Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Surgery

Prognostic Relevance of Pre- and Postoperative Arterial Blood Lactate Measurements, Procalcitonin and pH as Predictors of Outcomes in Secondary Peritonitis

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DOI: 10.36347/sjams.2022.v10i06.016 | **Received:** 02.05.2022 | **Accepted:** 07.06.2022 | **Published:** 21.06.2022

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Abstract **Original Research Article**

Secondary peritonitis is the most common form that follows an intra-peritoneal source usually from perforation of hollow viscera. Acute generalized peritonitis due to underlying hollow viscous perforation is a critical & life-threatening condition. It is a common surgical emergency in most of the general surgical units across the world. It is often associated with significant morbidity and mortality. In the present study Perforation peritonitis is associated with 12.8% mortality. Initial lactate, postoperative (24 hours) lactate is significant variables for mortality with critical values up to 3.78 mmol/L and 3.67 mmol/L respectively. Initial lactate, postoperative (24 hours) lactate values up to 2.29 mmol/L and 1.45 mmol/L respectively were reported in case of survivors. The lactate value of more than 2.5 mmol/L ascertained to have 64 % mortality. Initial pH, postoperative (24 hours) pH are significant variables for mortality with critical value of 7.16 and 7.17 respectively. Initial pH, postoperative (24 hours) pH value of 7.36 and 7.38 respectively were reported in case of survivors. Procalcitonin values of more than 2.58 ng/ml (normal range 0.01-0.05 ng/ml) ascertained to have 56.25 % mortality.

Keywords: Prognostic Relevance Postoperative Arterial Blood Procalcitonin.

INTRODUCTION

Peritonitis is defined as inflammation of a portion or all of the parietal and visceral peritoneum. Peritonitis may be acute or chronic, septic or aseptic, primary or secondary, localized or generalized [1]. Secondary peritonitis is the most common form that follows an intra-peritoneal source usually from perforation of hollow viscera. Acute generalized peritonitis due to underlying hollow viscous perforation is a critical & life-threatening condition. It is a common surgical emergency in most of the general surgical units across the world. It is often associated with significant morbidity and mortality [2].

The multifaceted nature of abdominal surgical infections makes it difficult to precisely define the disease and to assess its severity and therapeutic progress. Both the anatomic source of infection and to a greater degree, the physiologic compromise it inflicts, affects the outcome. High-risk patients require timely and aggressive treatment especially in severe peritonitis. To select them reasonably well, evaluation through a prognostic scoring system is the approach of choice. Early prognostic evaluation is desirable so as to be able to select high-risk patients for more aggressive treatment especially in severe peritonitis [3]. The prognosis and outcome of peritonitis depend upon the interaction of several factors, which includes patient-related factors, disease-specific factors, diagnostic and therapeutic interventions. Categorizing patients into different risk groups would help prognosticate the outcome, select patients for intensive care and determine operative risk, thereby helping to choose the nature of the operative procedure, e.g. damage control vs. definitive procedure [4]. Metabolic acidosis characterized by a reduction in pH and the increased base deficit is also common in peritonitis [5].

Broder and Weil in 1964 [6] for the first time suggested use of lactate as a clinical prognostic tool; since then, sepsis-associated hyperlactatemia (SAHL) has firmly established itself as a reliable indicator of mortality in critically ill patients. Lactic acid normally exists in an ionized form as lactate at physiological pH; produced daily by muscle fibers, brain, skin, red blood cells and intestine as an end product of glycolysis.

Hemodynamic changes accompanying peritonitis is associated with lactic acidosis and reduced lactate clearance. Metabolic acidosis is associated with increased morbidity and mortality. Hyperlactatemia is seen in a variety of conditions such as sepsis, shock, cardiac arrest, tissue hypoxia, burns, some pharmacological agents (linezolid, metformin, theophylline etc., multiple organ failure and is associated with increased morbidity and mortality [6, 7].

Elevated blood lactate levels have been used to define the prognostic value of occult hypoperfusion in critically ill patients without signs of clinical shock [8]. Vorwerk *et al.*, [9] reported a specificity of 74.3% for mortality with lactate levels of ≥ 4 mmol/l in patients with sepsis. Mikkelsen *et al.*, [10] reported that intermediate and high lactate levels are independently associated with mortality in severe sepsis, independent of organ failure and shock. Nichol *et al*., [11] performed both - static and dynamic measurements of plasma lactate in critically ill patients (36,673 lactate measurements in 5,041 patients) and found that dynamic lactate measurement was most predictive of mortality.

In 2001 at the International Conference on Definitions of Sepsis, pro-calcitonin was recognized as the most important marker for the diagnosis in the initial stages of the inflammatory response to infection, and enumerating its severity of sepsis [12]. Procalcitonin (PCT) is a prohormone of protein origin, similar to calcitonin, of which it is the precursor peptide. Under normal conditions, it is produced and secreted by C cells in the thyroid gland. It is also secreted by neuroendocrine cells in the lung and intestine; these last two sources of PCT provide its true clinical utility, since they increase its production in response to a pro-inflammatory stimulus. Procalcitonin is a biomarker of sepsis, whose concentrations increase when some endotoxin enters the bloodstream. It is used, among other things, to discriminate the etiology of infections, increase or decrease the antibiotic spectrum, and predict mortality. The diagnostic value of markers of inflammation could differentiate infectious processes that are not, and predicting the severity of a disease process or condition, which would initiate appropriate therapeutic and measure its response [12, 13].

The peritoneal cavity is the largest cavity in the human body, the surface area of its lining membrane called peritoneum is (2 m2 in an adult) nearly equal to that of the skin which is largest serous smooth membrane of human body. It can be divided into parietal and visceral portions. The parietal layer lines the abdominal and pelvic cavities and the abdominal surface of the diaphragm. The visceral layer covers the abdominal and pelvic viscera and includes the mesenteries. The peritoneum consists of a fibrous layer (the tunica sub serosa) and a surface layer of mesothelium (the tunica serosa) [14]. The parietal peritoneum is only loosely connected with the body wall, separated from it by an adipose layer, the tela sub-serosa; whereas the visceral peritoneum is usually tightly attached to the organs it covers [15].

The large surface area of the peritoneal cavity allows infection and malignant disease to spread easily throughout the abdomen. If malignant cells enter the peritoneal cavity by direct invasion (e.g. from colon or ovarian cancer) spread may be rapid. The peritoneal cavity can also act as a barrier to, and container of disease. Intra-abdominal infection therefore tends to remain below the diaphragm rather than spread into other body cavities [16].

History and Definition

Peritonitis has been deadly and ominous during the course of the antiquity of the human development, references of which can be traced so far from the ancient Egyptians era. The treatment of peritonitis was firstly done by the German surgeon M. Kirshner in 1926, and since then, in the treatment of this deadly disease, an urgent and fundamental place has been allocated for urgent and timely surgery. Peritonitis is the inflammation of a portion or all of the parietal and visceral peritoneum and peritonism is generalized rigidity of the abdomen. “Défence musculaire” or abdominal rigidity in abdominal palpation with involuntary contraction of abdominal muscles is one of the diagnostic features of peritonitis, suggesting intra-abdominal issues, yet sensitivity/specificity is poor. Nociceptive stimuli on the peritoneal lining cause activation of visceral afferent pathways that activate a reflex loop to the abdominal wall musculature. The result is the splinting of the abdominal wall using the abdominal skeletal muscle in response to viscerosomatic pain [17-19].

Pathogenesis and classification

“Peritonitis” is the physical finding that unifies a wide range of pathologies within the abdominal compartment, the actual significance and implications for morbidity and mortality. It is one of most common surgical emergencies which present to surgery department. In spite of the conspicuous progress in the surgical treatment of acute surgical diseases of the abdominal organs, the incidence of widespread peritonitis remains high, and the mortality rate for it varies from 25 to 41.5%. In research approaches and practical solutions to the problem of widespread peritonitis, new promising trends have recently begun to appear. First of all, this affected the issues of pathogenesis and classification of peritonitis, which determine the choice of optimal surgical tactics and an effective complex of intensive care measures [17, 20].

While the origins of the peritoneal irritants that result in peritonitis are many, it is frequently a sign of catastrophe and if left untreated, brings a grim

prognosis. The pathogenesis of generalized peritonitis is a complex, dynamic process of progression of pathophysiological disorders. The nature of morphological and functional changes, the age of patients, the degree of body resistance, the severity of concomitant diseases and other risk factors contribute to this process.

The clinical classification of the stages of generalized peritonitis

- Stage I - endogenous intoxication;
- Stage II - abdominal sepsis (joins from 2-4 days);
- Stage III - septic shock (joins from 3-7 days).

The clinical classification in terms of prevalence: Local peritonitis and widespread. Since it is almost impossible to determine the boundaries of inflammatory changes in the peritoneum during the operation. The concept of "general (total) peritonitis" was gradually excluded from use due to the similarity in many criteria (mechanism of pathogenesis, clinical manifestations and treatment tactics) with diffuse peritonitis [17, 20].

Classification on the basis of various stages of the host's response

Phase I of peritonitis involves the rapid removal of contaminants from the peritoneal cavity into the systemic circulation. It occurs because contaminated peritoneal fluid moves cephalad in response to pressure gradients generated by the diaphragm. The fluid passes through stomata in the diaphragmatic peritoneum and is absorbed into lymphatic lacunae. The lymph flows into the main lymphatic ducts via the sub sternal nodes. The resultant septicaemia predominantly involves gram-negative facultative anaerobes and is associated with high morbidity [21].

Phase II of peritonitis involves synergistic interactions between aerobes and anaerobes as they encounter host complement and phagocytes. The activation of complement is a first-line event in peritonitis and involves innate and acquired immunity; activation occurs mainly by the classical pathway, with the alternative and lectin pathways in support. Phospholipid surfactants produced by the peritoneal mesothelial cells work synergistically with complement to increase opsonisation and phagocytosis. Peritoneal mesothelial cells are also potent secretors of pro-inflammatory mediators, including interleukin-6, IL-8, monocyte chemo-attractant protein-1, macrophage inflammatory protein-1α and tumor necrosis factor-α. Therefore, peritoneal mesothelial cells play a central role in the cell signalling pathways leading to the recruitment of phagocytes to the peritoneal cavity and the up regulation of mast cells and fibroblasts in the sub-mesothelium [22].

Phase III of peritonitis is an attempt by host defences to localize infection, mainly via production of fibrinous exudates that traps microbes within its matrix and promotes local phagocytic effectors mechanisms. It also serves to promote the development of abscesses. Regulation of the formation and degradation of fibrinous exudates is vital to this process. The plasminogen-activating activity generated by peritoneal mesothelial cells determines whether the fibrin that forms after peritoneal injury is lysed or organized into fibrinous adhesions. In particular, tumor necrosis factor-α stimulates the production of plasminogen activator-inhibitor-1 by peritoneal mesothelial cells, which inhibits degradation of fibrin [23].

Peritonitis, defined as inflammation of the peritoneum may be localised or generalised and is usually caused by invasion of the peritoneal cavity by bacteria [24]. Peritoneum becomes inflamed secondary to bacterial invasion. Pathogenic organisms reach the peritoneal cavity through viscus perforation, through intra-peritoneal visceral suppuration, from abdominal wound, through the blood; lymphatic's or via open ends of fallopian tubes. The commonest organisms are *Escherichia coli*, aerobic and anaerobic S*treptococci*, and *Bacteroides*. Less frequently *Clostridium welchii* is found; still less frequently *staphylococci* or *Klebsiella pneumoniae* (Friedländer's bacillus) [23].

Peritonitis can be divided into three subtypes: primary, secondary and tertiary peritonitis. Out of three Secondary peritonitis is most common. Primary peritonitis can be defined as peritonitis in the absence of an intra-abdominal source resulting from bacterial translocation, haematogenous spread, or the iatrogenic contamination of the abdomen without a macroscopic defect in the gastrointestinal tract. Primary peritonitis is a very rare disorder amongst individuals who are otherwise healthy and without comorbidities and accounts for 1% of all peritonitis. It is usually associated with patients with underlying autoimmune disease such as systemic lupus erythematosus (SLE), immunosuppression, chronic liver disease, especially those with ascites, and chronic kidney disease. Secondary resulting from direct contamination of the peritoneum by spillage from the gastrointestinal or urogenital tracts such as bowel perforation and ischemia or their associated solid organs. Lastly, tertiary peritonitis is characterized by persistent or recurrent secondary peritonitis that persists for more than 48 h after an attempt at surgical source control, usually with organisms of low intrinsic virulence, and predisposed in immunocompromised patients. It is usually associated with progressive organ dysfunction leading to high mortality [24-26].

Secondary peritonitis, typically originating from a breach in the gastrointestinal tract, is a global problem as it may manifest as intra-abdominal sepsis (IAS). [17] Cases operated on as abdominal emergencies with the presence of secondary peritonitis were more likely to increase intra-abdominal pressure (IAP) than

other cases, especially when considering elective cases. The appearance of IAH is common in bacterial peritonitis, and in cases where the disease advanced, the manifestation of IAH becomes more frequent, contributing to the appearance of changes in the organs and an increase in mortality [27]. The mortality rate in patients with sepsis is 15–25% and can be as high as 18–55% when gram-positive Cocci are present. These are also associated with a higher rate of early deaths. Peritonitis is the cause of sepsis in 5–70%. [28] Secondary peritonitis is defined as the irritation of the abdominal peritoneal lining caused by direct contact with a peritoneal contaminant from intra-abdominal or intra-pelvic source of hollow viscus perforation, bowel ischemia/necrosis, or nonbacterial source resulting in an inflammatory reaction. It occurs most commonly from a physical or functional disruption of the integrity of the gastrointestinal tract and thus the bacterial contribution to secondary peritonitis is commonly polymicrobial and can leads to severe sepsis with organ failure. While gastrointestinal perforation causes direct spillage, secondary peritonitis can also be seen due to ischemic gut, volvulus, or blood in the peritoneal cavity secondary to trauma. There is a bimodal distribution of secondary peritonitis with peaks in age groups of 20–30 years and 50–60 years. Appendicular perforation dominates in the age ranging from 10 to 40 years and gastric perforation dominates from 50 to 80 years. The most common site of perforation causing secondary peritonitis is the appendix followed by the stomach and duodenum [17, 24, 29].

Peritonitis due to perforation of the gastrointestinal tract is one of the most common surgical emergencies all over the world [30]. There is paucity of data from India regarding its etiology, prognostic indicators, morbidity, and mortality patterns [31]. Despite advances in surgical techniques, antimicrobial therapy, and intensive care support, management of peritonitis continues to be highly demanding, difficult, and complex (Fig.1) [32]. Diagnosis of peritonitis is made largely by clinical evaluation. Routine investigations add little information in evaluation. Once diagnosis is confirmed patient's general condition is improved so that he/she can with stand surgery [1]. Origin of the peritonitis and effects of antimicrobial treatment are the main factors influencing the severity of peritonitis and its outcome. Mortality and morbidity of sepsis or severe peritonitis can be reduced by state of the art critical care medicine, including fluid resuscitation, vasopressor therapy and surgical or interventional source control. Early empiric antibiotic treatment and surgical source control can reduce mortality. [33] Improved intensive care and surgical management as well as more targeted diagnostics of peritonitis have reduced mortality from 90% in 1900 to 15–25% [34]. However, due to increasing microbial resistance, appropriate antibiotic treatment is getting more and more challenging, especially empiric treatment. Commonly, the empiric treatment of secondary peritonitis includes a combination of antibiotics, such as second or third generation Cephalosporins (Cefuroxime/Ceftriaxone), plus Metronidazole or Piperacillin/Sulbactam. In patients with severe sepsis, broad-spectrum antibiotics, such as Meropenem are frequently used [25]. Rapid diagnosis and early management of peritonitis remain a challenge for physicians in emergency medicine, surgery and critical care. Grading the severity of acute peritonitis has assisted in no small way in decision-making and has improved therapy in the management of severely ill patients (Fig.1). [24].

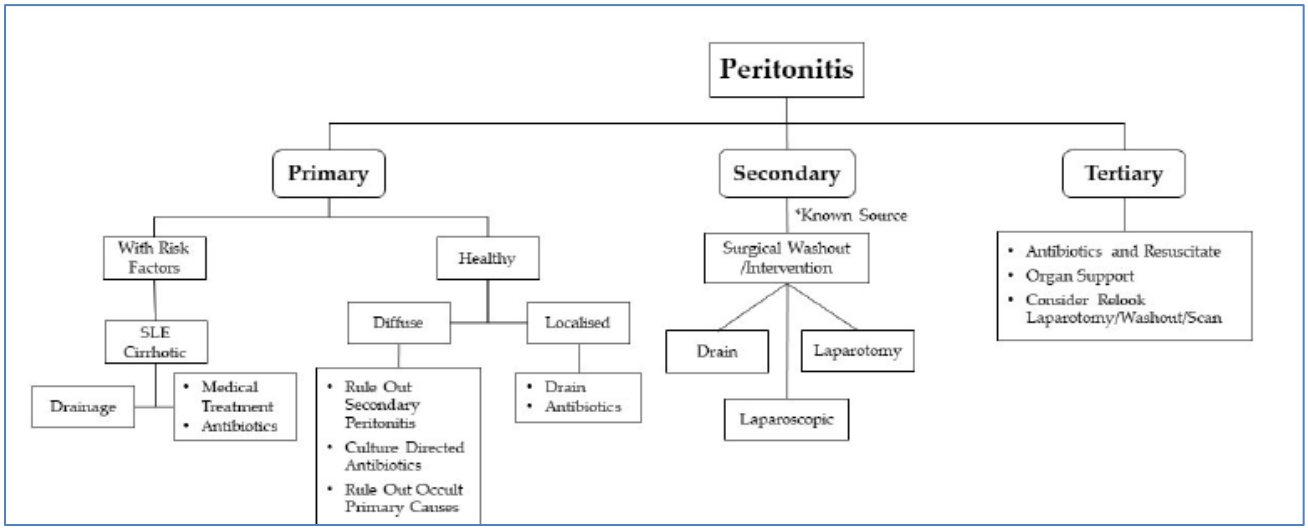

Fig-1: General approach to peritonitis [25].

In the gastrointestinal tract, lactate is increased in acute abdominal conditions such as bowel perforation, gangrene, acute pancreatitis, intestinal obstruction and appendicular perforation. Moreover, reduced lactate clearance may occur due to microcirculatory disarray, which could affect oxygen utilization by mitochondria at the tissue level and due to deranged renal function from sepsis or hypovolemia

[35]. Reversal of organ dysfunction in septic patients has been suggested to be part of a protective regulatory process, which induces a temporary hypo-metabolic state resembling hibernation that may protect the cells from dying and allow the possibility of functional recovery. Although increased blood lactate levels have been documented as a risk factor for mortality in peritonitis [36], both a single value of lactate and lactate clearance have been reported as a prognostic marker in various clinical scenarios.

Lactate level has been established as a good predictor of mortality in severe sepsis/septic shock, as it is elevated due to tissue hypoxia, excess adrenergic stimulation, or decreased clearance from hepatic dysfunction. It correlates well with indices of end-organ perfusion and has been investigated as a resuscitation end point in few randomized controlled trials. Surviving sepsis campaign guidelines suggest that, in septic shock, resuscitation should be guided to normalize lactate levels, suggesting potential correlation between lactate and the outcome. Higher lactate value 6 hours after admission is the best lactate metric associated with increased risk of early mortality and need for a higher level of care in children experiencing severe sepsis/septic shock in resource-poor regions [37]. Durrance RJ *et al*., [38] reported that Lactic acid levels have correlation to both severity of disease and mortality. Jabin *et al*., [39] reported that preoperative, immediate postoperative and 24-h postoperative lactate value independently predict 28- day mortality in perforation peritonitis patients undergoing emergency laparotomy.

Procalcitonin (PCT) is a prohormone which is a precursor of hormone calcitonin produced by cleavage of preprocalcitonin by endopeptidase. It is composed of 116 amino acids produced by parafollicular cells of thyroid and to a lesser extent, other neuroendocrine cells throughout the body of healthy individual. PCT is expressed in the central nervous system very early in fetal development, but the function of PCT itself is unclear; it is converted in the thyroid to calcitonin, a hormone involved in calcium homeostasis. Because PCT is nearly exclusively produced in the thyroid under normal physiological conditions, it is typically undetectable in the serum in healthy individuals [40].

Although several biomarkers have been proposed, no single clinical or biological indicator of sepsis has gained general acceptance. The procalcitonin (PCT) is one of the most widely studied biomarkers in patients with suspected sepsis. PCT commonly used in clinical practice, but have limited ability to distinguish bacterial sepsis of other inflammatory conditions [41]. PCT at presentation can be a very good tool for predicting the bowel ischaemia and gangrene as an early indicator and also it can be used as a marker for need for surgery in patients managing conservatively for intestinal obstruction. The advantage of PCT lies in its high specificity, with little or no increase in viral infection, the shock cardiogenic syndrome non-infectious inflammatory response. Procalcitonin is a useful marker of inflammation and useful as an early predictor and prognostic tool on infections, sepsis, acute pancreatitis like conditions including the post-operative complications [13].

Although the PCT has a role established as a biomarker in septic patients, the diagnostic accuracy of its systematic measurements has been questioned because of the variable and inconsistent results depending on the severity of the disease and infection in the patient population studied. **[41]** Additionally, because PCT is produced by tissues in the setting of bacterial infection, in addition to immune cells, it should be reliably produced in both immunocompetent and immunocompromised patients [40].

PCT however is secreted during systemic infection causing to its increase in serum levels allowing it to be dependable to distinguishing sepsis and non-infectious systemic inflammatory response syndrome. PCT may be a prognostic predictor to guide the empirical antimicrobial therapy in order to decrease the in-hospital mortality and the frequency of complications [42], since its levels are impeded by IFN-gamma in viral infection and its amount correlate with presence of bacterial infection. Procalcitonin immediately increases in 3 to 6 hours resulting in bacterial infection proving the capacity to distinguish between localized and systemic infections [43]. PCT-guided antibiotic treatment in ICU patients with infection results in improved survival and shorter antibiotic treatment duration. Effects were similar in sepsis patients and among subgroups based on sepsis severity, sepsis treatment modalities, and type of infection [44].

Normal PCT concentrations in healthy humans are <0.1 ng / ml. Secretion of PCT by neuroendocrine cells in the lung and intestine, provide its true clinical utility, since they increase its production in response to a pro-inflammatory stimulus especially in bacterial origin. It is therefore considered as an acute phase reactant protein. The half-life of procalcitonin is between 18 to 24 hours with a peak at 24 hours. In kidney failure patients it lies between 24 to 30 hours. Procalcitonin levels at presentation and followed up at timely intervals of 24, 48 and 72 hrs regularly is a very good tool for managing the patients with acute intestinal obstruction. It also helps us to decide on when to operate and continue the conservative treatment for obstruction cases is decided by timely monitoring of procalcitonin levels [13]. PCT values can rise to more than 400 times the baseline (> 4 ng / ml) rapidly when an endotoxin enters the bloodstream. It has been suggested that the PCT value can determine the risk and severity of an infection: with PCT <0.5 ng / ml, there is no risk of infection; with PCT of 0.5-2 ng / ml, the risk

of infection is moderate; with PCT of 2-10 ng / ml, there is a high risk of progression to a serious systemic infection; and with PCT> 10 ng / ml there is a high probability of severe sepsis or septic shock.

There are numerous indications for the use of PCT as a marker:

- Diagnosis of bacterial infection in the presence of systemic inflammatory response syndrome with a higher specificity than other acute phase reactants [45].
- Monitoring of antibiotic therapy and evolution of bacterial infection.
- Differential diagnosis of inflammatory diseases and fever of unknown origin.
- Predict mortality [12].

Romualdoa *et al*. [46] reported that the PCT clearance showed moderate performance as a prognostic factor. According to Mustafić *et al*., [47] concentration of procalcitonin and monitoring of PCT elevation reveal the severity of sepsis and it could also predict fatal outcome in patients with sepsis. Maseda *et al*. [48] reported that critically ill patients with secondary peritonitis PCT-guidance produced 50% reduction in AB duration ($P < 0.001$, log-rank test). Jiang et al. [49] reported that procalcitonin concentrations were positively correlated with APACHE II score in patients with sepsis, and therefore reflected disease severity. APACHE II score and procalcitonin concentration at 24 h are independent risk factors for death in patients with sepsis. The measurements of PCT in sepsis may help in clinical decision-making, as non-survivors of sepsis often showed a rising trend in PCT levels. PCT value on day 5 is a better predictor of mortality in patients with sepsis than the baseline value. Therefore, serial measurements of PCT rather than a single measurement will provide a better idea about the prognosis and response to treatment [50]. It is important to keep in mind that procalcitonin values may be influenced by pre-existing comorbid conditions such as chronic kidney disease and congestive heart failure, which have been shown in studies to be associated with higher PCT values at baseline. Indeed, procalcitonin can provide invaluable information when viewed as one piece of a clinical puzzle, and must always be interpreted in the clinical context [45].

Till beginning of 21st century peritonitis was considered as fatal condition. Despite spectacular advances in understanding pathogenesis of disease, in diagnostic modalities discovery of broad spectrum antibiotics, invention of modern advance equipments like ventilators, advancement of knowledge in surgical and anaesthesiology field, peritonitis still poses major problem for surgeons as far as morbidity and mortality is concerned [1]. Acute secondary peritonitis is one of the most dangerous pathologies that challenge surgeons. Although doctors have made significant progress in the management of patients with acute peritonitis in recent decades, the mortality rate of these patients are still reported to be between 19 and 70%.The cause of 90% of deaths in these patients were the delay in the transfer and emergency surgery in the hospital [51]. Researches show that the main causes of acute secondary peritonitis are perforation of hollow organs caused by acute inflammatory diseases, trauma, and intestinal obstruction, malignant and begin tumors. Complications like surgical infection, abdominal abscess, faecal fistulas, and thoracic complications are the causes of mortality and morbidity among them [52-54]. The aim of this study is to assess the prognostic relevance of pre- and postoperative arterial blood lactate measurements and pH as predictors of outcomes in secondary peritonitis.

MATERIAL AND METHODS

This study was conducted in the Department of Surgery IGMC, Shimla over a period of twelve months from January 2021 – December 2021.

Inclusion Criteria

- All adult patients (> 18 years of age) presenting with the clinical diagnosis of perforation peritonitis of either sex.
- All Patients willing to participate in the study.

Exclusion Criteria

- Patients operated elsewhere before presentation.
- Patients unwilling to participate in the study.
- Patients on drugs which alter the level of arterial lactate (ANNEXURE-1)

Study Methodology

- The proposed study was a longitudinal, prospective study with two time measurement of arterial lactate levels at 24 hours interval.
- All patients presenting to the Department of Surgery, IGMC, Shimla with a diagnosis of secondary peritonitis and fulfilling the inclusion and exclusion criteria were recruited.
- The diagnosis of secondary peritonitis was established based on clinical examination, investigations and operative findings.
- Informed and written consent was taken from the patient / relative.
- Resuscitation, preoperative and postoperative treatment was performed according to the established protocol for perforation peritonitis.
- Relevant information was collected as per study performa.
- ABG analysis was performed twice to assess arterial lactate levels and pH, once initially, on admission (preoperative), and the other, 24 hours after surgery (postoperative).

- 2 ml of blood sample drawn for ABG sampling from either the radial or femoral artery in a pre-heparinized syringe.
- Arterial Blood Lactate level and pH measured by using Siemens Rapid Point 500 e Analyzer which is available in the hospital and estimates the whole blood lactate level based on potentiometric measuring principles.
- AL_I was the preoperative reading of arterial lactate levels.
- AL_{24} was postoperative reading and absolute clearance as well as percentage lactate clearance calculated using the formula –

Absolute lactate clearance (mmol/L)	$AL_I - AL_{24}$
Percentage of lactate clearance (%)	$(AL_I - AL_{24}) \times 100\ AL_I$

- Serum procalcitonin estimation of the patient was done at the time of admission into hospital.
- For the determination of change in lactate level following peritonitis, preoperative and post-operative lactate values were statistically compared and Correlation of these values measured with t-test and Chi-square test.
- For the determination of correlation between PCT and outcome t-test and Chi-square test were performed.
- For the determination of change in pH following peritonitis, preoperative and postoperative pH values were statistically compared and Correlation of these values measured with t-test and Chi-square test.

RESULT AND DISCUSSION

In the gastrointestinal tract, lactate is increased in acute abdominal conditions such as bowel perforation, gangrene, acute pancreatitis, intestinal obstruction and appendicular perforation. Although increased blood lactate levels have been documented as a risk factor for mortality in peritonitis [55].

Lactate levels are routinely used to assess circulatory function and tissue perfusion. Higher levels are thought to be associated with circulatory dysfunction and impaired tissue perfusion. But, there is no clear-cut relationship and interpretation of results should be performed cautiously. Persistent hyperlactatemia may be result of decreased clearance instead of increased production. Also, when adrenalin is administered to the patients, production of lactate can be increased in the presence of adequate tissue oxygenation. Lactate may be a substrate for metabolism, may be increased in liver dysfunction and finally, may persist with or without tissue hypo perfusion [56]. Lactate levels were statistically significantly higher in non-survivors on the 3rd day and at that time-point demonstrated statistically significant discriminative power regarding outcome; lactate levels higher than cut-off values were good predictors of lethal outcome. These results are in accordance with other similar studies [57-59].

The present study was prospective and purely observational, relying upon two measurements of arterial lactate (once on admission i.e. preoperative and the other 24 h post-operatively), to establish lactate values that could prognosticate mortality exclusively in secondary peritonitis.

The two static values of preoperative lactate and 24 h post-operative lactate were used to calculate lactate clearance to give a dynamic value of percent lactate clearance that was an indicator of trend or change in lactate value over the first 24 h after surgery. A fall in post-operative lactate and increased percent lactate clearance can be perceived as successful management of the patient, indicative of good resuscitation, source control, management of peritonitis and reversal of organ dysfunction, whereas a rise indicates the opposite or worsening of condition. In the present study, percent lactate clearance increase was reported. SPSS analysis reported there was difference in the lactate levels of survivors and non-survivors indicating significant role in prediction of mortality in case of secondary peritonitis. According to the present study lactate level is directly related to the change in the pH.

In present study it was reported that there was significant elevation of percent lactate clearance levels on obstruction patients and secondary peritonitis and has significant role in the prediction of mortality. However it was studied in literature that percent lactate clearance levels are more related with the prediction of sepsis instead of morbidity in case of secondary peritonitis. Harindranath *et al*. (2021) reported elevated percent lactate clearance levels in patients with bacterial infection. Role of procalcitonin can also be explained by understanding the Patho physiology of ischaemia. Ischaemia is defined as decreased blood flow through the vessels inflammatory reaction then triggers the release of reactive oxygen species which in turn promotes the releases of inflammatory mediators like interferon. Interleukins, resulting oxidative stress damage the mucosa of intestine increasing the permeability of the intestinal wall then indigenous bacteria then proliferate and produce the endotoxinsthat ultimately promote the release of procalcitonin from the liver [60].

DEMOGRAPHIC PROFILE

In this retrospective study total 250 patients with diagnosis of perforation peritonitis were evaluated.

Table-1: Demographic and clinical data of patients under study

Parameter	Values
Total no. of patients	250
Age (mean, range), years	47.28 (18 – 87)
Sex, (n) Total Male Female	 250 205 (82%) 45 (18%)
Survivors (n) Total Male Female	 218 (87.2%) 186 (90.7%) 32 (71.1%)
Non-survivors (n) Total Male Female	 32 (12.8%) 19 (9.35%) 13 (28.8%)

1. GENDER DISTRIBUTION

- Total patients: 250
- Males: 205 (82%)
- Females: 45 (18%)

Table-2: Gender Distribution

	Frequency	Percentage
Male	205	82%
Female	45	18%
Total	250	100 %

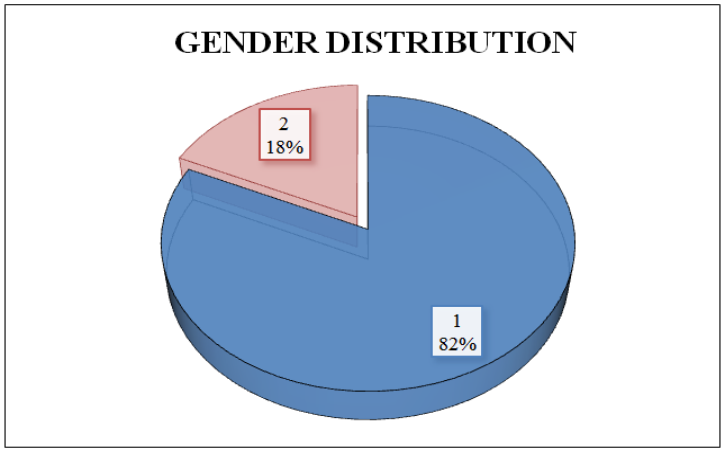

Fig-1: Gender Distribution

Table-3: Association between Gender and Outcome

OUTCOME	Male		Female		Total	
	N	%	N	%	N	%
EXPIRED	19	9.3	13	28.9	32	12.80
DISCHARGE	186	90.7	32	71.1	218	87.20
Total	205	100.0	45	100.0	250	100.00
Chi-square value = 12.727 P value = 0.000 Not Significant						

Statistical Analysis: Chi-square test. P<0.05: Statistically significant; P>0.05: Not significant.

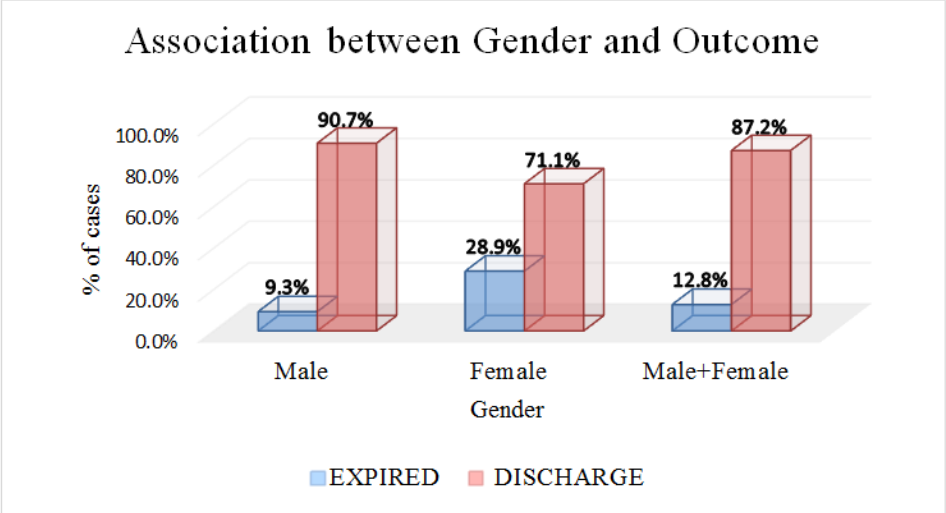

Fig-2: Association between gender and outcome

2. AGE DISTRIBUTION

- Mean age of the patients: 47.28±17.34 years
- Total patients with age < 40: 99 patients, Male: 93, Female: 6
- Total patients with age > 41: 151 patients, Male: 112, Female: 39
- Maximum age: 18 years
- Minimum age: 87 years

Table-4: Age distribution

Age (Years)	< 40	> 41
Male	93 (93.93%)	112 (74.17%)
Female	16 (6.06%)	39 (25.82%)
Total	99 (39.6%)	151 (60.4%)

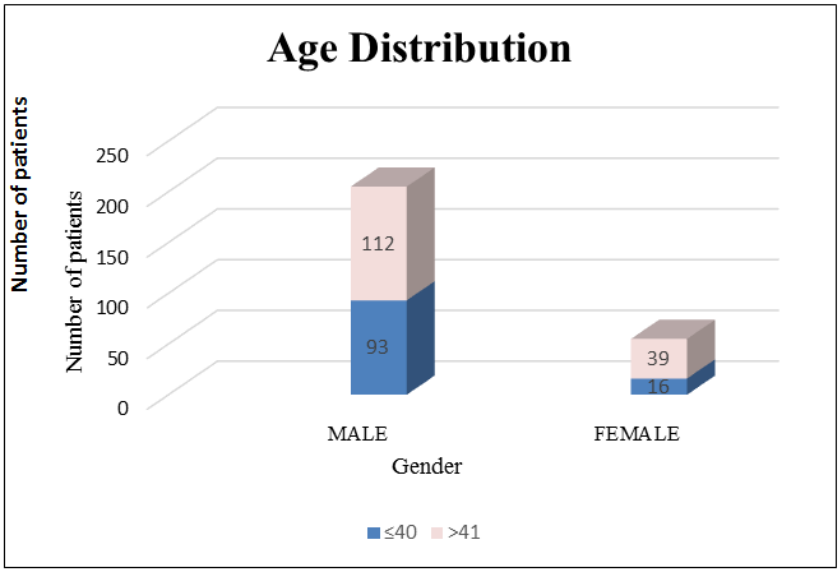

Fig-3: Age Distribution

Table-5: Mean age comparison between Outcome Expired and Outcome Discharge.

OUTCOME	N	Mean age	SD of age	P value
EXPIRED	32	59.16	13.32	<0.001 Significant
DISCHARGE	218	45.49	16.96	

Statistical Analysis: Independent sample t test. P<0.05: Statistically significant; P>0.05: Not significant.

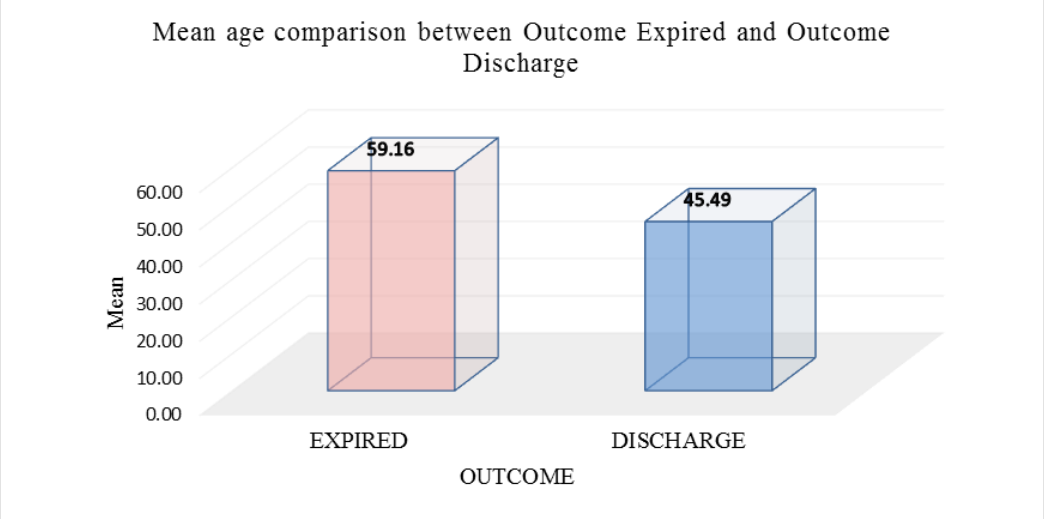

Fig-4: Association between ages with outcome

3. BMI

Table-6: Average BMI in Males and females of the study participants.

Gender	Mean BMI	SD of BMI
Male	21.93	3.00
Female	20.68	2.46
Overall	21.88	2.91

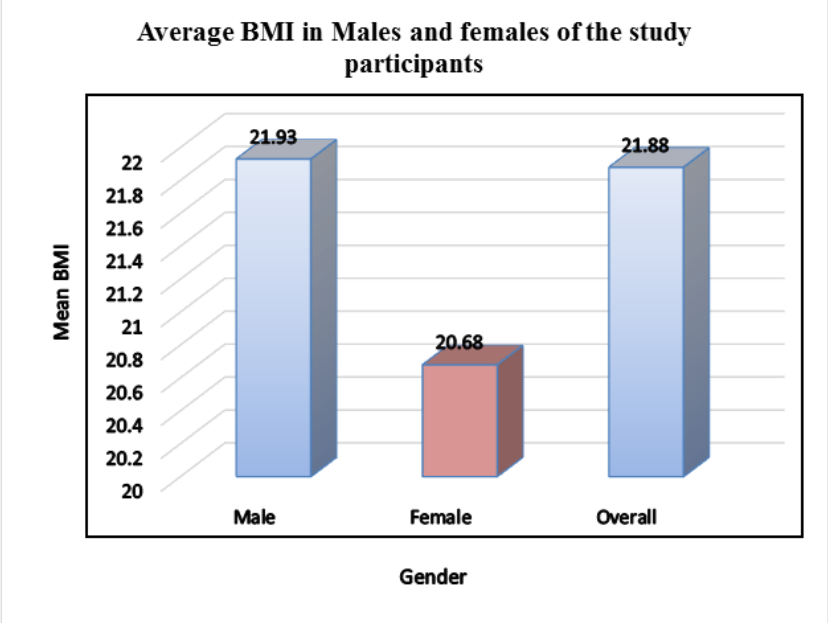

Fig-5: BMI groups

Table-7: Mean BMI comparison between Outcome Expired and Outcome Discharge.

OUTCOME	N	Mean	Std. Deviation	P value
EXPIRED	32	22.69	3.54	0.092
DISCHARGE	218	21.76	2.80	Not significant

Statistical Analysis: Independent sample t test. P<0.05: Statistically significant; P>0.05: Not significant.

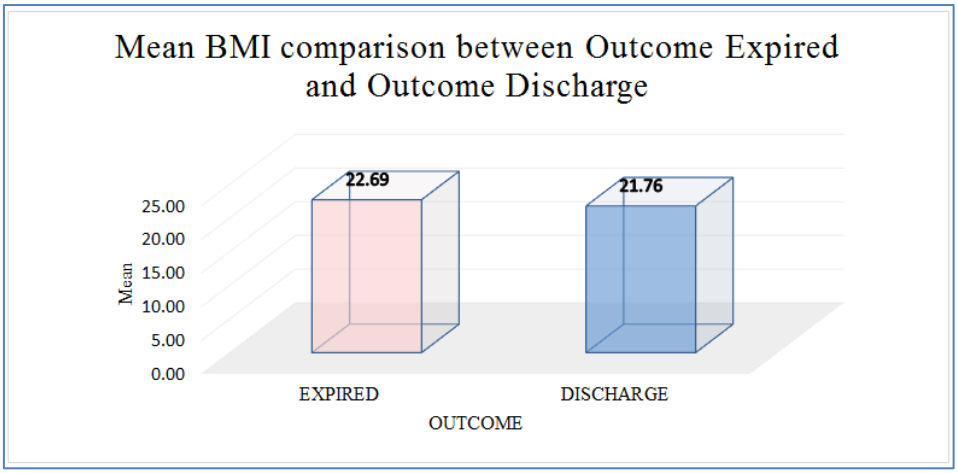

Fig-6: BMI groups

4. ASA GRADES

Table-8: Distribution of ASA grades among the study participants.

ASA	Number of patients	% of patients
Grade 1	114	45.60
Grade 2	107	42.80
Grade 3	22	8.80
Grade 4	7	2.80
Total	250	100.00

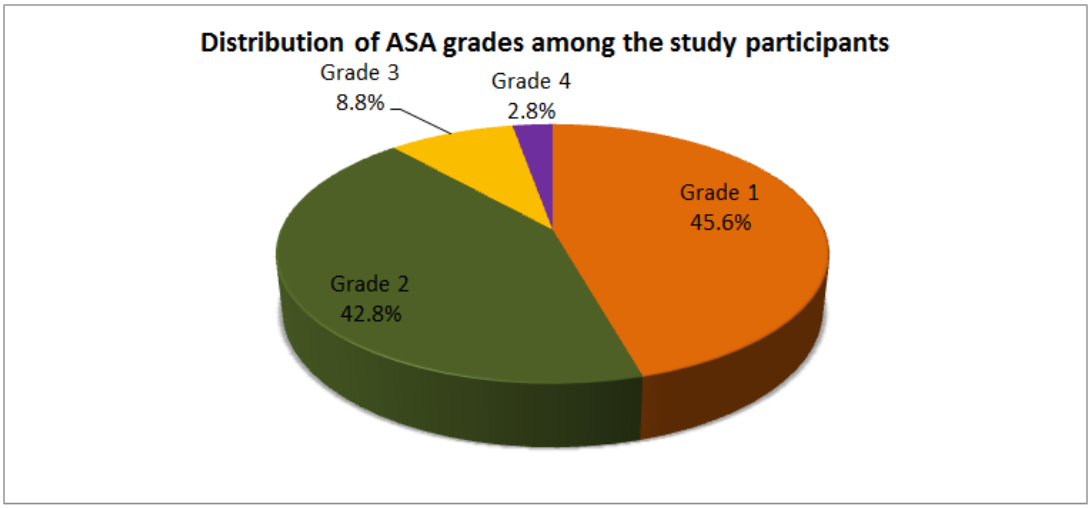

Fig-7: ASA grades

Table-9: Association between ASA and Outcome.

ASA	OUTCOME				Total	
	Expired		Discharge			
	N	%	N	%	N	%
Grade 1	2	6.3	112	51.4	114	45.6
Grade 2	19	59.4	88	40.4	107	42.8
Grade 3	9	28.1	13	6.0	22	8.8
Grade 4	2	6.3	5	2.3	7	2.8
Total	32	100.0	218	100.0	250	100
Chi-square value = 31.950; P value = 0.000 Significant						

Statistical Analysis: Chi-square test.

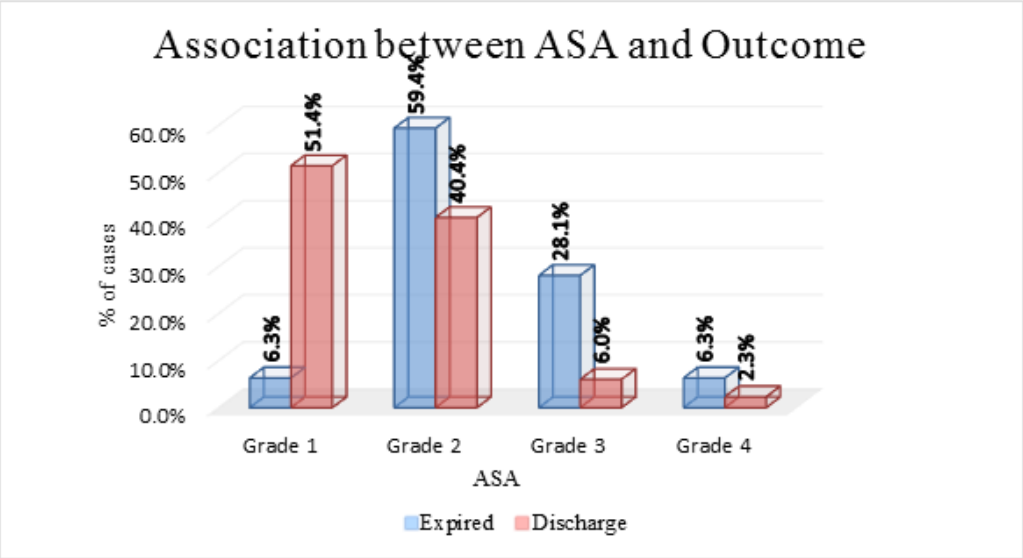

Fig-8: Association between ASA and outcome.

5. MORTALITY

- Total patients under study: 250 patients
- Died: 32 patients, Mortality rate: 12.8 %
- Discharged: 218 patients

Table-10: Distribution of Outcome of the study participants

OUTCOME	Total	
	N	%
EXPIRED	32	12.8
DISCHARGE	218	87.2
Total	250	100.0

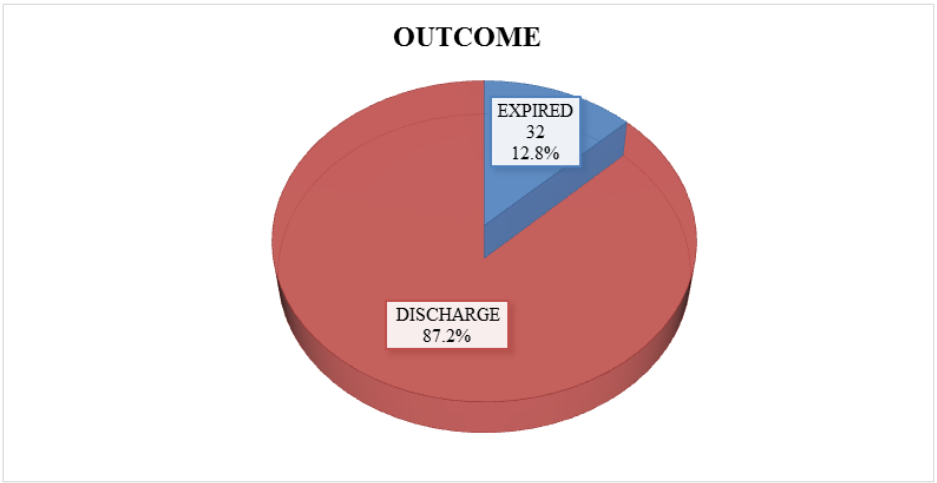

Fig-9: Mortality

6. TOTAL STAY IN HOSPITAL

Table-11: Distribution of Total stay (in days)

TOTAL STAY (in days)				
N	Minimum	Maximum	Mean	Std. Deviation
250	1.00	40.00	8.99	6.07

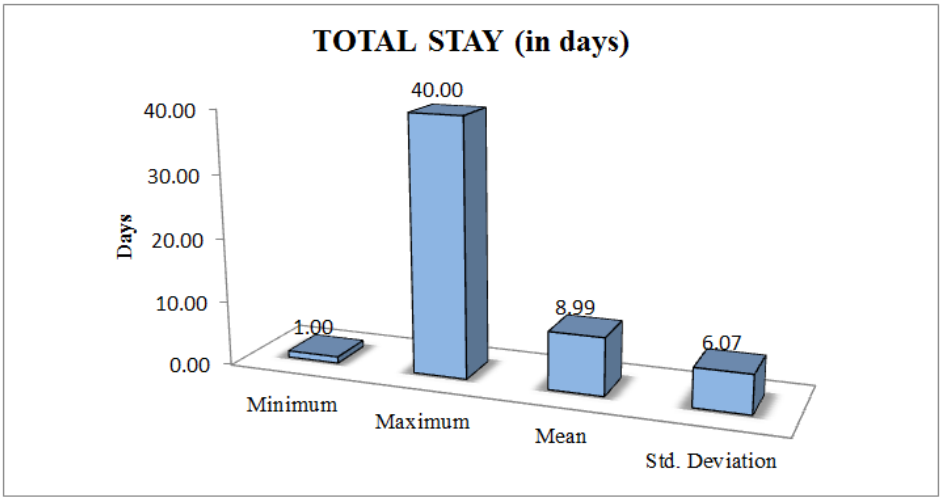

Fig-10: Total stay in hospital

Table-12: Mean comparison of Total stay in hospital between Outcome Expired and Discharged.

Variable	Outcome	N	Mean	Std. Deviation	P value
TOTAL STAY (in days)	EXPIRED	32	9.19	8.26	0.843 Not significant
	DISCHARGE	218	8.96	5.70	

Statistical Analysis: Independent sample t test. P<0.05: Statistically significant; P>0.05: Not significant.

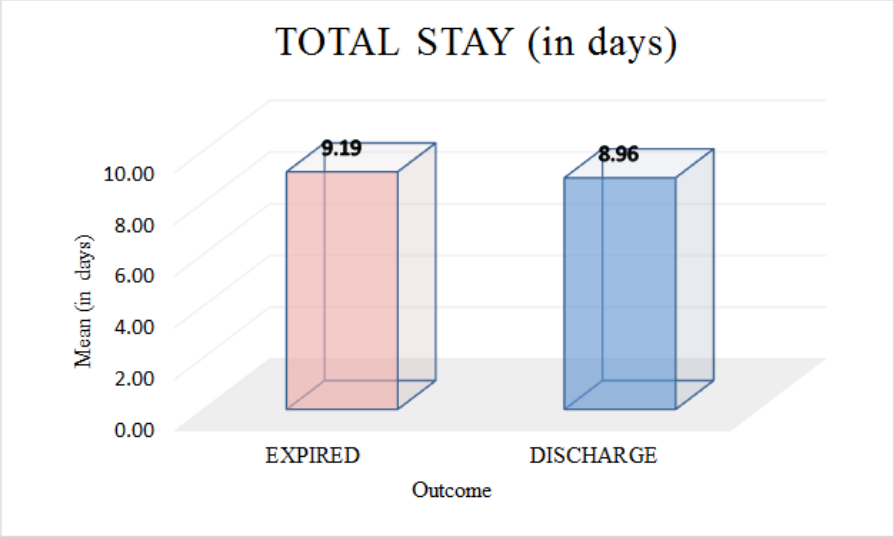

Fig-11: Comparison between total stay and outcome.

7. DIAGNOSIS (SITE OF PERFORATION)

- Most common cause: Duodenal perforation 91 patients (36.4%)
  Gastric perforation: 83 patients (33.2%),
  Ileal perforation: 32 patients (12.8%)
  Jejunal perforation: 16 patients (6.4%)
- Other: 28 patients (11.2%)

Table-13: Distribution of Diagnosis of the study participants

Diagnosis	Number of study participants	% of study participants
ILEAL PERFORATION	32	12.8
GALL BLADDER PERFORATION	3	1.2
RECTOSIGMOID JUNCTION PERFORATION	5	2
DUODENAL PERFORATION	91	36.4
JEJUNAL PERFORATION	16	6.4

Diagnosis	Number of study participants	% of study participants
GASTRIC PERFORATION	83	33.2
ILEAL PERFORATION,APPENDICULAR PERFORATION,CAECAL PERFORATION	1	0.4
ILEAL PERFORATION,APPENDICULAR PERFORATION,CAECAL PERFORATION,ASCENDING COLON PERFORATION	1	0.4
ILEAL PERFORATION,CAECAL PERFORATION	2	0.8
APPENDICULAR PERFORATION	7	2.8
APPENDICULAR PERFORATION,CAECAL PERFORATION	2	0.8
CAECAL PERFORATION	3	1.2
CAECAL PERFORATION,ASCENDING COLON PERFORATION	2	0.8
ASCENDING COLON PERFORATION	1	0.4
TRANSVERSE COLON PERFORATION	1	0.4
Total	250	100

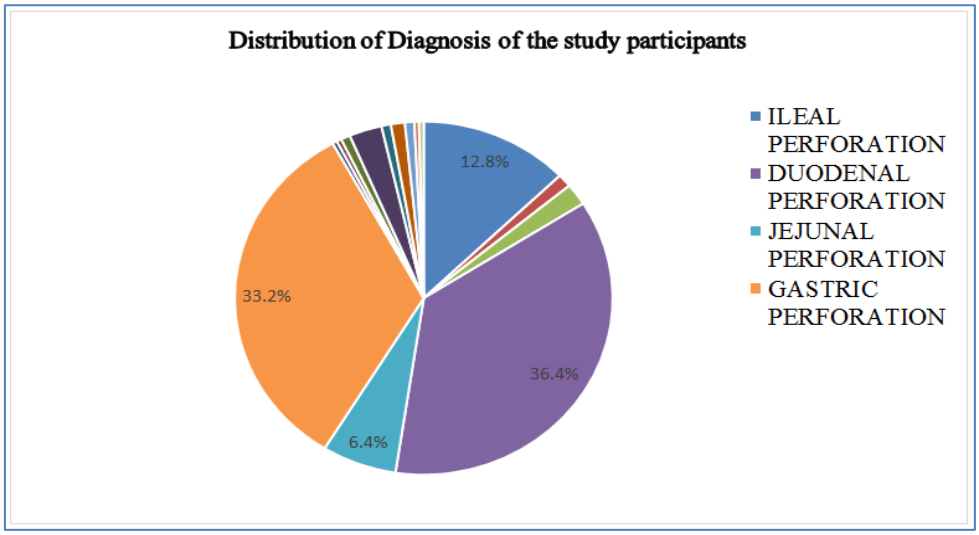

Fig-12: Diagnosis (Site of perforation)

Table-14: Association between Diagnosis and Outcome.

Diagnosis	Outcome				Total	
	Expired		Discharge			
	N	%	N	%	N	%
Ileal perforation	5	15.6	27	12.4	32	12.8
Gall bladder perforation	1	3.1	2	0.9	3	1.2
Rectosigmoid junction perforation	1	3.1	4	1.8	5	2
Duodenal perforation	9	28.1	82	37.6	91	36.4
Jejunal perforation	2	6.3	14	6.4	16	6.4
Gastric perforation	12	37.5	71	32.6	83	33.2
Ileal perforation,appendicular perforation,caecal perforation	1	3.1	0	0.0	1	0.4
Ileal perforation,appendicular perforation,caecal perforation,ascending colon perforation	0	0.0	1	0.5	1	0.4
Ileal perforation,caecal perforation	0	0.0	2	0.9	2	0.8
Appendicular perforation	0	0.0	7	3.2	7	2.8
Appendicular perforation,caecal perforation	0	0.0	2	0.9	2	0.8
Caecal perforation	0	0.0	3	1.4	3	1.2
Caecal perforation,ascending colon perforation	0	0.0	2	0.9	2	0.8
Ascending colon perforation	0	0.0	1	0.5	1	0.4
Transverse colon perforation	1	3.1	0	0.0	1	0.4
Total	32	100.0	218	100.0	250	100

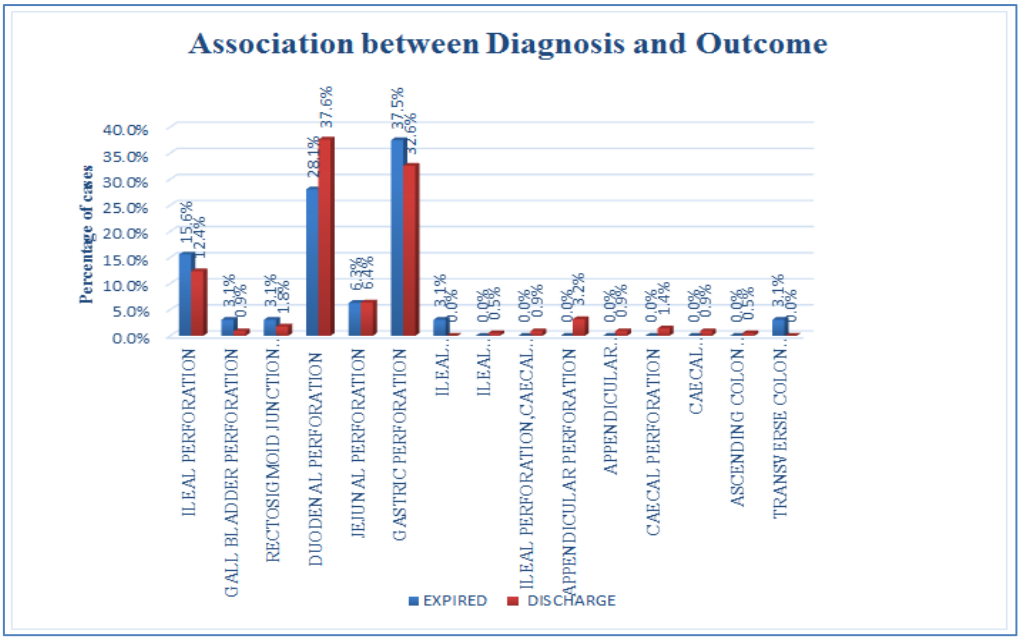

Fig-13: Association between diagnosis and outcome.

8. PROCEDURE

Table-15: Distribution of Procedure of the study participants

Procedure	Number of patients	% of study participants
Cellan jones repair	89	35.6
Loop ileostomy	43	17.2
End ileostomy	27	10.8
Cellan jones repair.F	19	7.6
Primary repair of any perforation,Loop ileostomy	16	6.4
Primary repair of any perforation	11	4.4
Appendectomy	6	2.4
End ileostomy,Limited ileocaecal resection	5	2
Primary repair of any perforation,End ileostomy	3	1.2
Primary repair of any perforation,Colostomy end	3	1.2
Cholecystectomy	3	1.2
Resection and anastomosis	2	0.8
Resection and anastomosis.F	2	0.8
Tube repair.F	2	0.8
Jejunostomy	2	0.8
Loop colostomy	2	0.8
Limited ileocaecal resection,End ileostomy	2	0.8
Right hemicolectomy,End ileostomy	2	0.8
Primary repair of any perforation,Appendectomy	1	0.4
Cellan jones repair ,End ileostomy	1	0.4
Cellan jones repair .T	1	0.4
Tube repair	1	0.4
Total gastrectomy with oesophagojejunostomy, rouex en y jj with fj.F	1	0.4
Rectus abdominal repair	1	0.4
Gastrojejunostomy	1	0.4
End ileostomy,Right hemicolectomy	1	0.4
Limited ileocaecal resection	1	0.4
Gastrectomy with loop gastrojejunostomy	1	0.4
Gastrectomy with loop gastrojejunostomy,Loop ileostomy	1	0.4
Total	250	100

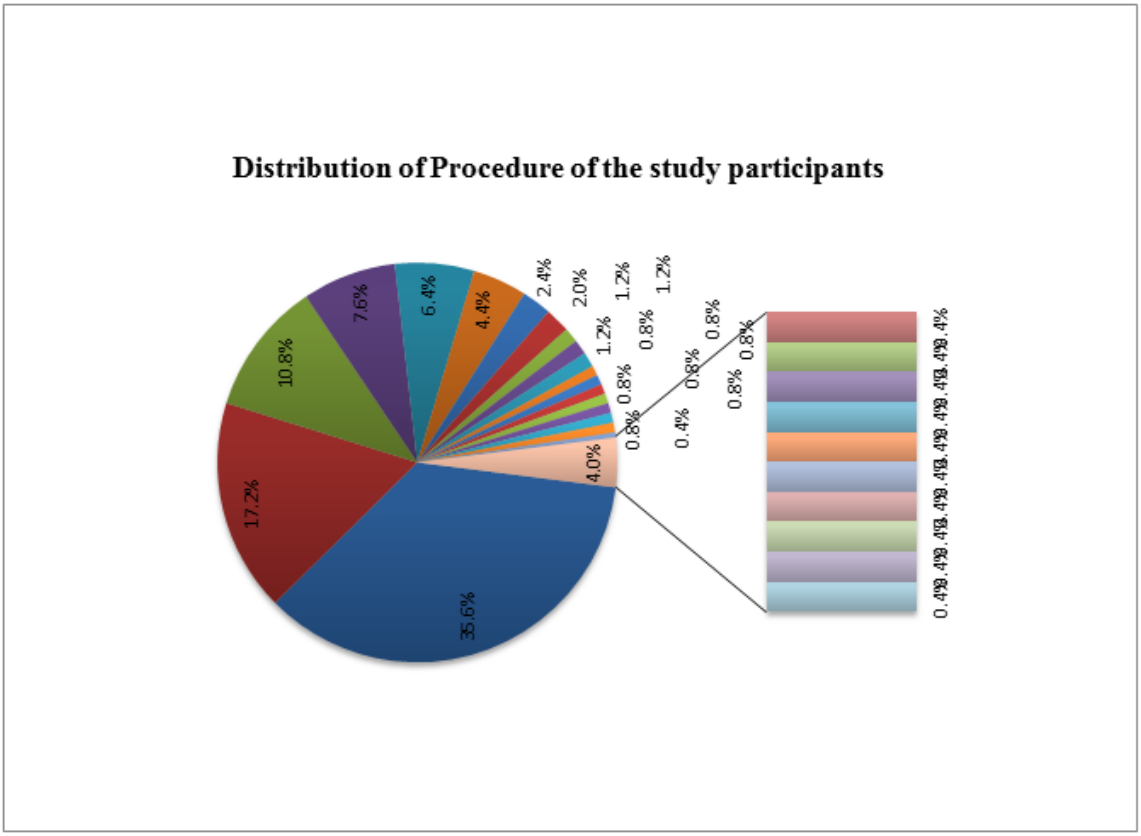

Fig-14: Procedure

9. LACTATE LEVEL

Table-16: Mean comparison of AL1 and AL24.

	N	Mean	Std. Deviation	Difference (AL1 - AL24)	P value
AL1	250	2.48	1.42	0.74	<0.001 Significant
AL24	250	1.74	1.52		

Statistical analysis: Paired t test. P<0.05: Statistically significant.

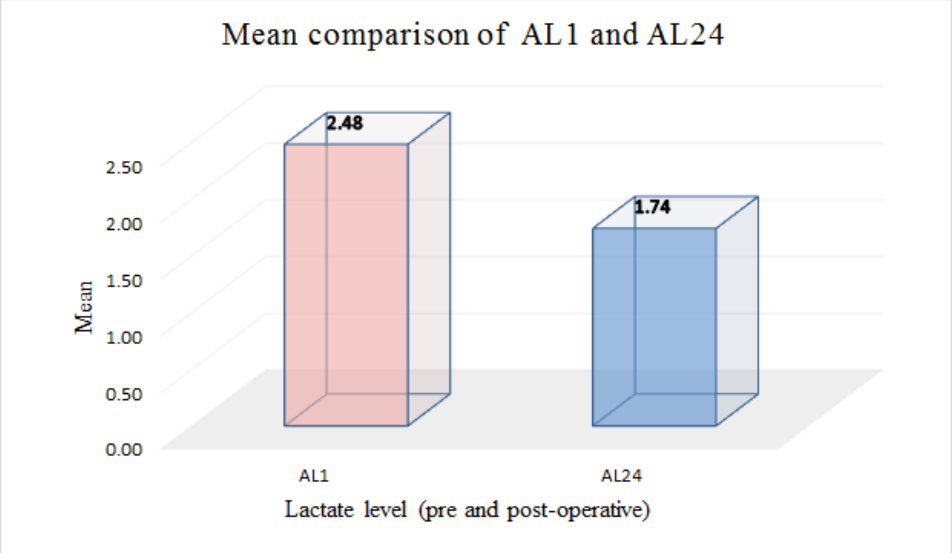

Fig-15: Comparison between pre and postoperative lactate level.

Table-17: Mean comparison of AL1, AL24 and AL1-AL24 between Outcomes.

Variable	Outcome	N	Mean	Std. Deviation	P value
AL1	EXPIRED	32	3.78	2.24	<0.001 Significant
	DISCHARGE	218	2.29	1.15	
AL24	EXPIRED	32	3.67	3.18	<0.001 Significant
	DISCHARGE	218	1.45	0.76	
AL1-AL24	EXPIRED	32	0.11	2.79	0.007 Significant
	DISCHARGE	218	0.84	1.10	

Statistical Analysis: Independent sample t test. P<0.05: Statistically significant; P>0.05: Not significant.

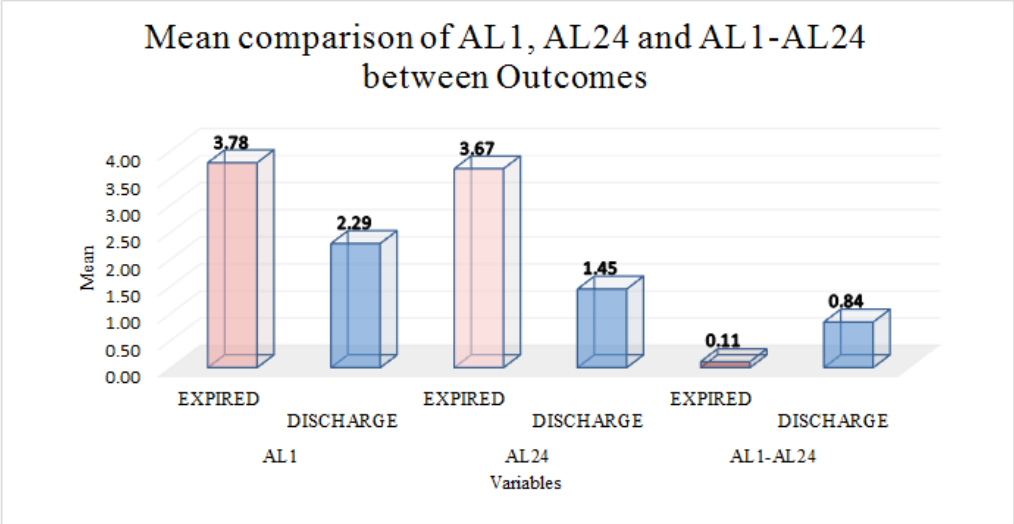

Fig-16: Comparison lactate level and lactate clearance.

13. pH AND PROCALCITONIN VALUES

Table-18: Minimum, Maximum, Mean and SD values of pH1, pH24 and Procalcitonin (ng/ml)

Variables	N	Minimum	Maximum	Mean	Std. Deviation
pH1	250	6.99	7.52	7.33	0.10
pH24	250	6.83	7.55	7.35	0.11
Procalcitonin (ng/ml)	250	0.06	5.08	0.88	0.80

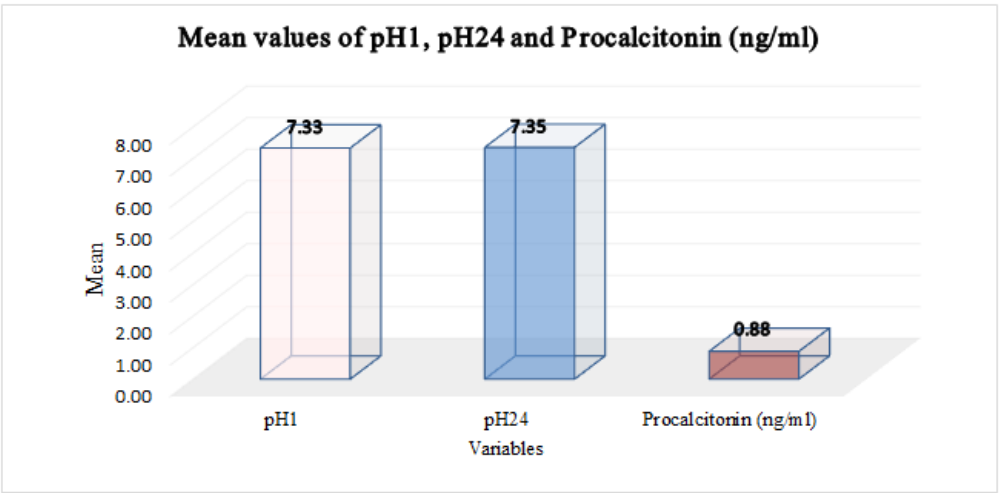

Fig-17: pH and procalcitonin levels.

Table-19: Mean comparison of PH1 and PH24 between Outcome expired and Outcome Discharged.

Variable	Outcome	N	Mean	Std. Deviation	P value
pH1	EXPIRED	32	7.16	0.09	<0.001 Significant
	DISCHARGE	218	7.36	0.08	
pH24	EXPIRED	32	7.17	0.13	<0.001 Significant
	DISCHARGE	218	7.38	0.07	

Statistical Analysis: Independent sample t test. P<0.05: Statistically significant; P>0.05: Not significant.

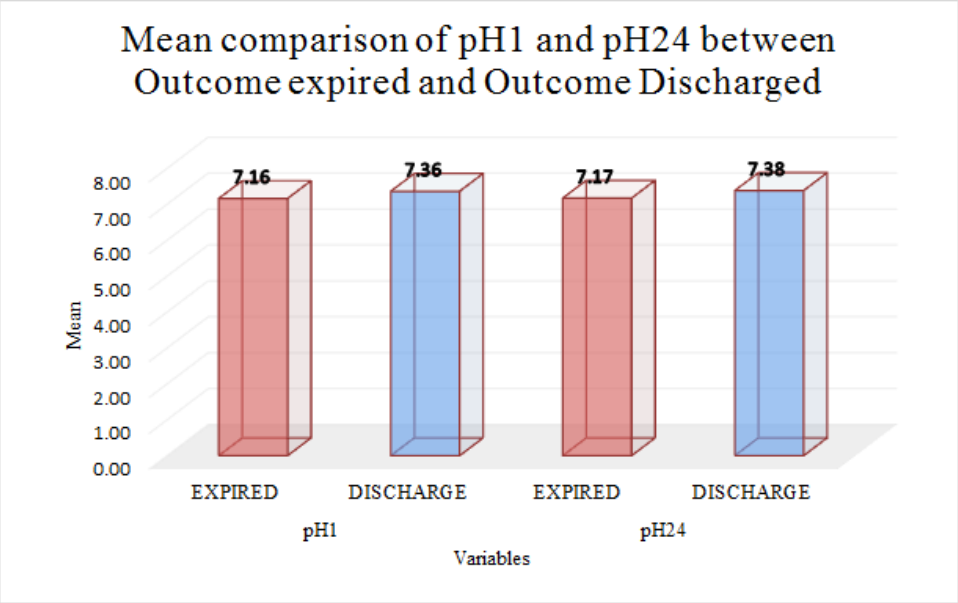

Fig-18: Comparison between pre and postoperative pH levels.

Table-20: Mean comparison of Procalcitonin (ng/ml) between Outcome Expired and Discharge.

Variable	Outcome	N	Mean	Std. Deviation	P value
Procalcitonin (ng/ml)	EXPIRED	32	2.58	1.26	<0.001 Significant
	DISCHARGE	218	0.63	0.18	

Statistical Analysis: Independent sample t test. P<0.05: Statistically significant; P>0.05: Not significant.

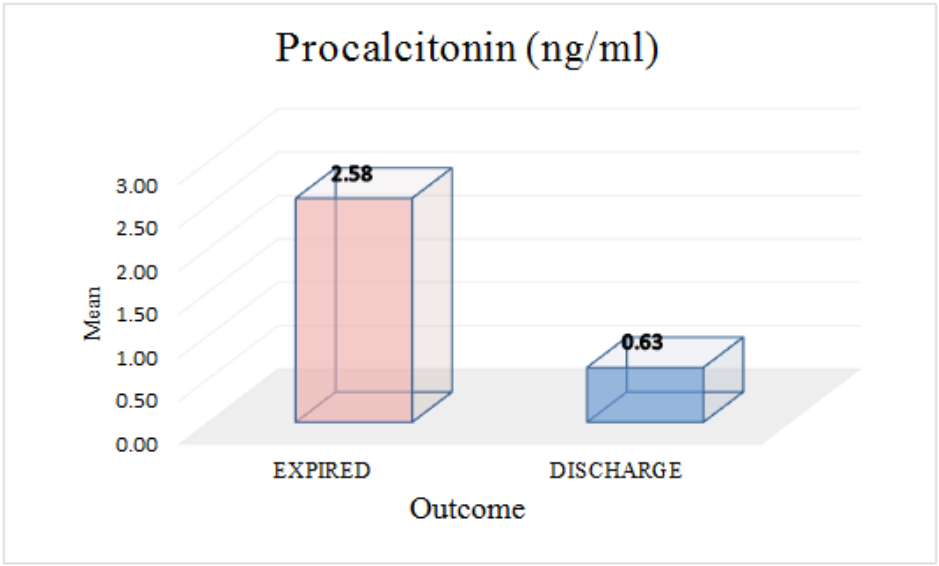

Fig-19: Comparison between procalcitonin level and outcome.

1. Gender distribution

Out of 250 patients included in the study 203 patients (81 %) were male while only a small fraction i.e. 47 patients (18.8%). This predominance in incidence of secondary peritonitis in males has been reported in most of the studies. Ghosh et al (2016) observed 84.58% incidence in male in their study of 545 patients. [61] Similar results were seen by Jhobta et al (2006) where incidence in male population was 84%. [62] This high incidence in males is attributed to more prevalence of lifestyle risk factors like smoking, alcohol intake, prone to gastrointestinal infections like typhoid, helicobacter because of preoccupation in outdoor activities, more chances of roadside accidents and assault leading to traumatic perforations. [61]

2. Age distribution

In our study mean age was 47.25 years ranging from 18-87 years, minimum age as per protocol was 18 years so patients below this age were excluded from the study. Jhobta *et al*. (2006) studied 504 patients age ranging from 3-90 years where mean age was 36.8 years and most of the patients were in the age group 31-50 years and Singh *et al*. (2011) reported mean age of 40.04 years (14-70 years) in 84 patients of perforation peritonitis [62-63].

3. BMI

Shin *et al*. (2016) analyzed 117 patients of intestinal perforation and observed mean BMI of 21.7 Kg/m^2, 16 patients (13.67%) had BMI < 18 kg/m^2 and 95 (81.19%) had > 18 Kg/m^2 [64].

4. ASA grade

Mabewa *et al*. (2015) reported 58 (59.79%) of patients in ASA grade III and 24 (24.74%) in grade IV [65]. Salamone *et al*. (2016) studied 104 elderly patients, out of these 31.7% were in ASA grade II, 45.2% in grade III and 23.1% in grade IV [66].

5. Cause/ site of perforation

Most common site for perforation peritonitis is duodenal perforation (36.4%) followed by gastric (33.2%), Ileal perforation (12.8%) and Jejunal perforation: 16 patients (6.4%). Ghosh *et al.* (2016) reported that gastroduodenal perforation was most common site for secondary peritonitis, out of 545 patients evaluated over a period of 3 years 264 (48.44%) had gastroduodenal perforation and small gut perforation was the second most common site. But in their study, they found appendicular perforation as the leading cause in small bowel in 105 patients (18.53%), ileal perforation was seen in 47 (8.62%) cases [61]. Jhobta *et al*. (2006) reported gastroduodenal perforation as leading cause in 57 % patients followed by small bowel perforation in 30% patients (most common ileal in 15% cases) [62]. Tolonen *et al*. (2016) reported colonic perforation as the commonest cause of perforation in 122 patients (54.7%) followed by gastroduodenal perforation in 61 (27.4%) patients and small bowel in 40 (17.9%) patients [67]. Most of the studied from developing world have reported gastroduodenal perforation as most common cause for perforation peritonitis, while in developed world it is the distal bowel, this variance is because of high prevalence of infectious disease in developing countries and that of inflammatory and diverticulitis in developed countries [62].

6. Procedure

Gupta *et al*. (2005) performed Cellan- jones repair in 119 patients out of 162 patients, jejunal patch repair in 5 patients, pyloroplasty in 3 patients, antrectomy and Bilroth II in 1 patient [68]. Leeman *et al*. (2013) also reported Cellan jones repair as the most common surgery performed for perforated peptic ulcer disease [69]. For ileal perforations most common procedure done in our study was stoma formation in almost 90 percent case, primary repair of the ileal perforation was done in 10% patients when the intraperitoneal contamination was minimal and period of presentation was less than 24 hours, similar in cases of traumatic perforations. In patients with late presentation resulting in contamination of peritoneal cavity, low BMI and malnutrition, ileostomy is more preferred surgical procedure when compared with primary repair [70]. Other procedures limited ileo-caecal resection with ileostomy, appendectomy, colostomy, right hemicolectomy, and cholecystectomy was performed as per indication.

7. Duration of hospital stay

In our study mean duration of stay was 8.99 days, maximum duration of stay was 40 days and minimum 1 day. 49 patients (21.87%) were admitted to ICU postoperatively because of inability to extubate, non-maintenance of saturation leading to ventilatory support, need of intensive monitoring of vitals and bad chest condition. Khan et al (2016) evaluated 110 cases over a period of 2 years and reported 7.85 days of mean duration of hospital stay ranging from 3- 40 days. [71] Postoperative complications requiring re-exploration like leak at primary repair site, retraction of stoma or gangrene of stoma, burst abdomen and major respiratory complications and cardiac events increase the duration of stay while minimum stay of 1 day was attributed to death of the patient within 1 day of surgery.

8. Mortality

Overall mortality rate in our study was 12.8% i.e. 32 patients, which is similar to the mortality rate of 6- 36% in various studies on secondary peritonitis in Asia and developed world. Jhobta *et al*. (2006) [62] reported overall mortality of 10% in 504 cases, similar results were obtained by Memon *et al*. (2012) [72] where overall mortality was 16.7%.

CONCLUSION

Perforation peritonitis is associated with 12.8% mortality. Most common site for perforation peritonitis is duodenal perforation (36.4%) followed by gastric (33.2%), Ileal perforation (12.8%) and Jejunal perforation: 16 patients (6.4%). Initial lactate, postoperative (24 hours) lactate are significant variables for mortality with critical values up to 3.78 mmol/L and 3.67 mmol/L respectively. Initial lactate, postoperative (24 hours) lactate values up to 2.29 mmol/L and 1.45 mmol/L respectively were reported in case of survivors. The lactate value of more than 2.5 mmol/L ascertained to have 64 % mortality. Initial pH, postoperative (24 hours) pH are significant variables for mortality with critical value of 7.16 and 7.17 respectively. Initial pH, postoperative (24 hours) pH value of 7.36 and 7.38 respectively were reported in case of survivors. Procalcitonin values of more than 2.58 ng/ml (normal range 0.01-0.05 ng/ml) ascertained to have 56.25 % mortality. Other than the variables mentioned above ASA grade is independent variables for mortality. Gender, sex, BMI, site of perforation, procedure performed, and duration of hospital stay are not significant factors for mortality.

ACKNOWLEDGEMENTS

The author would like to express their sincerest gratitude to the Professor U.K.Chandel for mentoring and supervision throughout the research work.

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