COMPARISON OF PROCALCITONIN (PCT) AND C-REACTIVE PROTEIN (CRP) PLASMA CONCENTRATION AT DIFFERENT SOFA SCORES DURING THE COURSE OF SEPSIS

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Abstract

Background: Hassling clinical features had been found in sepsis and non-infectious systemic inflammatory response syndrome (SIRS), with neither sensitive nor specific physiologic parameters and time-exhausting microbiological data, which may also be inconclusive. Aim of the work: To compare the clinical informative value of procalcitonin (PCT) and C-reactive protein (CRP) plasma concentration in the early detection of sepsis and to relate these biomarkers to other scoring systems. Patients and method: One hundred thirty-eight patients 77 males and 61 females with a mean age of 55.6+19 years were enrolled in our study. All were subjected to PCT, CRP, and sequential organ failure assessment (SOFA) scores daily for 7 days (day 1 starting symptoms). Blood samples were collected before starting antibiotics. The acute physiology and chronic health evaluation (APACHE) II score was used to determine the initial severity of illness. All patients were followed up for 28 days and were assigned to three groups: group I: SOFA 2–7, group II: SOFA 8–10, and group III: SOFA ≥ 11.

Results: Underlying clinical diagnosis revealed pneumonia in 72 patients, urinary tract infections in 8, bloodstream infection in 4, and other infections in 23, while infection could not be traced in 25 patients. The mean PCT was 3 ng/ml (95% CI 1–4), 12 ng/ml (95% CI 9.1–14), and 19 ng/ml (95% CI 16.3–22.3) in groups I, II, and III respectively, with a statistically significant difference in the mean PCT level among the 3 groups ($P < 0.0001$). On the other hand, CRP mean level did not significantly differentiate between the groups (147.1 mg/L in group II, which was even higher than the level of group III, 138.4 mg/L). We found statistically significant positive correlation between PCT and APACHE II scores by using a Spearman correlation test that could not be achieved between CRP and APACHE II.

Conclusion: Given PCT's patronage display over a wide spectrum of insults, it seems to do better than CRP in predicting the SOFA groups.

Keywords: sepsis, SOFA, procalcitonin, CRP, APACHE II score

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CONTENT

TABLE AND GRAPHIC LIST

ABBREVIATION

LOS	Length Of Stay
LPS	Lipopolysacharraide
LRTI	Lower Respiratory Tract Infection
MAP	Mean arterial pressure
mcg	Microgram
mL	Milliliter
mm^3	Cubic Millimeter
mmHg	Millimeter Mercury
mmol	Millimol
MODS	Multi Organ Dysfunction Syndrome
MPM	Mortality Probability Model
NEMS	Nine equivalents of nursing manpower use score
ng	Nanogram
Pao_2/F_IO_2	Partial pressure of Arterial Oxygen
PCT	Procalcitonin
PCWP	Partial Capillary Wedge Pressure
ROC	receiver operating characteristic
SAPS	Simplified Acute Physiology Score
SBP	Systolic Blood Pressure
SCCM	Society of critical care medicine
SD	Standard Deviation
SIRS	Systemic Inflammatory Response Syndrome
SOAP	Sepsis Occurrence in the Acutely Ill Patients
SOFA	Sequential Organ Failure Assessment
TISS	Therapeutic Intervention Scoring System
TNF	Tumor necrosis factor
uL	Micro litter
umol	Micro milimol
US	United state
UTI	Urinary tract infection
VAP	Ventilator associated pneumonia
vs	versus
WBC	White blood cell
$	US Dollar

ACCP	American College of Chest Physicians
AIDS	Acquired immune deficiency syndrome
AKI	Acute kidney injury
APACHE	Acute Physiology and chronic health evaluation
aPTT	Activated Partial Thromboplastin Time
ARDS	Acute Respiratory Distress Syndrome
ATS	American Thoracic society
AUC	Area under curve
BAL	Bronchoalveolar Lavage
BSI	Blood stream infection
BP	Blood pressure
cAMP	Cyclic Adenosine monophosphate
CAP	Community Acquired pneumonia
CI	Cardiac Index
COPD	Chronic Obstructive Pulmonary Disease
CRP	C-Reactive protein
CVP	Central Venous Pressure
CVVH	Continuous Veno-Venous Hemofiltration
^oC	Celsius degree
DIC	Disseminated Intravascular Coagulation
dl	Deciliter
e.g.,	For example
EEG	Electroencephalographic
ESICM	European society of intensive care medicine
fig	Figure
F_IO_2	Fraction of Inspired Oxygen
hr	Hour
HR	Heart Rate
ICU	Intensive Care Unit
IgG	Immunoglobulin G
IL	Interleukin
INR	International Normalized Ratio
kg	Kilogram
L	Liter

INTRODUCTION

One of the prime events that may hit the critically ill patients is fever. Identifying the offender is of magnificent prominence, as it will direct the way of treatment towards bacterial, fungal or viral etiology.

C-reactive protein (CRP) is known as a very sensitive inflammatory marker irrespective of the cause, which is definitive when the case is immunocompromised patient. Procalcitonin (PCT) had been widely studied as a marker for bacterial infection. The utility of this marker in severe sepsis is now widely admitted. Limper et al. had described it, as a differentiating biomarker between infectious from non-infectious fever (1).

Two or more of the following conditions characterize systemic inflammatory syndrome (SIRS): Temperature >38.5°C or <35.0°C; Heart Rate of >90 beats/min; Respiratory Rate of >20breaths/min or $PaCO_2$ of <32 mm Hg; and White Cell Count (WBC) of >12,000cells/mL, <4,000cells/mL, or >10% immature (band) forms (2).
Infection as SIRS inducer has been marked to be an important factor. Sepsis and its sequelae are common causes of mortality in Intensive Care Unit (ICU), and delayed diagnosis and treatment are associated with increased mortality (3).

The clinical features of sepsis and non-infectious SIRS are very close. Physiologic parameters such as criteria for SIRS are neither specific nor sensitive for sepsis.
Microbiologic data are time consuming and may be non-diagnostic, as negative cultures do not exclude infection, and the microbiologic diagnostic procedure requires at least 1–2 days for providing accurate quantitative results. Furthermore, viral infections are even more difficult to assess (4).

Therefore a rapidly obtainable marker that is capable of discriminating sepsis from non-infectious SIRS would be clinically useful. An ideal marker of infection would be highly specific, highly sensitive, easy to measure, rapid, inexpensive, and correlated with the severity and prognosis of infection.

In critically ill patients, confined information usually could be retrieved from CRP measurement due to relatively long clinical half-life, misleading assay in reinfection, and the delayed response (5).

Procalcitonin plasma level increase severe bacterial or fungal infections or sepsis and concentrations as high as 1000ng/ml had been reported in sepsis and septic shock, however localized bacterial infections, viral infections, autoimmune and allergic disorders are not PCT inducers (6).

Procalcitonin (PCT) is a 116 amino acid protein with a molecular mass of 13 kDa, it is a precursor of calcitonin hormone. The increased level of PCT in bacterial sepsis was first mentioned by Assicot et al., (1993) which seems to be related to the degree of microbial invasion (7). It is not known exactly where the originating site of PCT production, but the liver seems to be the major site of production. A large amount of PCT had been produced after stimulation of human hepatocytes with tumor necrosis factor α (TNFα) and interleukin 6 (IL-6) (8). Under normal physiological conditions, the PCT serum level is extremely low, usually below 0.01 ng/ml, and in viral infection and inflammation concentrations are slightly increased, but rarely above 1ng/ml (9), However level up to 500ng/ml or more had been described in bacterial infections (10).

Critical care outcome predictors include clinical, diagnostic, and physiologic variables that are well identified. The acute physiology and chronic health evaluation II (APACHE II) scoring system is commonly used in intensive care population for outcome prognostication, and to acuity comparing of medical care in different

intensive care units (ICU), it was created for assessing disease severity in adult patients admitted to ICU (11,12).

The relation between PCT concentrations and the severity of organ dysfunction assessed by sepsis-related organ failure assessment (SOFA) score in patients with multiorgan dysfunction (MOD) secondary to systemic inflammation of infectious or noninfectious origin need to be studied. We hypothesize that PCT is a better stigma for sepsis than CRP and may have a predictive rule in early or late sepsis related mortality.

The aim of this work is to compare the clinical informative value of PCT and CRP plasma concentration in the detection of infection/sepsis and investigate the relation between both markers and the severity of organ dysfunction assessed by the SOFA score, and to study the mortality predictive power of PCT versus CRP.

Aim Of The Work

1. Compare the clinical informative value of Procalcitonin and C-Reactive Protein plasma concentration in the detection of infection/sepsis and investigate the relation between Procalcitonin and C-Reactive protein concentration and the severity of organ dysfunction assessed by the sepsis-related organ failure assessment (SOFA) score.

2. Compare Procalcitonin and C-Reactive Protein plasma concentration prognostic value in prediction of early (7 days) or late (28 days) mortality.

Chapter I

SEPSIS OVERVIEW

Sepsis is a clinical syndrome that complicates severe infection and is characterized by systemic inflammation and widespread tissue injury. In this syndrome, tissues remote from the original insult display the cardinal signs of inflammation, including vasodilation, increased microvascular permeability, and leukocyte accumulation. Although inflammation is an essential host response, current beliefs regarding the onset and progression of sepsis center upon a "dysregulation" of the normal response, with a massive and uncontrolled release of pro-inflammatory mediators creating a chain of events that leads to widespread tissue injury.

Noninfectious disorders (e.g., acute pancreatitis or pulmonary contusion) may also be complicated by tissue injury secondary to activation of the inflammatory system. The term systemic inflammatory response syndrome (SIRS) is used in this setting to refer to the consequences of a dysregulated host inflammatory response when infection is not present.

Therefore, distinguish between an underlying disease (infection or pancreatitis) and the host's response (sepsis or SIRS) is possible. This distinction is important clinically since it is the latter, not the primary disease, that is responsible for the multiple organ dysfunction syndrome (MODS). MODS is the usual explanation for the high mortality rates associated with these syndromes.

DEFINITIONS:

The American College of Chest Physicians (ACCP) and Society of Critical Care Medicine (SCCM) convened a consensus panel in 1992 to define SIRS, sepsis, severe sepsis, and septic shock (13). These definitions were reconsidered in 2001 during an

international sepsis definitions conference that included representatives from the ACCP, SCCM, European Society of Intensive Care Medicine, American Thoracic Society, and Surgical Infection Society (2). A practical modification of the definitions has since been published, which provides exact hemodynamic definitions for septic shock (14).

Tab.1: Definitions of systemic inflammatory response syndrome and different degrees of severity of sepsis. (From 2)

Condition	Description
Systemic inflammatory response syndrome	Two or more of the following conditions: 1. Temperature >38.5°C or <35.0°C; 2. Heart rate of >90 beats/min; 3. Respiratory rate of >20 breaths/min or $PaCO_2$ of <32mmHg; 4. WBC count of >12,000 cells/mL, <4000 cells/mL, or >10% immature (band) forms.
Sepsis	SIRS in response to: • Documented infection (culture or Gram stain of blood, sputum, urine, or normally sterile body fluid positive for pathogenic microorganism; or • Focus of infection identified by visual inspection, e.g. ruptured bowel with free air or bowel contents found in abdomen at surgery, wound with purulent discharge).
Severe sepsis	Sepsis and at least one of the following signs of organ hypoperfusion or organ dysfunction: 1. Areas of mottled skin; 2. Capillary refilling of ≥3s; 3. Abrupt change in mental status or abnormal EEG findings; 4. Acute lung injury/ARDS; 5. Cardiac dysfunction (echocardiography) 6. Urinary output of <0.5 mL/kg for at least 1h or renal replacement therapy; 7. Lactate >2 mmol/L; 8. Platelet count of <100,000 cells/mL; 9. Disseminated intravascular coagulation.
Septic shock	Severe sepsis and one of the following conditions: 1. Systemic mean BP of <60mmHg (<80mmHg if previous hypertension) after: • 20 to 30 mL/kg starch or • 40 to 60 mL/kg saline solution, or • PCWP between 12 and 20 mmHg; 2. Need for Dopamine of >5mcg/kg/min, or Norepinephrine or Epinephrine of <0.25mcg/kg/min to maintain mean BP at >60mm Hg (80mmHg if previous hypertension).
Refractory septic shock	Need for Dopamine at >15mcg/kg/min, or Norepinephrine or Epinephrine at >0.25 mcg/kg/min to maintain mean BP at >60mmHg (80 mmHg if previous hypertension).

- **Infection**:

  Infectionis characterized by an inflammatory response to microorganisms or the invasion of normally sterile host tissue by those organisms.

- **Bacteremia**:

  Bacteremia is defined as the presence of viable bacteria in the blood.

- **Systemic inflammatory response syndrome (SIRS)**:

  SIRS refers to the consequences of a dysregulated host inflammatory response.

  It is clinically recognized by the presence of two or more of the following:

  1. Temperature >38.5ºC or <35ºC,
  2. Heart rate >90 beats/min,
  3. Respiratory rate >20breaths/min or $PaCO_2$<32 mmHg,
  4. WBC >12,000cells/mm^3, <4000cells/mm^3, or >10% immature (band) forms.

  SIRS can result from a variety of conditions, such as autoimmune disorders, pancreatitis, vasculitis, thromboembolism, burns, or surgery.

- **Sepsis**:

  It exists if two or more of the following abnormalities are present, along with either a culture-proven or visually identified infection:

  1. Temperature >38.3ºC or <36ºC,
  2. Heart rate >90 beats/min,
  3. Respiratory rate >20 breaths/min or $PaCO_2$<32 mmHg,
  4. WBC >12,000 cells/mm^3, <4000 cells/mm^3, or >10% immature (band) forms.

  The severity of sepsis is graded according to the associated organ dysfunction and hemodynamic compromise.

- **Severe sepsis:**

  Severe sepsis exists if there is sepsis plus at least one of the following signs of organ hypoperfusion or dysfunction:

  1. Areas of mottled skin,
  2. Abrupt change in mental status,
  3. Abnormal EEG findings,
  4. Acute lung injury or ARDS
  5. Urine output <0.5mL/kg for at least one hour, or renal replacement therapy,
  6. Cardiac dysfunction, as defined by echo-cardiography or direct measurement of the Cardiac index,
  7. Disseminated Intravascular Coagulation
  8. Platelet count <100,000 platelets/mL,
  9. Lactate >2mmol/L.

- **Septic shock:**

  Septic shock is one type of vasodilatory or distributive shock. It results from a marked reduction in systemic vascular resistance, often associated with an increased in cardiac output.

  Septic shock exists if there is severe sepsis plus one of the following:

  1. Systemic MAP is <60mmHg (or <80mmHg if the patient has baseline hypertension) despite adequate fluid resuscitation, and/or
  2. Maintaining the systemic mean blood pressure >60mmHg (or >80mmHg if the patient has baseline hypertension) requires Dopamine >5mcg/kg/min, Nor-epinephrine <0.25mcg/kg/min, or Epinephrine <0.25mcg/kg/min despite adequate fluid resuscitation.

  Adequate fluid resuscitation is defined as infusion of 20 to 30 mL/kg of starch, infusion of 40 to 60 mL/kg of saline solution, or a measured pulmonary capillary wedge pressure (PCWP) of 12 to 20mmHg.