of treatment failure.

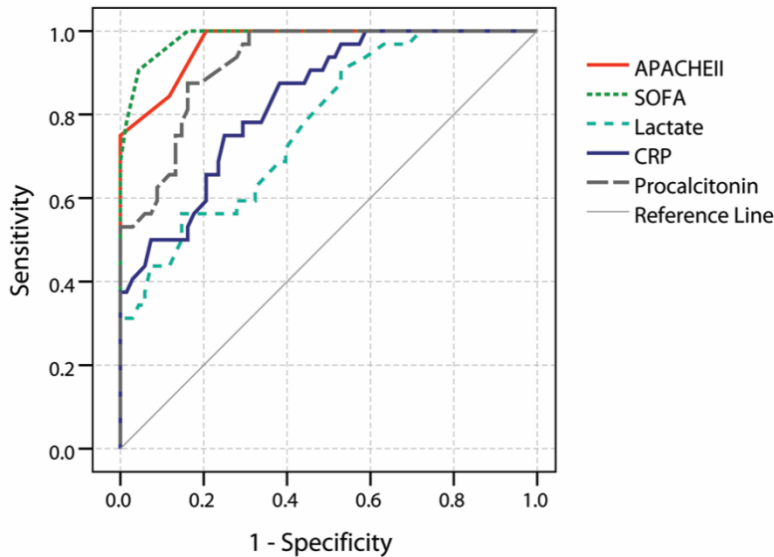


Fig 1 ROC curves in predicting mortality from APACHE II, SOFA score, Lactate, CRP, and Procalcitonin

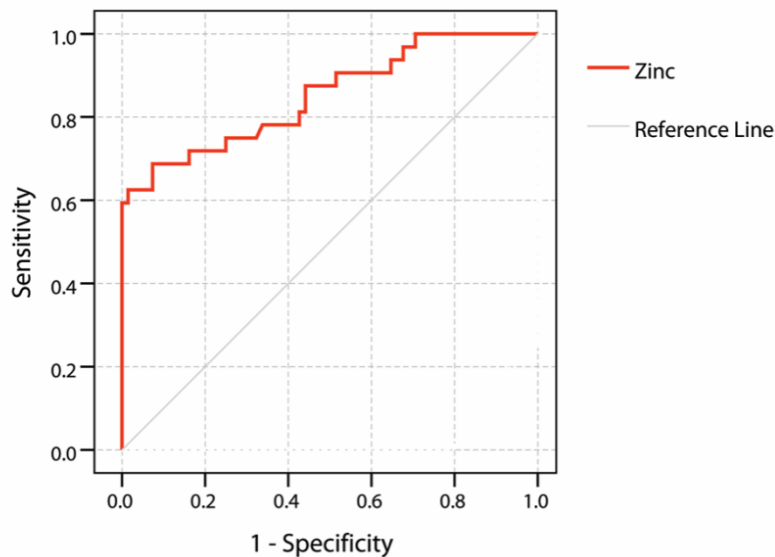


Fig 2 ROC curves in predicting mortality from Zinc

Table 1: Patients characteristics

Study variables	Median (IQR) / Frequency (%)
Age (years)	62 (55 – 71.7)

Male sex	69 (69)
Culture positive	90 (90)
APACHE II score (0-71)	18 (13–20)
SOFA score (0-24)	6 (4–10)
Lactate (mg/dl)	31.5 (23–46)
CRP (mg/dl)	70 (45–94)
Procalcitonin (ng/ml)	5.9 (3.5–8.2)
Zinc (µg/dl)	48.6 (43–62.7)
Mortality	32 (32)

Table 2: Areas under the receiver operating characteristic curves (AUC) in predicting mortality

	AUC (95% CI)	Cut-off point	Sens	Spec	PPV	NPV
APACHE II	0.969 (0.914 – 0.993)	18	100	79.4	69.6	100
SOFA	0.986 (0.939 – 0.999)	8	90.6	95.6	90.6	95.6
Lactate	0.775(0.681– 0.853)	43	56.2	85.3	64.3	80.6
CRP	0.835 (0.748 – 0.902)	78	75	75	58.5	86.4
Procalcitonin	0.925 (0.855 – 0.968)	6.3	87.5	83.8	71.8	93.4
Zinc	0.851(0.766– 0.915)	43.5	68.7	92.6	81.5	86.3

Conclusion:-

Low serum zinc levels may be one of the predictors of mortality in septic patients.

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