Adiponectin as a Predictor for the Severity of Sepsis in ICU Patients

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Abstract: Sepsis is widely diagnosed In ICU patients. The sepsis markers are numerous with variable sensitivity and specificity. Adiponectin is a protein hormone that is secreted from adipose tissue into the bloodstream. It is a key substance in metabolic syndrome and has an anti-inflammatory property. The relationship between adiponectin and sepsis is unclear. In the current study, we aim to demonstrate that low plasma adiponectin level could be an early predictor for morbidity and mortality of sepsis by its comparison with c-reactive protein, serum lactate and procalcitonine. Thirty patients admitted to the intensive care unit with picture clinically suggesting sepsis were enrolled in the study. Predisposition, insult/infection, response, and organ dysfunction (PIRO) score was used to follow the course of the septic process. Plasma adiponectin level, serum lactate level, procalcitonin level(PCT), c-reactive protein(CRP) were checked on day1 then day 4 then day 7 and so on until ICU discharge or demise for a total of 28 days . PIRO score was able to expect sepsis prognosis with high statistical significance. Procalcitonin, serum lactate and adiponectin were valuable in follow up the sepsis prognosis with P value (0, 0.01 & 0 respectively) on the contrary CRP had poor prognostic value in sepsis follow up (P value 0.16).We conclude that PIRO score is an effective model for staging of sepsis and predict mortality. Measuring serial procalcitonin levels may be the most useful in order to understand the trend, identify the peak, and be able to identify resolution of sepsis. Early high lactate level is a predictor for poor prognosis of sepsis. Adiponectin is similar to procalcitinin in early detection of sepsis & can be used as a prognostic indicator with considering that adiponectin level could be affected by other metabolic disorders.

Keywords: Sepsis, Sepsis Markers, PIRO Score, Adiponectin

1. Introduction

Approximately 40% of all intensive care unit patients have sepsis on admission to the intensive care unit or experience sepsis during their stay in the intensive care unit [1]. Crude in-hospital mortality rates ranged from 16.9% in uninfected patients to 53.6% in patients who were infected [2].

Systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock were initially defined by the American College of Chest Physicians (ACCP) and Society of Critical Care Medicine (SCCM) [3]. These definitions were reconsidered in 2001 during an International Sepsis Definitions Conference [4]. A practical modification of the definitions has since been published, which provides exact hemodynamic definitions for septic shock [5].

Systemic inflammatory response syndrome is the clinical syndrome that results from a dysregulated inflammatory response to a noninfectious insult. It requires that two or more of the following abnormalities be present, temperature >38.3ºC or <36ºC, heart rate >90 beats/min, respiratory rate >20 breaths/min or PaCO2 <32 mmHg, WBC >12,000 cells/mm3, <4000 cells/mm3, or >10 percent immature (band) forms. Sepsis is the clinical syndrome that results from a dysregulated inflammatory response to an infection. Severe sepsis refers to sepsis plus at least one of the signs of hypoperfusion or organ dysfunction. Septic shock

exists if there is severe sepsis plus one or both of the following, systemic mean blood pressure is <60 mmHg despite adequate fluid resuscitation and maintaining the systemic mean blood pressure >60 mmHg requires dopamine >5 mcg/kg per min, norepinephrine >0.25 mcg/kg per min, or epinephrine >0.25 mcg/kg per min despite adequate fluid resuscitation [6].

A number of risk factors exist for the development and progression of sepsis, including advanced age, compromised immune system response, chronic illness, broad-spectrum antibiotic use, and exposure to infection risk associated with surgical and invasive procedures [7].

Many believe that sepsis develops as a result of exuberant production of proinflammatory molecules, lysosomal enzymes, superoxide-derived free radicals, vasoactive substances, such as platelet-activating factor (PAF), tissue factor (TF), and plasminogen activator inhibitor-1 (PAI-1) [8]. This occurs in conjunction with increases in the expression of inducible nitric oxide (NO) synthase, increasing production of NO resulting in coagulopathy, endothelial dysfunction, vascular instability, and eventually to apoptosis (i.e. programmed cell death) and multi-organ failure [8].

A marker of sepsis has been defined as a measure that predicts the presence or severity of the disease. To be a useful, the substance being measured must rise above normal levels early in the course of the infectious process [9].

Sepsis biomarkers have included procalcitonin (PCT) [10], various interleukins (ILs) [10], eosinophil count [11], adrenomedullin (ADM) and pro-ADM [12], atrial natriuretic peptide (ANP) and pro-ANP, [13], pro-vasopressin (copeptin) [12], interferon-γ (IFN-γ) [14], triggering receptor expressed on myeloid cells 1 (TREM-1) [14], resistin [15] and CD64 expression on the neutrophil membrane [16&17].

C-Reactive Protein (CRP) is acute-phase protein released by the liver after the onset of inflammation or tissue damage. Some studies showed the value of CRP as a marker of sepsis [18] and other studies showed a limited value of CRP as a marker of sepsis [19].

Procalcitonin PCT has been studied as a possible marker of sepsis with a superior sensitivity and specificity [20] and, in some countries, is now being included in routine clinical practice and guideline recommendations [21]. PCT is a propeptide of calcitonin and is normally produced in the C-cells of the thyroid gland and the normal PCT levels are very low (<0.2 ng/ml). During sepsis, PCT is produced by extrathyroid tissues (monocytes, liver) resulting in high levels [22&23].

The normal blood lactate concentration in unstressed patients is 0.5-1 mmol/L. Hyperlactatemia is defined by lactate concentrations above 2mmol/L and in patients with septic shock lactate levels are more than (5 mmol/L) [24]. A single venous lactate measurement above 4 mmol/l predicted short-term and in-hospital risk for death in patients with suspected infection [25].

Adiponectin is an anti-inflammatory adipokine secreted by adipose tissue. Its deficiency is associated with increased mortality and morbidity in septic patients [26& 27]. Adiponectin contains 247 amino acids. The circulating plasma range of adiponectin in human subjects is 3-30 μg/mL [28]. The secretion of adiponectin by adipocytes appears to be hormone regulated [29]. Compared to other adipokines such as leptin and resistin, both considered being proinflammatory [30&31].

Adiponectin deficiency may cause the severe systemic inflammatory response and high mortality [32]. The degree of decreasing plasma adiponectin levels during sepsis might depend on the insult severity. It has been reported that recombinant adiponectin improved mortality in sepsis [33].

The aim of our study is to demonstrate that low plasma adiponectin level could be an early predictor for morbidity and mortality of sepsis by its comparison with CRP, serum lactate and procalcitonin levels.

2. Patients and Methods

The study involved thirty patients admitted to the ICU with picture suggesting sepsis. Inclusion criteria, age ≥19 years [below this age group the adiponectin levels are not stable in relation to body fat cells], body mass index (BMI) equals or more than 25kg/m², informed consent given by the patient or first degree relative and sepsis criteria, [clinically suspected infection confirmed infection and 2 or more of the following; Temperature >38ºC or <36ºC, heart rate (HR) > 90/min, Respiratory rate (RR) > 20/min or PaCO2 < 32 mmHg, White blood cell count > 12,000/mm³ or < 4000/m³]. Exclusion criteria, age < 19 years, BMI < 25kg/m², chronic renal failure [adiponectin level is double fold elevated in chronic renal failure].

Each was subjected to; detailed history, physical examination and laboratory investigations (CBC, serum creatinine, urea, AST, ALT, total proteins, albumin, total bilirubin, coagulation profile and ABGs). These routine laboratories investigations were withdrawn on study day 1 and subsequently thereafter every day until ICU discharge or demise. Specific laboratory investigations include plasma adiponectin level, serum lactate level, procalcitonin level (PCT) and C-reactive protein (CRP). These specific Labs were done on day1, day 4, day 7 and so on until ICU discharge or demise for a total of 28 days.

Microbiological studies included pan cultures (sputum, blood, urine or biological fluid) and imaging studies were done to identify the source of sepsis.

Clinical data; length of ICU stay, final outcome and need for organ supportive measures (vasopressors, mechanical ventilation and/or hemodialysis) were reported for all patients until ICU discharge or demise.

Scoring system; *Predisposition, insult/infection, response and organ dysfunction (PIRO) score* is an effective model for staging of sepsis and seems to be predictive of mortality.

Table (1). *variants and scoring parameters on which PIRO score depends.*

Predis-position	P0: Age _46 yrs	P1: Age 46–64 yrs, no CLD	P2: Age 64–85 yrs, no CLD and no congestive cardiomyopathy	P3: Age 46–64 yrs with CLD or 64–85 yrs with Congestive cardiomyopathy	P4: Age 64–85 yrs with CLD or age _85 yrs
Insult/ infection	I0: CA-UTI Gramnegative	I1: CA-UTI not Gramnegative	I2: CA infection except CA-UTI or nosocomial Grampositive	I3: Nosocomial acquired infection except Gram-positive or nosocomial fungal nonabdominal infection	I4: Nosocomial abdominal fungal infection
Response	R0: No tachycardia and/or no tachypnea	R1: Both tachycardia and Tachypnea			
Organ dysfunction	O0: 2 OF	O1: 3 OF, 1 hepatic	O2: 3 OF, none hepatic	O3: 4 OF	O4: 5 OF

CLD, chronic liver disease; CA-UTI, community-acquired urinary tract infections; OF, organ failures.

PIRO gives the patient scale from 0-13 according to the parameters explained in the table and the higher the scale the more the morbidity and mortality from the septic process. The data collected was tabulated and statistically analyzed.

Statistical methods:

IBM SPSS statistics (V. 20.0, IBM Corp., USA, 2011) was used for data analysis. Data were expressed as the mean ± standard deviation (SD) for numerical variables. $P \leq 0.05$ was considered to be statistically significant and $P < 0.01$ considered being highly statistically significant.

3. Results

The study involved thirty patients admitted to the ICU with picture suggesting sepsis. Fifteen from the included patients were discharged safely from the ICU while fifteen died.

Table (2). *Demographic data of the cases (n=30):*.*

	N	Min	Max	Mean	SD
Age(years)	30	29	97	65.33	14.528
Weight (Kg)	30	58	160	93.1	18.578
Height(m)	30	151	178	164.67	9.36
BMI(Kg/m²)	30	29.1	62.5	35.47883	7.222227

Table (3). *Comparison between discharged and died patients as regards BW, Ht & BMI*.*

	Out-Come	N	Mean	SD	T	P	Sig.
BW	Disch.	15	85.53	22.196			
	Died	15	100.67	9.978	2.408	0.026	S
Ht	Disch.	15	165.53	9.613			
	Died	15	163.8	9.352	0.501	0.621	NS
BMI	Disch.	15	33.2167	8.785592			
	Died	15	37.745	4.45596	1.782	0.089	NS

*Independent t test. * Data are presented as mean ± standard deviation.
BW: body weight, Ht: height, BMI: body mass index

There was positive correlation between the mortality versus the body weight with P-value (0.026), while no significant correlation was detected versus the height or the BMI.

Table (4). *Sex Outcome Cross tabulation:*.*

		Outcome		Total
		Disch.	Died	
Female	Count	6	5	11
	% within Outcome	40.0%	33.3%	36.7%
Male	Count	9	10	19
	% within Outcome	60.0%	66.7%	63.3%
Total	Count	15	15	30
	% within Outcome	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	P
Pearson Chi-Square	.144a	.705

It was found that the gender had no significant relation to the outcome.

Table (5). *Correlations between adiponectin (µg/L) versus other variables in cases (n=30): *.*

		Age	Wt	Ht	BMI
Adiponectin_dC	R	-0.31	-0.394	0.141	0.24
	P	0.095	0.031	0.459	0.201
	Sig.	NS	S	NS	NS

*dC = delta change: for correlation with other variables

There was negative correlation between adiponectin (µg/L) versus BW with P-value 0.031.

Table (6). *Correlations between adiponectin (µg/L), CRP (mg/L), Procalcitonin (µg/L), Lactate (mmol/L) versus PIRO score in cases (n=30): *.*

		PIRO_dC
CRP_dC	R	0.121
	P	0.525
	Sig.	NS
Procal_dC	R	0.672
	P	0
	Sig.	HS
Lact_dC	R	0.434
	P	0.016
	Sig.	S
Adipo_dC	R	-0.524
	P	0.003
	Sig.	HS

*dC = delta change : for correlation with other variables

There was negative correlation between adiponectin (µg/L) versus PIRO score with highly significant P-value 0.003. There was positive correlation between prcalcitonin (µg/L)

versus PIRO score with significant P-value 0.

There was positive correlation between lactate (mmol/L) versus PIRO score with highly significant P-value 0.016.

While no significant correlation was detected between CRP(mg/L) versus PIRO score.

Table (7). Prognostic value of PIRO score.

	PIRO_Sc_day 1	PIRO_Sc_day 4	PIRO_Sc_day 7	PIRO_Sc_day 10	PIRO_Sc_day 13	PIRO_Sc_day 17	PIRO_Sc_day 20	PIRO_Sc_day 23	PIRO_Sc_day 27	PIRO_dC
Z	-1.888	-3.333	-3.559	-3.298	-0.748	-1.528	-1.557	-1.528	-0.748	-3.054
P	0.059	0.001	0	0.001	0.455	0.127	0.12	0.127	0.455	0.002
Sig.	NS	HS	HS	HS	NS	NS	NS	NS	NS	HS

* Wilcoxon Rank Sum Test

On comparing the values of PIRO score that were serially detected in all cases those who were discharged & those who died the score was able to expect the prognosis with high statistical significance during days 4, 7 & 10 with P values 0.001, 0 & 0.001 respectively.
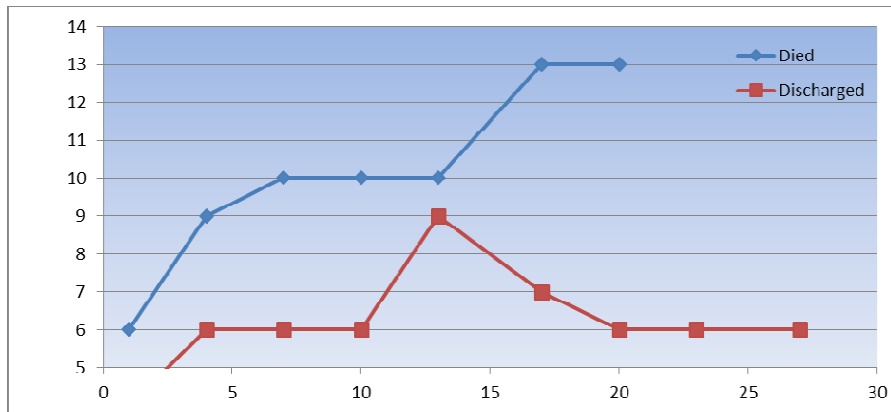
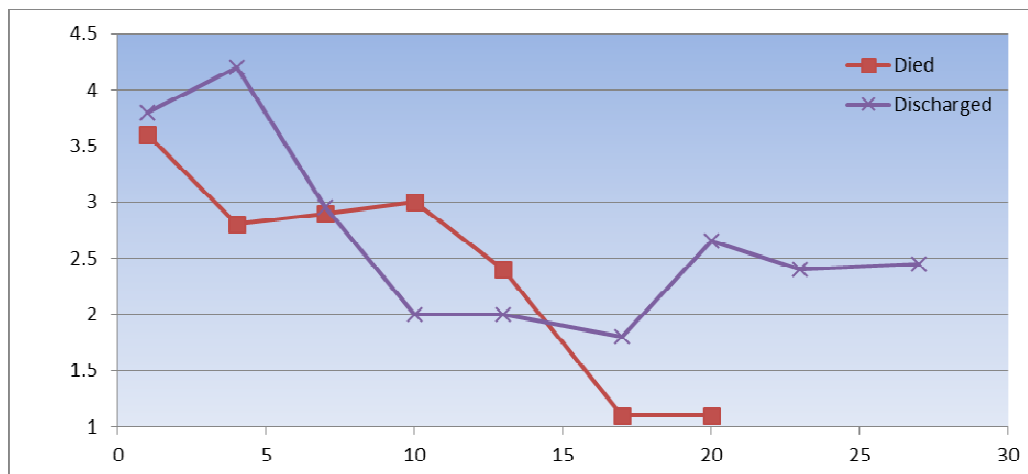*Figure (1). Follow-up chart to study PIRO score pattern among different times for both died discharged patients.*

Table (8). Prognostic value of S. adiponectin (µg/L).

	Adipo_day 1	Adipo_day 4	Adipo_day 7	Adipo_day 10	Adipo_day 13	Adipo_day 17	Adipo_day 20	Adipo_day 23	Adipo_day 27	Adipo_dC
Z	-0.146	-1.455	-0.679	-0.753	-0.298	-1.528	-1.5	-1.455	-0.146	-4.21
P	0.884	0.146	0.497	0.451	0.766	0.127	0.134	0.146	0.884	0
Sig.	NS	NS	NS	NS	NS	NS	NS	NS	NS	HS

* Wilcoxon Rank Sum Test

On comparing the values of Adiponectin that were serially detected in all cases those who were discharged & those who died The degree of change due to follow-up study (delta change or dC) that reflects the actual different changes through the follow-up study was highly significant with P-value 0 .

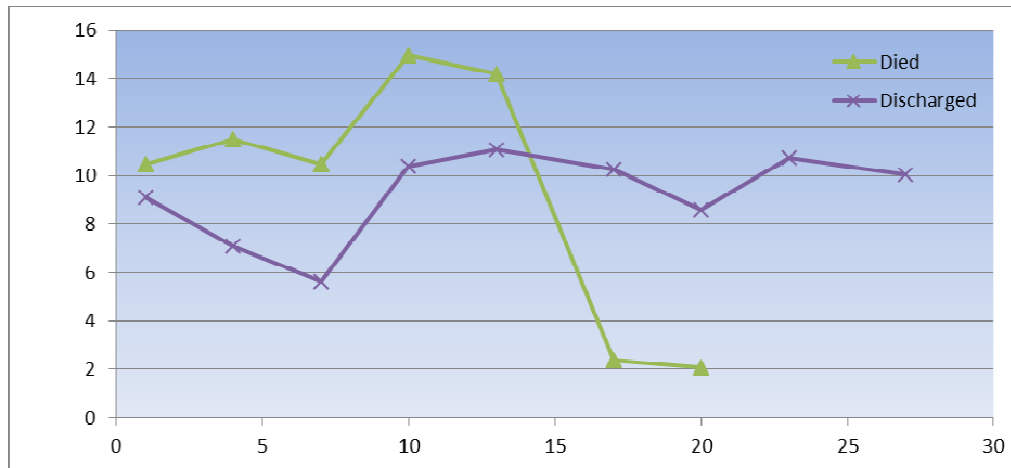*Figure (2). Follow-up chart to study Adipo. Pattern among different times for both died discharged patients.*

Table (9). Prognostic value of S. Procalcitonin (μg/L).

Z	Procal_day 1	Procal_day 4	Procal_day 7	Procal_ day 10	Procal_ day 13	Procal_day 17	Procal_day 20	Procal_day 23	Procal_day 27	Procal_dC
P	-0.062	-1.742	-1.57	-0.883	-0.293	-1.514	-1.5	-1.514	-1.57	-3.588
Sig.	0.95	0.081	0.116	0.377	0.77	0.13	0.134	0.13	0.116	0
	NS	NS	NS	NS	NS	NS	NS	NS	NS	HS

* Wilcoxon Rank Sum Test

On comparing the values of Procalcitonin that were serially detected in all cases those who were discharged & those who died The degree of change due to follow-up study (delta change or dC) that reflects the actual different changes through the follow-up study was highly significant with P-value 0 .
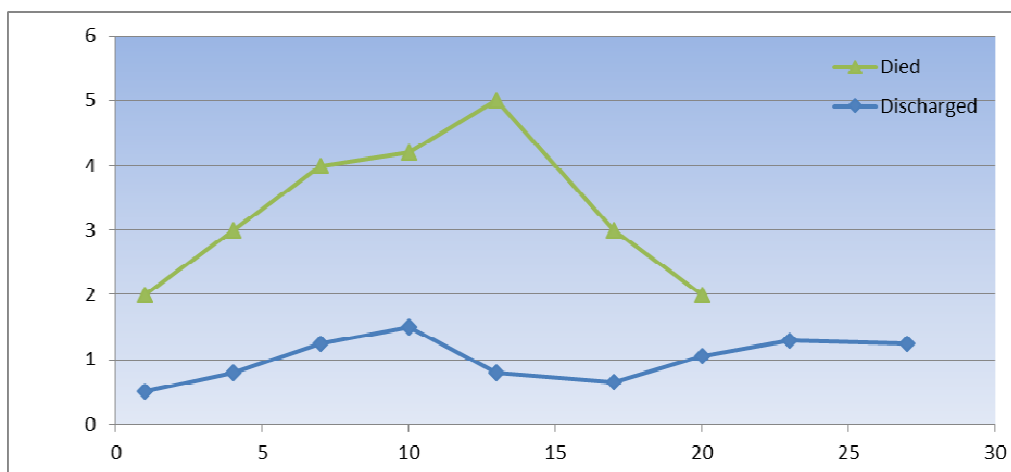

Figure (3). Follow-up chart to study Procal.pattern among different times for both died discharged patients.

Table (10). Prognostic value of S. Lactate (mmol/l).

	Lactate_day 1	Lactate day_4	Lactate_day7	Lactate_day10	Lactate_day13	Lactate_day17	Lactate_day 20	Lactate_day 23	Lactate_day 27	Lact_dC
Z	-2.009	-3.433	-3.352	-3.19	-1.794	-0.509	-0.757	-2.009	-2.009	-2.554
P	0.045	0.001	0.001	0.001	0.073	0.611	0.449	0.045	0.045	0.011
Sig	S	HS	HS	HS	NS	NS	NS	S	S	S

* Wilcoxon Rank Sum Test

On comparing the values of Lactate that were serially detected in all cases those who were discharged & those who died although the values detection serially had variable significance The degree of change due to follow-up study (delta change or dC) that reflects the actual different changes through the follow-up study was significant with P-value 0.011 .

Figure (4). Follow-up chart to study Lactate pattern among different times for both died discharged patients.

Table (11). Prognostic value of CRP (mg/dl).

	CRP_ day 1	CRP_ day 4	CRP_ day 7	CRP_ day 10	CRP_ day 13	CRP_ day 17	CRP_ day 20	CRP_ day 23	CRP_ day 27	CRP_dC
Z	-0.291	-1.639	-0.246	-0.132	-0.588	-1.514	-1	-0.132	-0.588	-1.39
P	0.771	0.101	0.806	0.895	0.557	0.13	0.317	0.895	0.557	0.165
Sig.	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

CRP follow up has no significant correlation versus the prognosis of sepsis although it was high in most cases on following the disease .
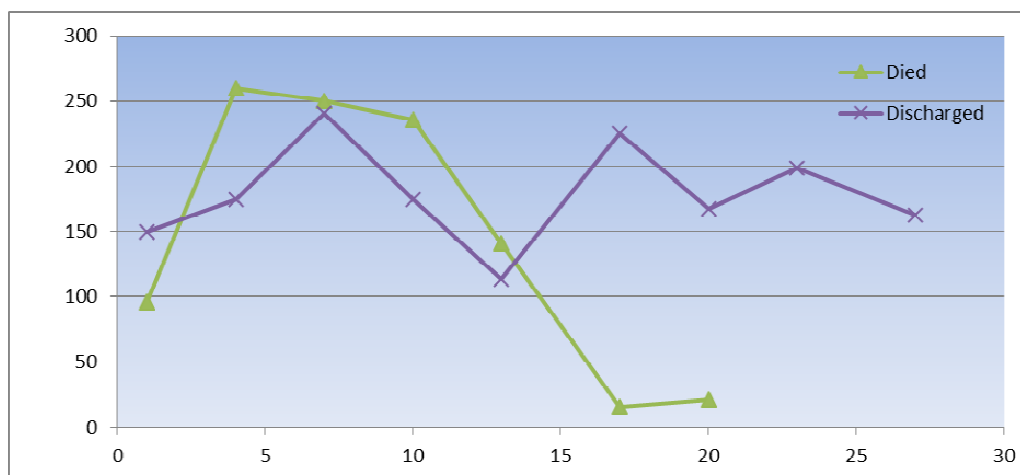
Figure (5). Follow-up chart to study CRP pattern among different times for both died discharged patients.

4. Discussion

Sepsis is the clinical syndrome that results from a dysregulated inflammatory response to an infection [6]. A marker of sepsis has been defined as a measure that predicts the presence or severity of the disease. Procalcitonin (PCT), in some countries, is now being included in routine clinical practice and guideline recommendations [21]. A single venous lactate measurement above 4 mmol/l predicted short-term and in-hospital risk for death in patients presenting at the emergency unit with suspected infection [25]. Adiponectin is an anti-inflammatory adipokine secreted by adipose tissue [34] and its deficiency is associated with increased mortality and morbidity in septic patients [26].

The current study that was conducted on 30 critically ill patients admitted to the Intensive Care unit with sepsis. 15 were discharged safely from ICU while 15 were died.

Mean body weight (BW) of patients who were died was 100.67Kg while it was 85.35 Kg for those who were discharged giving positive correlation between the mortality versus the body weight with P-value (0.026), confirming the study of [26] which mentioned that obesity is associated with increased mortality and morbidity in septic patients.

In the current study there was negative correlation between adiponectin levels (μg/L) versus patients' BW with (P-value 0.031). This meets what was mentioned by [28] that obesity is considered a known adiponectin deficient state and another case-control study, in which confounding factors such as obesity were adjusted, significantly lower concentrations of circulating adiponectin were present in patients with obesity compared to those without [35].

Predisposition, insult/infection, response, and organ dysfunction (PIRO) score is an effective model for staging of sepsis and seems to be predictive of mortality [36]. Rello and his colleagues found that PIRO score performed well as 28-day mortality prediction tool in community acquired pneumonia patients requiring ICU admission [37]. Furtado and his colleagues on the other hand suggested that PIRO score was not a good predictor of intensive care unit mortality in their study [38]. While Orlando and Endaya, confirmed the validity and simplicity of PIRO score as a tool for assessing risk of severity for patients with sepsis in the ICU and may guide clinicians in managing patients. PIRO score was used in the current study to follow the course of the septic process in each patient with maximum 28 days, the score was able to expect the prognosis with high statistical significance during days 4, 7 & 10 with P values 0.001, 0 and 0.001 respectively [39].

Póvoa and his colleagues measured CRP daily after starting the antibiotic course for community acquired sepsis and found that it was useful as early as day 3 in identification of community acquired sepsis patients with poor outcome. The rate of CRP decline during the first five ICU days was markedly associated with prognosis [40]. While Gokmen and his colleagues demonstrated that CRP had low predictive value regarding gram positive and gram negative infection and isn't a good early marker for sepsis. In the current study we found CRP follow up had no significant correlation versus the prognosis of sepsis although it was high in most cases on following the disease [41].

The current study prospectively looked at every 72hs PCT measurements in patients with sepsis and correlated the results

with prognosis guided by PIRO score during the ICU stay. On comparing the values of procalcitonin that were serially detected in all patients, the degree of change due to follow-up study (delta change or dC) that reflects the actual different changes through the follow-up study was highly significant with P-value 0. These results are meeting with the results of both Giamarellos-Bourboulis and his colleagues *and* Jensen and his colleagues that PCT has an important value in follow up the prognosis of the septic process [42]& [43] and thus supports the suggestion of Schuetz and his colleagues that PCT can be a guide for early use of antibiotics and also early discontinuation [44].

Regarding serum lactate when prospectively measured at every 72hs in patients with sepsis and correlated the results with their prognosis guided by PIRO score during the ICU stay we found that there was positive correlation between lactate (mmol/L) versus PIRO score with highly significant P-value 0.016. On comparing the values of Lactate that were serially detected in all patients, the values detected serially had variable significance with the higher significant values achieved on following the lactate on days 1,4,7 and 10. The degree of change due to follow-up study (delta change or dC) that reflects the actual different changes through the follow-up study was significant with P-value 0.011. The results are with study published by Bakker and Jansen, showed that venous lactate predicted 28-day in-hospital mortality [45]. Nguyen and his colleagues observed the evolution of serial lactate levels in patients with severe sepsis during the first 6 h of treatment. In their study, a 10% decrease in lactate levels during the 6-h study period was related to an 11% decrease in the likelihood of mortality [46].

In the current study, there was negative correlation between adiponectin (μg/L) versus PIRO score with highly significant P-value 0.003 meaning that the lower the adiponectin the more severe the sepsis. Teoh and his colleagues found that low adiponectin was associated with a heightened inflammatory response. So the authors suggested that low adiponectin may guide to a high risk for sepsis-related complications [33]. Van Meurs and his colleagues induced experimental sepsis in mice, circulating adiponectin is reduced in mice with endotoxemic challenge compared with healthy control mice [47].

In the current study the values of adiponectin that were serially detected in all patients that reflects the actual different changes through the follow-up study (delta change or dC) was highly significant with P-value 0 meaning that adiponectin measurement could have a good prognostic value. These results are meeting with the study of *(Uji et al., 2010)* who found that the plasma adiponectin levels decreased at the early period of polymicrobial sepsis and early detection of low adiponectin may help in management of patients with sepsis as an assessment of the severity of septic process [48]. A recent study by Yamamoto and his colleagues found that adiponectin ratio could be the most useful predictor for postoperative infection in comparison with CRP [49].

We concluded in these studies that sepsis carries a high risk of multiorgan dysfunction syndrome and death in critically ill patients. PIRO score is an effective model for staging of sepsis

and seems to be predictive of mortality Measuring serial procalcitonin levels may be the most useful, in order to understand the trend, identify the peak, and be able to identify resolution of sepsis. Early high lactate level is a predictor for poor prognosis of sepsis. Adiponectin is similar to procalcitonin in early detection of sepsis and can be used as a prognostic indicator with considering that adiponectin level could be affected by other metabolic disorders.

We recommend further studies with greater number of patients to ensure these results and other studies to assess the role of recombinant adiponectin in improving mortality in patients with sepsis.

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