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Original Article

PROCALCITONIN FOR IMPROVED ASSESSMENT AND AN ANSWER TO SEPSIS DILEMMA IN CRITICALLY ILL - A MYTH, A HYPE, OR A REALITY ?

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Abstract :

Background and objectives: "Sepsis is a major cause for mortality in critically ill patients all over the world. The number of patients presenting with sepsis, septic shock is gradually increasing in daily clinical practice. Mortality in sepsis is mainly due to a delay in diagnosis and initiation of specific therapy(antibiotics).This is in turn mainly attributed to the difficulty in differentiating infectious trigger(sepsis) from non infectious triggers as both present with similar clinical features. Lack of specific marker adds to this dilemma of differentiating infectious and non infectious factors in critically ill patients.

Recently there are some reports from European countries on role of Procalcitonin (PCT) in critically ill patients. Draw backs of these studies are galore mainly due to the difficulties in interpretation of results, as varying definitions for sepsis are used. But also there is paucity of data on Procalcitonin from Indian sub continent. Hence in the present single centre prospective observational study conducted at tertiary care medical college hospital , A total of 50 adult patients with sepsis fulfilling ACCP/SCCM guidelines were included, out of which 23 were in SIRS/Sepsis, 14 in severe sepsis and 13 in septic shock. Procalcitonin was evaluated in the first 24 hours after admission and before initiation of any antibiotic therapy. The role of procalcitonin was analyzed in relation to confirming sepsis, assessing the severity of sepsis and assessing the prognosis(possible out come) of sepsis. Combined role of procalcitonin with other indicators especially ESR, SOFA Score, Blood/relevant material culture was explored.

Results: Our study confirmed the importance of procalcitonin in critically ill patients particularly in improving the predictive power while solving the sepsis dilemma.

Conclusions: From our study, we conclude that Procalcitonin is not a myth nor a hype but it is a hard reality and is an answer to sepsis dilemma. It is therefore preferable to add Procalcitonin into the standard workup of critically ill patients with suspected sepsis in every day clinical practice.

Keywords : Procalcitonin, PCT, SOFA Score, Sepsis, Septic shock, ACCP/SCCM guidelines, Sepsis dilemma

Introduction :

Sepsis refers to the systemic response to serious infection by any class of micro organism. Sepsis can be simply defined as a spectrum of clinical manifestations caused by immune response of a patient to infection by micro organism [1]. It ranges from systemic inflammatory response(SIRS) to multiple organ dysfunction(MODS) and ultimately death.

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Recently there is an increase in the incidence of sepsis and septic shock mainly due to (A) an increase in infections due to antibiotic resistant organisms, (B) increased use of invasive devices such as intra venous catheters, (C) wide spread use of cyto toxic and immunosuppressive drug therapies for cancer and transplantations, (D) increased life span of patients with Hiv, cancer, and diabetes who are more prone to develop sepsis[2,3].

The source of infection is an important determinant of clinical outcome. The most frequent source, sites and portal of entry of micro organisms causing sepsis are genito

urinary tract(25%), respiratory tract and lungs(20%), biliary tract and abdomen(5%), and other sources being skin, soft tissue, central nervous system, miscellaneous and uncertain sites [4]. Patients with nosocomial pneumonia, intra abdominal infection and poly microbial bacteria are at significant risk for severe sepsis. Bacteraemia associated with intra vascular catheters or indwelling urinary catheters carries a lower risk of developing septic shock [5,6].

Micro organisms that are commonly implicated in sepsis and sepsis related conditions(SIRS, Septic shock) include S epidermidis, S aureus, Bacillus species, Corynebacterium species, and the organisms that contaminate hands of medical personnel such as pseudomonas aeruginosa, acinetobacter species, candida species, klebsiella, and entero bacter species [3,7]. Recently Gram Positive pathogens seems to have largely superseded Gram Negative pathogens in inducing sepsis [8].

Sepsis is reported to be the most common cause of death in intensive care units, particularly among elderly, immunocompromised, and critically ill. Approximately 25-35% of patients with severe sepsis and 40-45% of patients with septic shock die within 30 days [2]. Gram Negative bacteria cause more deaths due to sepsis [7] and pathogens associated with highest mortality rate are entero bacteriaceae and P aeruginosa [8].

Sepsis Dilemma

Early diagnosis of sepsis is of prime and paramount importance as early institution of appropriate anti microbial therapy is associated with better outcomes. More over it also helps in avoiding wide spread and irrelevant administration of antibiotic therapy which further helps in preventing antibiotic resistance, drug toxicity, and higher cost. In some cases, history and physical examination with or without routine laboratory tests may be enough to diagnose sepsis. But it is often difficult to distinguish critically ill patients with systemic infection, sepsis, organ dysfunction or shock from patients with similar clinical signs and laboratory findings without infections [9,10]. Even though culture positivity for causative organism is considered to be the gold standard, microbiological evidence for infection may not develop at the same time [11]. Blood cultures yield bacteria or fungi in approximately 20-40% of severe sepsis cases and 40-70% of cases of septic shock [12]. Microbial cultures require more time and negative results donot exclude sepsis.

Rationale and Need for the Present Study

In view of the above facts, there is an urgent need for an effective, appropriate, sensitive and specific early marker of infection to accurately solve the sepsis dilemma(diagnostic, therapeutic, and prognostic dilemma). Recently Procalcitonin(PCT) has caught the attention of researchers world wide as an interesting possible marker of systemic inflammatory response to infection, sepsis [13].

PROCALCITONIN (PCT) is the 116 amino acid pro hormone of calcitonin which is normally produced in the C cells of the thyroid gland. Normally all procalcitonin is cleaved by specific proteases and none is released in to the blood stream. PCT levels are thus undetectable (< 0.1 ng/ml) in healthy humans. However during severe infections with systemic manifestations, PCT levels may increase to over 100 ng/ml [3]. PCT is thus an integral part of the inflammatory response to infection [15,16.] The exact origin of PCT during sepsis is uncertain but probably produced by extra thyroid tissues also [13,14]. Study on PCT kinetics involving volunteers revealed PCT levels started to raise in 3-4 hours after insult, peaking by 14 hours and high values(of 4ng/ml) remaining up to 24 hours, with a half life of 25-30 hours. The same PCT kinetics is expected to occur in all sepsis and septic shocks [14,15,16,17].The temporal relationship between the onset or control of infection and PCT concentrations, as well as its patho physiological role in sepsis and exact position within the inflammatory mediator cascade are poorly understood [8,17,18].

There are few studies trying to identify the role of PCT and its superiority to c- reactive protein(CRP) in diagnosing and assessing the severity of sepsis . But all of them are from European or western countries [2,13,19,20,21,22,23].The draw backs of these studies is the difficulties in the interpretation of results mainly due to varying definitions for the used terms

Keywords: Procalcitonin, PCT, SOFA Score, Sepsis, Septic shock, ACCP/SCCM guidelines, Sepsis dilemma - Raghava Sharma

like infection, bacteraemia, sepsis, septic shock. At the same time there is paucity of data on PCT from Indian subcontinent.

Hence the present study was undertaken to evaluate the role of PCT in effectively solving the sepsis dilemma among critically ill patients by strictly adhering to the criteria by American college of chest physicians, Society of critical care medicine(ACCP/SCCM) [24] and also to correlate the same to SOFA (sepsis related organ failure assessment) score [10] to reinforce sepsis severity assessment.

Methodology :

The present prospective, cross sectional, observational study was undertaken in a tertiary care medical college hospital at Mangalore, coastal Karnataka after it was approved and permitted by the ethical committee of the institute. In the present study it was aimed to analyze (i) Role of PCT in diagnosing and confirming sepsis, (ii) Role of PCT in identifying severity of sepsis, (iii) Role of PCT in correlating severity of sepsis to SOFA scores, (iv) Role of PCT as a prognostic marker in sepsis and its importance in outcome and mortality. A total of 50 adult patients aged more than 18 & less than 80 years who fulfilled the criteria for definition of SIRS/sepsis, severe sepsis, septic shock as defined by ACCP/SCCM (Table 1) were selected and included in the study. Patients with age < 18 years, > 80 years, with co morbidities like major trauma, surgery, burns and malignancy were excluded from the study as these conditions could lead to a rise in PCT levels. Detailed symptoms history and detailed physical examination was undertaken for each included patient . The patients were grouped in to the following severities namely SIRS, sepsis, severe sepsis, and septic shock in accordance with the criteria from the guidelines of ACCP/SCCM [24]. SOFA (sepsis related organ failure assessment score) [10] was calculated for all the patients included in the study as described in Table 2, and Mean score was calculated for SIRS/sepsis severe sepsis, and septic shock. PCT level was estimated by using BRAHMS PCT-Q test(technique fully described under appendix -1 below)in all the 50 patients included in the study and was correlated and compared with SOFA score and degree of sepsis(as per ACCP/SCCM criterias).The following PCT cut offs were employed for therapeutic intervention and analysis of outcome –

PCT < 0.5 ng/ml : Local bacterial infection possible, systemic infection(sepsis) unlikely.

PCT > 0.5 & < 2 ng/ml : Suggests systemic infection(sepsis).

PCT > 2 & < 10 ng/ml : Suggests severe sepsis.

PCT > 10 ng/ml : Suggests almost exclusively septic shock.

From all the study population , for the definitive etiological diagnosis(isolation of micro organism) at least two blood samples were collected by aseptic precaution and subjected to culture. Materials from primary site of infection inclusive of urine, sputum, pleural fluid, ascetic fluid, pus were sent for Gram stain and culture. All the samples for culture were obtained immediately once sepsis was suspected, within 24 hours of admission to hospital and before starting antibiotic treatment. Other relevant lab parameters particularly Haemoglobin, White blood cell count, Platelet count, ESR, Prothrombin time, INR(international normalization ratio), Renal function test, and Liver function test were performed in all the included subjects. The data thus obtained were tabulated and then analyzed.

Appendix 1:

BRAHMS PCT-Q Test (PCT estimation technique) [18] : An immuno chromatographic test for the semi quantitative detection of PCT(procalcitonin) with an incubation period of only 30 minutes, which neither depends on apparatus nor needs calibrating. The test uses a monoclonal mouse anti catacalcin antibody conjugated with colloidal gold(tracer) and a polyclonal sheep anti calcitonin antibody(solid phase). These two antibodies rules out cross reactivity. After the patient sample(serum) has been applied to the test strip, the tracer binds to the PCT in the sample and marked antigen antibody complex forms. This complex moves by means of capillarity through the test system and in the process passes through the area containing the test band. Here the marked antigen antibody complex binds to the fixed anti calcitonin

antibodies and forms a sandwich complex. At a PCT concentration > 0.5 ng/ml, this sandwich complex can be seen as a reddish band. The colour intensity of the band is directly proportional to the PCT concentration of the sample. By comparing with the reference card thus PCT concentration in the sample can be obtained as (a) < 0.5 ng/ml, (b) > 0.5 & < 2 ng/ml, (c) >2 & < 10 ng/ml, (d) > 10 ng/ml. Non bound tracer diffuses in to the control band zone, where gets fixed and produces an intensely red coloured control band. The functional ability of the test system is checked by means of this control band.

Observations and Results

In this study, total of 50 patients were selected who were fitting in to the inclusion criteria as described in the methodology.

- Out of 50 patients, Procalcitonin was positive in 47(94%) patients.(Fig 1)
- 52% of the study patients were males and 48% were females.(Table 3)
- Maximum number of study patients were in the age group of 51-60 years.(Fig 2, Table 4)
- Out of total 50 patients, 23(52%)patients were in the group of SIRS/sepsis, 14(26%) patients were in group of severe sepsis, while 13(22%) were in group of septic shock.(Table 5)
- Most common symptom in patients with sepsis was fever.(table 6)
- Most common signs in patients with sepsis were Tachycardia(91%), followed by high temperature(76%) and then tachypnoea(65%).(Table 7)
- Among other laboratory parameters , almost all patients with sepsis had leucocytosis and high ESR.(Table 8)
- Most common identified source of sepsis was respiratory tract infection(40%), followed by urinary tract infection(20%).(Fig 3, Table 9)
- Increase in level of PCT was clearly evident as the severity of sepsis (as per ACCP/SCCM criterias) increased , irrespective of the source of sepsis.(Table 10, 11, 12)
- Out of total 50 patients 20(40%) were culture positive and among those 14(70%) grew Gram negative organisms in culture. Most common Gram negative organism grown was E.Coli, while most common Gram positive organism grown was MRSA.(Fig 4, Table 13)
- Culture of Blood, Urine, Sputum, Pus, and Ascitic fluid were collectively responsible for the 40% positivity. All culture positive cases had PCT levels > 0.5 ng/ml while all culture negative cases had low PCT levels < 0.5 ng/ml.(Table 14)
- Even in culture negative sepsis patients , high PCT levels was evident and consistent with severity of sepsis.(Fig 5, Table 15)
- PCT was positive in 47 out of total 50 patients and high levels of PCT (> 10 ng/ml) was characteristically noted in patients with severe sepsis and septic shock.(Fig 6, Table 16)
- Mean SOFA score was 4.9 for SIRS/sepsis, 10.2 for severe sepsis, and 11.8 for septic shock. Thus increasing level of Mean SOFA score was clearly evident and correlated well with increasing severity of sepsis.(Table 17)
- Correlation of PCT level and Mean SOFA score clearly demonstrated a progressively increasing PCT level corresponding well to progressively increasing Mean SOFA scores. Thus PCT level and Mean SOFA scores correlated well with sepsis severity.(Table 18)
- Correlation of PCT to ESR in all the included subjects demonstrated that , although ESR was high in patients with sepsis , it did not correlate well with severity of sepsis.(Table 19)
- All sepsis patients who had mortality had very high PCT level (> 10 ng/ml) at the time of admission.(Fig 7, Table 20)

FIGURE 1: Procalcitonin positivity

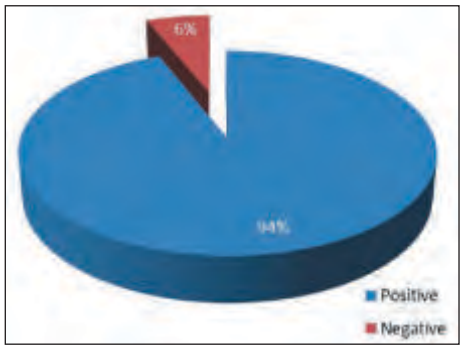

FIGURE 2 : Age distribution.

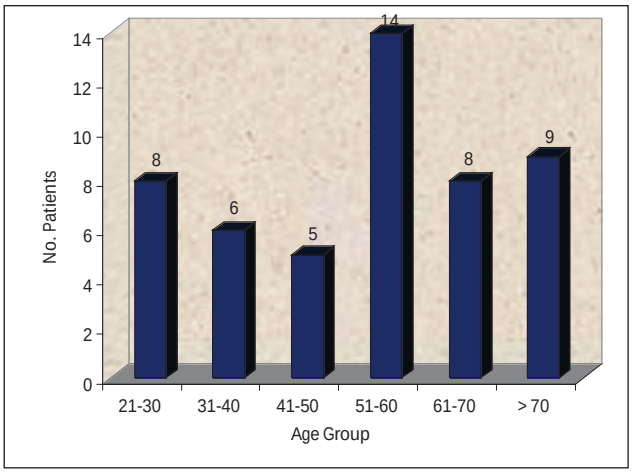

FIGURE 3 : Source of sepsis.

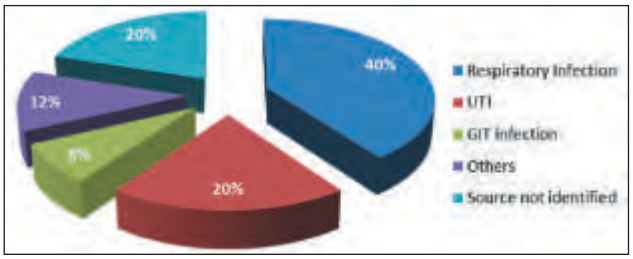

FIGURE 4 : Organism grown in culture.

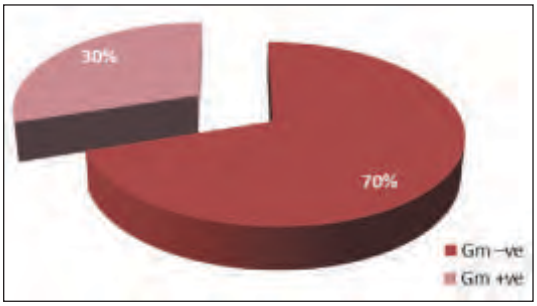

FIGURE 5 : Culture and PCT in relation to severity of sepsis.

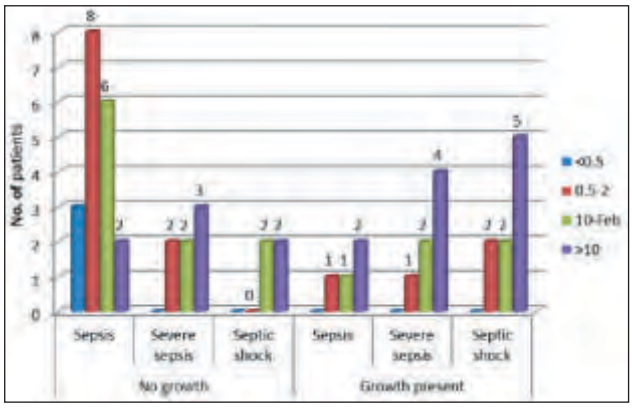

FIGURE 6 : Diagnostic value of PCT for severity of sepsis.

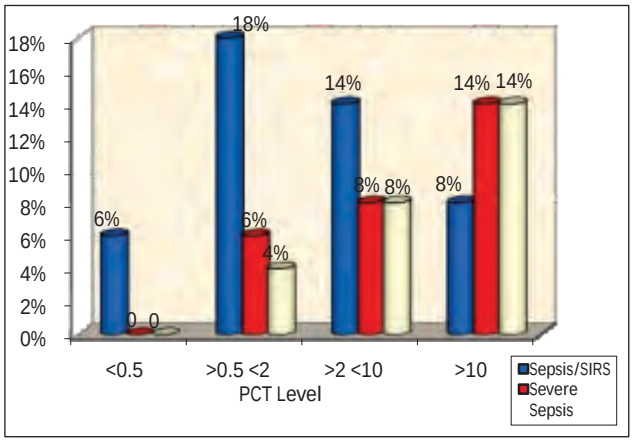

FIGURE 7 : PCT Vs Mortality.

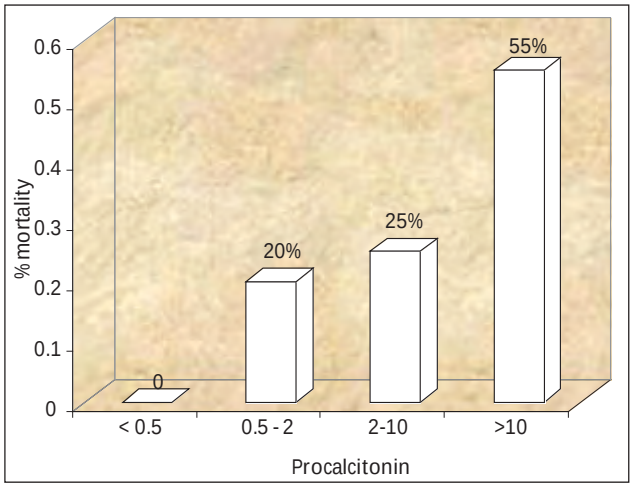

TABLE 1 : ACCP/SCCM CONSENSUS GUIDELINES [24]

CLINICAL STATUS.	CONSENSUS GUIDE LINES/CRITERIAS
A. Infection	Microbial phenomenon characterized by an inflammatory response to the presence of micro organism or the invasion of normally sterile host tissue by those organisms.
B. Bacteraemia	The presence of viable bacteria in the blood as evidenced by positive blood culture.
C. Systemic inflammatory response syndrome (SIRS)	The systemic inflammatory response to a variety of insults, manifested by two or more of the following: (i) Temperature > 38*C or < 36* C (ii) Heart rate > 90 beats/minute (iii)Respiratory rate >20 breaths/min or PaCo2 < 32 mmHg (iv)White blood cell count > 12000/cu mm, < 4000/cu mm, > 10% immature forms.
D. Sepsis	SIRS Plus suspected or documented infection site by positive culture for the organism from that site.
E. Severe sepsis	Sepsis with one or more signs of organ dysfunction – (i) Cardiovascular: Arterial systolic blood pressure < 90 mmHg or Mean arterial pressure < 70 mmHg that responds to administration of intravenous fluids, Pulmonary artery wedge pressure >12 mmHg or central venous pressure > 8 mmHg after adequate fluid resuscitation. (ii) Renal: Urine output < 0.5 ml/kg per hour for 1 hour despite adequate fluid resuscitation. (iii)Respiratory: Pao2/Fio2 < 250 or < 200 if lung is the only dysfunctional organ. (iv)Haematological: Platelet count < 80000/mcL or 50% decrease in platelet count from highest value recorded over previous 3 days. (v) Metabolic acidosis: Ph < 7.3 or a base deficit > 5 & plasma lactate level > 1.5 times upper limit of normal for reporting lab.
F. Septic shock	Sepsis with hypotension despite adequate fluid resuscitation, along with presence of perfusion abnormalities that may include lactic acidosis, oliguria, or an acute alteration in mental status.
G. Refractory septic shock	Septic shock that lasts for more than 1 hour and does not respond to fluid or vaso pressor administration.

Table 2 : SOFA SCORING SYSTEM[10,25]

By European Society of Intensive Care Medicine in 1994. Six organ systems/variables evaluated in a scale of 0- 4 each. The arithmetical sum of these six is the value of SOFA score.

	SOFA Score				
Variable	0	1	2	3	4
Respiratory -PaO2/FiO2 mmHg	> 400	301 – 400	201 – 300	101 – 200	≤ 100
Coagulation – Platelet (lakh / dl)	<1.2 (<20)	1.2-1.9 (20 – 32)	2.0-5.9 (33 – 100)	6.0-11.9 (101 – 203)	>12 (> 203)
Hepatic -Bilirubin, mg/dL (µmol/L)	<1.2 (<20)	1.2-1.9 (20 – 32)	2.0-5.9 (33 – 100)	6.0-11.9 (101 – 203)	>12 (> 203)
CVS - Hypotension	MABP > 70 mmHg	MABP < 70 mmHg without ionotropes	Dop ≤ 5	Dop 6 – 15 or Epi ≤ 0.1 or Norepi ≤ 0.1	Dop >15 or Epi > 0.1 or Norepi > 0.1
CNS - Glasgow Coma Score	15	13 - 14	10 - 12	6 - 9	< 6
Renal - Creatinine, mg/dL (µmol/L)	< 1.2 (<106)	1.2-1.9 (106 – 168)	2.0-3.4 (169 - 300)	3.5-4.9 (301 – 433)	> 5 (> 434) or anuria

MABP – Mean Arterial Blood Pressure, Dop – Dopamine Epi – Epinephrine Norepi – Norepinephrine
SOFA score >13 is associated with high mortality.

Keywords: Procalcitonin, PCT, SOFA Score, Sepsis, Septic shock, ACCP/SCCM guidelines, Sepsis dilemma - Raghava Sharma

Table 3: Sex Distribution

Sex	No. Patients (n=50)	Percentage
Male	26	52%
Female	24	48%

Table 4: Age distribution

Age group	No. Patients	Percentage
21-30	8	16
31-40	6	12
41-50	5	10
51-60	14	28
61-70	8	16
> 70	9	18

Table 5: Severity of sepsis

Sepsis	No. Patients (n=50)	Percentage
Sepsis / SIRS	23	52
Severe sepsis	14	26
Septic shock	13	22

Table 6: Frequency of symptoms in patients

Symptoms	Percentage(%)
Fever	83
Chills	15
Cough	40
Breathlessness	35
Altered Sensorium	32
Vomiting	21
Loose stools	13
Pain abdomen	12
Jaundice	7
Headache	6
Burning micturition	6
Swelling of lower limb	6
Seizures	3

Table 7: Frequency of Common Signs in Patients

Signs	Percentage
Febrile-High temperature	76
Tachycardia	91
Tachypnoea	65
Hypotension	37
Pallor	43
Edema	33
Icterus	30
Altered sensorium	30
petechiae	7
Subconjunctival hemorrhage	6
Lymphadenopathy	2

Table 8: Other Lab parameters

Lab parameters	Percentage
Decreased Hemoglobin (<10gm %)	49
Leucoytosis (>12,000)	78
Leucopenia (< 4,000)	6
Thrombocytopenia (<1,50,000)	55
Prolonged PT/INR	47
Altered RFT	67
Altered LFT	50
Raised ESR	73

Table 9: Source of sepsis

Respiratory Tract Infection	20 (40%)
Urinary tract infection	10 (20%)
Gastro intestinal tract infection	5 (10%)
Others	5 (10%)
Source not identified	10 (20%)

Table 10: Relationship between procalcitonin and sepsis in respiratory tract infection
Total no. of respiratory tract infections = 20 (40%, n=50).

Procalcitonin (ng/ml)	Sepsis	Severe sepsis	Septic shock
< 0.5 1	-	-	
> 0.5 < 2	4	1	1
>2 <106	-	1	
>10 3	1	2	

Table 11: Relationship between procalcitonin and sepsis in Urinary tract infections.
Total no. of patients with UTI = 10 (20%, n=50).

Procalcitonin (ng/ml)	Sepsis	Severe sepsis	Septic shock
< 0.5	1	0	0
> 0.5 < 2	2	0	1
>2 <10	1	0	1
>10	2	1	1

Table 12: Relationship between procalcitonin and sepsis in gastro intestinal tract infections
Total no. of patients with GIT infections = 5 (10%, n=50).

Procalcitonin (ng/ml)	Sepsis	Severe sepsis	Septic shock
< 0.5	0	0	0
> 0.5 < 2	1	0	0
>2 <10	1	1	1
>10	1	0	0

Table 13: Organism grown in culture
Total number of positive cultures = 20 (40 %).

Gm –ve	14 (70%)
Gm +ve	6 (30%)

Table 14: Relationship between procalcitonin and cultures in patients with sepsis
Total no. of positive cultures = 20 (40 %)

Procalcitonin (ng/ml)	Blood C/S	Urine C/S	Sputum C/S	Pus C/S	Ascitic fluid C/S
< 0.5	0	0	0	0	0
> 0.5 < 2	2	1	1	0	0
>2 <10	2	1	1	1	0
>10	3	3	2	2	1
Total	7	5	4	3	1

Table 15: Culture and PCT in relation to severity of sepsis

		<0.5	>0.5,< 2	>2,<10	>10
No growth	Sepsis	3	8	6	2
	Severe sepsis	0	2	2	3
	Septic shock	0	0	2	2
Growth	Sepsis	0	1	1	2
present	Severe sepsis	0	1	2	4
	Septic shock	0	2	2	5

Table 16: Severity of sepsis & Diagnostic value of Procalcitonin

Procalcitonin (ng/ml)	Sepsis/SIRS	Severe Sepsis	Septic shock
<0.5	3(6%)	0	0
>0.5 <2	9(18%)	3(6%)	2(4%)
>2 <10	7(14%)	4(8%)	4(8%)
>10	4(8%)	7(14%)	7(14%)

Table 17: SOFA score and Severity of sepsis

Severity	Mean SOFA Score
SIRS, Sepsis	4.9
Severe Sepsis	10.2
Shock	11.8

Table 18: PCT V/s SOFA Correlation

Procalcitonin(ng/ml)	Mean SOFA Score
< 0.5	6
0.5-2	8.4
2-10	10.6
> 10	12.2

Table 19: PCT V/s SOFA V/s ESR Correlation

Procalcitonin(ng/ml)	Mean SOFA Score	Mean ESR
< 0.5	6	30
0.5-2	8.4	50
2-10	10.6	42
> 10	12.2	53

Table 20: PCT V/s Mortality Correlation

Procalcitonin (ng/ml)	Frequency (n=50)	No. of deaths (n=20)	% mortality
< 0.5	3	0	0
0.5 – 2	14	4	20%
2 -10	15	5	25%
>10	18	11	55%

Conclusions :

Summarily, the observations and results from the present study confirm that Procalcitonin(PCT) is a promising marker of sepsis especially at the time of admission itself among critically ill patients.

PCT measurement appears to be a better predictor to distinguish patients with sepsis and patients without sepsis when compared to ESR.

PCT is an excellent marker providing the additive effect to improve the predictive power for diagnosing sepsis , for assessing severity of sepsis , and also for predicting the outcome/prognosis especially during the first 24 hours of admission.

It is all about “confidence” and confidence comes through PCT while managing critically ill patients, as a quick PCT estimation by BRAHMS- PCT Q test (reports available within 30 minutes and is independent of observer bias) is a boon.

Thus from the present study we conclude that :

- Addition of procalcitonin (PCT) into the workup of critically ill patients with suspected sepsis will aid definitive diagnosis and also help in quick complex patient management.
- Procalcitonin(PCT) is not a myth nor a hype and definitely not an innocuous laboratory curiosity but it is a hard reality and is an answer to sepsis dilemma.

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