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Role of Perioperative C - Reactive Protein and Procalcitonin in Predicting 30 Day Mortality after Major Surgery

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ABSTRACT

INTRODUCTION

Outcome predictors following major surgery have been till date based on scoring systems like sepsis score, Sequential Organ Failure Assessment (SOFA), Acute Physiology and Chronic Health Evaluation (APACHE II, APACHE III) score etc. These scores either can be applied to a single set of data or repeated overtime. APACHE and SOFA are some of the most popular scoring systems. Of late the pathophysiology of stress response in major surgery has been well understood. The final common pathway of stress response is final and common to most of the stress situations like surgery, trauma and serious illness. Response to surgery is part of the integrated, organized systemic reaction that encompasses a wide range of endocrine, immunological, inflammatory and hematological components. The inflammatory response to injury and activation of cellular process are inherently designed to restore tissue function and eradicate invading microorganisms. In response to tissue injury acute phase proteins are released by liver, stimulated by cytokines which is known as acute phase response.

Among those acute phase proteins C-reactive protein (CRP) was the first to be described in 1930. Surgical trauma induces a significant increase in CRP level, which can reduce its predictive value for the diagnosis of infection in early postoperative period. Despite this, an interest in CRP as an infection monitoring tool in perioperative setting has increased since it was reported that, values higher than 140 mg/l on the post op day 3-4 well predicts infectious complications after colorectal surgery. Procalcitonin (PCT), the pro hormone was described as the bio chemical marker for infection in 1993. Procalcitonin is more suitable as an infection monitoring tool in the perioperative setting. Recent studies in surgical patients have also shown PCT was better for detecting post-operative infection than CRP after orthopedic, cardiac and thoracic surgery. But the literature available on these markers regarding perioperative utility in predicting 30 day mortality after major surgery is very limited. Hence this study was planned to know the role of C-reactive protein and Procalcitonin in predicting 30 day mortality after major surgery.

AIMS AND OBJECTIVES

Primary objective

To determine the role of perioperative C- reactive protein, Procalcitonin in predicting 30-day mortality after major surgery.

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Secondary objective

To correlate level of C-reactive protein and Procalcitonin with APACHE II Scores.

MATERIAL AND METHODS

Place of study

Meenakshi Mission Hospital and research center, Madurai.

Biochemical markers

Estimation of CRP, Procalcitonin in perioperative period.

Scoring system

APACHE II.

METHODOLOGY

Blood samples collected

CRP Levels estimated on day before surgery & On 3rd POD.

Procalcitonin levels estimated on day before surgery & on 3rd POD.

Scoring system

On day before surgery & on 3 POD.

CRP

Particle enhanced immuno turbidometric immunoassay (PETIA).

Principle

Synthetic particles coated with antibody to C-reactive protein (abpr) aggregate in the presence of C-reactive protein in the sample. The increase in turbidity which accompanies aggregation is proportional to the C-reactive protein concentration.

CRP + abpr ⟶ Aggregates.

Flex reagent cartridges are used (SIEMENS).

Assay range: 0.5 mg/l - 250 mg/l or 0.05 mg/l - 25mg/dl.

Procalcitonin

Electro chemilumionesence immuno assay

Elecsys BRAHMS PCT kits were used (COBAS).

Sandwich principle

1st Incubation: Antigen in the sample (30 mic.l), a biotinylated monoclonal PCT-specific antibody, and a monoclonal PCT specific antibody labeled with a ruthenium complex react to form a sandwich complex.

2nd Incubation: After addition of streptavidin coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin. The reaction mixture is aspirated into the measuring cell where the microparticles are

magnetically captured onto the surface of the electrode. Unbound substances are then removed with procell. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier. Results are determined via a calibration curve which is instrument - specifically generated by 2-point calibration and a master curve provided via the reagent barcode.

Measuring range

0.02 ng/ml - 100 ng/ml

Values below the detection limit reported as <0.02 ng/ml

Values above the measuring limit reported as >100 ng/ml

Duration

24 Months

Number of patients

N = 90

Sample size

The sensitivity of Procalcitonin is 67% (two consecutive maximum PCT levels correlation with death), precision is 10% and 95% confidence interval the minimum required sample size is 85 subjects.

Reference (based on this study sample size calculated)

Rau BM, Frigerio I, Büchler MW, et al. (2007) Evaluation of procalcitonin for predicting septic multiorgan failure and overall prognosis in secondary peritonitis: A prospective, international multicenter study. Archives of Surgery 142(2): 134-142.

A PROSPECTIVE, INTERNATIONAL MULTICENTER STUDY

Statistical analysis

The data was recorded in Microsoft excel. Statistical analysis was performed by using STATA 11.1 (College Station TX USA) and SPSS.20 Version statistical analysis system. Categorical variables were expressed as frequency and percentage. Continuous variables were expressed in terms of mean and standard deviation. Independent t test was used to compare two groups' means. Paired t test was applied for comparison within the group. Karl-Pearson correlation was used between two related variables to find correlation coefficient. Logistic regression was used to predict the dependent variables from independent variables. Diagnostic accuracy of CRP and PCT concentrations for prediction of postoperative 30 days mortality was assessed by receiver operating characteristics (ROC) curve analysis. The area under the curve presented a direct measure of the diagnostic accuracy of the test. P value <0.05 was considered significant.

Design of study

Prospective cohort study.

RESULTS

53.3% of the patients were below 50 years and 46.7% of them were above 50 years.

65.54% of the patients were male and 34.44% patients were female.

There was no statistically significant difference between survivors and non survivors in terms of age (p = 0.53). There was statistically significant difference of ICU Stay between survivors and non survivors (p = <0.001).

Statistically significant difference of total hospital stay observed between survivors and non survivors (Survivors -6.40 ± 1.82 days, Non survivors -11.33 ± 4.93 days; p<0.001).

No significantly different C - reactive protein levels were seen pre operatively among survivors and non survivors (2.37 ± 2.02 *vs*. 3.31 ± 2.42; p = 0.433). Whereas Post operatively there was significantly different CRP levels were observed (4.52 ± 4.07 *vs*. 16.2 ± 7.83; p<0.001). But when compared with non survivors, survivors had significantly different preoperative and postoperative CRP levels (p = 0.154 *vs*. p ≤ 0.001).

No significantly different Procalcitonin levels were observed pre operatively between survivors and non survivors (1.605 ± 1.22 *vs*. 2.01 ± 1.23; p = 0.574). Whereas post operatively there was significantly different Procalcitonin levels were seen among them (3.89 ± 3.40 *vs*. 34.50 ± 27.53; p <0.001). But when compared with non survivors, survivors had significantly different preoperative and postoperative Procalcitonin levels (p = 0.189 *vs*. p ≤ 0.001).

There was no significantly different APACHE Scores were observed pre operatively among survivors and non survivors (6.28 ± 1.91 *vs*. 8.33 ± 4.04 p = 0.083), whereas significantly high scores observed post operatively among them (8.55 ± 2.61 *vs*. 16.67 ± 2.31; =<0.001). In the survivors group there was significantly high scores seen postoperative period when compared with preoperative period (p = <0.001) but this was not observed in survivors group (p = 0.054).

When all factors (confounding) were taken into account & logistic regression used no individual factor was found to have any significant bearing on final outcome.

CONCLUSION

Postoperative (Third POD) C reactive protein and procalcitonin levels can be used to predict 30 days mortality after major abdominal surgery.

CRP and PCT levels were correlating with APACHE II Scores. These can be used to predict morbidity after major surgery instead of APACH II.

KEYWORDS

C- reactive protein; APACHE II; Surgery

INTRODUCTION

Outcome predictors following major surgery have been till date based on scoring systems like sepsis score, Sequential Organ Failure Assessment (SOFA), Acute Physiology And Chronic Health Evaluation (APACHE II, APACHE III) score etc. These scores either can be applied to a single set of data or repeated overtime. APACHE and SOFA are some of the most popular scoring systems. Of late the pathophysiology of stress response in major surgery has been well understood. The final common pathway of stress response is final and common to most of the stress situations like surgery, trauma and serious illness. Response to surgery is part of the integrated, organized, systemic reaction that encompasses a wide range of endocrine, immunological, inflammatory and hematological components. The inflammatory response to

injury and activation of cellular process are inherently designed to restore tissue function and eradicate invading microorganisms. In response to tissue injury, acute phase proteins are released by the liver, stimulated by cytokines, which is known as an acute phase response.

Among those acute phase proteins C-reactive protein (CRP) was the first to be described in 1930. Surgical trauma induces a significant increase in CRP level, which can reduce its predictive value for the diagnosis of infection in early postoperative period [1-3]. Despite this, an interest in CRP as an infection monitoring tool in perioperative setting has increased since it was reported that , values higher than 140 mg/l on the post op day 3-4 well predicts infectious complications after colorectal surgery [4]. Procalcitonin (PCT), the pro hormone was described as the biochemical marker for infection in 1993 [5]. Procalcitonin is more suitable as an infection monitoring tool in the perioperative setting [6,7]. Recent studies in surgical patients have also shown PCT was better for detecting post operative infection than CRP [8-10] after orthopedic, cardiac and thoracic surgery. But the literature available on these markers regarding perioperative utility in predicting 30 days mortality after major surgery is very limited. Hence this study was planned to know the role of C-reactive protein and Procalcitonin in predicting 30 day mortality after major surgery.

AIMS AND OBJECTIVES

Primary Objective

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Secondary Objective

To correlate level of C-reactive protein and Procalcitonin with APACHE II Scores.

REVIEW OF LITERATURE

Prediction of post-operative outcome after major abdominal surgery has been a challenge in the practice of medicine. Lack of reliable predictors were responsible for the use of some scoring systems in Intensive Care Units. There is no agreed classification of these systems. Most commonly used APACHE and SOFA scores include a combination of multiple clinical and serum markers. The predictability of mortality with the effectiveness of these systems yet to be validated .The main drawback of these systems is that they should be repeated overtime. In search of simple and reliable markers, researchers are inclined to understand the surgical stress response and response due to sepsis.

Response to severe stress like major surgery, major trauma and sepsis have a universal common pathway from initial neutrophil activation, followed by macrophage recruitment to release of multiple cytokines and chemokine's, which participate in multi cascadal cell promoting and perpetuating cycles of cell signaling leading to either dysfunction cell or death of a cell. Response to trauma is part of the integrated, organized, systemic reaction that encompasses a wide range of endocrine, immunological, inflammatory and hematological components. The inflammatory response to injury and activation of cellular process are inherently designed to restore tissue function and eradicate invading microorganisms. The stress response involves the hormonal, immunological and cellular response to injury which results in metabolic and nutritional alterations. The integrity of central nervous system is the main key of integrity of inflammatory response. Inflammation originating from a specific location sends afferent signals to the hypothalamus, which in turn rapidly relays opposing anti-inflammatory message to the site of inflammation to reduce inflammatory mediator release by immunocytes. Basic and initial endocrine response is characterized by increased secretion of pituitary hormones and activation of

the sympathetic nervous system. All these trigger cellular and immunological response which cause release of inflammatory mediators (cytokines, heat shock proteins, reactive oxygen metabolites, eicosanoids, fatty Acid metabolites, serotonin, histamine, kallikreins) and acute phase proteins. TNF, IL-1b and IL-6 are the cytokines that mediate the initial response of the innate immune system to injury or infection. TNF and IL-1b both activate endothelial cells, attracting circulating polymorpho-nuclear leukocytes (PMNs) to the site. They also enter the circulation, causing fever and other systemic symptoms. IL-6 enhances the liver's production of the so-called acute phase reactants, including CRP, and also stimulates a shift in the production of cells in the bone marrow so that more PMNs are produced. Therefore, these three cytokines are essentially responsible for the features of SIRS and could be potentially useful as biomarkers of sepsis. In response to the tissue injury release of acute phase proteins is known as the 'acute phase response' (Figure 1). These proteins act as inflammatory mediators, anti-proteinases and scavengers in tissue repair [11,12]. Some of these proteins play a supportive role and enhance inflammation (e.g. complement), while others appear to protect the host from inflammatory tissue injury (e.g. protease inhibitors).

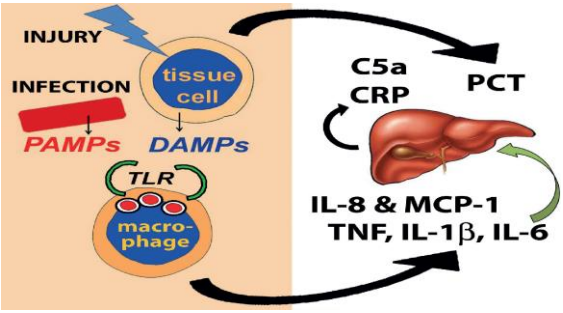

Figure 1: Sepsis begins with either infection or tissue injury. PAMPs from invading organisms or DAMPs from injured tissue cells (or both) are recognized by macrophage receptors such as the TLRs. This results in the production of pro-inflammatory cytokines such as TNF, IL-1b and IL-6 and chemokines such as IL-8 and MCP-1. IL-6 stimulates the liver to produce CRP and complement proteins. Many cells in the body also produce PCT in response to both infection and injury. PAMP: Pathogen-associated molecular pattern; DAMP: damage-associated molecular pattern; TLR: toll-like receptors; TNF: tumor necrosis factor; MCP-1: monocyte chemo attractant protein-1; IL: interleukin.

Many acute phase reactant proteins fall within one of three broad groups: (I) anti-infectious agents, such as complement components, C-reactive protein (CRP), and serum amyloid P (SAP); (II) proteins that promote the increased breakdown of lipids and glycogen, fatty acid synthesis, and gluconeogenesis; and (III) pro-coagulation factors like CRP, fibrinogen, 2-macroglobulin and other anti-proteinases. The acute phase proteins are nonspecific biochemical markers produced by hepatocytes in response to tissue injury, infection, or inflammation. Interleukin - 6 is a potent inducer of acute phase reactants that can include proteinase inhibitors, coagulation, complement proteins and transport proteins [13].

There are groups of proteins whose synthesis in the liver is up-regulated by IL-6 like CRP, complement proteins and procalcitonin (PCT). PCT and CRP are both proteins produced in response to infection and/or inflammation. The final end products like levels of CRP, procalcitonin, total leucocyte count, micro ESR have been studied as reasonably reliable markers of severity of illness. The direct determination of proteins and/or proinflammatory cytokines in serum has been used to perform the prognosis and diagnosis of several critical illnesses; among these C reactive protein (CRP) is the most widely used and the most accessible.

C Reactive Protein

This protein belongs to the pentatraxin family; it has five identical subunits codified by only one gene which is located in chromosome 1 (figure 2). These units associate themselves to form a stable pentameric unit, with a molecular weight of approximately 18 KD. Its synthesis in the liver is up-regulated by IL-6. CRP's role during acute inflammation is not entirely clear. It may bind the phospholipid components of microorganisms (and damaged host cells), facilitating their removal by macrophages. Other functions includes prevention of the adhesion of granulocytes on endothelial cells, synthesis of superoxide and its stimulation of the production of

interleukin-1 receptor antagonists. Because the levels of CRP rise much more significantly during acute inflammation than the levels of the other acute phase reactants, the test have been used for decades to indicate the presence of significant inflammatory or infectious disease, especially in pediatrics and, more recently, as a biomarker of the inflammation that accompanies atherosclerosis and cardiovascular disease.

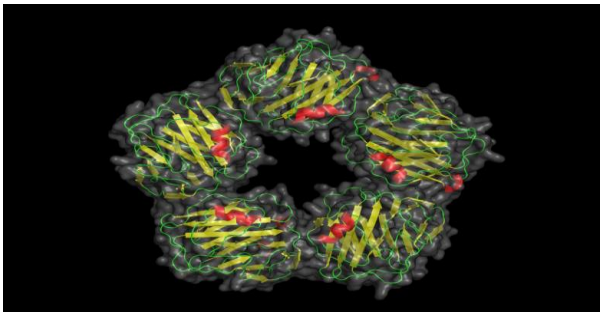

Figure 2: Five identical subunits codified by only one gene which is located in chromosome 1.

Although its low specificity may be its primary drawback as a biomarker of sepsis in adults, it is commonly used to screen for early onset sepsis (occurring during the first 24 hour of life) as its sensitivity is generally considered to be very high in this setting. Plasma levels of CRP reach its peak not before 48 hours. CRP plasma levels may remain elevated upto several days even after elimination of the infectious focus. CRP is found to be raised in noninfectious conditions like autoimmune diseases, rheumatic disorders, acute coronary syndromes, malignant tumors and after surgery. CRP is also often used to monitor patients after surgery; levels are typically elevated compared to pre-operative levels, but they fall quickly unless post-operative infection is present. Many studies have suggested that the CRP cutoff value between 5 & 10 mg/dl. CRP is of poor predictive value for the diagnosis of sepsis [14-17]. It does not present a gender difference and values are not affected by other conditions such as anemia, polycythemia or erythrocyte morphology.

Elevated preoperative CRP was considered an independent predictor of poor prognosis in patients with hepatocellular, pancreatic and colon cancer. This inflammatory marker was also used in detecting pancreatic necrosis and in monitoring the severity of patients with acute pancreatitis. Together with clinical signs and other inflammatory markers, CRP has been evaluated as an indicator of an unfavorable postoperative course, including surgical and non-surgical complications. Recently, this protein was identified as an early predictor of septic complications after esophageal, pancreatic and rectal resection. Given the potential complications associated with anastomotic leakage in colorectal surgery, particular emphasis has also been given to this marker in this area [18-21].

The changes observed in postoperative CRP levels in patients who developed complications demonstrate the presence of an inflammatory process and the activation of hepatic synthesis of CRP immediately after the surgical procedure (and before the occurrence of clinical manifestations). As the synthesis of this inflammatory marker is dependent only on the liver function and not compromised by any other organ failure, the rate of CRP production actually reflects the intensity of the inflammatory process.

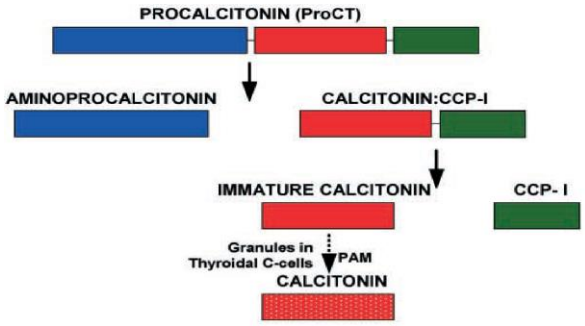

Figure 3: Schematic illustration of the human calcitonin precursors (procalcitonin and its constituent peptides), which are found in the free form in normal human serum. Mainly in thyroidal C-cells, immature calcitonin is amidated into mature calcitonin by the enzyme peptidylglycine- amidating-monooxygenase (PAM). CCP-I denotes calcitonin carboxypeptide-I.

Procalcitonin

'Calcitonin' was first identified during studies of parathyroid function in dogs - A new parathyroid hormone

that caused transient hypocalcaemia. Subsequently demonstrated in the human serum of patients with medullary thyroid carcinoma, its heterogeneity hinted at the existence of multiple forms of this new hormone and of a precursor prohormone. The identification of this procalcitonin (PCT) in the hypocalcaemia of Staphylococcal toxic shock syndrome first drew the association of PCT with sepsis and inflammatory states, which was confirmed by subsequent studies.

Procalcitonin is a 116 amino acid, 13 kDa protein, encoded by the CALC-1 gene on the short arm of chromosome 11. Its exact site of production is unclear, but thought to be liver is a major source. It is also produced in the C-cells of the thyroid gland as a prohormone of calcitonin. It undergoes successive cleavage in the neuroendocrine cells of the thyroid, lung and pancreas to form three distinct molecules; calcitonin, katacalcin and N-terminal fragment called amino procalcitonin. This was first described by Assicot in sepsis in 1993 and he stated that procalcitonin, not calcitonin is the marker of stress response [22].

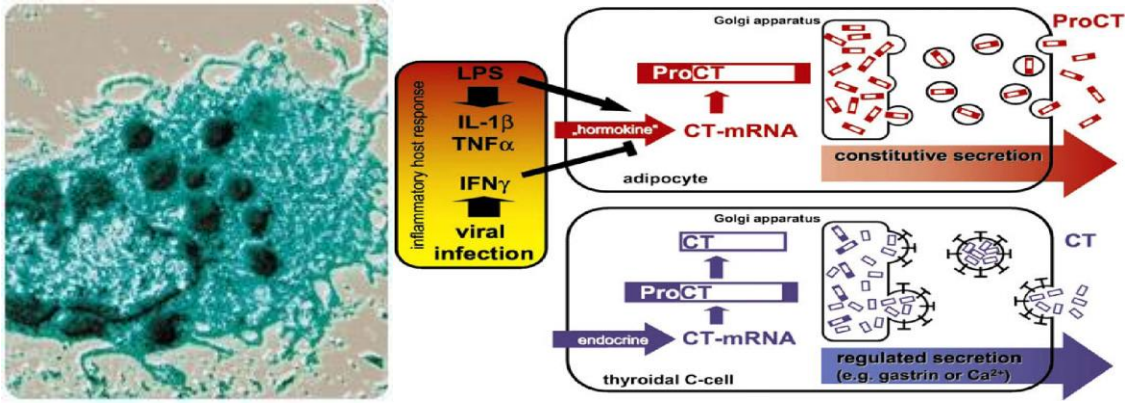

Figure 4: Procalcitonin (ProCT) as a ‘‘hormokine.’’ Calcitonin 1 (CALC 1) expression is restricted to neuroendocrine cells, specifically C cells of the thyroid, in the normal state. In sepsis, constitutive synthesis and release occurs in response to the host inflammatory response. (Adapted from Linscheid P, Seboek D, Nylen ES,et al. In vitro and in vivo calcitonin I gene expression in parenchymal cells: a novel product of human adipose tissue.)

The first prospective study of PCT in children with sepsis revealed a rapid and dramatic increase in the levels of PCT, which normalized with appropriate antibiotic therapy. Elevated PCT has been demonstrated following the injection of endotoxin into healthy volunteers that is detectable at 4 hours with a peak at 6 hours post administration.

Procalcitonin levels are elevated in bacterial infections, major surgery, severe trauma or burns. PCT elevation is recognized in septic shock and sepsis within 2 hours after endotoxemia or bacteremia [23]. Many studies confirm PCT as a marker of severe infection and sepsis [24]. PCT <0.5 unlikely to have sepsis, >2 indicates high risk for sepsis [25]. PCT levels more than 10ng/ml is usually observed in patients with organ failure remote to the site of infection [26]. Sequential elevation of PCT following major surgery or trauma, may help to suspect septic complications early. PCT may distinguish between infectious and noninfectious causes of organ dysfunction or shock than other markers and increases the sensibility and specificity of the diagnosis of sepsis when used in addition to clinical criteria [27].

PCT may also be helpful to differentiate between bacterial and viral Infections [28], infectious and noninfectious causes of the acute respiratory distress syndrome, graft rejection from systemic fungal or bacterial infections in patients after liver or kidney transplantation [29]. PCT is also found to be elevated in septic patients with chemotherapy [30]. In patients with necrotizing

pancreatitis, the PCT was a superior predictor of infection of the pancreatic necrosis when compared to the CRP and IL-8 with a predictive power almost equal to the gold standard of FNAC [31]. PCT proved to be superior to tumor necrosis factor, IL-8 and CRP in polytrauma patients, initially elevated PCT levels indicated a risk for developing septic complications and multiple organ failure [32,33].

The use of PCT as an antimicrobial stewardship tool is extremely attractive in the current climate of increasingly antibiotic resistant microbes. The theory is that with daily or serial PCT measurements, antibiotics can be safely stopped once the PCT level declines below a certain cut-off point or reduces to a certain percentage of its initial value. The use of PCT in the avoidance of antibiotic initiation and in reducing antibiotic course length has been extensively studied outside of the critical care environment. Several large, high-quality randomized controlled trials have demonstrated significant decreases in antibiotic use without any apparent increase in harm in lower respiratory tract infection, exacerbations of chronic obstructive pulmonary disease and community-acquired pneumonia.

Complications after major abdominal surgeries are associated with increased morbidity and mortality. Recognition of patients at risk for complications before presentation of full-blown symptoms could lead to early diagnosis and treatment which may improve outcome. However, the early recognition of complications by clinical characteristics and parameters in individual patients remains difficult, except perhaps for pulmonary complications. After major surgery, surgical stress itself induces a strong inflammatory response, and the value of the systemic inflammatory response syndrome (SIRS) criteria i.e. fever, leukocytosis, tachypnea, and tachycardia for the early diagnosis of complications is limited. On the other hand, inflammatory biomarkers like C-reactive protein (CRP) and procalcitonin (PCT) might be useful in the early diagnosis of not yet clinically symptomatic post-operative complications.

D. Mokart, M. Merlin, A. Sannini, J. P. Brun et al. (34)studied early (first postoperative day) changes in Interleukin 6 (IL-6), Procalcitonin (PCT) and C-reactive protein (CRP) serum concentrations and the occurrence of subsequent septic complications after major surgery prospectively over a period of 10 months in a cancer hospital in 50 consecutive patients undergoing elective major surgical procedures. They found that Sixteen patients developed septic complications during the first five postoperative days (group 1), and 34 patients developed no septic complications (group 2). On day 1, PCT and IL-6 levels were significantly higher in group 1 (P-values of 0.003 and 0.006, respectively) but CRP levels were similar. They concluded that PCT and IL-6 appear to be early markers of subsequent postoperative sepsis in patients undergoing major surgery for cancer. These findings could allow identification of postoperative septic complications.

Liliana Simon, France Gauvin, Devendra K. Amre et al. [35] performed. A meta-analysis to evaluate the accuracy of determination of Procalcitonin (PCT) and C-Reactive Protein (CRP) levels for the diagnosis of infective *vs.* non-infective causes of inflammation using 10 studies from all over the world in 905 cases. Patients varied from neonates to old age including medical and surgical cases. PCT level was more sensitive (88% [95% confidence interval {CI}, 80%-93%] *vs.* 75% [95% CI, 62%-84%]) and more specific (81% [95% CI, 67%-90%] *vs.* 67% [95% CI, 56%-77%]) than CRP level for differentiating bacterial from non-infective causes of inflammation. They concluded that the overall accuracy of PCT markers is higher than that of CRP markers, both to differentiate bacterial infections from viral infections and to differentiate bacterial infections from other non-infective causes of systemic inflammation.

Bernard Uzzan, MD; Régis Cohen, MD, PhD; Patrick Nicolas, Pharm D, Ph et al. [36] done meta-analysis of all 49 published studies in medical, surgical, polyvalent intensive care units and postoperative wards in adults after surgery or trauma, to quantify the accuracy of serum procalcitonin as a diagnostic test for sepsis, severe sepsis, or septic shock alone and compared with C-reactive protein. The summary receiver operating characteristics curve for procalcitonin was better than for C-reactive protein. They concluded that Procalcitonin represents a good biological diagnostic marker for sepsis, severe sepsis and septic shock in critically ill patients.

Gian Paolo Castelli, Claudio Pognani, Michael Meisner et al [37] studied role of C Reactive Protein, Procalcitonin during systemic inflammatory syndrome, sepsis, organ dysfunction in 150 adult intensive care patients over 10 days. PCT, CRP and infection parameters were compared among various groups like no SIRS group (n-15), SIRS (n-15), sepsis (n-71) and trauma patients [49]. PCT and CRP were higher in patients in whom infection was diagnosed at comparable levels of organ dysfunction, although correlation with the SOFA score was weak (R-0.254, p <0.001 for PCT and R-0.292, p <0.001 for CRP). CRP levels were near their maximum during lower SOFA scores, whereas maximum PCT concentrations were found at higher score levels (SOFA>12).They concluded that the PCT and CRP levels are related to the severity of organ dysfunction, but concentrations are still higher during infection. Different sensitivity and kinetics indicate a different clinical use for both parameters.

Severity Scoring Systems

Two main types of severity scoring system have been developed for use in the ICU patient: Those primarily focused on a single end-point like survival and those focusing on describing morbidity as it evolves (example: Organ dysfunction scores) [38]. Some of the early systematic attempts to define the severity of the surgical infection and the risk of death derived from the observation that patients dying after surgical infection often followed a clinical course characterized by sequential organ failures [39].

Scoring Systems can provide:

1. Case-mix adjustment for evaluative research.
2. A tool for comparative audit - SMR.
3. A mechanism to decide resource allocation.
4. An aid for the clinical management of patients.

Initially Scoring Systems developed for trauma pts as anatomical and physiological scoring systems.

- Specific anatomical scores: Eg. Abbreviated injury score(1969), Burns score (1971), Injury severity score(1974).
- Specific physiological scores: Eg. Trauma index (1971), Glasgow coma scale (1974), Trauma score (1981), Sepsis score (1983).

The scoring systems basically are classified into Anatomical (ISS), Therapeutic waited scores (TISS), Organ Specific Scoring (SOFA), Physiological assessment (APACHE), Disease specific (Ransons-for acute pancreatitis, Child Pugh- Liver failure, MELD-ESLD). An ideal scoring system need to have easily recordable variables, needs to be well calibrated with high levels of discrimination and be applicable to all patient populations and could be used across all countries. Such an ideal Scoring System is not currently available.

Fry and associates showed in 1980 that death after major operative procedures or severe trauma was usually due to infection and became more likely as the number of failed organs increased i.e. the mortality rate with no organ failures was 3%, rising to 30% with one organ failure and 100% with four organ failures [40]. Sweet and associates noted the synergistic relation between acute renal failure or respiratory failure and mortality [41]. Knaus and co-workers extended these observations and again confirmed the increasing mortality rate associated with an increased number of failed organs and in addition showed a strong relation between the duration of organ failure and likelihood of death [42]. Pine and associates confirmed the

relation between increased numbers of failed organs and an increased mortality rate. They also noted a number of other risk factors thought to influence the development of organ failure or death and identified clinical shock at any time, malnutrition, alcoholism and age as important predictive factors [43]. Stevens recognized the need for more precision and for a greater range of potential values and devised a scoring system to represent the magnitude and severity of organ failure. He defined seven organ systems and assigned a score from 0 to 5 in each system. Scores were calculated by squaring the value assigned to each organ system and adding the three highest scores to arrive at the "Septic Severity Score" [44] .

With the aim of classification of patients on the basis of severity of illness and for the comparison of outcomes after therapy the physiological scoring systems were developed. Amongst them APACHE II has been validated in both general and surgical intensive care patients. Some studies have found the APACHE II score to have the best prognostic characteristics when applied to emergency patients, as opposed to elective surgical and non-surgical patients. Out of all the scoring systems like SOFA, APACHE II, APACHE III, POSSUM the most validated and commonly used scoring system is APACHE II in surgical patients.

***Acute Physiology and Chronic Health Evaluation Ii*: (APACHE II)**

This system developed by Knaus et.al in 1981, was used for measuring severity of illness in groups of critically ill patients. This system consists of two parts- the acute physiological assessment and the chronic health evaluation. Hence the name APACHE. The acute physiologic assessment examines abnormalities among 34 possible measurements obtained during the first day of admission to the ICU. The chronic health evaluation examines the patient's preadmission health by reviewing the medical history for details concerning functional status, productivity, and medical attention during the 6 months before admission [45].

PHYSIOLOGIC VARIABLE†		POINT SCORE								
		+4	+3	+2	+1	0	+1	+2	+3	+4
1	Temperature, core (°C)	≥ 41°	39–40.9°	—	38.5–38.9°	36–38.4°	34–35.9°	32–33.9°	30–31.9°	≤ 29.9°
2	Mean arterial pressure (mm Hg)	≥ 160	130–159	110–129	—	70–109	—	50–69	—	≤ 49
3	Heart rate	≥ 180	140–179	110–139	—	70–109	—	55–69	40–54	≤ 39
4	Respiratory rate (nonventilated or ventilated)	≥ 50	35–49	—	25–34	12–24	10–11	6–9	—	≤ 5
5	Oxygenation:									
	a) F_{IO_2} ≥ 0.5: use A-aDO_2	≥ 500	350–499	200–349	—	< 200	—	—	—	—
	b) F_{IO_2} < 0.5: use P_{AO_2} (mm Hg)	—	—	—	—	> 70	61–70	—	55–60	< 55
6	Arterial pH	≥ 7.7	7.6–7.69	—	7.5–7.59	7.33–7.49	—	7.25–7.32	7.15–7.24	< 7.15
7	Serum Na (mmol/L)	≥ 180	160–179	155–159	150–154	130–149	—	120–129	111–119	≤ 110
8	Serum K (mmol/L)	≥ 7	6–6.9	—	5.5–5.9	3.5–5.4	3–3.4	2.5–2.9	—	< 2.5
9	Serum creatinine (mg/dL); double point score for **acute** renal failure	≥ 3.5	2–3.4	1.5–1.9	—	0.6–1.4	—	< 0.6	—	—
10	Hct (%)	≥ 60	—	50–59.9	46–49.9	30–45.9	—	20–29.9	—	< 20
11	WBC (in 1000s)	≥ 40	—	20–39.9	15–19.9	3–14.9	—	1–2.9	—	< 1
12	Glasgow coma score (GCS)	Score = 15 minus actual GCS								
Acute physiology score is the sum of the 12 individual variable points.										
Add 0 points for age <44; 2 points, 45–54 yr; 3 points, 55–64 yr; 5 points, 65–74 yr; 6 points ≥ 75 yr.										
Add chronic health status points: 2 points if elective postoperative patient with immunocompromise or history of severe organ insufficiency; 5 points for nonoperative patient or emergency postoperative patient with immunocompromise or severe organ insufficiency.‡										
(13)§	Serum HCO_3 (venous–mmol/L)	≥ 52	41–51.9	—	32–40.9	22–31.9	—	18–21.9	15–17.9	< 15

Figure 5: APACHE II Score Model.

APACHE II score, a revised and simplified version introduced in 1985, uses a point score based on initial values of 12 routine physiologic measures, age, and previous health status to provide a general measure of

severity of disease. The different variables used in APACHE II are Temperature (rectal in °C), Mean arterial pressure (mm Hg), Heart rate, Respiratory rate (non-ventilated or ventilated), Oxygenation (in mm Hg), Arterial pH, Serum Sodium (in mmol/L), Serum Potassium (in mmol/L), Serum Creatinine (mg/dl), Haematocrit (%), White cell count and Serum HCO3 (venous-mmol/L) [46]. It ranges from 0-71. Bion and Chang were the first to explore the possibility of using APACHE II as a dynamic scoring system. Bion used a modified APACHE II in the Sickness Score System in which the day 1 score was compared with day 4 and risk of mortality was predicted [47]. Change on the other hand used the product of daily APACHE II scores with a Modified Organ Failure Score and calculated thresholds above which individual patient mortality was predicted [48].

Though these scoring systems can predict morbidity and mortality in postoperative intensive care settings, in view of their complexity and less cost effectiveness various molecular markers are now being studied. Hence we have evaluated the role of peri-operative CRP and PCT in predicting 30 days mortality after major surgeries and also want to know correlation between these molecular markers and APACHE II scoring system.

MATERIAL AND METHODS

Methodology

- Blood samples collected.
- CRP Levels estimated on day before surgery & On 3rd POD.
- Procalcitonin levels estimated on day before surgery & on 3rd POD.
- Scoring system: On day before surgery & on 3rd POD.

CRP: Particle Enhanced Immuno Turbidometric Immunoassay (PETIA)

Principle

Synthetic particles coated with antibody to C-reactive protein (AbPR) aggregate in the presence of C-reactive protein in the sample. The increase in turbidity which accompanies aggregation is proportional to the C-reactive protein concentration.

- CRP + AbPR Aggregates.
- Flex reagent cartridges are used (SIEMENS).
- Assay range: 0.5 mg/l - 250 mg/l or 0.05 mg/l - 25mg/dl.

Procalcitonin

- Electro Chemilumionesence Immuno Assay.
- Elecsys BRAHMS PCT kits were used (COBAS).

Principle

Sandwich Principle

1st Incubation: Antigen in the sample (30 mic.l), a biotinylated monoclonal PCT-specific antibody, and a monoclonal PCT specific antibody labeled with a ruthenium complex react to form a sandwich complex.

2nd Incubation: After addition of streptavidin coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin. The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with procell. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier. Results are determined via a calibration curve which is instrument- specifically generated by 2-point calibration and a master curve provided via the reagent barcode.

- Measuring range- 0.02 ng/ml -100 ng/ml
- Values below the detection limit reported as <0.02ng/ml
- Values above the measuring limit reported as >100ng/ml
- Duration: 24 Months
- Number of patients: n=90

- Sample Size: The sensitivity of Procalcitonin is 67 % (1) (two consecutive maximum PCT levels correlation with death), precision is 10% and 95% confidence interval the minimum required sample size is 85 subjects.
- A Prospective, International multicentre study.

Statistical Analysis

The data were recorded in Microsoft excel. Statistical analysis was performed by using STATA 11.1 (College Station TX USA) and SPSS.20 Version statistical analysis system. Categorical variables were expressed as frequency and percentage. Continuous variables were expressed in terms of mean and standard deviation. Independent t test was used to compare two groups means. Paired t test was applied for comparison within the group. Karl-Pearson correlation was used between two related variables to find correlation coefficient. Logistic regression was used to predict the dependent variables from independent variables. Diagnostic accuracy of CRP and PCT concentrations for prediction of postoperative 30 day mortality was assessed by receiver operating characteristics (ROC) curve analysis. The area under the curve presented a direct measure of the diagnostic accuracy of the test. P value <0.05 was considered significant.

Design of Study

Inclusion Criteria

Surgeries included:

1. Esophagectomy.
2. Esophagogastrectomy.
3. Total gastrectomy.
4. Hepatic resection.
5. Whipples Procedure.
6. Radical Cholecystectomy.
7. Colectomy.
8. APR.
9. AR.

II. Both benign and malignant cases

III. All age groups

Exclusion Criteria

Preexisting organ failure.

(CRF/CLD).

RESULTS

Age Distribution

Age	n	%
<24	3	3.33
25-49	45	50
50-75	41	45.56
>75	1	1.11
Total	90	100

Table 1: 53.3% of the patients were below 50 years and 46.7% of them were above 50 years.

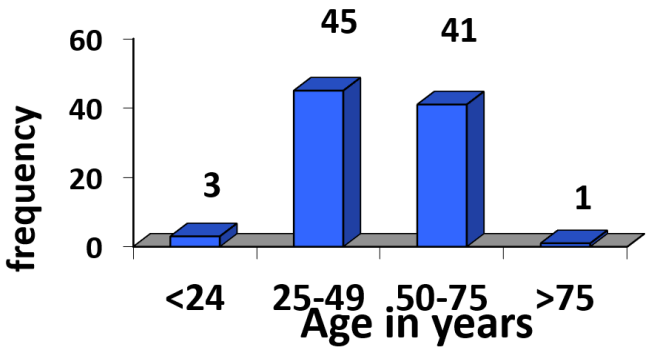

Figure 5: Age distribution.

Sex Distribution

Sex	n	%
Male	59	65.54
Female	31	34.44
Total	90	100

Table 2: 65.54% of the patients were male and 34.44% patients were female.

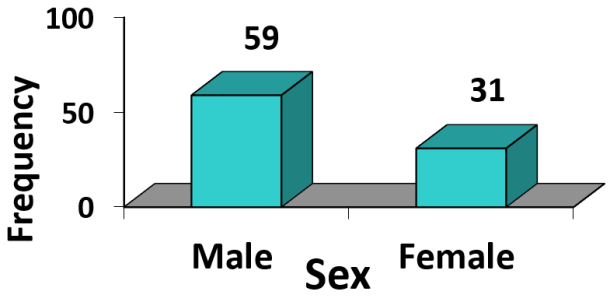

Figure 6: Sex distribution.

Age Distribution between Survivors and Non-Survivors

Age	Survivors			Non-Survivors			
	n	Mean	SD	N	Mean	SD	P-Value #
	87	48.62	13.75	3	53.67	7.67	0.53

#-unpaired t-test, *-p<0.001 significant

Table 3: There was no statistically significant difference between survivors and non survivors in terms of age (p=0.53).

ICU-Stay between Survivors and Non-Survivors

ICU Stay	Survivors			Non-Survivors			
	N	Mean	SD	n	Mean	SD	P-Value #
	87	2.79	0.82	3	7.33	2.08	P<0.001***

#-unpaired t-test *-p<0.001 significant

Table 4: There was statistically significant difference of ICU Stay between survivors and non survivors (p=<0.001).

Total Stay between Survivors and Non-Survivors

Total Stay	Survivors			Non-Survivors			
	n	Mean	SD	n	Mean	SD	P-Value #
	87	6.40	1.82	3	11.33	4.93	P<0.001***

#-unpaired t-test, *-p<0.001 significant

Table 5: Statistically significant difference of total hospital stay observed between survivors and non survivors (Survivors -6.40±1.82 days, Non survivors -11.33 ± 4.93 days. p<0.001).

C - Reactive Protein Levels Between Survivors and Non survivors

CRP	Survivors			Non-Survivors			
	n	Mean	SD	n	Mean	SD	P-Value #
CRP Preoperative	87	2.37	2.02	3	3.31	2.42	0.433
CRP Postoperative	87	4.52	4.07	3	16.2	7.83	P <0.001*
P-value ^	87	P <0.001*		3	P = 0.1546		

^-paired t-test, #-unpaired t-test, *-p<0.001 significant

Table 6: No significantly different C- reactive protein levels were seen pre operatively among survivors and non survivors (2.37 ± 2.02 *vs.* 3.31 ± 2.42. p = 0.433). Whereas Post operatively there was significantly different CRP levels were observed (4.52 ± 4.07 *vs.* 16.2 ± 7.83. p <0.001). But when compared with non survivors, survivors had significantly different Pre-operative and postoperative CRP levels (p = 0.154 *vs.* p = <0.001).

Procalcitonin levels among Survivors and Non Survivors

PCT	Survivors			Non survivors			
	n	Mean	SD	N	Mean	SD	P-Value #
PCT Preoperative	87	1.605	1.22	3	2.01	1.23	0.574
PCT Postoperative	87	3.89	3.40	3	34.50	27.53	P<0.001*
P-value	87	P<0.001*		3	P= 0.189		

#-unpaired t-test, *-p<0.001significant

Table 7: No significantly different Procalcitonin levels were observed pre operatively between survivors and non survivors (1.605 ± 1.22 *vs.* 2.01 ± 1.23. p = 0.574). Whereas post operatively there was significantly different Procalcitonin levels were seen among them (3.89 ± 3.40 *vs.* 34.50 ± 27.53. p<0.001). But when compared with non survivors, survivors had significantly different preoperative and postoperative Procalcitonin levels (p = 0.189 *vs.* p = <0.001).

Standardization in Training and Practice

APACHE II Scores among Survivors and Non Survivors

APACHE score	Survivors			Non survivors			
	N	Mean	SD	N	Mean	SD	P-Value#
APACHE preoperative	87	6.28	1.91	3	8.33	4.04	0.083
APACHE postoperative	87	8.55	2.61	3	16.67	2.31	P <0.001*
p-value	87	P <0.001*		3	0.054		

#-unpaired t-test, *-p<0.001 significant

Table 8: There was no significantly different APACHE Scores were observed pre operatively among survivors and non survivors (6.28 ± 1.91 *vs.* 8.33 ± 4.04 p = 0.083), whereas significantly high scores observed post operatively among them (8.55 ± 2.61 *vs.* 16.67 ± 2.31, =<0.001). In the survivors group there was significantly high scores seen postoperative period when compared with preoperative period (p = <0.001) but this was not observed in survivors group (p = 0.054).

Logistic Regression between Factors and Outcome

Factor	Co-Efficient	Standard Error	Sig	Odds Ratio
Age	-0.415	814.001	1.0	0.66
Sex	-2.09	32256.02	1.0	0.124
ICU STAY	17.45	18175.38	0.99	37944390.9
TOTAL STAY	-7.5	15368.736	1	0.001
CRP_PRE_OP	0.096	1360.268	1	1.101
CRP_DAY3	0.11	1862.477	1	1.117
PCT_PRE_OP	-4.382	20509.185	1	0.012
PCT_DAY3	1.619	2499.845	0.99	5.046
APACHE_PRE_OP	2.678	5890.74	1	14.556
APACHE_DAY3	0.727	4229.4	1	2.069
Constant	-39.994	122309.1	1	0.000*

Table 9: When all factors (confounding) were taken into account & logistic regression used no individual factor was found to have any significant bearing on final outcome.

ROC Curves of Various Factors

To determine the predictive ability of studied variables in predicting outcome (mortality), ROC curves were used. An area under curve (AUC) of more than 0.7 was considered to be significant.

When ROC was applied on individual variable factors such as ICU Stay, total stay, C - reactive protein, Procalcitonin and APACHE II scores on third postoperative day were having significant area under curve. Whereas age and preoperative CRP, Procalcitonin, APACHE II were not having significant area under curve.

Factor	AUC	95% Confidence Interval	P-value
Age	0.636	0.435-0.837	0.425
ICU STAY	0.996	0.984-1	0.004
TOTAL STAY	0.898	0.787-1	0.019
CRP_PRE_OP	0.642	0.343-0.940	0.406
CRP_DAY3	0.962	0.907-1	0.007
PCT_PRE_OP	0.626	0.33-0.92	0.458
PCT_DAY3	0.989	0.964-1	0.004
APACHE_PRE_OP	0.663	0.377-0.949	0.339
APACHE_DAY3	0.990	0.969-1	0.004

Table 10: ROC Curves of Various Factors.

Standardization in Training and Practice

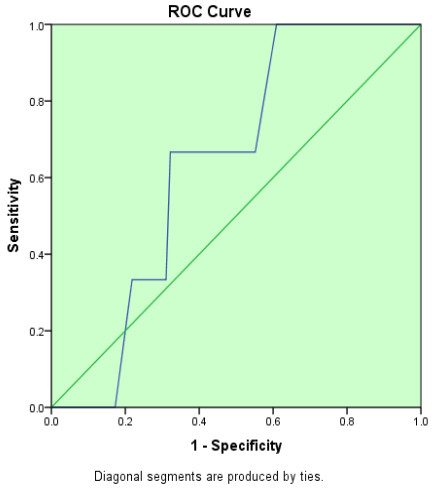

Figure 7: Age *vs.* mortality.

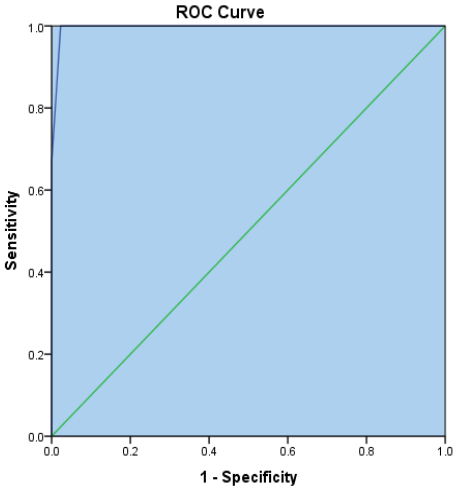

Figure 8: ICU stay *vs.* mortality.

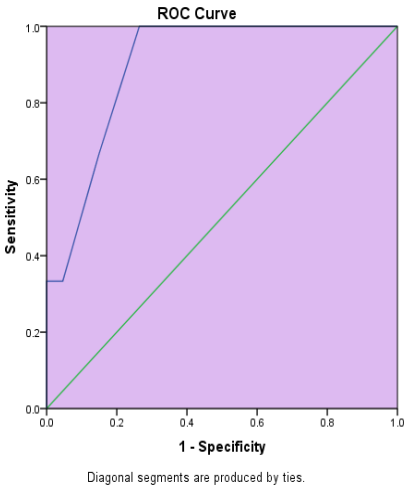

Figure 9: Total stay *vs.* mortality.

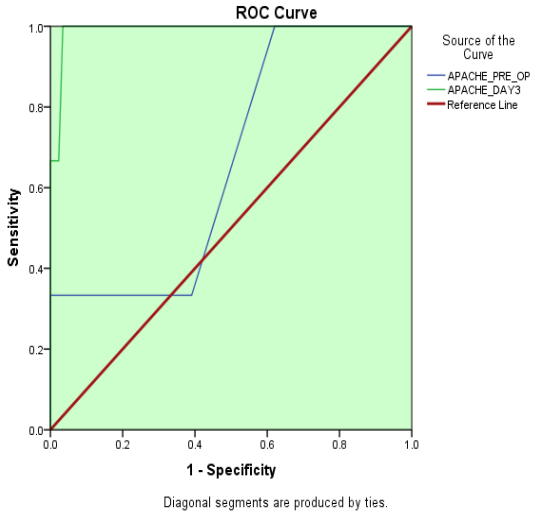

Figure 10: APACHE *vs.* mortality.

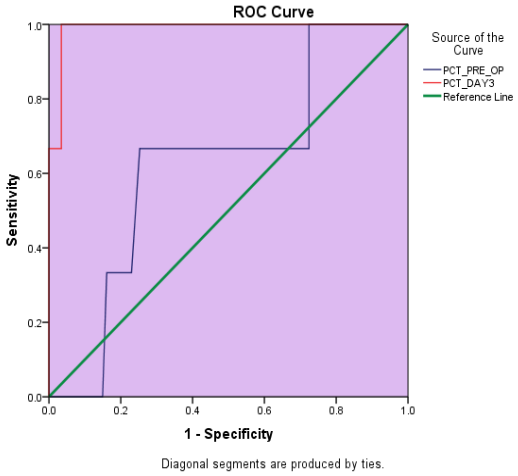

Figure 11: Procalcitonin *vs.* mortality.

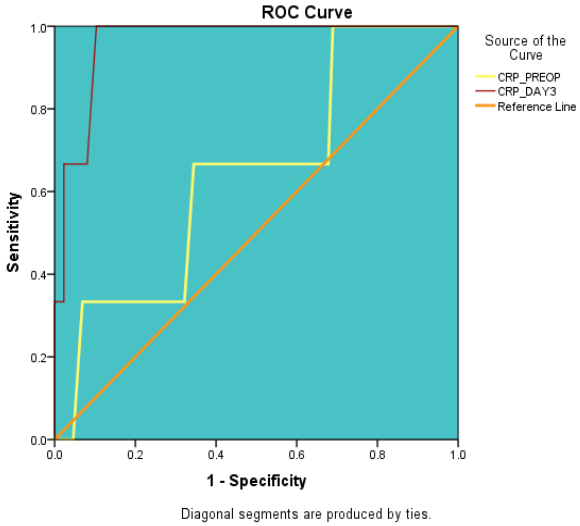

Figure 12: CRP *vs.* mortality.

Pearson correlation coefficient was applied to find out correlation between two variables.

Correlation between CRP and PCT

Variables	'R'-value	P- value
Crp Pre - Pct Pre	0.04	0.712
Crp Post 3rd Day Pct Post 3rd Day	0.66	P<0.001*

Table 11: Preoperatively positive correlation found between C-reactive protein and Procalcitonin, though it was not statistically significant(r = 0.04, p = 0.712).Whereas positive and significant correlation was found postoperatively(r = 0.66, p = <0.001).

Correlation between CRP and APACHE II

Variables	'R'-value	P-value
Crp Pre –Apache	0.09	0.375
Crp Post 3rd Day Apache Post 3rd Day	0.45	P<0.001*

Table 12: Preoperatively positive correlation found between C-reactive protein and APACHE II, though it was not statistically significant(r=0.09, p=0.375).Whereas positive and significant correlation found between these two variables on postoperative day three(r = 0.45, p = <0.001).

Correlation between PCT and APACHE II

Variables	'R'-value	P-value
Pct Pre -Apache	0.226	0.033*
Pct Post 3rd Day Apache Post 3rd Day	0.503	P<0.001*

Table 13: Preoperatively positive correlation found between Procalcitonin and APACHE II, though it was not statistically significant(r = 0.226, p = 0.033).Whereas positive and significant correlation found between these two variables on postoperative day three(r = 0.503, p = <0.001).

DISCUSSION

Postoperative morbidity and mortality are the important concerns till date after major abdominal surgery. The Majority of postoperative mortalities is related to postoperative complications which may lead to sepsis and multi organ dysfunction. Surgical and traumatic injuries in different areas of the body induce C reactive protein (CRP) and Procalcitonin (PCT) secretion of varying degree, and an increase in its serum concentration depends primarily on the extension of the local tissue damage. These conditions are associated with the risk of damaging the intestinal barrier and the possibility of bacterial contamination or translocation resulting in endotoxemia. The prevailing opinion is that the penetration of endotoxins and other microbial products into the bloodstream is responsible for the increased secretion of PCT under such circumstances. Not only the complications, the postoperative stress can also causes a rise of acute phase reactants. Jerko Barbi et al. investigated the kinetics of changes in serum concentrations of PCT and CRP after abdominal surgeries in 41 patients. Plasma concentrations of PCT and CRP were measured in all the patients before surgery and at the postoperative day 1 (POD1), postoperative day 2 (POD2) and postoperative day 3 (POD3). Systemic release of the PCT, and CRP was present in all the measured time points after the abdominal surgery. Median concentrations of PCT (17 pg/ml) production was measured highest at POD1 and the median of CRP (147 mg/L) was measured at highest POD2. They found that CRP at POD3 was a good predictor of SIRS (AUC was 0.76) and PCT is a good marker for stress caused by surgical injury without sepsis [49]. In our study when preoperative and postoperative (POD 3) levels of CRP and PCT were compared, it was statistically significant in survivors (CRP -2.37 ± 2.02 *vs.* 4.52 ± 4.07, p = <0.001 and PCT -1.605 ± 1.22 *vs.* 3.89 ± 3.40, p = <0.001). In non survivors, though there was a trend of increase in levels of CRP and PCT on POD 3 it was not statistically significant. This may be due to very small number of non survivors (3/90).Positive and significant correlation was found between CRP, PCT and APACHE on postoperative day three (Correlation between CRP and APACHE II - r = 0.45, p = <0.001, correlation between PCT and APACHE II - r = 0.503, p = <0.001) which shows an indirect evidence of stress response.

Similarly Joana Silvestre et al. also conducted a single-center, prospective, observational study in 50 patients submitted to elective colorectal surgery with primary anastomosis. CRP and PCT were measured daily and they compared infected and non-infected patients. They

observed that, after a major elective surgical insult both CRP and PCT serum levels increased independently of the presence of infection. Besides serum CRP time-course showed to be useful in the early detection of an infectious complication whereas PCT was unhelpful [50].

This has been validated in many other major surgeries like neuro and cardiac surgeries. Talat Syeda et al. estimated the concentration of C-reactive protein in pre- and post-operative serum samples of brain tumor patients in order to detect the potential risks of post-operative infections and concluded that pre-operative serum C-reactive protein concentrations of 28% of the patients were elevated, suggesting an association with brain tumors [51]. Post-operative serum concentrations were significantly higher than those noted before the surgery. Absence of a fall of concentration from peak value on post-operative Day 2 or a secondary rise from post-operative Day 7 could be alarming for inter-current infection.

Christoph Sponholz et al. [52] performed a review of the literature with the aim of describing the evolution of serum procalcitonin (PCT) levels after uncomplicated cardiac surgery, characterizing the role of PCT as a tool in discriminating infection, identifying the relation between PCT, organ failure, and severity of sepsis syndromes, and assessing the possible role of PCT in detection of postoperative complications and mortality. They found that uncomplicated cardiac surgery induces a postoperative increase in serum PCT levels. Peak PCT levels are reached within 24 hours postoperatively and return to normal levels within the first week. This increase seems to be dependent on the surgical procedure and on intra operative events. PCT values reported in infected patients are generally higher than in non-infected patients after cardiac surgery and the dynamics of PCT levels over time may be more important than absolute values.

Early detection of postoperative complications followed by immediate management significantly reduces mortality associated with abdominal sepsis. Apart from stress response these markers have been utilized to detect postoperative complications like anastamotic leak early after colorectal surgeries. A.B. Almeida et al [53] reviewed the daily postoperative serum CRP and white blood cell counts in 173 patients who underwent surgery for colorectal disease with anastomosis. Patients with anastamotic leakage (Group A, n = 24) were compared to patients without leakage (Group B, n = 149).They found that daily average values of serum CRP were significantly higher in group A starting at the 2nd POD and remained significantly elevated until the diagnosis of leakage ($p = 0.003$). Postoperative mortality was high in anastamosis leakage group when compared to no anastamosis leakage group (12.5% *vs.* 2.7, $p=0.02$). Recently Freek Daams et al. [54] conducted a systematic review of sixty nine articles to find out predictive factors for anastomotic leakage after colorectal surgery and concluded that C-reactive protein measurement at postoperative day 3-4 is helpful.

These observations have initiated to use these markers for the early prediction of complications after esophagectomy by Sandra H. Hoeboer et al. [55]. They measured CRP and PCT on post-operative days 0, 1, 2, and 3 in 45 consecutive patients of elective esophagectomy with gastric tube reconstruction. Among them Twenty-eight patients developed a post-operative complication (5 surgical, 14 infectious, 9 combined surgical/infectious, including anastamotic leakage), presenting on day 3 or later. This small study suggests that high or increasing CRP levels may precede the clinical diagnosis of general or surgical/infectious complications after esophagectomy. Elevated PCT levels may more specifically and timely precede combined surgical/infectious complications mainly associated with anastamotic leakage.

Similarly, in our study, though we did not evaluate the complications like anastamotic leak, we found that on

post-operative day three, CRP levels were good predictors of mortality with high area under curve (CRP- AUC-0.962). There was a high correlation between CRP, and APACHE on post-operative day. Which is predictive of morbidity also.

Lorant Kiss et al [56] evaluated the levels of PCT and APACHE II on the day of sepsis diagnosis in 160 septic patients after abdominal and thoracic surgery. CRP results, pre and postoperatively were recorded, with considerations of comorbidity and surgical procedure. They observed a CRP peak at postoperative day two or three, and then it fell. The multivariate analysis showed that APACHE II score and PCT level were independent early predictive markers to indicate the severe lethal sepsis. The predictive power of both parameters (PCT, APACHE II score) in combination was shown to be superior to that of either single parameter.

In the present study no significantly different C - reactive protein, PCT levels and APACHE II Scores were seen pre operatively among survivors and non survivors (CRP - 0.433,PCT - p = 0.574,APACHE - p = 0.083). On post-operative day 3 CRP, PCT levels and APACHE II scores were significantly elevated in survivor group but not in non survivors.

Whereas Post operatively there were significantly different CRP, PCT level and APACHE II scores observed ($p<0.001$) between survivors and non survivors. C - reactive protein, Procalcitonin and APACHE II scores on third postoperative day was having a significant area under the curve on ROC curve analysis. When all factors (confounding) were taken into account & logistic regression used no individual factor was found to have any significant bearing on the final outcome.

Mitsuro Kanda et al. [57] in 153 post pancreatectomy patients C-reactive protein (CRP), procalcitonin levels measured in search of novel diagnostics for aggravating pancreatic fistulas in the acute phase. In their observation ROC curve analysis revealed that changes in CRP levels from POD 1 to POD 3 had the greatest area under the curve value (0.767) and that an elevated CRP level of 28.4 mg/L yielded the most optimal predictive value for clinically relevant POPFs. In Multivariate analysis they found elevation of the CRP level (≥28.4 mg/L, from POD 1 to POD 3) as independent diagnostic factors for clinically relevant POPFs (OR 4.82, 95%; CI: 1.25 - 20.2, P = 0.022).They concluded that a steep rise in the CRP level was a highly diagnostic factor for clinically relevant POPFs and may be helpful in selecting the appropriate management for POPFs. In our study when the ROC was applied C - reactive protein, Procalcitonin and APACHE II scores on third postoperative day were having significant area under curve. Whereas a preoperative CRP, Procalcitonin, APACHE II were not having significant area under curve. These findings confirm predictability of the markers on the final outcome and morbidity, but the cause of morbidity was not individually analyzed.

The evidence for using the PCT to predict mortality in patients after surgery is more complicated to interpret because studies have found markedly different cut-off points. In our series because of small sample size and low mortality, we could not calculate criterion values to predict mortality. But, Schneider et al [58] found an optimum cut-off point of 1.44 mg/mL in their study of 220 unselected post-surgery patients requiring postoperative critical care. Using this cut-off for a serum PCT measured on the day after surgery, the ROC curve for combined mortality and morbidity was 0.75 (95% CI 0.66 - 0.85) and for the APACHE II score was 0.69 (95% CI 0.59 - 0.78). In contrast, in a study of post-elective coronary bypass patients, Fritz et al [59] found a cut-off for mortality prediction at 2.5 mg/mL, whereas Rau et al [60] found a cut-off of 16 mg/mL in patients who had undergone surgery for peritonitis.

Elıas Domınguez-Comesan et al. [61] conducted a prospective observational study including 67 patients operated for colorectal, gastric and pancreatic cancer to evaluate the association between serum levels of procalcitonin and C-reactive protein, on the first 3 postoperative days, and the appearance of postoperative intraabdominal infection. They found that serum CRP levels at 72 hours, serum PCT serum at 24 hours, 48 hours and 72 hours and the ratio between serum levels of CRP at 72 hours and serum levels of CRP at 48 hours (CRP D3/CRP D2) were significantly associated with the appearance of postoperative intra-abdominal infection. The highest sensitivity corresponded to PCT at 72 hours (88.9%); the highest specificity and positive predictive value corresponded to the ratio CRP D3/CRP D2 (96.49% and 71.4%, respectively); the highest negative predictive value to procalcitonin at 72 hours and 24 hours. But in present study post operatively only on third post-operative day CRP, PCT levels were estimated. Neverthless, CRP and PCT levels on third day were correlating well with APACHE II on third day, suggests that these markers can predict post-operative morbidity.

Based on the above evidence in literature, does CRP and PCT add anything to the already established clinical methods of prognostic assessment in post-operative management? APACHE II and SOFA scores have been validated for mortality risk stratification, but are clinically unwieldy and tend to be used more for audit and research than clinical decision making. A rapidly available biochemical test that provides similar prognostic information could therefore be useful to help discussions about prognosis with patients' relatives and decisions regarding earlier interventions.

Although these markers can rise in different inflammatory processes of a non-infectious etiology, they are quite specific markers for infection. To date it has been used to assess the prognosis of patients with sepsis and also detect postoperative complications after major abdominal surgeries. In literature none of the studies directly correlated these markers and thirty day mortality after major abdominal surgery. In the present study C reactive protein and Procalcitonin levels were measured to detect thirty day mortality which could indirectly address post-operative complication burden too. Post-operative raise of these levels were observed in majority of our cases, and third day values were predictive of morbidity as well as mortality which were shown by ROC curve analysis. But usefulness of pre-operative evaluation of these proteins was questionable as per our observations. The important drawback in this study was, correlation of these markers with post-operative complications were not evaluated and also raise of these markers whether it was due to surgical stress response or due to complications was not made out. We consider that it is necessary to perform similar studies with a bigger sample size because correlations are related to the sample size and possibly a greater number of patients could give us a better correlation with greater statistical weightage.

CONCLUSION

1. Postoperative (Third POD) C reactive protein and procalcitonin levels can be used to predict 30 days mortality after major abdominal surgery.
2. CRP and PCT levels were correlating with APACHE II Scores. These can be used to predict morbidity after major surgery instead of APACH II.

LIMITATIONS OF STUDY

1. Small sample size with low mortality rate.
2. Criterion values could not be derived.
3. Correlation between these markers and cause of death were not analyzed.

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