



**ORIGINAL ARTICLE**

**Value of Pro-Adrenomedullin in Critically Ill Septic Children in Zagazig University Hospital**

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**ABSTRACT**

**Introduction:** Sepsis is a life-threatening condition which affects many children regardless of some underlying healthcare issues. Assessment risk of mortality in critically ill septic children in pediatric intensive care units (PICUs) can be done by measuring levels of certain new biomarkers. Adrenomedullin (ADM) has been recently proposed as a useful biomarker for evaluating disease severity and risk of death. **Objective:** The purpose of this study was to measure sensitivity and specificity of ADM in assessment risk of mortality in septic children in comparison to other traditionally used biomarkers in PICUs as CRP and procalcitonin. **Method:** A prospective Cross sectional study was carried out at pediatric intensive care unit of the pediatric Department and clinical pathology department at Zagazig University Children Hospitals during the period from July 2018 to January 2019, Thirty eight infant and children patients were recruited in the study, they were selected from the pediatric intensive care unit population who suffered septicemia, blood samples withdrawn to measure sepsis markers as ADM, CRP and PCT. **Results:** There is statistically significant difference between the outcome of the studied patients and our biomarkers CRP, procalcitonin and ADM levels, we found that sensitivity of ADM 83.3%, specificity was 75% PCT sensitivity was 77.8% and specificity was 65% however 72.2% sensitivity, 65% specificity of CRP. **Conclusion:** MR-pro-ADM level have shown higher positive-predictive values than PCT and CRP levels with high sensitivity and specificity so, this study came to support MR-pro-ADM as new biomarker for evaluating individual disease severity and risk of death in critically ill septic children.

**Key words:** Pediatric intensive care unit; sepsis; MR; pro-ADM.

**INTRODUCTION**

Sepsis is a critical condition which affects many children regardless of some underlying healthcare issues [1]. Sepsis is one of the main causes of death among children even in developed countries.

For the past two decades, sepsis has been defined as “systemic inflammatory response syndrome (SIRS) caused by infection” both for adults and children [2].

In PICUs, new biomarkers have been recently used to assess risk of mortality in critically ill septic children. Mortality risk can be assessed by multiple risk scores such as

PRISM III (Pediatric Risk Mortality Score), Pediatric Multiple Organ Dysfunction Score, Sepsis-Related Organ Failure Assessment and PELOD (Pediatric Logistic Organ Dysfunction). However these scores are useful, their utility on individual level seems to be very limited [3]. Thus, combination of clinical and laboratory criteria are used for the diagnosis of sepsis. Adrenomedullin (ADM) is one of the recently used biomarker in assessment of mortality risk.

Adrenomedullin (ADM), a peptide with 52 amino acids, has immune modulating, metabolic, bactericidal and vascular actions

[4] . It is important for maintaining blood supply to organs as it is potent vasodilator [5] . Moreover, ADM also has a role in regulation and modulation of complement activity [6].ADM serum levels were shown to be increased in sepsis and monitoring of its levels is important in diagnosis and prognosis of sepsis. Regarding its immunometric analysis, it is extremely challenging as it is masked by (complement factor H) and also being rapidly cleared from the circulation [7] . Recently, scientists overcome this obstacle by measuring the more stable mid-regional fragment of pro-adrenomedullin (MR-proADM), which directly reflects levels of the rapidly degraded active peptide ADM, this fragment was found in plasma of septic children [8].

### PATIENTS AND METHODS

#### Patients and study design

A prospective Cross sectional study was performed at pediatric intensive care unit of the pediatric Department and clinical pathology department at Zagazig University Children Hospitals during the period from July 2018 to January 2019, thirty eight infant and children patients were recruited in the study ,they were selected from the pediatric intensive care unit population who suffered septicemia , a written informed consent was taken from all the patients before the start of the study. The largest percentage of the studied patients was female with age ranged from 1 to 156 months.

The study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

**Patients: Inclusion criteria** were sepsis confirmed through clinical/laboratory screen and positive culture, and diagnosed according to the International guidelines of sepsis[9] .

**Exclusion criteria** were chronic chest disease , following cardiac surgery and immunodeficiency. These diseases were excluded as they may interfere and affect levels of ADM [10] .

**Methods: Each Patient is subjected to** complete history taking including personal, past history of disease, drug, operation and present history of fever, localizing signs of sepsis, convulsion. Complete examination for patients admitted in PICU which is done for assessment of body systems including general examination for vital signs, abnormal colors e.g jaundice, pallor, skin mottling, petechiae and sclerema .Also neurological , cardiovascular and respiratory assessment was done.

**Laboratory investigation** either routine laboratory investigation as CBC ,CRP ,PCT by ELISA technique [11] and blood culture or special laboratory investigation as Mid-regional Pro-Adrenomedullin by ELISA technique were done.

#### Data analysis:

#### Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences version SPSS for Window) 16.0s 16.0, Inc., Chicago, IL, USA).

Regarding quantitative parameters, the data was tested for normality using Shapiro wilk test that revealed that data was not normally distributed. So, non parametric tests were used. Results were expressed as Median and (first quartile “Q1” -third quartile “Q3”). Mann-Whitney (MW) test was used to compare one variable in two groups. Kruskal Wallis (KW) test was used to compare one variable in more than two groups.

Categorical data are presented as absolute numbers and percentages within  $\chi^2$  -brackets. A chi<sup>2</sup> analysis or Fisher exact test was used to compare these ected cell frequency was variables when exp .less than five

Diagnostic Accuracy of CRP, Pro-calcitonin, and Mid-regional pro-adrenomedullin was assessed through receiver operating characteristics (ROC) analysis. Area under the curve (AUC), specificity and sensitivity were calculated.

Correlations between non parametric data are done using spearman correlation coefficient.

All P values were based on a 2-tailed distribution, and the corresponding P :value

- Non-significant (NS) difference if  $P > 0.05$ .
- Significant(S) difference if  $P < 0.05$ .
- Highly significant (HS) difference if  $P < 0.001$ .

### Results

The largest percentage of the studied patients was female (63.2%) with age ranged from 1 to 156 months with mean age 33.79 as shown in **Table (1)**.

There is significant difference between patients who need and those who don't need mechanical ventilation and serum Midregional pro-adrenomedullin, also patients who need inotrope had higher levels of serum Midregional pro-adrenomedullin ( $p > 0.05$ ) as shown in **Table (2)**.

The largest percentage of studied patients were alive by the end of the study , also there is statistically non-significant difference between the outcome of the studied patients and demographic characteristics (the largest percentage in each group were female).

**Table (3)** shows type of organism detected in blood cultures; 36.8% of patients had klebsiella, 26.3% patients had pseudomonas, 18.4% of patients had staph hemolytics, 15.8% patients had acenitobacter

baumanni and 2.6% of patients had staph aureus.

There is statistically non-significant difference between the outcome of the studied patients regarding TLC and hemoglobin while there is statistically significant difference between them concerning platelet count which was lower in patients who died as shown in **Table (4)**.

There is statistically significant difference between the outcome of the studied patients and both CRP and procalcitonin levels (were lower among patients who died by the end) , also there is statistically significant difference between the outcome of the studied patients and serum MR pro-adrenomedullin level as shown in **Table (5)**.

**Figure (1)** Boxplot showing serum MR proadrenomedullin level in relation to outcome of the studied patients.

**Figure (2):** ROC curve showed performance of serum midregional pro-adrenomedullin in predicting mortality in the studied patients.

The best cutoff of serum MR-proadrenomedullin in prediction in mortality of the studied patients is  $\geq 196.431$  with area under curve 0.842 and sensitivity 83.3%, specificity 75%, PPV 75%, NPV 83.3%, positive likelihood ratio 3.33 and negative likelihood ratio 0.22 with accuracy 87.9 %.

**Table (1): Distribution of the studied patients according to demographic characteristics:**

	N	%	
<b>Gender:</b>			
Male	14	36.8	
Female	24	63.2	
	<b>Mean <math>\pm</math> SD</b>	<b>Median</b>	<b>Range</b>
Age (months)	33.79 $\pm$ 40.02	21	1 – 156

**Table (2): Relation between need for MV and inotropes and serum midregional pro-adrenomedullin in the studied patients:**

	Midregional pro-adrenomedullin		
	Mean $\pm$ SD	Z	P
<b>Mechanical ventilation:</b>			
No	55.9 $\pm$ 21.79	-3.296	<0.001**
Yes	480.62 $\pm$ 363.36		
<b>Inotrope:</b>			
No	244.67 $\pm$ 314.15	-1.446	0.148
Yes	450.42 $\pm$ 376.02		

**Table (3): Distribution of the studied patients according to disease and blood culture:**

	N	%
<b>Disease:</b>		
Aspiration pneumonia	3	7.9
Bronchopneumonia	9	23.7
Pneumonia	12	31.6
CMV pneumonitis	2	5.3
CNS infection	7	18.4
Gastroenteritis	3	7.9
Enterocolitis	1	2.6
<b>Bacteria:</b>		
Acenitobacter	6	15.8
Klebseilla	14	36.8
Pseudomonas	10	26.3
Staph aureus	1	2.6
Staph hemolyticus	7	18.4

**Table (4): Comparison between outcomes of the studied patients regarding CBC findings:**

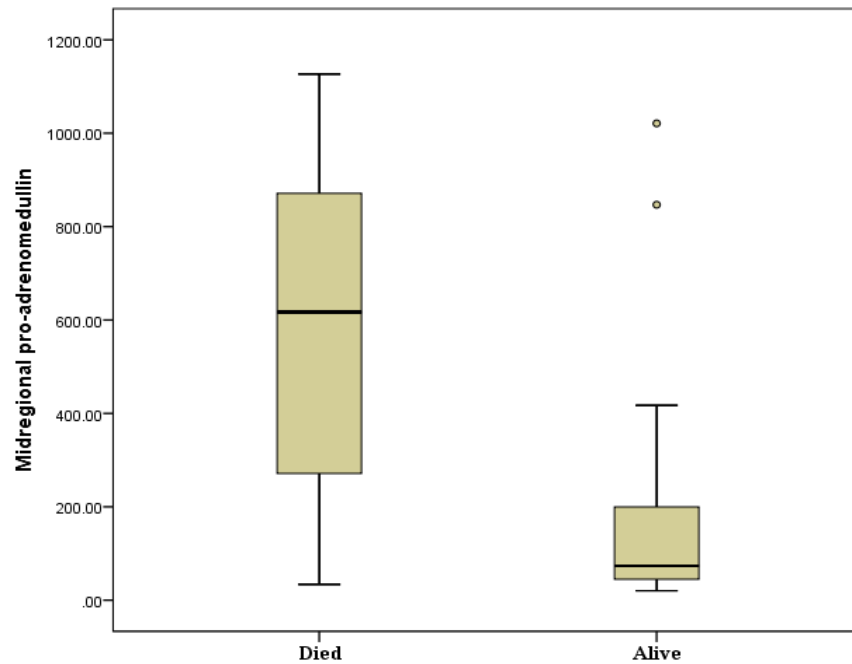
	Died (18)		Alive (20)		Z	P
	Mean ± SD	Median	Mean ± SD	Median		
TLC (X1000/ $\mu$ L)	13.72 ± 11.81	12.15	12.38 ± 5.22	12.4	-0.38	0.704
Hemoglobin (g/dl)	10.76 ± 1.77	11.1	10.14 ± 1.34	9.95	t(1.225)	0.229
Platelet count (X1000/ $\mu$ L)	156.67 ± 155.65	95	300.6 ± 207.42	253.5	-2.5	0.012*

Z Mann Whitney test t independent sample t test \*p<0.05 is statistically significant

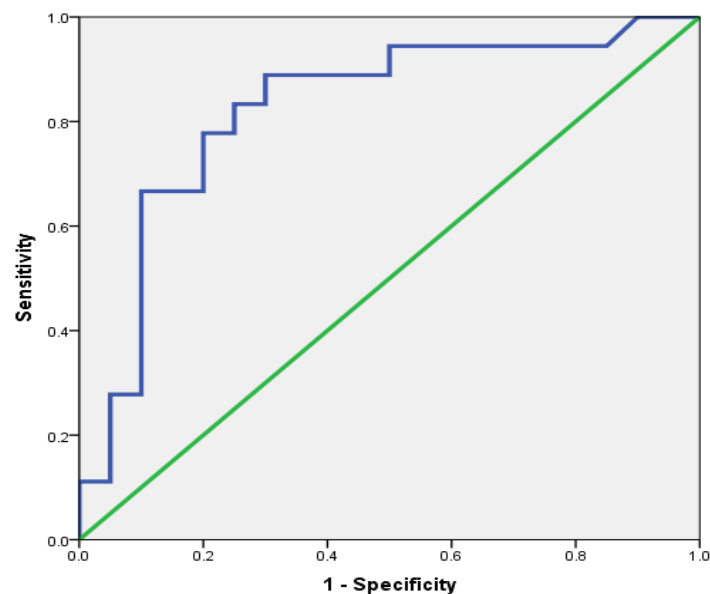
**Table (5): Comparison between outcome of the studied patients regarding CRP and procalcitonin and ADM levels:**

	Died (18)		Alive (20)		Z	p
	Mean ± SD	Median	Mean ± SD	Median		
CRP (mg/dl)	127.8 ± 100.75	126.68	58.76 ± 56.77	38.97	-2.222	0.026*
Procalcitonin (ng/ml)	9.83 ± 14.16	4.89	3.07 ± 4.51	0.78	-2.384	0.017*
MR pro ADM (pg/ml)	585.45 ± 344.83	617.1	195.15 ± 278.63	73.58	-3.406	0.001**

SFR



**Figure (1):** Boxplot showing serum MR proadrenomedullin level in relation to outcome of the studied patients.



**Figure (2):** ROC curve showed performance of serum midregional pro-adrenomedullin in prediction of mortality in the studied patients.

## DISCUSSION

The study included 38 patients with septicemia with median age 21 months 63.2% of them were female. Our data showed that there was no statistical significant difference between patient age and MR-pro-ADM level, those results are in agreement with **Angeletti et al.** [12].

Cases of the study showed high percentage of pneumonia 44.8% followed by bronchopneumonia 23.7 %, CNS infection

18.4 %, 7.9% for GE and only 2.6% for enterocolitis. This may be due to timing of the study with high prevalence of chest diseases at that time and random selection by the candidate.

Cultures are the gold standard test for diagnosis of sepsis according to site of infection; in our study we studied 38 patients with sepsis. The main etiological agents were gram negative organisms (30/38). The most prevalent organism was *Klebsiella pneumoniae*

(36.8%). This comes in agreement with the study of **Dzwonek et al.** [13], in which nearly half of the positive blood cultures grew *Klebsiella pneumonia*, also in the study of **De Benedetti et al.** [14], the isolated pathogens included *Klebsiella pneumonia* (47.5%) in neonatal intensive care unit.

In contrast to our study, **São Pedro et al.** [15] studied 115 patient with sepsis in pediatric ICU 40 of them were culture positive, most prevalent organism was *Staph. aureus* (27.5%). This variation may be attributed to differences in the environment, the microbial etiology of sepsis and supportive care practice between centers.

In our study, mean hemoglobin was 10.43 and mean platelet count was 232.42 while mean total leucocytic count in the studied patients was 13.01, **Alcoba et al.**, [16] stated that mean TLC was 15 and this may be attributed to different mean age in his study and severity of sepsis.

Also in our study, there is statistically non-significant positive correlation between serum MR- proadrenomedullin level and both TLC and platelet count while there is statistically non-significant negative correlation between it and hemoglobin level.

The hematological system is important in the response to sepsis and also plays an important role in the resolution of severe sepsis [17]

**Simon et al.**, [18] found that mean PCT 4.07 while that of CRP was 71, these values are in line with our results that showed that, mean CRP in the studied patients was 91.46, mean procalcitonin was 6.27 while that of MR-pro-ADM was 380.01 ranged from 20.21 to 1126.39.

CRP which is one of the acute phase proteins, is highly sensitive but poorly specific for bacterial infections. Despite being poorly specific for infections, it is still used as a screening test for early onset neonatal sepsis [19].

In the current study, Twenty nine patients underwent ventilation. Mean duration of ventilation in days in the studied patients was 7.86, ranged from 1 to 30 days with statistically non-significant positive correlation between serum MR-

proadrenomedullin level and ventilation duration (in days), this was supported by other investigators such as **Jordan et al.**, [20] who concluded that median values of MR-pro-ADM levels were significantly higher when patients needed mechanical ventilation.

One proposed mechanism for explanation of those results is development of ARDS in those patients who needed mechanical ventilation which was supported by **Luhr et al.**, [21].

The largest percentage of studied patients were alive by the end of the study, 18 were died (47.4%) and 20 were alive (52.6%) with no significant difference between the outcome of the studied patients and demographic characteristics (the largest percentage in each group were female).

Regarding relation between outcome of the studied patients and CBC parameters, there is statistically non-significant difference between the outcome of the studied patients regarding TLC and hemoglobin while there is statistically significant difference between them concerning platelet count which was lower in patients who died.

Similar to our results, **Abdel Motalib et al.**, [22] found that there was significant difference about platelet count only but not RBCS count in study about neonatal sepsis.

Our observation is explained by **Acikgoz et al.**, [23] who said that sepsis associated thrombocytopenia is multifactorial. Inflammatory mediators and bacterial endotoxin can enhance platelet reactivity and adhesivity, also autoantibodies to specific platelet antigen had been detected.

The best single biomarker such as CRP, procalcitonin, interleukin 6, interleukin 8, presepsin or their combination has not been identified. Therefore, it was recently suggested that additional studies are necessary to identify more accurate biomarkers of sepsis [24].

In the present study, there is statistically significant difference between the outcome of the studied patients and both CRP and procalcitonin levels, also there is statistically significant difference between the outcome of the studied patients and serum MR

pro-adrenomedullin level. These results come in agreement with that of **Albrich et al.**, [25] who found that ADM levels have been significantly higher in cases of hospital mortality.

In our study, there is statistically significant difference between the outcome of the studied patients and duration of ventilation (in days). The patients who died had longer duration of ventilation. These results are consistent with that of **Christ-Crain M and Opal SM** [26]. This finding could be attributed to development of VAP in those patients as **Boomer et al.**, [27].

Regarding performance of our three biomarkers in the current study in predicting mortality in the studied patients: The best cutoff of serum MR-proadrenomedullin is  $\geq 196.431$  with area under curve 0.842 and sensitivity 83.3%, specificity 75%, PPV 75%, NPV 83.3%, that of PCT is  $\geq 1.06$  with area under curve 0.726 and sensitivity 77.8%, specificity 65%, PPV 66.7%, NPV 76.5%, While that of CRP is  $\geq 50.25$  with area under curve 0.711 and sensitivity 72.2%, specificity 65%, PPV 65%, NPV 72.2%.

Those results are similar to **Christ-Crain M and Opal SM** [26] who stated that MR-pro-ADM levels showed higher PPVs than PCT and CRP (31 vs 21.6% and 15.8%, respectively).

### Conclusion

MR-pro-ADM level exhibited higher positive-predictive values than PCT and CRP levels with high sensitivity and specificity so, this study came to support MR-pro-ADM as new biomarker for evaluating individual disease severity and risk of death in critically ill septic children, ADM levels have been significantly higher in those patients having the worst forms of disease: need of mechanical ventilation and use of inotropes.

### Recommendations

MR-pro-ADM can be used as a new biomarker for sepsis in infant and children, this biomarker can be measured at the first moment of patient admission, and it is simple and fast to determine. CRP and PCT are still valuable markers for sepsis, further studies on large number of cases and with serial

measurement are needed to discover accuracy of MR-pro-ADM to assess prognosis of sepsis.

### Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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### REFERENCES

- 1-Watson RS, Carcillo JA, Linde-Zwirble WT, Clermont G, Lidicker J, Angus DC.** The epidemiology of severe sepsis in children in the United States. *Am J Respir Crit Care Med* 2003; 167(5):695–701.
- 2-Goldstein B, Giroir B, Randolph A.** International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics *Pediatr Crit Care Med* 2005; 6: 2–8.
- 3-Lacroix J, Cotting J.** For the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) network. *Pediatr. Crit. Care. Med* 2005; 126–134.
- 4-Linscheid P, Seboek D, Zulewski H, Keller U, Müller B.** Autocrine/paracrine role of inflammation-mediated calcitonin gene-related peptide and adrenomedullin expression in human adipose tissue. *Endocrinology* 2005; 146:2699–708.
- 5-Eto T.** A review of the biological properties and clinical implications of adrenomedullin and proadrenomedullin N-terminal 20 peptide (PAMP), hypotensive and vasodilating peptides. *Peptides* 2001; 22:1693-1711.
- 6-Martínez A, Pío R, Zipfel PF, Cuttitta F.** Mapping of the adrenomedullin-binding domains in human complement factor H. *Hypertens Res* 2003; 55-59.
- 7-Kato J, Tsuruda T, Kitamura K, Eto T.** Adrenomedullin: a possible autocrine or paracrine hormone in the cardiac ventricles. *Hypertens Res* 2003; 113-119.
- 8-Struck J, Tao C, Morgenthaler NG, Bergmann A.** Identification of an adrenomedullin precursor fragment in plasma of sepsis patients. *Peptides* 2004; 25:1369-72.
- 9-Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R et al.** Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock. *Crit. Care Med* 2008; 6, 296–327.
- 10-Abella R, Satriano A, Frigiola A, Varrica A, Gavilanes A, Zimmermann LJ et al.** Adrenomedullin alterations related to cardiopulmonary bypass in infants with low cardiac output syndrome. *J. Matern. Fetal Neonatal Med* 2012 ; 25(12), 2756–2761.

- 11-Abdel Mohsen A, Kamel BA.** Predictive values for procalcitonin in the diagnosis of neonatal sepsis. *Electron Physician* 2015; 7:1190-1195.
- 12- Angeletti S, Battistoni F, Fioravanti M, Bernardini S, Dicuonzo G.** Procalcitonin and mid-regional pro-adrenomedullin test combination in sepsis diagnosis. *Clin Chem Lab Med* 2013; 51(5): 1059–1067.
- 13- Dzwonek AB, Neth OW, Thiébaud RI.** The role of mannose-binding lectin in susceptibility to infection in preterm neonates. *Pediatr Res* 2008; 63 (6) :680-685.
- 14-De Benedetti F, Auriti C, D'urbano LE.** Low serum levels of mannose binding lectin are a risk factor for neonatal sepsis. *Pediatr Res* 2007; 61: 325-328.
- 15- São Pedro TC, Morcillo AM, Baracat EC.** Etiology and prognostic factor of sepsis among children and adolescents admitted to the intensive care unit. *Rev Bras Ter Intensiva* 2015; 27 (3): 240-246.
- 16-Alcoba G, Manzano S, Lacroix L ,Galletto-Lacour A, Gervaix A.** Proadrenomedullin and copeptin in pediatric pneumonia: a prospective diagnostic accuracy study. *BMC Infect Dis* 2015; 15:347.
- 17- Aird WC .** The hematologic system as a marker of organ dysfunction in sepsis. *Mayo Clin Proc* 2003; 78(7): 869-881.
- 18- Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J.** Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. *Clin Infect Dis* 2004;39:206 – 17.
- 19- Pizzolato E, Ulla M, Galluzzo C, Lucchiari M, Manetta T, Lupia E et al.** Role of presepsin for the evaluation of sepsis in the emergency department. *Clin Chem Lab Med* 2014; 52(10): 1395-1400.
- 20-Jordan I, Corniero P, Balaguer M, Ortiz J, Vila D, Velasco J et al.** Adrenomedullin is a useful biomarker for the prognosis of critically ill septic children. *Biomark. Med* 2014; 1065–1072.
- 21-Luhr OR, Antonsen K, Karlsson M, Aardal S, Thorsteinsson A, Frostell CG et al.** Incidence and mortality after acute respiratory failure and acute respiratory distress syndrome in Sweden, Denmark and Iceland. *Am. J. Respir. Crit. Care Med* 1999; 159:1849–1861.
- 22-Abdel Motalib T , Khalaf FA,El Hendawy G, E Kotb SE, Ali AM, El Sharnoby A.** Soluble CD14-subtype (Presepsin) and hepcidin as diagnostic and prognostic markers in early onset neonatal sepsis. *Egypt J Med Microbiol* 2015; 24 (3): 45-52.
- 23- Acikgoz S, Akduman D, Eskici Z, Can M, Mungan G, Guven B et al .**Thrombocyte and erythrocyte indices in sepsis and disseminated intravascular coagulation. *J Med Biochem* 2012; 31: 60-64.
- 24- Poggi C, Bianconi T, Gozzini E, Generoso M, Dani C.** Presepsin for the Detection of Late-Onset Sepsis in Preterm Newborns. *Pediatrics* 2015; 135: 68-76.
- 25- Albrich WC, Dusemund F, Rüegger K, Christ-Crain M, Zimmerli W, Bregenzer T et al.** Enhancement of CURB65 score with proadrenomedullin (CURB65-A) for outcome prediction in lower respiratory tract infections: derivation of a clinical algorithm. *BMC Infect. Dis* 2011; 11, 112–123.
- 26- Christ-Crain M, Opal SM.** The role of biomarkers in the diagnosis and management of community-acquired pneumonia. *Crit. Car* 2010; 14(1), 203–213.
- 27-Boomer JS, To K, Chang KC, Takasu O, Osborne DF, Walton AH, et al.** Immunosuppression in patients who die of sepsis and multiple organ failure. *Jama* 2011; 306(23):2594–605.

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