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Clinical Evaluation of plasma Gelsolin as a novel marker for sepsis: comparison with Procalcitonin regarding early diagnosis and prognosis in septic patients

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ABSTRACT

Gelsolin is an actin-binding plasma protein that is part of an 'actin-scavenging' system. Gelsolin serves a protective role against tissue injuries and may play a crucial role in the pathophysiology of sepsis. The present study was designed to evaluate the diagnostic utility and the prognostic value of pGSN in the critically ill septic patients. A total of 80 critically ill septic patients and another 40 critically ill non septic patients were included in this observational prospective randomized study. All patients were subjected to a measurement of pGSN and the PCT at fashioned time intervals. Septic patients showed significantly lower admission pGSN level (169.5±74.4 ng/l) compared to nonseptic critically ill patients (227.3±84.7 ng/l, p = 0.01). Also, patients with septic shock had significantly lower pGSN levels than those with severe sepsis and sepsis; furthermore, non-survivors had significantly lower pGSN levels compared to survivors. Septic patients had significantly higher PCT level, APACHE II and SOFA scores. pGSN level were significantly negatively correlated with ICU stay, PCT level, APACHEII & SOFA scores. APACHE II score has shown best ability to predict mortality with AUC 0.913 followed by PCT with AUC 0.828, while the pGSN was the least in the ability to predict mortality with AUC only 0.378 despite significant difference between pGSN levels between survivals & non-survivals. So pGSN might serve as efficient complementary marker in sepsis. However, its prognostic role in mortality requires further investigation in larger studies.

Kew word: Gelsolin; Procalcitonin; Sepsis; APACHE II, SOFA score

INTRODUCTION

Sepsis is a leading cause of mortality in critically ill patients. Delay in diagnosis and initiation of antibiotics have been shown to increase mortality. However, differentiating sepsis from non-infectious triggers of the systemic inflammatory response syndrome is difficult, especially in critically ill patients who may have systemic inflammatory response syndrome for other reasons.

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It is this conundrum that predominantly drives broad-spectrum antimicrobial use and the associated evolution of antibiotic resistance in critical care environments. It is perhaps unsurprising, therefore, that the search for a highly accurate biomarker of sepsis has become one of the holy grails of medicine. (Becker K *et al*., 2008).

Among promising novel biomarkers is plasma gelsolin (pGSN), which is an actin-binding plasma protein that is part of an “actin-scavenging” system that buffers potentially harmful actin molecules released from injured tissues. Gelsolin is a calcium-dependent actin-binding protein that severs actin filaments and caps their fast-growing "barbed" ends. An isoform normally present in plasma may serve to fragment actin filaments leaking out of damaged cells and block further elongation of

their barbed ends (Janmey P *et al*., 1987, Kwiatkowski D *et al*., 1988). After binding actin, these complexes are cleared from the circulation, thereby protecting the host from further injury (Lind S *et al*., 1986, Goldschmidt-Clermont P *et al*., 1988).

The pathophysiological role of actin, leaked from damaged cells, as a major contributor to the propagation of organ injury after an initial insult is under increasing scrutiny (Lee W and Galbraith R *et al*., 1992). Actin is the principal component of the microfilaments that form the cytoskeleton of all motile and phagocytic eukaryotic cells. It is the most abundant protein in the cytosol of these cells, constituting > 10% of the total protein. When cells are lysed in vivo by any pathological process, cytoplasmic actin is released into an extracellular milieu that is favorable for the polymerization of actin (Lee W *et al*., 1989, Smith D *et al*., 1988). Filamentous actin may then cause secondary injury to already damaged organs by occluding the microvascular circulation and by activating platelets and the clotting cascade (Smith D *et al*., 1987). There has been accumulated evidence that decreases in a circulating actin-binding protein, pGSN to critical levels precede and therefore predict complications (Dahl B *et al*., 1999, Lee P *et al*., 2006).

In humans, extensive tissue injury in trauma, acute respiratory distress syndrome, hematopoietic stem cell transplantation, acute hepatic failure, and myonecrosis lead to pGSN decrements, and in critically ill surgical patients, very low pGSN levels predict poor outcomes. Low circulating levels of pGSN may indicate significant depletion of this actin-scavenger system and may serve as a marker of injury severity in critically ill patients (Mounzer K *et al*., 1999, Lind S *et al., 1988,* DiNubile M *et al*., 2002, Suhler E *et al*., 1997). Little is known about the course of pGSN levels over time in patients with severe sepsis.

The aim of this work is to compare the clinical informative value of pGSN level in the diagnosis of sepsis and investigate its relation with other inflammatory marker, the severity of organ dysfunction assessed by APACHE II and SOFA scores, and to study its mortality predictive power.

PATIENTS AND METHODS

Patients:

Eighty patients who had been diagnosed with sepsis according to ACCP/SCCM criteria (Levy, M *et al*., 2003) admitted to the Critical care department at Cairo university hospital and the intensive care unit at Theodor Bilharz Research Institute, Egypt from October 2015 to September 2016 were enrolled in this prospective observational multicenter study. The study was approved by the institution review board at Cairo University. This study did not interfere with normal routine patient management. Informed consent given by the patient or immediate relative (first degree). ACCP/SCCM criteria include: **(a)** clinically suspected infection as per the treating physician or confirmed infection and **(b)** 2 or more of the following: Temperature >38ºC (100.4ºF) or <36ºC (96.8ºF), HR > 90/min, RR > 20/min or PaCO2 < 32 mmHg, White blood cell count > 12,000/mm3 or < 4000/mm3 or > 10% immature neutrophils. ***Severe sepsis*** is defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion. ***Septic shock*** is defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation. ***Sepsis-induced hypotension*** is defined as a systolic blood pressure < 90 mmHg or mean arterial pressure (**MAP**) < 70 mmHg or a systolic blood pressure decrease > 40 mmHg in the absence of other causes of hypotension**.**

Exclusion criteria included patients < 18 years, trauma, burns, postoperative patients, and patients with a history of chronic liver disease, malignancy or on chronic hemodialysis.

Patients who were diagnosed as having sepsis at ICU admission and did not met any of the exclusion criteria were included into the study on the day of ICU admission, and subsequently followed up until the day of hospital discharge or demise.

The blood samples were also collected from forty consecutive non-specific age and sex matched subjects as a control. Patients were followed during ICU stay and only patients who didn't develop infection were enrolled. This group included patients admitted with acute coronary syndrome, heart failure, arrhythmias, acute pulmonary edema, obstetric emergencies (eclampsia), patients with cerebrovascular accident, epilepsy, pulmonary embolism and others.

Evaluation of Patients:

All included patients were subjected to the following:

Full Clinical Evaluation:

Including a history and physical examination with a special emphasis on vital signs (BP, HR, Temperature and RR) and GCS; these were evaluated on the day of admission and then followed up daily (every 2 hours for vital signs and once daily for GCS).

Imaging investigations:

chest X-ray, CT brain, or abdominal sonography were done when needed.

Laboratory investigations:

Routine Labs:

CBC (complete blood count), *Kidney Function Tests:* Na, K, serum creatinine, and blood Urea; *Liver Function Tests*: ALT (Alanine aminotransferase), AST (Aspartate aminotransferase), total bilirubin and albumin; and arterial blood gas (ABG). These routine Labs were withdrawn on study day 1 and subsequently thereafter every day until ICU discharge or demise.

Microbiological studies: including pan cultures (sputum, blood, urine or biological fluid according to clinical suspicious) prior to antibiotic administration or after discontinuation of antibiotic for 48 hours

Labs specific for this study: Plasma Gelsolin (pGSN) (Zoltán H *et al*., 2016, Wang H *et al., 2008*) and procalcitonin (PCT) (Wacker C *et al., 2008*): They were measured by using a double- antibody sandwich enzyme- linked immune sorbent assay (ELISA) on the day of admission thereafter every day for 5 days. Collected heparinated blood sample was centrifuged within one hour and stored at – 70°C. Then, samples were added to the appropriate microtiter plate wells pre-coated with the specific biotine-conjugated polyclonal antibody enzyme specific for GSN or PCT. Next, Avidin conjugated to Horseradish Peroxidase is added to each microplate well and incubated. Then a TMB substrate solution is added to each well. Only those wells that contain GSN, biotin-conjugated antibody and enzyme-conjugated Avidin will exhibit a change in color. The enzyme-substrate reaction is terminated by the addition of a stop solution (sulphuric acid solution) and the color change is measured spectrophotometrically at a wavelength of 450 nm. The concentration of the GSN or PCT in the samples is then determined by comparing the O.D. of the samples to the standard curve. This assay has high sensitivity and excellent specificity for detection of GSN and human PCT.

Clinical data:

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

Application of scoring System:

Acute Physiology and Chronic Health Evaluation II (APACHE II) score (Beck D *et al.,* 1997), which is a severity of disease classification system, was evaluated on the day of admission. After admission, an integer score is computed based on several measurements; higher scores imply a more severe disease and a higher risk of death. Sepsis-related Organ Failure Assessment (SOFA) score (Vincent J *et al.,* 1996) was evaluated on study day 1 and serially every day until ICU discharge or demise. This score determines the extent of a person's organ function or rate of failure.

The statistics:

Continuous variables were summarized using range and mean ± SD. Categorical variables were summarized using frequencies and relative frequencies. Continuous variables were compared using nonparametric Mann Whitney *U* test for those which aren't normally distributed. Categorical variables were compared using the Chi-square and exact test was used when the expected frequency was less than 5. Receiver operator characteristic (ROC) analysis was used to determine the optimum cut off value for the studied diagnostic markers. Correlation between various variables was done using Person correlation equation for non-normal variables. A probability value (*p* value) of less than 0.05 was considered statistically significant. All statistical calculations were done using SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 22 for Microsoft Windows.

RESULTS

Demographic and baseline clinical data at ICU admission: (Table 1, Fig. 1,2)

pGSN and baseline clinical characteristics:

The mean ICU admission pGSN level for the septic patients was significantly lower than that in control subjects, (169.5±74.4 (42-320) vs 227.3±84.7 (85-390) , P= 0.010). There was a significant change from admission pGSN to 2nd day pGSN (169.5±74.4 vs 157.3±72.2, P = <0.001) and from 3rd day pGSN to 4th day pGSN (152.9±66.7 vs 148.8±58.9, P = 0.013). However there were no significant changes from 2nd day pGSN 2 to 3rd day pGSN (P= 0.623) and from 4th day pGSN to 5th day pGSN (P = 0.582). Moreover, the levels of pGSN in the studied septic patients decreased with the increasing severity of the septic condition at ICU admission. (Table 2, Fig. 3).

Figure-1. The etiology of sepsis in the study group

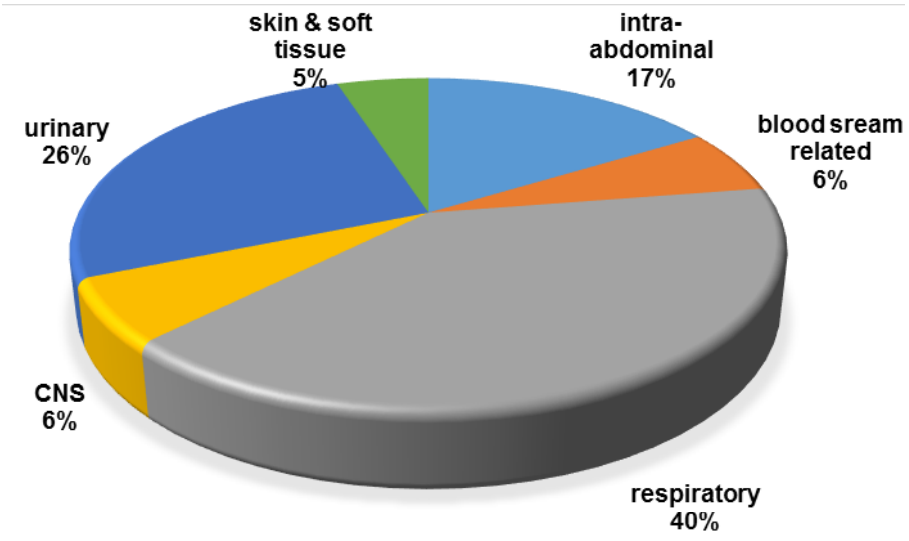


Figure-2. Microscopic examination to identify potential pathogen in septic cases

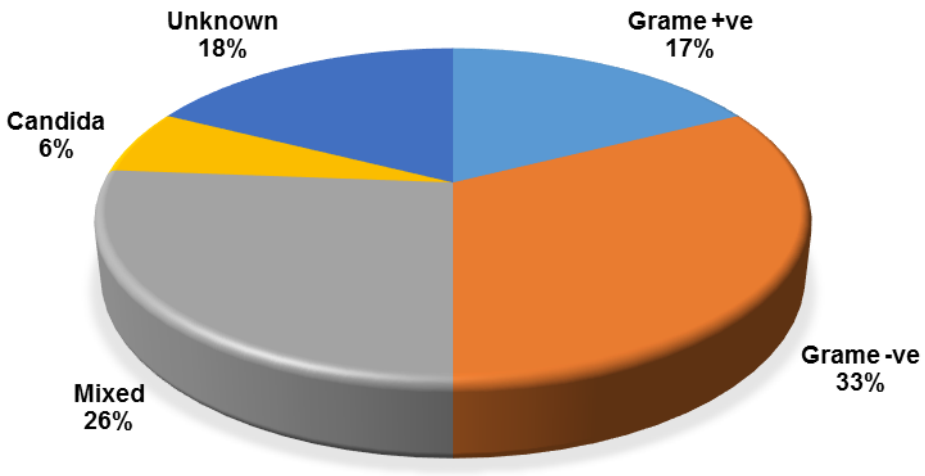
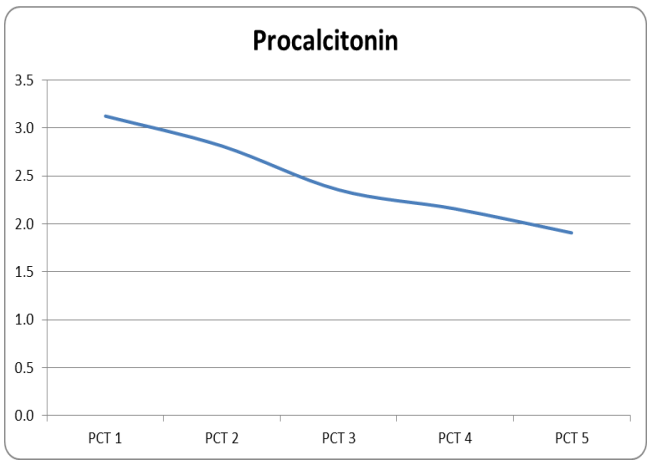
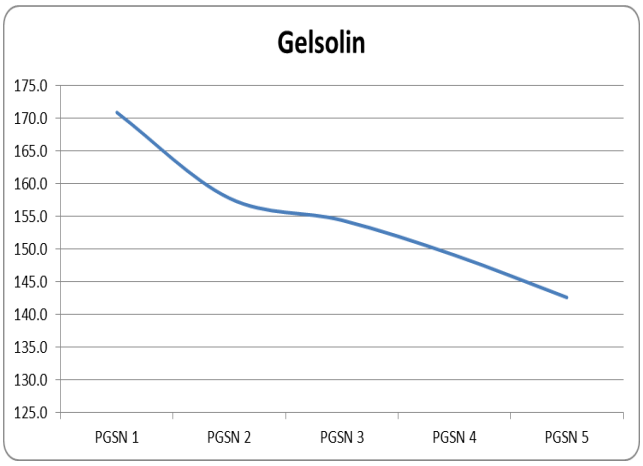


Figure-3. Time course for PCT and GSN levels in the septic patients





pGSN and severity of illness during ICU stay (Need for organ supportive measures):

The mean pGSN levels were significantly higher in patients who required MV (39 patients), required vasopressor support (52 patients) and required hemodialysis (28 patients) than those who did not require them (41, 28, 52 patients respectively). (Table 3)

Correlation between the pGSN and length of ICU stay, the scoring systems and PCT levels:

A significant negative correlation was found between admission pGSN level and the length of ICU stay, (r = -0.323, p = 0.028). Also, a significant negative correlation was found between pGSN levels and the PCT levels and the scoring systems. (Table 5).

pGSN and final outcome:

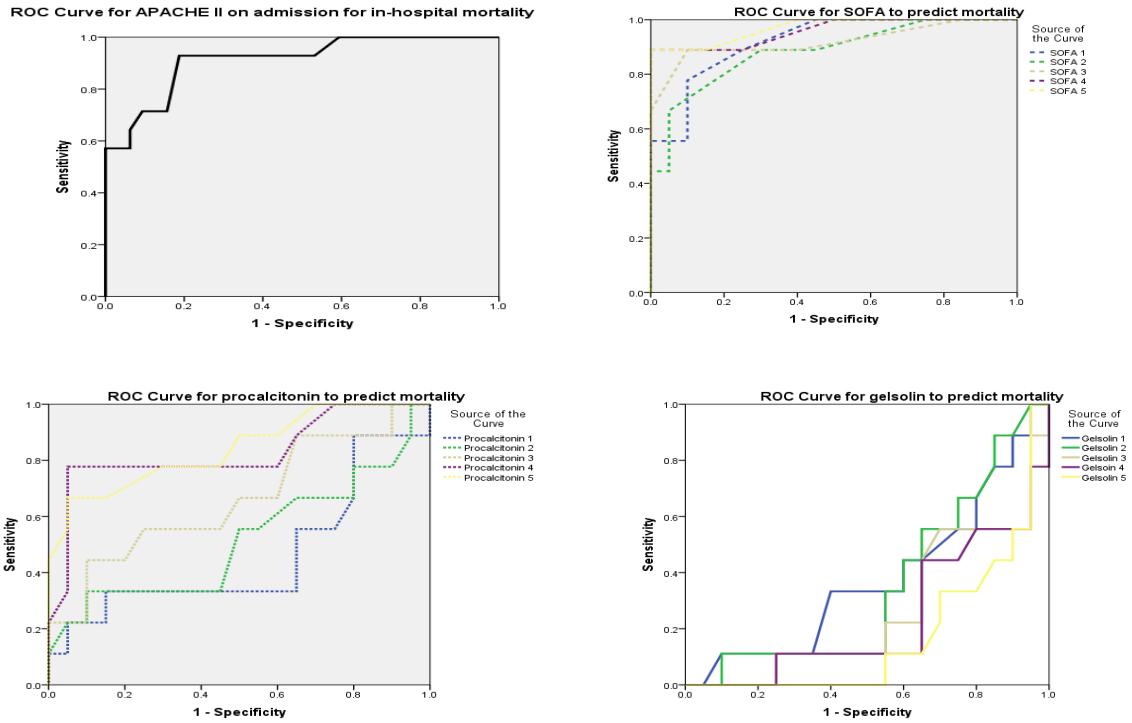
The ICU mortality rate was 35% (28 of 80 septic patients). The mean pGSN levels in non-survivors were significantly higher than that in survivors (Table 3).

Prognostic ability of pGSN:

The receiver operator characteristic (ROC) curve was calculated for the use of admission pGSN level as a predictor of ICU mortality. The area under the ROC (AUROC) curve for admission pGSN to predict ICU mortality was 0.376 (p = 0.300). The optimal cutoff value for admission pGSN to predict ICU mortality was 129 ng/l. This cutoff value gave a sensitivity of 44.4% and a specificity of 40.0% for ICU mortality (Table 4).

AUROC curves were also calculated for PCT, APACHE II and SOFA scores in the prediction of ICU mortality. The best AUROC curve for PCT was 0.825 (p = 0.005); the best cut-off value to predict ICU mortality was with 4th day PCT which was 2.4 mg/L with a sensitivity of 77.8% and a specificity of 95.0%. The best AUROC curve for SOFA score was 0.950 (p = < 0.001); the best cutoff score was with 4th day SOFA which was 5 with a sensitivity of 88.9% and a specificity of 90%. The AUROC curve for APACHE II score was 0.911 (p = < 0.001); the optimal cut-off score was 24 with a sensitivity of 92.9% and a specificity of 81.2%. (Table-4, Fig-4).

Figure-4. ROC curve analysis of APACHE IV and SOFA scores and PCT and GSN levels for prediction of mortality.



DISCUSSION

The challenges of diagnosing and treating sepsis seem more daunting as incidence increases, patients become older and sicker, and pathogenic organisms evolve. Early and appropriate antibiotic therapy is critical. Likewise, limiting exposure when infection is absent will become exceedingly important as drug resistance increases (Martin G et al., 2003, Annane D et al., 2003).

These complexities have led to the search for the ‘‘troponin’’ of sepsis, a biomarker or set of biomarkers with compelling sensitivity and specificity for effectively identifying the disease, patients at risk for untoward outcomes, and reliably guiding treatment. So the aim of the present study was to investigate pGSN as biomarker for sepsis in comparison to an established biomarker procalcitonin in septic patients in regard to its diagnostic and prognostic value.

Both septic and non-septic included patients were comparable with no significant differences as regard their demographic, clinical data and co-morbidities, except baseline temperature which was significantly higher in sepsis group and mean arterial pressure which was significantly lower in sepsis group. This was in agreement with study by Giuliano et al. (2007) and Liu et al. (2010) who found that the presence of an elevated temperature was associated with the highest risk of sepsis. Shapiro et al (2009) however concluded that this was not pathognomonic to sepsis and may also be observed in a wide variety of non-infectious inflammatory conditions.

The current study revealed a significant difference between septic and non- septic patients for their neurologic impairment (GCS), need for mechanical ventilator, renal replacement therapy and vasoactive support.

This was also shown by Wilson et al. (2003) who proved that advanced sepsis can cause brain damage and that milder cases may recover without neurological problem and this may be related to the reversible mechanisms of what is called sepsis-associated encephalopathy. However more advanced cases of sepsis may have neuron-killing complications. Also, Lagu et al. (2012) reported that non septic patients were less likely to receive a code for respiratory failure than patients with sepsis or to receive a code for shock or other cardiovascular failure.

Moreover, length of ICU & hospital stay was significantly higher in septic than non-septic patients. This was consistent with Melville et al. (2015) who concluded that patients with sepsis needed longer ICU care, with the average length of stay almost doubled.

The current study reported a higher degree of disease severity and organ failure in sepsis group as indicated by significantly higher SOFA and APACHE II scores in septic patients, also, septic patients with severe sepsis and septic shock have higher scores. Liu et al. (2013) showed no difference in APACHE II score between sepsis and no sepsis groups; however it was significantly higher in severe sepsis and septic shock

Table-1. Demographic and clinical data between septic patients and control:-

Variables		Sepsis (N: 80)	Control (N: 40)	P value
Age (years)	Mean±SD (Range)	50.7 ± 15.2 (20-80)	50.9 ± 14.5 (28-79)	0.978
Male: Female sex	(Ratio)	39: 41 (0.95)	21: 19 (1.1)	0.698
Diabetes mellitus	N (%)	41 (51.3 %)	19 (47.5 %)	0.698
Baseline hemodynamic				
Heart rate (beat/minute)	Mean±SD	121.1 ± 27.9	120.0 ± 29.1	0.978
Respiratory rate (breath/minute)	Mean±SD	32.8 ± 7.4	32.1 ± 6.6	0.707
Temperature (^{0}C)	Mean±SD	38.6 ± 1.4	37.4 ± 0.7	0.002
Mean blood pressure (mmHg)	Mean±SD	61.4 ± 19.8	82.4 ± 27.4	< 0.001
GCS (<8)	N (%)	26 (32.5%)	16 (40%)	0.416
Baseline Laboratory investigations				
Hematocrit (%)	Mean±SD	38.9 ± 5.2	40.2 ± 5.8	0.442
Leucocytes (cell/mm^3)	Mean±SD	18.7 ± 10.7	8.7 ± 3.2	<0.001
Platelet count (cell/mm^3)	Mean±SD	206.5 ± 114.4	262.4 ± 94.0	0.034
ALT (U/L)	Mean±SD	37.60 ± 8.44	34.22 ± 10.00	0.074
AST (U/L)	Mean±SD	29.62 ± 7.37	28.87 ± 9.69	0.671
Total bilirubin (mg/dl)	Mean±SD	1.9 ± 1.7	1.2 ± 0.5	0.013
Albumin (g/dl)	Mean±SD	3.1 ± 0.6	3.2 ± 0.7	0.697
Blood urea (mg/dl)	Mean±SD	112.0 ± 28.5	106.6 ± 23.8	0.278
Serum creatinine (mg/dl)	Mean±SD	1.8 ± 1.0	1.3 ± 0.5	0.017
Sodium (mEq/L)	Mean±SD	136.1 ± 7.7	141.5 ± 4.8	0.010
Potassium (mEq/L)	Mean±SD	4.6 ± 0.9	4.1 ± 0.5	0.005
PaO_2 (FiO_2 50%)	Mean±SD	69.6 ± 15.9	79.2 ± 15.7	0.008
PH	Mean±SD	7.3 ± 0.1	7.4 ± 0.1	0.014
HCO_3 (mEq/L)	Mean±SD	18.2 ± 6.6	22.2 ± 3.9	0.006
Clinical coarse and outcome				
Need for mechanical ventilation	N (%)	39 (46.7%)	10 (25%)	0.009
Need for vasopressor support	N (%)	52 (65%)	9 (22.5%)	<0.001
Need for hemodialysis	N (%)	28 (35%)	7 (17.5%)	0.053
Duration of ICU stay (day)	Mean±SD	8.7 ± 5.8	3.4 ± 2.2	<0.001
Duration of post ICU stay (day)	Mean±SD	3.1 ± 2.6	1.7 ± 1.2	0.005
APACHE II	Mean±SD	21.9 ± 13.2	11.8 ± 7.6	<0.001
SOFA (1st day)	Mean±SD	5.5 ± 3.3	2.7 ± 1.7	<0.001
SOFA (2nd day)	Mean±SD	6.5 ± 3.9	2.9 ± 1.7	<0.001
SOFA (3rd day)	Mean±SD	5.8 ± 3.5	2.8 ± 1.5	<0.001
SOFA (4th day)	Mean±SD	5.5 ± 3.4	2.8 ± 1.6	<0.001
SOFA (5th day)	Mean±SD	5.4 ± 3.7	2.7 ± 1.5	<0.001
Mortality	N (%)	28 (35%)	5 (12.5%)	0.096
Inflammatory markers				
Admission PCT	Mean±SD	3.1 ± 2.5	0.6 ± 0.5	0.009
Admission pGSN	Mean±SD	169.5 ± 74.4	227.3 ± 84.7	0.010

N: *number;* ***ST:*** *standard deviation;* ***ALT:*** *alanine aminotransferase,* ***AST:*** *aspartate aminotransferase;* ***GLS:*** *Glasgow coma scale;* ***PaO_2:*** *partial pressure of arterial oxygen;* ***FiO_2:*** *fraction of inspired oxygen;* ***APACH II:*** *Acute Physiology And Chronic Health Evaluation;* ***SOFA:*** *Sepsis-related Organ Failure Assessment;* ***PCT:*** *procalcitonin;* ***pGSN:*** *plasma gelsolin*

than in sepsis. Yousef and Suliman (2013) showed higher SOFA score in sepsis patients. Moreover, Daviaud and coworkers (2015) investigated causes of death in septic shock of 543 patients and concluded that higher admission SOFA score remained an independent risk factor of early death, which was defined within the first 3 days of ICU admission.

Procalcitonin has been studied extensively to diagnose sepsis and provides prognostic insights for sepsis. The level of PCT rises in a response to a proinflammatory stimulus, especially of bacterial origin. In this case, it is produced mainly by the cells of the lung and the intestine (Wacker C et al., 2013, Boysen A et al., 2013). Current study demonstrated a significantly higher admission PCT level in the septic patients when

Table-2. Demographic and clinical data of the patients with different grades of sepsis.

Variables			Sepsis (N: 25)	Severe sepsis (N: 21)	Septic shock (N: 34)	P value
Age (years)		Mean±SD	50.4 ± 16.3	52.4 ± 9.6	53.4 ± 14.4	0.152
Male: Female sex		(Ratio)	12: 13 (0.92)	10: 11 (0.91)	17: 17 (1.0)	0.751
Diabetes mellitus		N(%)	10 (40 %)	9 (42.8 %)	22 (64.7 %)	0.208
Baseline hemodynamic						
Heart rate (beat/minute)		Mean±SD	113.8 ± 13.2	121.2 ± 23.1	123.6 ± 35.6	0.567
Respiratory rate (breath/minute)		Mean±SD	31.6 ± 5.1	32.7 ± 7.4	33.9 ± 8.6	0.718
Temperature (^{0}C)		Mean±SD	38.6 ± 0.7	38.7 ± 0.5	38.4 ± 2.0	0.822
Mean blood pressure (mmHg)		Mean±SD	75.6 ± 7.9	77.3 ± 11.8	44.9 ± 12.3	<0.001
GCS (< 8)		N(%)	1 (4.0%)	8 (38%)	17 (50%)	<0.001
Baseline Laboratory investigations						
Hematocrit (%)		Mean±SD	40.8 ± 4.6	40.7 ± 4.8	37.0 ± 4.9	0.056
Leucocytes (cell/mm^3)		Mean±SD	14.7 ± 6.4	14.1 ± 7.2	21.5 ± 12.9	0.121
Platelet count (cell/mm^3)		Mean±SD	213.4 ± 66.6	242.3 ± 127.9	177.3 ± 125.4	0.292
ALT (U/L)		Mean±SD	36.08 ± 10.15	37.66 ± 8.39	39.97 ± 5.19	0.097
AST (U/L)		Mean±SD	27.48 ± 5.79	28.90 ± 9.33	31.44 ± 6.22	0.158
Total bilirubin (mg/dl)		Mean±SD	1.1 ± 1.0	1.8 ± 1.7	2.4 ± 1.9	0.095
Albumin (g/dl)		Mean±SD	3.3 ± 0.4	3.5 ± 0.5	3.1 ± 0.7	0.053
Blood urea (mg/dl)		Mean±SD	98.5 ± 21.7	111.0 ± 24.8	121.5 ± 31.8	0.010
Serum creatinine (mg/dl)		Mean±SD	1.1 ± 0.5	1.8 ± 0.7	2.3 ± 1.1	0.002
Sodium (mEq/L)		Mean±SD	135.9 ± 6.2	138.8 ± 6.7	134.8 ± 8.9	0.432
Potassium (mEq/L)		Mean±SD	4.1 ± 0.7	4.1 ± 0.4	5.0 ± 0.9	0.001
PaO_2 (FiO_2 50%)		Mean±SD	75.6 ± 16.3	63.4 ± 13.5	64.2 ± 15.9	0.201
PH		Mean±SD	7.3 ± 0.1	7.4 ± 0.1	7.2 ± 0.1	0.014
HCO_3 (mEq/L)		Mean±SD	23.1 ± 2.3	18.3 ± 5.9	15.8 ± 6.9	0.007
Clinical coarse and outcome						
Need for mechanical ventilation		N(%)	1 (4.0%)	14 (66.6%)	24 (70.6%)	<0.001
Need for vasopressor support		N(%)	3 (12%)	15 (71.4%)	34 100%)	<0.001
Need for hemodialysis		N(%)	0 (0.0%)	5 (23.8%)	23 (67.6%)	<0.001
APACHE II		Mean±SD	10.9 ± 5.1	19.6 ± 9.7	29.8 ± 13.2	<0.001
SOFA	(day1)	Mean±SD	1.9 ± 1.6	5.0 ± 2.6	7.9 ± 3.3	<0.001
	(day2)	Mean±SD	1.6 ± 1.8	6.3 ± 1.9	9.4 ± 3.7	<0.001
	(day3)	Mean±SD	1.6 ± 1.3	5.4 ± 2.1	8.1 ± 4.4	0.002
	(day4)	Mean±SD	1.4 ± 1.1	4.4 ± 2.6	7.9 ± 5.7	0.012
	(day5)	Mean±SD	1.5 ± 0.8	4.1 ± 2.5	7.6 ± 5.5	0.057
Mortality		N(%)	0 (0.0%)	4 (19%)	24 (70.5%)	<0.001
Inflammatory markers						
PCT	(1st day)	Mean±SD	2.5 ± 1.3	2.9 ± 2.2	3.6 ± 2.7	0.380
	(2nd day)	Mean±SD	1.5 ± 0.9	2.5 ± 1.5	3.8 ± 2.5	0.012
	(3rd day)	Mean±SD	1.2 ± 0.6	2.0 ± 1.0	3.1 ± 2.1	0.058
	(4th day)	Mean±SD	1.1 ± 0.7	1.7 ± 0.8	2.8 ± 2.2	0.054
	(5th day)	Mean±SD	0.9 ± 0.5	1.6 ± 1.0	2.3 ± 1.9	0.199
pGSN	(1st day)	Mean±SD	217.2 ± 58.8	178.9 ± 79.7	132.5 ± 70.8	0.009
	(2nd day)	Mean±SD	204.9 ± 52.7	171.6 ± 66.0	122.5 ± 68.5	0.002
	(3rd day)	Mean±SD	205.1 ± 49.2	170.4 ± 72.1	120.7 ± 54.9	0.003
	(4th day)	Mean±SD	200.3 ± 24.6	155.2 ± 63.8	127.9 ± 55.8	0.014
	(5th day)	Mean±SD	195.8 ± 20.9	155.7 ± 62.8	121.6 ± 65.7	0.069

N: *number; ST: standard deviation; ALT: alanine aminotransferase, AST: aspartate aminotransferase; GLS: Glasgow coma scale; PaO2: partial pressure of arterial oxygen; FiO2: fraction of inspired oxygen; APACH II: Acute Physiology And Chronic Health Evaluation; SOFA: Sepsis-related Organ Failure Assessment; PCT: procalcitonin; pGSN: plasma gelsolin*

Table-3. Distribution of the PCT and pGSN levels with organ dysfunction and mortality in the patients entered the study.

Ventilatory support									
Variables (Mean±SD)		No 41 (51.3%)	Yes 39 (48.7%)	P value	Variables (Mean±SD)		No 41 (51.3%)	Yes 39 (48.7%)	P value
PCT	(1st day)	1.8 ± 1.2	3.7 ± 2.2	0.017	pGSN	(1st day)	204.9 ± 76.6	141.4 ± 77.6	0.005
	(2nd day)	2.1 ± 1.4	3.8 ± 1.9	0.033		(2nd day)	174.4 ± 70.7	134.5 ± 69.8	0.074
	(3rd day)	1.6 ± 1.0	3.2 ± 1.5	0.023		(3rd day)	171.0 ± 60.8	131.9 ± 68.9	0.079
	(4th day)	1.3 ± 0.8	3.2 ± 1.3	0.005		(4th day)	168.8 ± 47.8	125.9 ± 64.6	0.041
	(5th day)	1.1 ± 0.7	2.7 ± 1.4	0.021		(5th day)	159.4 ± 60.4	123.7 ± 65.5	0.143
Renal replacement therapy									
		No 52 (65%)	Yes 28 (35%)				No 52 (65%)	Yes 28 (35%)	P value
PCT	(1st day)	2.0 ± 1.3	4.0 ± 2.5	0.055	pGSN	(1st day)	202.7 ± 78.9	130.6 ± 64.4	0.003
	(2nd day)	2.3 ± 1.2	3.9 ± 2.2	0.088		(2nd day)	180.1 ± 62.9	109.4 ± 69.8	0.002
	(3rd day)	2.0 ± 1.1	3.0 ± 1.9	0.269		(3rd day)	175.4 ± 64.5	116.1 ± 56.2	0.012
	(4th day)	1.9 ± 1.0	2.6 ± 1.3	0.343		(4th day)	163.5 ± 56.8	125.7 ± 56.2	0.057
	(5th day)	1.8 ± 0.9	2.1 ± 0.9	0.737		(5th day)	162.3 ± 65.8	123.6 ± 60.7	0.293
Circulatory failure									
		No 28 (35%)	Yes 52 (65%)				No 28 (35%)	Yes 52 (65%)	P value
PCT	(1st day)	1.7 ± 1.3	3.6 ± 1.8	0.006	pGSN	(1st day)	211.8 ± 75.8	128.4 ± 13.9	<0.001
	(2nd day)	1.9 ± 1.0	3.8 ± 1.7	0.005		(2nd day)	199.6 ± 59.9	122.5 ± 68.5	<0.001
	(3rd day)	1.6 ± 0.8	3.0 ± 1.4	0.023		(3rd day)	188.9 ± 65.1	119.8 ± 56.3	0.002
	(4th day)	1.4 ± 0.7	2.8 ± 1.2	0.015		(4th day)	178.3 ± 52.7	125.4 ± 55.3	0.013
	(5th day)	1.3 ± 0.7	2.4 ± 1.2	0.068		(5th day)	170.5 ± 52.0	122.5 ± 65.7	0.042
Mortality									
		No 52 (65%)	Yes 28 (35%)				No 52 (65%)	Yes 28 (35%)	P value
PCT	(1st day)	2.7 ± 1.2	4.2 ± 2.5	0.138	pGSN	(1st day)	197.6 ± 73.8	124.2 ± 57.3	0.005
	(2nd day)	2.2 ± 1.0	4.4 ± 2.2	0.027		(2nd day)	177.1 ± 72.5	114.4 ± 50.7	0.008
	(3rd day)	1.7 ± 0.9	4.0 ± 1.8	0.021		(3rd day)	173.4 ± 65.7	108.1 ± 44.2	0.004
	(4th day)	1.4 ± 0.7	3.8 ± 1.4	0.012		(4th day)	167.9 ± 55.9	105.3 ± 46.2	0.006
	(5th day)	1.2 ± 0.7	3.5 ± 1.5	0.026		(5th day)	163.3 ± 61.6	96.4 ± 44.2	0.007

ST: standard deviation; PCT: procalcitonin; pGSN: plasma gelsolin

Table-4. Prognostic ability of the scoring systems, PCT and pGSN

Variables		AUC	Cut-off	Sensitivity	Specificity
APACHE II		0.911	24	92.9%	81.2%
	(1st day)	0.919	6.5	77.8%	90.0%
	(2nd day)	0.883	6.5	88.9%	70.0%
SOFA	(3rd day)	0.931	7.5	77.8%	95.0%
	(4th day)	0.950	5	88.9%	90.0%
	(5th day)	0.970	4.5	88.9%	90.0%
	(1st day)	0.458	2.2	55.6%	35.0%
	(2nd day)	0.518	1.9	66.7%	35.0%
PCT	(3rd day)	0.661	2	55.6%	55.0%
	(4th day)	0.825	2.4	77.8%	95.0%
	(5th day)	0.841	2.4	66.7%	95.0%
	(1st day)	0.376	129	44.4%	40.0%
	(2nd day)	0.360	121	55.6%	35.0%
pGSN	(3rd day)	0.263	127	44.4%	35.0%
	(4th day)	0.237	130	44.4%	35.0%
	(5th day)	0.172	122	33.3%	25.0%

UNC: area under the receiver operator characteristic curve; APACH II: Acute Physiology And Chronic Health Evaluation; SOFA: Sepsis-related Organ Failure Assessment; PCT: procalcitonin; pGSN: plasma gelsolin
ST: standard deviation; PCT: procalcitonin; pGSN: plasma gelsolin

Table-5. Correlation between pGSN and LOS, scoring systems and PCT.

Variables (correlation coefficient {p-value})		1st day pGSN	2nd day pGSN	3rd day pGSN	4th day Pgsn	5th day pGSN
LOS ICU		-0.323 {0.028}				
APACHE II		-0.583 {<0.001}				
	(1st day)	-0.573 {<0.001}				
	(2nd day)		-0.601 {<0.001}			
SOFA	(3rd day)			-0.575 {<0.001}		
	(4th day)				-0.541 {0.001}	
	(5th day)					-0.558 {0.002}
	(1st day)	-0.349 {0.011}				
	(2nd day)		-0.359 {0.015}			
PCT	(3rd day)			-0.355 {0.031}		
	(4th day)				-0.435 {0.013}	
	(5th day)					-0.518 {0.005}

***LOS:** length of stay; **ICU:** intensive care unit; **APACHE II:** Acute Physiology And Chronic Health Evaluation; **SOFA:** Sepsis-related Organ Failure Assessment; **PCT:** procalcitonin; **pGSN:** plasma gelsolin*

compared with the non-septic group (3.1±2.5 {0.2 – 10} vs 0.6±0.5 {0 – 2} ng/ml with p = 0.009). On the other hand, there was no significant changes among daily PCT measurements in different grades of sepsis except for the 2nd day level. This was consistent with study of Uchil S et al (2011) who showed no significant association between the level of serum PCT and grade of sepsis.

Among patients with sepsis we found higher need for ventilator support and use of vasopressors among patients with high PCT level, however need for renal replacement therapy was independent for PCT level. There was a pattern of daily detrimental changes in survivors and another pattern of non-detrimental changes in non-survivors. Importantly, the course of PCT levels over time, rather than absolute PCT values, affect the prognosis of systemic inflammation; continuously declining PCT levels indicate a better prognosis, even if the peak PCT values are very high. A persistent increase or failure to decline in the PCT levels has been related to higher mortality rates in various studies (Magrini L et al., 2013, Friederichs J et al., 2013).

Moreover PCT measurements could also predict mortality in the current study with the best cut off value was 2.4 ng/ml at 4th day which could be explained by the persistence of ongoing tissue damage and high PCT

levels which ensued higher morbidities and favored early mortality.

Gelsolin is a calcium dependent actin binding protein predominantly responsible in removal of actin filaments released into circulation upon cell injury. Diminished levels of pGSN were observed in human subjects affected with acute liver injury, myocardial infarction, sepsis and myonecrosis in comparison to the healthy people (Lee P et al., 2006, Mounzer K et al., 1999). The current study revealed that admission pGSN levels in sepsis patients were significantly lower than those in non-septic critically ill patients, also was significantly lower in patients with septic shock than in patients with severe sepsis and sepsis. Although plasma albumin levels in both septic group and non-septic critically ill group were below the normal value, there was no significant difference between the two groups. This indicates that the decrease in pGSN level was specific and not a simple consequence of systemic plasma protein loss or dilution.

Lee P et al (2007) examined the role of pGSN in animal models of sepsis. He documented the depletion of pGSN (25-50% of normal) in murine models of sepsis, associated with the presence of circulating actin within 6 hours of septic challenge. Repletion of pGSN led to solubilization of circulating actin aggregates and significantly reduced mortality in endotoxemic mice (survival rates were 88% in the gelsolin group vs. 0% in the saline group, $p < 0.001$).

In another study, Lee P et al., (2008) and Swapna Gurrapu (2016) were concluded that circulating actin and pGSN deficiency are associated with early sepsis. The degree of pGSN deficiency correlated with sepsis mortality. He proposed that reversing pGSN deficiency may be an effective treatment for sepsis. This observation go with the result done by Cohen T et al (2011) who stated that exogenous gelsolin could reduce morbidity from sepsis.

Wang H et al (2008) examined levels of pGSN in patients with severe sepsis. The admission pGSN levels were significantly lower in severe sepsis (20.6 ± 11.7 mg/l) compared with non-septic critically ill patients (52.3 ± 20.3 mg/l; $P < 0.001$) and healthy control individuals (126.8 ± 32.0 mg/l; $P < 0.001$). Survivors of severe sepsis exhibited substantial recovery of their depressed pGSN levels, whereas pGSN levels in non-survivors remained at or below their depleted admission levels.

In the current study we observed that almost all the patients with sepsis had decreased pGSN level, the lowest levels were associated with highest SOFA score and more complicated disease courses (severe sepsis and septic shock). Moreover, pGSN levels were lower in septic patients who required for ventilator support, renal replacement therapy and vasopressors.

Huang and coworkers (2011) also studied the prognostic implications of pGSN levels on the development of multiple organ dysfunction syndrome (MODS) and fatal outcome in a group of severely burn patients. The results showed that pGSN concentrations decreased markedly. Moreover, as the pGSN levels decreased, the incidence of septic complication as well as MODS remarkably increased.

Despite that there were significant changes in the daily patterns of pGSN measurements among survivors and non-survivors but diminished pGSN levels had a week ability to predict mortality in the current study. The area under the ROC curve to predict ICU mortality was 0.376%. The optimal cutoff value to predict ICU mortality was 129 with a sensitivity and specificity of 44.4% and 40% respectively.

Mounzer et al, (1999) and Lingaiah et al (2014) were demonstrated that low admission pGSN levels were associated with increased risk for adverse outcomes, including prolonged length of hospital stay and death in patients who had undergone surgery or who had suffered trauma. Also, Lee et al., (2006) examined pGSN levels in critically ill patients and concluded that low pGSN levels were associated with increased risk of death occurring in the ICU. pGSN levels lower than 61 ng/l predicted longer ICU stay, prolonged ventilator dependence, and increased overall in-hospital mortality.

Interestingly, Lee et al, (2009) studied pGSN level in chronic hemodialysis patients and noted that low pGSN and detectable circulating actin identify chronic hemodialysis patients at highest risk for 1-year mortality. The current study had shown that APACHE II score has shown best ability to predict mortality with AUC 0.911 followed by PCT with AUC 0.825. pGSN was the least in the ability to predict mortality with AUC only 0.376 despite significant difference between pGSN levels between survivals & non-survivals.

To our knowledge there are no studies assessing the predictive ability for pGSN in mortality from sepsis. However, late in 2016, Zoltán et al, (2016) studied the predictive value of serum actin, gelsolin and the recently defined actin/gelsolin ratio during sepsis by comparison it to classical clinical and inflammatory laboratory parameters. The study was done on 46 cases of severe septic patients. Ophthalmologic patients (n = 27) served as controls. In concordance with our results, the study found that septic patients showed significantly decreased 1st day pGSN levels and increased actin/gelsolin ratios compared to non-septic patients; furthermore, non-survivors had significantly lower gelsolin levels compared to survivors.

In contrary to our findings, Zoltán et al, (2016) and Rajendra Prasad Gujjeti et al (2014) were found that pGSN had similar prognostic value to PCT when assessing 7-day mortality and the predictive capacity of the first-day actin/gelsolin ratios was similar to that of APACHE II score regarding ICU mortality in severe sepsis. Possibly, the characteristics of patient population and the limited number of cases contributed to the conflicted results.

Sepsis causes high mortality, exceeding 30% for patients with severe sepsis and rising to over 50% for patients with septic shock. Figures have improved in the last decade, probably thanks to improved early recognition of sepsis. One crucial measure is early and correct identification of high-risk patients in need of early intervention. This study had shed lights on the novel

marker actin scavenger gelsolin for early detection of sepsis and as a prognostic tool in severity of the disease. It may also guide decision-making in countries with a shortage of ICU beds. In those settings, selection of patients in real need of intensive care should rely not only on clinical judgment but also on the proposed marker. Also, in a situation in which ICU beds are not available, this new stratification indicates which patients in the general ward should be intensively monitored. This applies even to patients who have uncomplicated sepsis but whose mortality remains between 5% and 10%, meaning that some will deteriorate over time.

Limitations of the study: The number of patients is inadequate to allow definitive conclusions to be drawn, and the study does not elucidate the role played by pGSN in sepsis or the association of pGSN with actin and cytokine.

CONCLUSION

pGSN (measured by ELISA) may be used as a rapid, simple and easy to perform and interpret test for the early prognosis and prediction of adverse outcome of septic patients at their ICU admission. It correlates with the severity of septic condition, and needs for mechanical ventilator, hemodynamic support and hemodialysis; however, it could not predict mortality with much accuracy compared to other parameters.

Recommendation:

1. Larger study group needed for studying the diagnostic and prognostic function of pGSN in sepsis,
2. Role of gelsolin as a therapeutic agent needs to be further investigated,
3. Future studies on role of pGSN in predicting mortality over extended period of time.

Conflict of Interests

Authors declare that there is no conflict of interests regarding the publication of this paper.

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