ANALYSIS OF DRAIN FLUID FOR PRESENCE OF PROCALCITONIN AND C-REACTIVE PROTEIN AS EARLY MARKERS OF INTESTINAL ANASTOMOTIC LEAKAGE

Submitted by

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B. L. D. E. ((Deemed to be University)

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In partial fulfilment of the requirements for the degree of

MASTER OF SURGERY

In

GENERAL SURGERY

UNDER THE GUIDENCE OF

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2018

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I hereby declare that this dissertation "**ANALYSIS OF DRAIN FLUID FOR PRESENCE OF PROCALCITONIN AND C-REACTIVE PROTEIN AS EARLY MARKERS OF INTESTINAL ANASTOMOTIC LEAKAGE"** is a bonafide and genuine research work carried out by me under the guidance of **DR. TEJASWINI VALLABHA,** Professor & HOD, Department of general surgery at BLDE (Deemed to be university) Shri B. M. Patil Medical College Hospital and Research Centre, Vijayapur.

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DR. PRADEEP JAJU

ABSTRACT

Introduction

Anastomotic leakage is an important complications causing significant mortality and morbidity in intestinal anastomosis. The diagnosis of anastomotic leak (AL) is difficult as many of the investigations are not specific and clinical presentation is usually late.

C-Reactive Protein (CRP) is an acute phase protein displaying rapid and pronounced rise of its serum concentration in response to infection and inflammation. Procalcitonin is one such biomarker present in fluid around the anastomosis draining through drain site can give rapid and objective diagnosis for detection of anastomotic leakage before its clinical presentation.

Aims and objectives

Procalcitonin & C-reactive protein are reliable & sensitive biomarkers of intestinal anastomotic leak in drain fluid.

Materials and Methods

Source of data

All eligible patients admitted at B.L.D.E(Deemed to be University) Shri. B. M. Patil Medical College Hospital& Research Centre, Vijayapur in Surgery Department during the study period. September 2016 to August 2018

Inclusion criteria

- All patients undergoing elective and emergency intestinal anastomosis (small intestinal anastomosis and colorectal anastomosis) were included.

Exclusion criteria

- Patients planned exclusively for ileostomies and colostomies were excluded.

Results

Total 48 cases underwent intestinal anastomosis. Sensitivity and Specificity of C-reactive protein is increasing as Post Operative Day (POD) 3,5,and 7 highest being 85.71% on POD5 and 97.56% on POD 7 respectively. Sensitivity of Procalcitonin is highest and equal to on POD3 and POD 5 i.e 71.43% and low on POD 7 i.e 28.57%, and Specificity of Procalcitonin is increasing as POD3,5 and 7 highest being 97.56% on POD 7.

Conclusion

Evaluation of C-reactive protein and Procalticonin in drain fluid on Pod3,5 and 7 were found to be associated with higher than normal values in anastomotic leakage patients. Positive predictive value of CRP is 83.33% on POD7. Negative predictive value of CRP is 95.24% on POD7.Accuracy of CRP is 93.75% on POD7 Positive predictive value of PCT is 66.67% on POD7 Negative predictive value of PCT is 94.74% on POD5 Accuracy of PCT is 87.50% on POD7.

Conservative management with good nutritional support helps in management of patients with anastomotic leaks. As in this study out of 7 patients with anastomotic leaks 5 were managed conservatively and 2 had to undergo relaparotomy.

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INTRODUCTION

Over the last 3 decades, surgical outcome of the patients with colorectal diseases and intestinal anastomosis has significantly improved. Despite improvement of surgical techniques, perioperative preparation, colorectal surgery is associated with 5% mortality rate and a morbidity of 20-40%.[1]

Anastomotic leakage is an important complication causing significant morbidity and mortality . Its incidence varies from 0-1.4% for right colonic surgeries and 8-24 % for low anterior resections. The diagnosis of anastomotic leakage (AL) is difficult as many of the investigations are non specific and clinical presentation is usually late. [1]

AL occurs within 7 days after surgery and delay in diagnosis can result in generalized peritonitis. The test to diagnose anastomotic leakage at early stage before it becomes clinically evident will allow early intervention and decrease morbidity and mortality.[2] Serum inflammatory markers like C - reactive protein (CRP), if elevated are not specific. Inflammatory mediators are present in peritoneal fluid in the vicinity of anastomosis. The levels of peritoneal fluid cytokines are much higher than in serum and may thus predict anastomotic leakage.[3,4]

Current diagnostic methods include observation of clinical features while confirmation is obtained by imaging. Clinical features, serum CRP and Leucocytosis are non-specific and are also increased in postoperative urinary tract infection and wound infections. By the time clinical signs are evident, patient is already ill and needs CT scan or contrast x rays for confirmation. It may take 8 days to 2 weeks for diagnosis. Such long intervals increase the mortality rate.[5] An objective laboratory test helps to decrease this interval and make an early diagnosis.

Procalcitonin is one such biomarker present in fluid around the anastomosis coming through drain site can give rapid and objective diagnosis for detection of anastomotic leakage before its clinical presentation. Such biomarker can be found in fluid obtained from intra-abdominal drains. Prophylactic drainage is often applied to prevent accumulation of blood and serum in the pelvic/peritoneal cavity and to allow faecal and purulent discharge to be drained out. Many studies have attempted to analyse the drain fluid in a more objective and sophisticated manner which can give information and assist in early diagnosis.[6-12]

CRP is an acute phase protein displaying rapid and pronounced rise of its serum concentration in response to infection and inflammation.[13] Procalcitonin (PCT) is a potential marker of acute inflammation released from different parenchymal tissues and differentiated cell types throughout body in response to serum interleukins increased in bacterial infections.[14, 15]

Procalcitonin (PCT) , a protein that consists of 116 aminoacids ,is the precursor of calcitonin which is synthesised by parafollicular cells of thyroid and involved in calcium homeostasis. PCT is also produced by neuroendocrine cells of lung and intestine and is released in response to inflammation ,especially those of bacterial origin. Procalcitonin released as an acute phase reactant does not result in its increased serum level. [16]

Several studies suggest that procalcitonin may be involved in metabolism of calcium, cytokine network and modulation of nitric oxide synthesis. Enzymes in plasma do not break down PCT. Its half life in plasma is 30hrs. In patients with sepsis, higher PCT levels are associated with greater risk of progression to severe sepsis and septic shock, worsening the prognosis. [17]

Techniques in anastomosis have no bearing on healing in general.[17] PCT and CRP have good negative predictor value of AL in 3rd ,5th and 7th postoperative days. Value of PCT and CRP were found to be high in drain fluid analysis suggesting AL.[18]

Colorectal Anastomotic Leak remains a poorly understood complication of colorectal surgery. Incidence of CAL is between 2.4 to 19% and mortality rate due to sepsis and multi organ failure is around 15%. With current screening and diagnostic methods the interval between construction of colorectal anastomosis and diagnosis of leakages varies between 6 and 13 days. Several studies have suggested that delay of diagnosis of CAL is associated with higher mortality rates. Early detection and management improves clinical outcome. A biomarker reflecting the local inflammation around the anastomosis is considered be an objective screening tool for AL in early phase.[19]

PCT and CRP can also increase in the drain fluid of small intestine resection and anastomosis. There are not many studies regarding analysis of drain fluid for biomarkers in small intestinal anastomosis.

In the above context, there is need for study of early detection of anastomotic leakage. In this study, we attempted to diagnose AL by using drain fluid biomarkers.

AIMS AND OBJECTIVE OF THE STUDY

To evaluate Procalcitonin & C-reactive protein are reliable & sensitive biomarkers of intestinal anastomotic leak in drain fluid.

RESEARCH HYPOTHESIS

Procalcitonin and C reactive protein are sensitive and reliable diagnostic tools in early diagnosis of anastomotic leak.

REVIEW OF LITERATUTE

HISTORICAL BACKGROUND

Only 90 cases of bowel anastomosis were reported before 1982. In the same period several suture techniques were described as the results were conflicting there was need for study in the field for the help of the patients, as a result of which many surgeons came with concepts of sutures, suture over prosthesis, suture materials and buttons.[20,21]

In 1893 Nicholas Senn from Chicago reviewed 60 different techniques for suturing intestine. He described them in the book "Ancient and Modern Methods". Among these only few were continued in the clinical practice. [22]

In 1895 R. Von Frey came with few more new techniques of intestinal anastomosis which showed the scope of further improvement in the clinical practice. [23]

Nowadays the high risk life threatening procedures are being turned in to safe procedures by improvising over the years in the intestinal anastomosis. Present techniques are made out of experimental operations and emerging of other medical branches. Present gastrointestinal anastomosis are outcome of production of fine suture materials, revising surgical principles and early surgical treatment for bowel disease. [24,25]

At the end of 19th century terminology for intestinal anastomosis was accepted in the surgical society. Terms evolved like circular bowel suture, bowel suture, anastomosis, anus praetornaturalis, bowel fistula. In the abdominal penetrating injuries, complete bowel lacerations were in majority. Those were sutured in simple bowel sutures.

Edward Albert (1897) discussed the terms Gastrorrhaphy, enterorrhaphy and etc. in his own article operations in the gastrointestinal tract.[26]

Circular bowel suture is called when two ends of bowel were sutured end to end fashion. Advantage of this is it completely restores the intestinal continuity after either resection of part of intestine or complete bowel transection. Bowel anastomosis was defined as surgical connection of bowel which are not in anatomical continuity. Gastroenterostomy was termed if there was an bypass of any intestinal obstruction.[23,26]

Bowel fistula in late 19th century was called as connection between two segments of bowel which are not surgically attached to each other. Phillipp Theophrast et al gave the term Anus Praeternaturalis for enterocutaneous fistula which was the common complication following penetrating abdomen injury or secondary to drainage of intraabdominal abscess. Later E. Albert replaced this by Greek term stoma (mouth opening). Many patients died during an operation of intestinal anastomosis in the ancient times. Main cause of death was due to shock, pain as there was no discovery of anasthesia and lack of knowledge in the techniques of anastomosis due to less animal studies. [26]

Significance of intestinal sutures and importance of suturing abdominal wall in layers for any bowel injury was shown by Giovanni de Vigo.[27]

Alexis Baron Boyer suggested few general measures like diet, laxatives should be added to treatment of bowel lacerations. [21] Significance of joining serosal surfaces was stressed in 1880 by French anatomist Marie-Franc and Lembert came up with the surgical technique of serosal approximantion in bowel anastomosis. [23]

In 1881, Ludwig R retrospectively studies all the reported cases of bowel anastomosis and came to conclusion that Lembert serosal apposition technique was not sufficient for bowel anastomosis. [20]

In 1887 William Stewart Halsted came to a conclusion by his animal experiment that sub mucosa gave sufficient mechanical strength for bowel sutures , and this conclusion brought an concept of single layer intestinal suture technique for bowel anastomosis. [28] Vitezslav C studied mechanical characteristics of bowel anastomosis. With his animal studies he came to conclusion that strength of bowel anastomosis was least during first 3 days post surgery and it gradually increases from 5th post operative day onwards and reaches the normal value by the end of 2nd week post surgery. [29]

CONCEPTS OF BASIC PRINCIPLES OF INTESTINAL ANASTOMOSIS

HEALING OF ANASTOMOSIS:

There is well balance between the rate of collagen synthesis and lysis in the wound healing and as well as integrity, strength and patency of intestinal anastomosis. [30]

In the initial 4 days after surgery it has been observed that rate of degradation of mature collagen is much higher than synthesis. About 60% strength is attained after 3/ 4 days. Collagen deposition predominates after 5 days and it gets peak on 7th POD. Full 100% strength is obtained after 1 week and remodelling of anastomosis occurs after 5 to 6weeks. [31]

HEALING FACTORS:

Factors affecting healing are vascular supply, tissue oxygenation, tissue tension and location of anastomosis. Patient factors like underling disease, nutritional status, immune status, are also important in healing of intestinal anastomosis. Adequate

blood supply provides fibroblasts, platelets and macrophages to the anastomosis to help in degradation and remodelling. Stomach and small bowel heal rapidly as they have rich blood supply. [32,33]

Hypovolemia, anaemia, low cardiac output, sustained postoperative hypotention, exposure to radiation, tension on the anastomosis and extensive mesenteric dissection are all factors for causing impairment in blood flow to the anastomotic site.Diseases like diabetes affect microvasculature of the bowel and which in turn cause poor healing. Location of anastomosis may increase the risk of poor healing. Low rectal anastomosis has increased chance of dehiscence due to increased tissue tension. Obesity is high risk for anastomotic dehiscence. [30,34]

Patients receiving immunosuppressants, monoclonal antibodies have poor healing of intestinal anastomosis. High dose corticosteroids impair wound healing due to immunosuppressive effect. [35]

Nutrition related factors like low albumin, anaemia, vitamin C deficiency ,zinc deficiency, influence on collagen synthesis and which affect the healing of anastomosis.[36,37] Intraabdominal abscess, underlying infection secondary to peritonitis are again poor prognostic factors of anastomotic healing. [37]

NUTRITION

Preoperative nutrition status of the patient is an important factor responsible for anastomotic dehiscence. Nutrition status is calculated by built of the patient, weight of the patient, serum albumin, serum protein levels, haemoglobin level etc. In malnourished patients, preoperative parenteral nutrition and blood transfusions are

shown to be beneficial. Poor nutrition impairs deposition of collagen and can lead to dehiscence in acute stage or stricture formation in excessive scar tissue. [38]

MECHANICAL BOWEL PREPARATION

Bowel preparation decreases the intraluminal stool load which decreases the soilage which later cause an anastomotic deciscence. In the study by Cochrane concluded that this procedure did not reduce anastomotic dehiscence and cannot be routinely recommended. [39]

ABDOMINAL DRAINS

Abdominal drains have been routinely placed at the anastomotic site to prevent accumulation of serous or bloody fluid, or early identification of anastomotic dehiscence if content is purulent. Basic principle of drains is in the fact that it creates negative pressure on the anastomotic site and absorbs the intra abdominal fluif collection postoperatively. It may also act as an port for entry of microbes and can thereby cause dehiscence. [40-42]

CHEMORADIATION

Patient with large malignant colonic mass or growth usually undergo preoperative chemoradiation to reduce the tumour burden . Chemoradiation can predispose to anastomotic leakage and thus can cause pelvic fibrosis ,following which neorectum will be stiff and non compliant. Following which patient develops tenesmes and fecal incontinence. Therefore many surgeons perform diverting stoma to minimise the complications of anastomotic leak post pelvic radiation. [43-46]

TECHNIQUES OF SUTURES

HAND SEWN TECHNIQUES

For many decades bowel anastomosis were performed by hand sewn techniques with ideal suture material which did not produce any inflammation., which retained strength throughout healing process, which had minimal tissue reaction and minimal attraction to bacteria. Suitable suture materials included silk, polypropylene, polyglycolic acid, catgut and poludioxane. silk was proved to show more tissue reaction, polydiaxone in one study showed least attractive to bacteria common flora of bowel such as Ecoli and Staphylococcus Aureus. [47,48]

Two layer bowel anastomosis is done , inner layer with continuous absorbable sutures and outer layer with interrupted non absorbable sutures. Alternatively single layer suture technique with non absorbable suture is done. [49]

STAPLED TECHNIQUES

In the 1970 surgeons started using intestinal staplers where initially they were able to divide tissues and later used for approximation of intestines.[50]

There are 3 main types of staplers

1. Transverse staplers
2. Linear stapling
3. End to end circular staplers

These devises are available in different depths for different intestinal thickness and as per the size of anastomosis.

COMPARISON OF HAND SEWN AND STAPLED TECHNIQUES

Stapling devices bring the intestinal walls in an everted fashion, while in hand sewn anastomosis the bowel wall is inverted.it was thought before that staplers cause more ischemia of tissues and has higher dehiscence rate. Staplers are been used increasingly because it has many advantages such as speed, minimal tissue reaction and standardisation of technique. [51]

In a randomised prospective study trial compared hand sewn techniques with circular stapled technique for colorectal anastomosis it was found that dehiscence rate was significantly higher in hand sewn group as compared with stapled group (14% verses 6%).[52]

SUTURELESS ANASTOMOSIS TECHNIQUES

These techniques are designed to create compression anastomosis by approximating loops of bowel without suture or staple. The results are promising and are comparable with hand sewn technique. [53-55]

BIOMARKERS IN PERITONEAL FLUID

IMMUNE PARAMETERS IN PERITONEAL FLUID

In the surgical trauma and infection cytokines such as interleukin (IL)-1,5,10 and tumour necrosis factor(TNF-a) are polypeptides that mediate systemic changes such as fever, neutrophilia, increased acute phase protein synthesis.[56]

In the few hours after surgery levels of cytokines are elevated in peritoneal fluid as a part of postoperative inflammatory response. [57]

If the postoperative period is uncomplicated then the cytokine levels in the peritoneal fluid will start to decrease within 24hrs. [57,58] In complications such as AL occur then there will be increase in IL-6 and TNF-a levels as early first postoperative day. [59]

It was observed that levels of IL-1 was significantly raised on POD-3 in patients with anastomotic leak. [59]

As a result of these observations it is suggested that monitoring of peritoneal cytokines could be important predictive marker for early diagnosis of postoperative complications. [60]

TISSUE PARAMETERS

Zinc dependent endopeptidases such as matrix metalloproteinases (MMP) which regulate the integrity and composition of extracellular matrix(ECM) in both pathological and physiological processes. [61]

In peritoneal fluid both active and inactive forms can be determined. The wound repair and tissue regeneration depends on balance between proteolysis by MMPs and their inhibitors like protein synthesis and tissue inhibitors of MMPs.[61]

Important targets of MMPs are the type I and type III collagen genes which are normally overexpressed at the anastomotic site. [62]

These studies can conclude that levels of MMPs in tissue or peritoneal fluid could serve as biomarker for AL.[19]

PARAMETERS FOR ISCHAEMIA

In the areas of anastomosis there is conversion of aerobic metabolism to anaerobic metabolism which leads to increased levels of lactate levels and increased carbon dioxide accumulation and decrease in pH. Decreased blood supply at the anastomotic site causes decrease glucose levels. These changes causes cell damage with breakdown of membranes and release of membrane phospholipids. [63]

Estimation of glucose, lactate, and glycerol in peritoneal fluid by microdialysis and indirectly by analysis of the diasylate. Diasylate will be equililibrium with the peritoneal fluid surrounding the drain, so the values corresponds to the levels of peritoneal fluid. The diasylate will correspond to levels of the peritoneal fluid. [64]

MICROBIOLOGICAL PARAMETERS

Microorganisms get colonised in the abdominal cavity due to contamination of peritoneal cavity either by intra-abdominal abscess or spillage of intestinal contents. Normally it will be removed by immune system and postoperatively there will be no complications. [19]

Intraperitoneal bacterial load is assessed both qualitatively and quantitatively to early diagnose AL. Lipopolysaccharides (LPS) were determines in peritoneal fluid as they form the outer wall of gram negative bacteria that are abundantly found in gut flora. [65]

Even analysis of pH,pCO2 and pO2 in the drainaige fluid shows early detection of infectious complications after surgery as early as POD4. [66]

ROLE OF ESTIMATION OF C-REACTIVE PROTEIN IN PERITONEAL FLUID

In some studies it is shown that the elevated c-reactive protein (CRP) in the postoperative period may predict an increased chance of postoperative infection and AL. [67]

As CRP begins to increase before the appearance of clinical signs as fever,tachycardia and pain it becomes the ideal predictor of postoperative infective complications. [68]

Peritoneal fluid is the filtrate of plasma and it is in equilibrium with serum.so the assumption is that values of CRP in drainaige fluid reflect values obtained in serum. [69]

CRP is produced by hepatocytes as a part of acute phase response upon stimulation by IL-6,TNF-a originating at the site of inflammation. It is a pentameric protein with

various molecular formations. Within 6hrs after stimulations, CRP levels exceed normal values and attain peaks about 48hr.CRP has a constant half-life of about 19hrs.[70]

In one study group of patients with AL ,high CRP persisted on POD 1,3,7. All the patients with CRP values in drainaige fluid above 108mg/dl on the POD5 and 93mg/dl on POD7 had AL. However as a non selective marker of inflammation and is not a completely reliable indicator of infection, CRP could be taken in to consideration only within clinical presentation. [71]

ROLE OF ESTIMATION OF PROCALCITONIN IN PERITONEAL FLUID

Procalcitonin (PCT) is produced primarily in neuroendocrine C cells of the thyroid. However PCT is shown to be released from different parenchymal tissues and other differentiated cell types throughout the body in presence of any bacterial infection. Serum levels of PCT has been suggested to be sensitive indicator of ongoing sepsis. [72]

In drain fluid significant difference was seen among patients with anastomotic leaks and patients without leak on POD 5 and POD 3. [72]

Procalcitonin works as a proharmone of calcitonin under normal metabolic conditions, its levels in the circulation are very low(0.05ng/ml). PCT increases fast in 2-3 hrs following infection and may rise 700ng/ml in severe sepsis and septic shock. [73]

When compared with CRP, PCT levels do not rise following inflammation of non infectious origin.PCT level rises before any clinical signs appear, therefore it is an ideal tool for early diagnosis of AL. [73]

MATERIALS AND METHODS:

SOURCE OF DATA:

All eligible patients admitted at B.L.D.E.(Deemed to be University) Shri. B. M. Patil Medical College Hospital& Research Centre, Vijayapur in Surgery Department during the study period. September 2016 to August 2018

SAMPLE SIZE

- As per the records of B.L.D.E (Deemed to be University) Hospital, Vijayapur, with 95% confidence level, anticipated prevalence of AL among all laparotomy patients as 20% and desired precision as ± 10%.the ,minimal sample size is 48 with finite population correction.
- The formula used

$$n = \frac{z2\ p(1-p)}{d^2}$$

where

z =z statistic at 5% level of significance

d is margin of error

p is expected prevalance rate.

STATISTICAL ANALYSIS

All characteristics were summarized descriptively. For continuous variables, the summary statistics of mean ± standard deviation (SD) were used. Chi-square (χ^2) test was used for association between two variables by following formula:

The formula for the chi-square statistic used in the chi square test is:

$$\chi_c^2 = \sum \frac{(O_i - E_i)^2}{E_i}$$

The subscript "c" are the degrees of freedom. "O" is observed value and E is expected value.

C= (number of rows-1)* (number of columns-1)

In cases of more than 30% cell frequency <5, Freeman-Halton Fisher exact test was employed to determine the significance of differences between groups for categorical data. The difference of the means of analysis variables between two independent groups was tested by unpaired t test.

The t statistic to test whether the means are different can be calculated as follows:

$$t = \frac{(\overline{x_1} - \overline{x_2}) - (\mu_1 - \mu_2)}{\sqrt{\frac{{s_1}^2}{n_1} + \frac{{s_2}^2}{n_2}}}$$

where $\bar{x}_1$ = mean of sample 1

$\bar{x}_2$ = mean of sample 2

n_1 = number of subjects in sample 1

n_2 = number of subjects in sample 2

$$s_1^2 = \text{variance of sample 1} = \frac{\Sigma(x_1 - \bar{x}_1)^2}{n_1}$$

$$s_2^2 = \text{variance of sample 2} = \frac{\Sigma(x_2 - \bar{x}_2)^2}{n_2}$$

Sensitivity- specificity was calculated to check relative efficiency.

sensitivity or true positive rate (TPR)

eqv. with hit rate, recall

$$TPR = TP/P = TP/(TP + FN)$$

specificity (SPC) or true negative rate

$$SPC = TN/N = TN/(FP + TN)$$

precision or positive predictive value (PPV)

$$PPV = TP/(TP + FP)$$

negative predictive value (NPV)

$$NPV = TN/(TN + FN)$$

If the p-value was < 0.05, then the results were considered to be statistically significant otherwise it was considered as not statistically significant. Data were analyzed using SPSS software v.23.0. and Microsoft office 2007.

INCLUSION CRITERIA

- All patients who underwent elective and emergency intestinal anastomosis (small intestinal anastomosis ,and colorectal anastomosis) were included.

EXCLUSION CRITERIA

- Patients who undergo exclusively ileostomies and colostomies were excluded.

METHOD OF COLLECTION OF DATA

The source of data were patients who were admitted in department of surgery of B.L.D.E.(Deemed to be University) Shri. B.M. Patil Medical College, Hospital and Research Center, Vijayapur, and underwent intestinal anastomoses.

Study period was SEPTEMBER 2016 – AUGUST 2018

Patients with clinical features of pain abdomen were evaluated

- History of patients were noted and detailed examination of the patient was done.
- Patients who underwent small intestinal anastomosis , colonic anastomosis, sigmoid resection, high anterior resection, low anterior resection & subtotal colectomy with ileorectal anastomosis were included.
- All patients received preoperative antibiotic prophylaxis & intra abdominal drain postoperatively and antibiotic therapy as per need. To obtain the drain fluid a drain was kept at the anastomotic site & was left in place during the first 7 post operative days.
- Drain fluid reservoirs were emptied 2 times a day with 12 hours interval, respecting the rules of sterility. The evening collection was disposed off, the morning collection was sent to the analysis for CRP and PCT. On the post operative day 3,5 and 7.
- Instrument used was mini VIDAS BLU for testing sample
- Technique – CLIA (Chemiluminesence Immunofluroscent Assay) .

RESULTS

48 patients with intestinal anastomosis were evaluated with estimation of Procaltitonin and C-reactive protein in drain fluid on POD3, POD-5 and POD-7 in Department of Surgery in BLDE(Deemed to be University) Shri. B. M. Patil Medical College, Hospital and Research Centre, Vijayapura. Period of study was from October 2016- March 2018.

Following factors were observed and tabulated as follows:

TABLE 1: DISTRIBUTION OF PATIENTS ACCORDING TO AGE

AGE(YRS)	N	%
21-30	10	20.8
31-40	9	18.8
41-50	10	20.8
51-60	12	25
>60	7	14.6
Total	48	100

FIGURE 1: DISTRIBUTION OF PATIENTS ACCORDING TO AGE

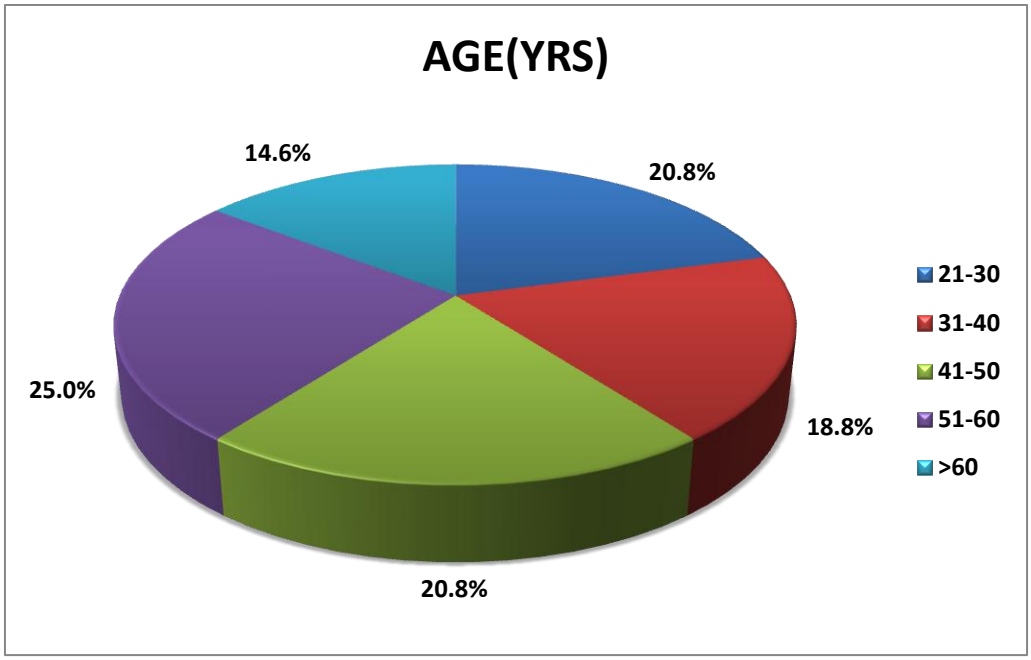

Figure 1 and Table 1 shows the distribution of patients according to age, Maximum number of cases fell in age group of 51-60 ie around 12 cases, followed by 41-50 yrs and 21-30 yrs age group ie 10 cases each . And 9 cases were in age group of 31-40 , 7 cases were >60yrs age.

TABLE 2: DISTRIBUTION OF PATIENTS ACCORDING TO GENDER

SEX	N	%
Male	37	77.1
Female	11	22.9
Total	48	100

FIGURE 2:DISTRIBUTION OF PATIENTS ACCORDING TO GENDER

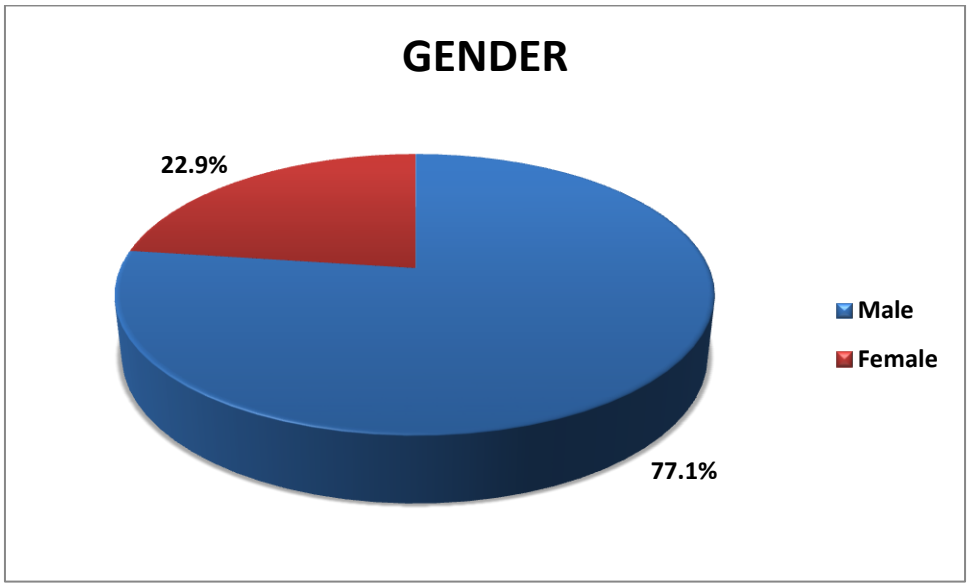

Table 2 and figure 2 shows the distribution of patients according to gender ie , In 48 cases 37 cases were male and 11 were female.

TABLE 3: ASSOCIATION OF AGE AND SEX

AGE(YRS)	Male		Female		p value
	N	%	N	%	
21-30	9	24.3	1	9.1	0.117
31-40	6	16.2	3	27.3	
41-50	5	13.5	5	45.5	
51-60	11	29.7	1	9.1	
>60	6	16.2	1	9.1	
Total	37	100.0	11	100.0	

FIGURE 3: ASSOCIATION OF AGE AND SEX

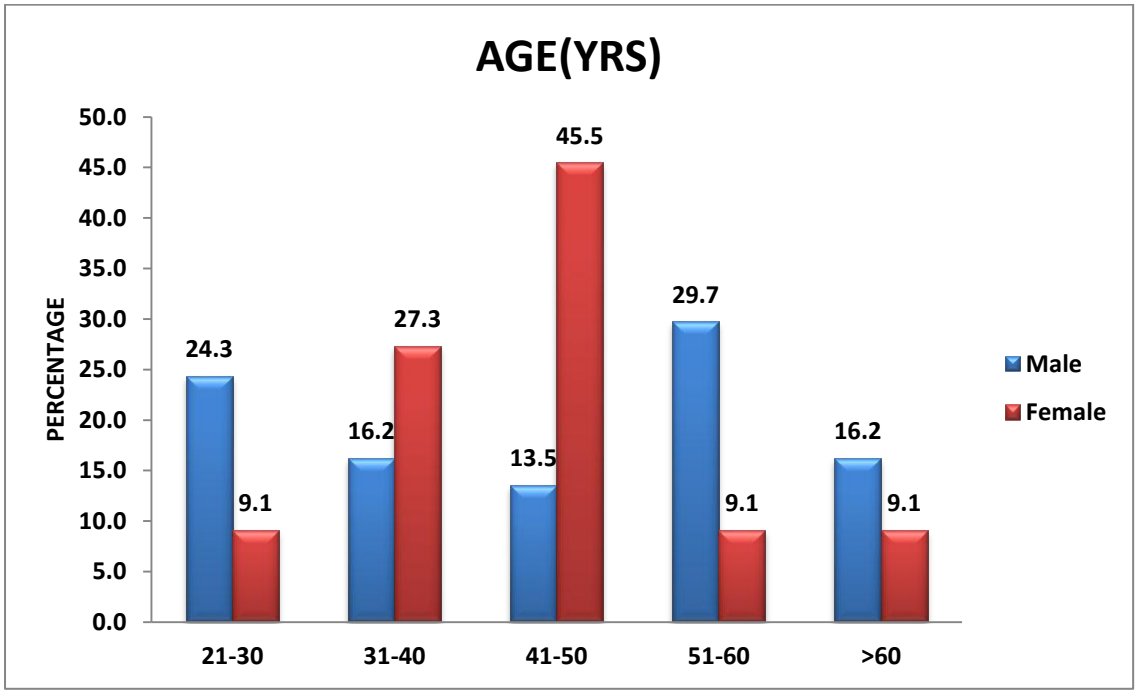

Chart 3 and figure 3 describes the association of age and sex ie, in the age group of 41-50 female were in higher percentage (45.5%) than males(13.5%) and with respect of 51-60 yrs age group highest percentage of males(29.7) than females (9.1%)

TABLE 4: DISTRIBUTION OF CASES ACCORDING TO ANASTOMOTIC LEAK

ANASTOMOTIC LEAK	N	%
NO	41	85.4
YES	7	14.6
Total	48	100

FIGURE 4: DISTRIBUTION OF CASES ACCORDING TO ANASTOMOTIC LEAK

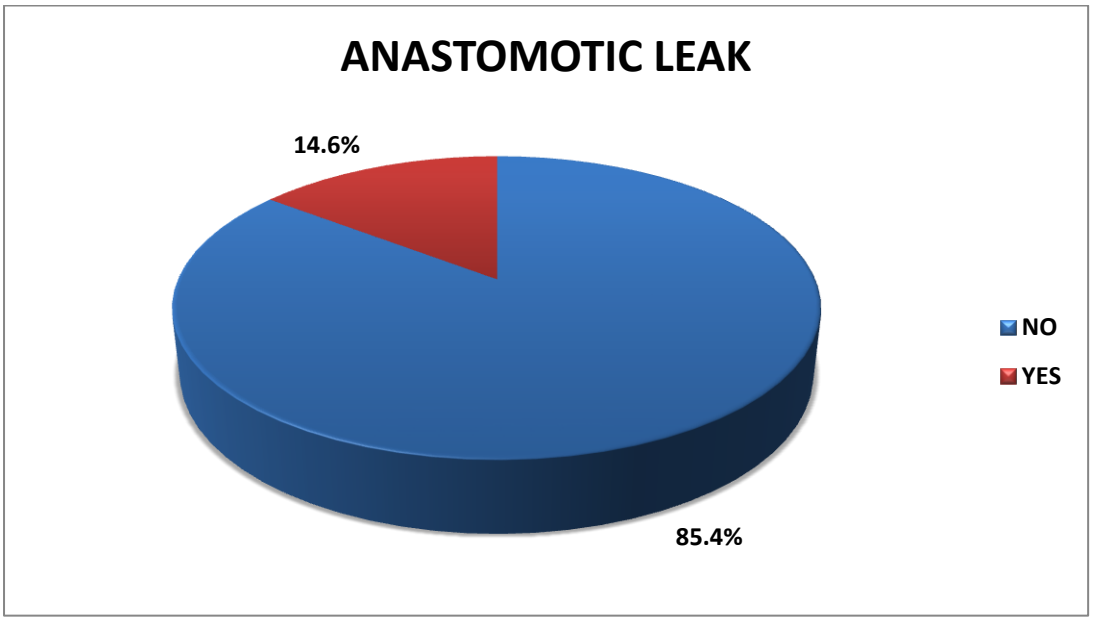

Table 4 and figure 4 shows distribution of cases according to anastomotic leak, out of 48 cases 41 cases had no anastomotic leak whereas 7 cases had anastomotic leak.

TABLE 5: DISTRIBUTION OF CASES ACCORDING TO MANAGEMENT

MANAGEMENT	N	%
CONSERVATIVE MANAGEMENT	5	71.4
SURGICAL MANAGEMENT	2	28.6
Total	7	100.0

FIGURE 5: DISTRIBUTION OF CASES ACCORDING TO MANAGEMENT

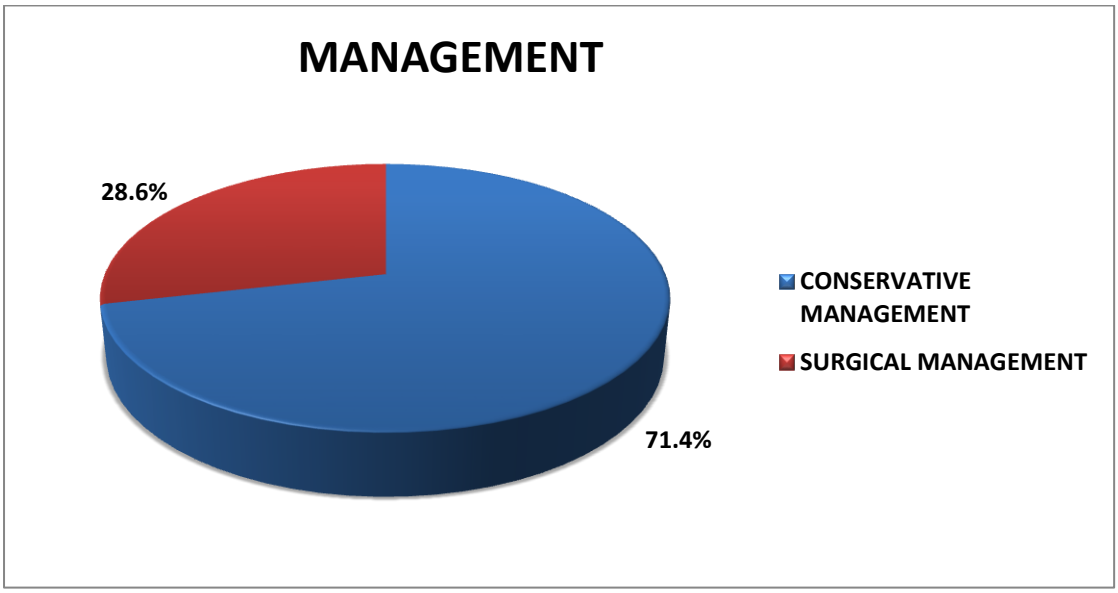

Table 5 and figure 5 shows distribution of cases according to management . in this study out of 7 anastomotic leaks 5 cases were managed conservatively where as 2 had to undergo surgery.

TABLE 6: MEAN C-REACTIVE PROTEIN ACCORDING TO ANASTOMOTIC LEAK

C-REACTIVE PROTEIN	ANASTOMOTIC LEAK				p value
	YES		NO		
	Mean	SD	Mean	SD	
POD-3	2.66	2.77	1.08	0.40	0.001*
POD-5	2.84	2.77	0.84	0.48	<0.001*
POD-7	2.83	3.06	0.59	0.31	<0.001*

Note: * significant at 5% level of significance (p<0.05)

FIGURE 6: MEAN C-REACTIVE PROTEIN ACCORDING TO ANASTOMOTIC LEAK

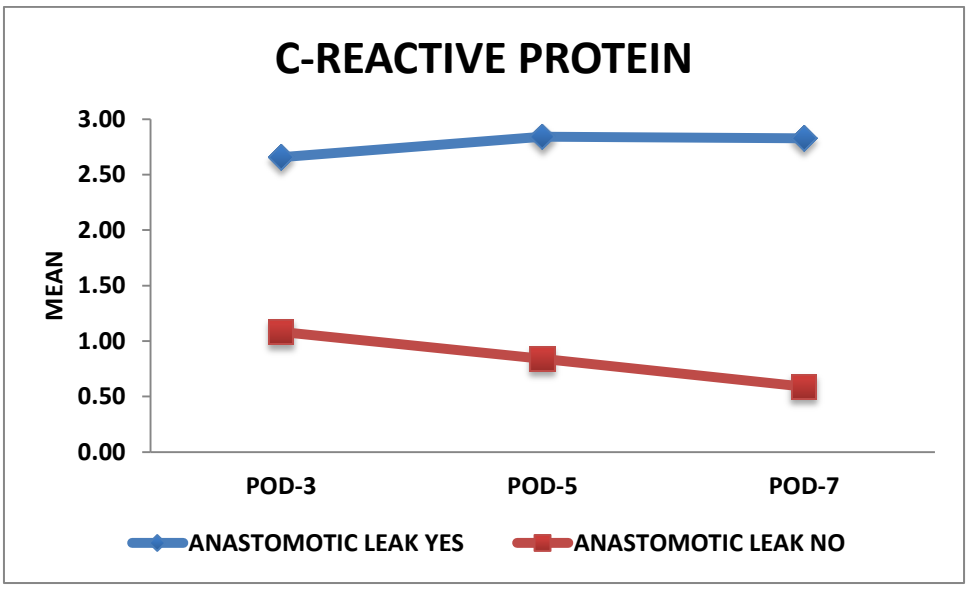

Table 6 and figure 6 shows mean c-reactive protein according to anastomotic leak, in the cases with no anastomotic leak mean CRP levels at POD-3,5,7 were 1.08,0.84.0.59 whereas mean value of CRP in anastomotic leak cases were higher i.e POD-3,5,7 were 2.66,2.84 and 2.83 with significant p value.

TABLE 7: MEAN PROCALCITONIN ACCORDING TO ANASTOMOTIC LEAK

PROCALCITONIN	ANASTOMOTIC LEAK				p value
	YES		NO		
	Mean	SD	Mean	SD	
POD-3	3.19	2.95	1.17	0.61	<0.001*
POD-5	1.62	0.65	0.98	0.61	0.015*
POD-7	1.07	0.79	0.67	0.41	0.046*

Note: * significant at 5% level of significance (p<0.05)

FIGURE 7: MEAN PROCALCITONIN ACCORDING TO ANASTOMOTIC LEAK

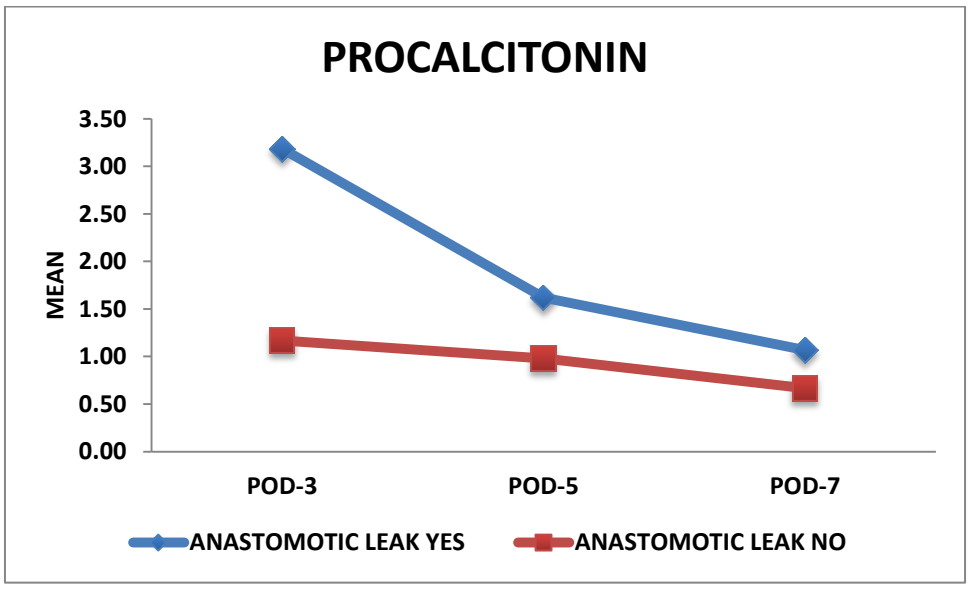

Table 7 and figure 7 shows mean Procalcitonin levels according to anastomotic leak. In the cases with no anastomotic leak mean PCT levels at POD-3,5,7 were 1.17,0.98.0.67 whereas mean value of PCT in patients with anastomotic leak were higher i.e POD-3,5,7 were 3.19,1.62 and 1.07 with significant p value.

TABLE 8: DIAGNOSTIC EFFICACY OF C-REACTIVE PROTEIN

C-REACTIVE PROTEIN	POD-3	POD-5	POD-7
Sensitivity	42.86%	85.71%	71.43%
Specificity	73.17%	82.93%	97.56%
PPV	21.43%	46.15%	83.33%
NPV	88.24%	97.14%	95.24%
Accuracy	68.75%	83.33%	93.75%

FIGURE 8: DIAGNOSTIC EFFICACY OF C-REACTIVE PROTEIN

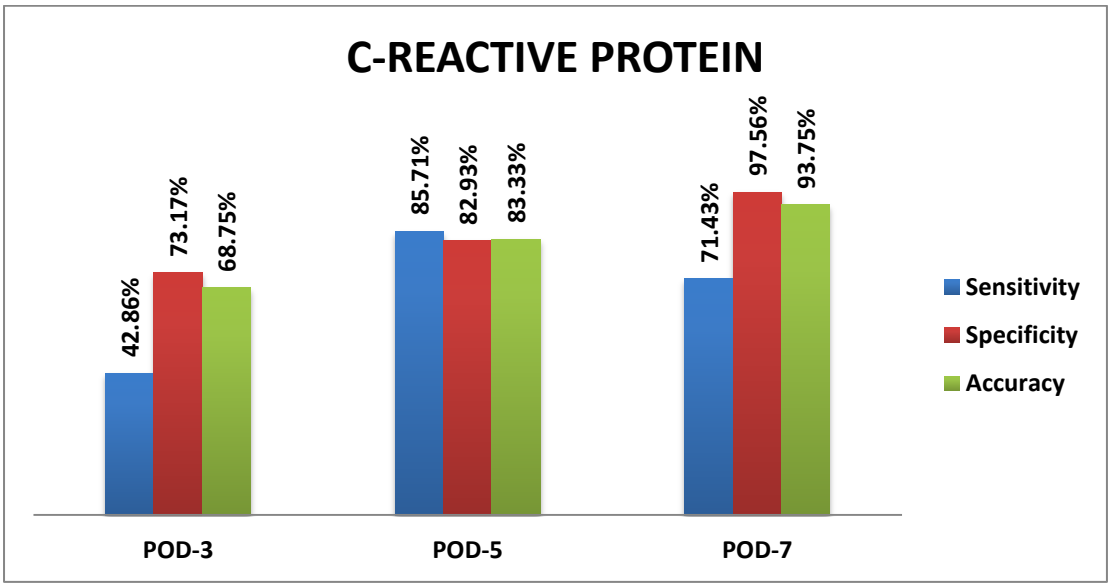

Table 8 and figure 8 shows Specificity, Sensitivity, PPV, NPV and Accuracy of C-reactive protein on POD3, POD-5 and POD7.

TABLE 9: DIAGNOSTIC EFFICACY OF PROCALCITONIN

PROCALCITONIN	POD-3	POD-5	POD-7
Sensitivity	71.43%	71.43%	28.57%
Specificity	73.17%	87.80%	97.56%
PPV	31.25%	50.00%	66.67%
NPV	93.75%	94.74%	88.89%
Accuracy	72.92%	85.42%	87.50%

FIGURE 9: DIAGNOSTIC EFFICACY OF PROCALCITONIN

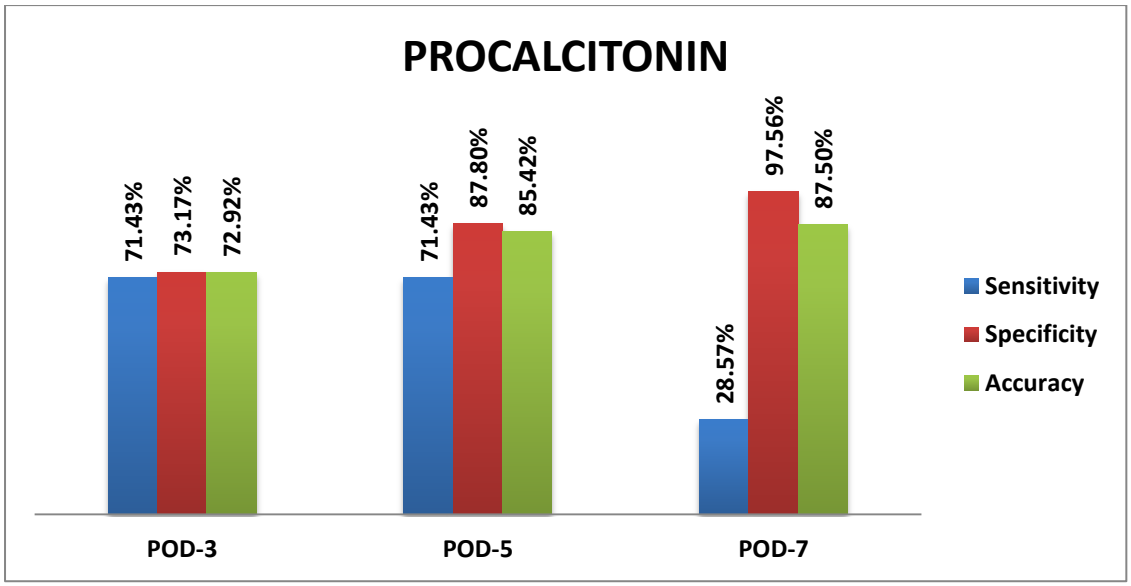

Table 9 and figure 9 shows Specificity, Sensitivity, PPV, NPV and Accuracy of Procalcitonin on POD3,POD-5 and POD7

TABLE 10: C-REACTIVE PROTEIN LEVEL AT POD 3 ACCORDING TO ANASTOMOTIC LEAK

C-REACTIVE PROTEIN AT POD 3	ANASTOMOTIC LEAK				TOTAL		p value
	YES		NO				
	N	%	N	%	N	%	
<1.5	4	57.1	30	73.2	34	70.8	0.389
≥1.5	3	42.9	11	26.8	14	29.2	
Total	7	100.0	41	100.0	48	100.0	

FIGURE 10: C-REACTIVE PROTEIN LEVEL AT POD 3 ACCORDING TO ANASTOMOTIC LEAK

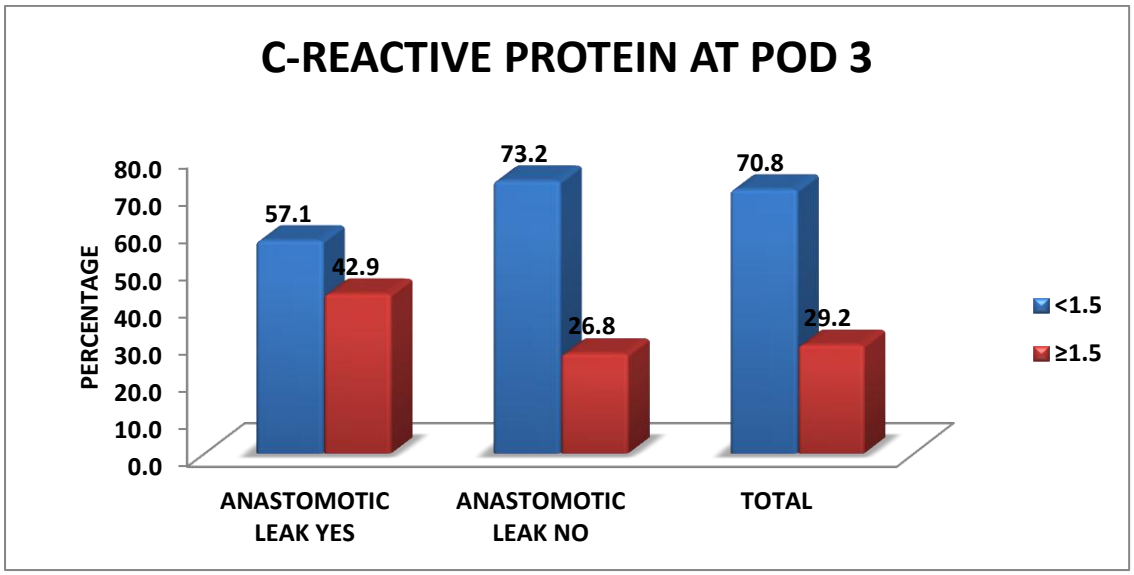

Table 10 and figure 10 shows CRP level at POD-3 according to anastomotic leak. Out of total 48 cases of study 34 cases(30 cases with no anastomotic leak and + 4 cases with anastomotic leak) had CRP value <1.5 , whereas 14 cases (11 cases with no anastomotic leak + 3 cases with anastomotic leak) had CRP levels > 1.5.

TABLE 11: C-REACTIVE PROTEIN LEVEL AT POD 5 ACCORDING TO ANASTOMOTIC LEAK

C-REACTIVE PROTEIN AT POD 5	ANASTOMOTIC LEAK				TOTAL		p value
	YES		NO				
	N	%	N	%	N	%	
<1.5	1	14.3	34	82.9	35	72.9	<0.001*
≥1.5	6	85.7	7	17.1	13	27.1	
Total	7	100.0	41	100.0	48	100.0	

Note: * significant at 5% level of significance (p<0.05)

FIGURE 11: C-REACTIVE PROTEIN LEVEL AT POD 5 ACCORDING TO ANASTOMOTIC LEAK

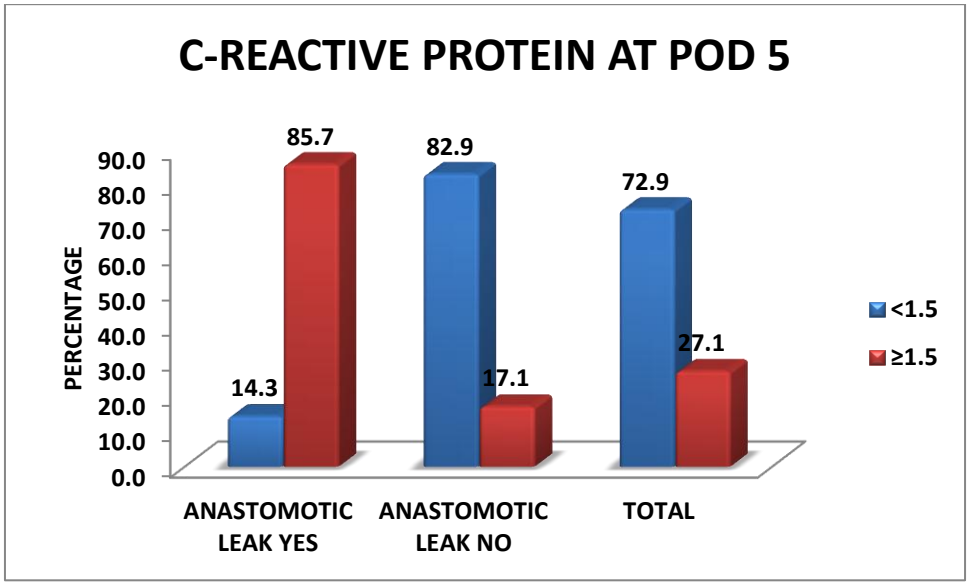

Table 11 and figure 11 shows CRP level at POD-5 according to anastomotic leak. Out of total 48 cases of study 35 cases (34 cases with no anastomotic leak and + 1 cases with anastomotic leak) had CRP value <1.5 , whereas 13 cases (7 cases with no anastomotic leak + 6 cases with anastomotic leak) had CRP levels > 1.5.

TABLE 12: C-REACTIVE PROTEIN LEVEL AT POD 7 ACCORDING TO ANASTOMOTIC LEAK

C-REACTIVE PROTEIN AT POD 7	ANASTOMOTIC LEAK				TOTAL		p value
	YES		NO				
	N	%	N	%	N	%	
<1.5	2	28.6	40	97.6	42	87.5	<0.001*
≥1.5	5	71.4	1	2.4	6	12.5	
Total	7	100.0	41	100.0	48	100.0	

Note: * significant at 5% level of significance (p<0.05)

FIGURE 12: C-REACTIVE PROTEIN LEVEL AT POD 7 ACCORDING TO ANASTOMOTIC LEAK

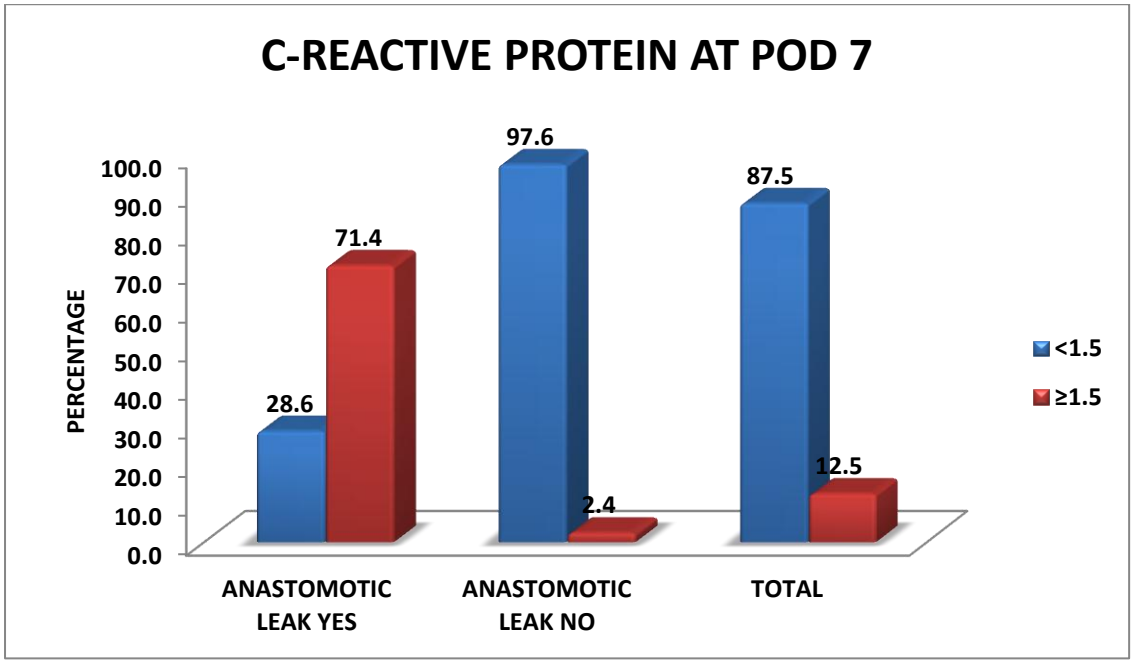

Table 12 and figure 12 shows CRP level at POD-7 according to anastomotic leak. Out of total 48 cases of study 42 cases(40 cases with no anastomotic leak and + 2 cases with anastomotic leak) had CRP value <1.5 , whereas 6 cases (1 case with no anastomotic leak + 5 cases with anastomotic leak) had CRP levels > 1.5.

TABLE 13: PROCALCITONIN LEVEL AT POD 3 ACCORDING TO ANASTOMOTIC LEAK

PROCALCITONIN AT POD 3	ANASTOMOTIC LEAK				TOTAL		p value
	YES		NO				
	N	%	N	%	N	%	
<1.5	2	28.6	30	73.2	32	66.7	0.021*
≥1.5	5	71.4	11	26.8	16	33.3	
Total	7	100.0	41	100.0	48	100.0	

Note: * significant at 5% level of significance (p<0.05)

FIGURE 13: PROCALCITONIN LEVEL AT POD 3 ACCORDING TO ANASTOMOTIC LEAK

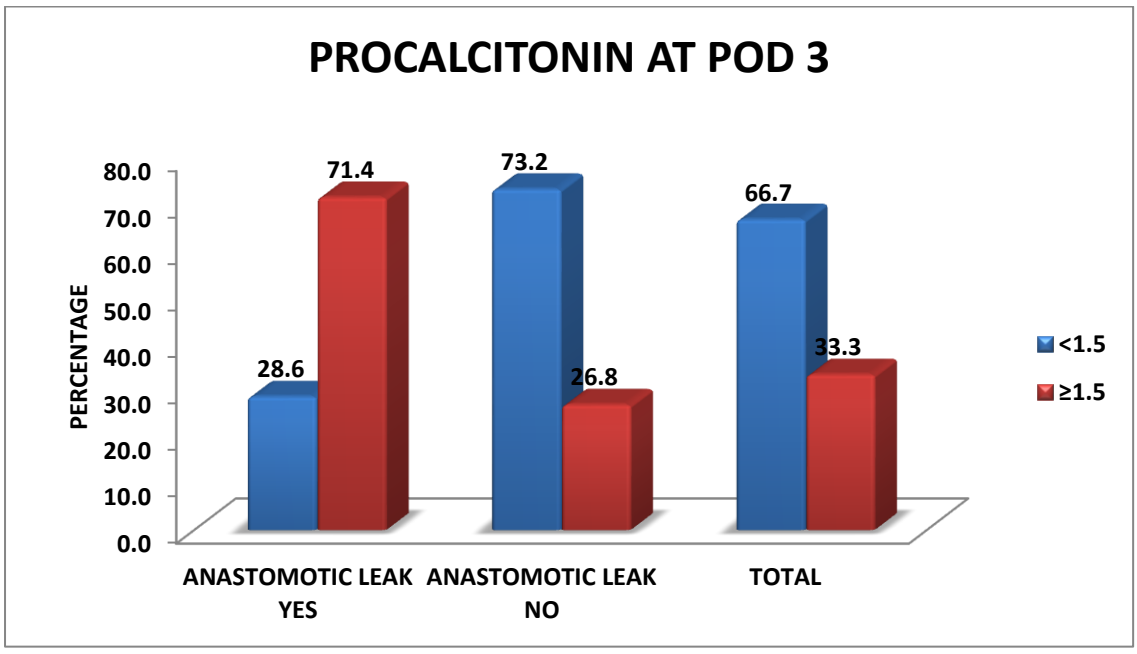

Table 13 and figure 13 shows PCT level at POD-3 according to anastomotic leak. Out of total 48 cases of study 32 cases(30 cases with no anastomotic leak and + 2 cases with anastomotic leak) had PCT value <1.5 , whereas 16 cases (11 cases with no anastomotic leak + 5 cases with anastomotic leak) had PCT levels > 1.5. with significant p value.

TABLE 14: PROCALCITONIN LEVEL AT POD 5 ACCORDING TO ANASTOMOTIC LEAK

PROCALCITONIN AT POD 5	ANASTOMOTIC LEAK				TOTAL		p value
	YES		NO				
	N	%	N	%	N	%	
<1.5	2	28.6	36	87.8	38	79.2	<0.001*
≥1.5	5	71.4	5	12.2	10	20.8	
Total	7	100.0	41	100.0	48	100.0	

Note: * significant at 5% level of significance (p<0.05)

FIGURE 14: PROCALCITONIN LEVEL AT POD 5 ACCORDING TO ANASTOMOTIC LEAK

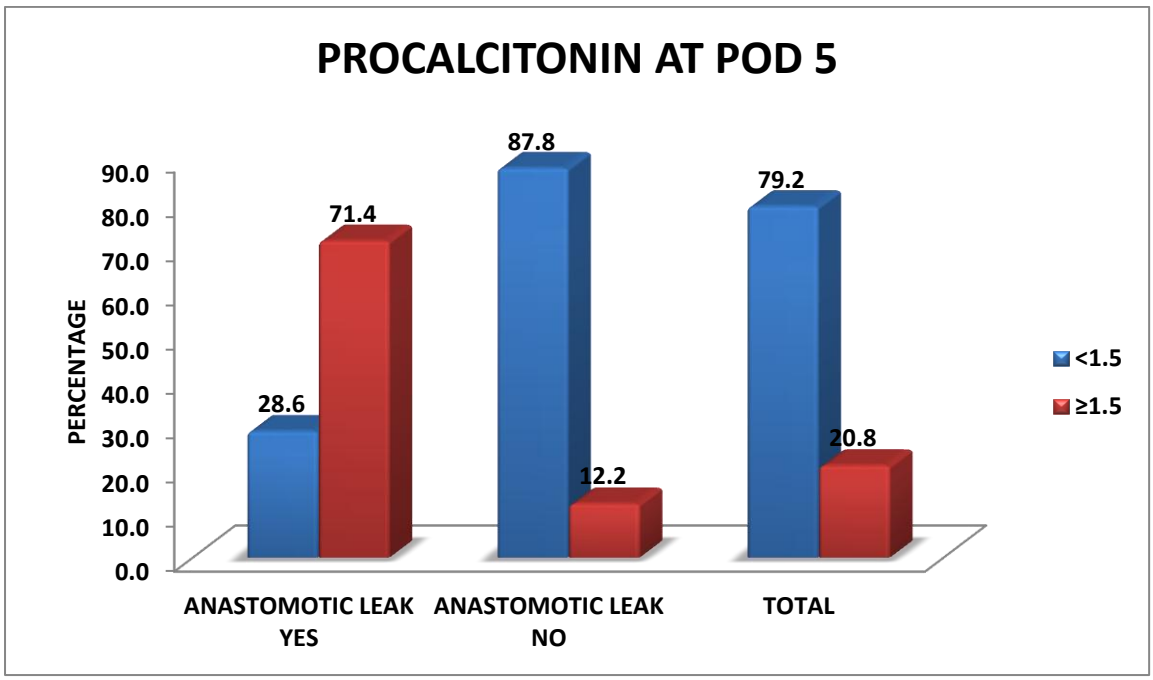

Table 14 and figure 14 shows PCT level at POD-5 according to anastomotic leak. Out of total 48 cases of study 38 cases(36 cases with no anastomotic leak and + 2 cases with anastomotic leak) had PCT value <1.5 , whereas 10 cases (5 cases with no anastomotic leak + 5 cases with anastomotic leak) had PCT levels > 1.5. with significant p value.

TABLE 15: PROCALCITONIN LEVEL AT POD 7 ACCORDING TO ANASTOMOTIC LEAK

PROCALCITONIN AT POD 7	ANASTOMOTIC LEAK				TOTAL		p value
	YES		NO				
	N	%	N	%	N	%	
<1.5	5	71.4	40	97.6	45	93.8	0.008*
≥1.5	2	28.6	1	2.4	3	6.3	
Total	7	100.0	41	100.0	48	100.0	

Note: * significant at 5% level of significance (p<0.05)

FIGURE 15: PROCALCITONIN LEVEL AT POD 7 ACCORDING TO ANASTOMOTIC LEAK

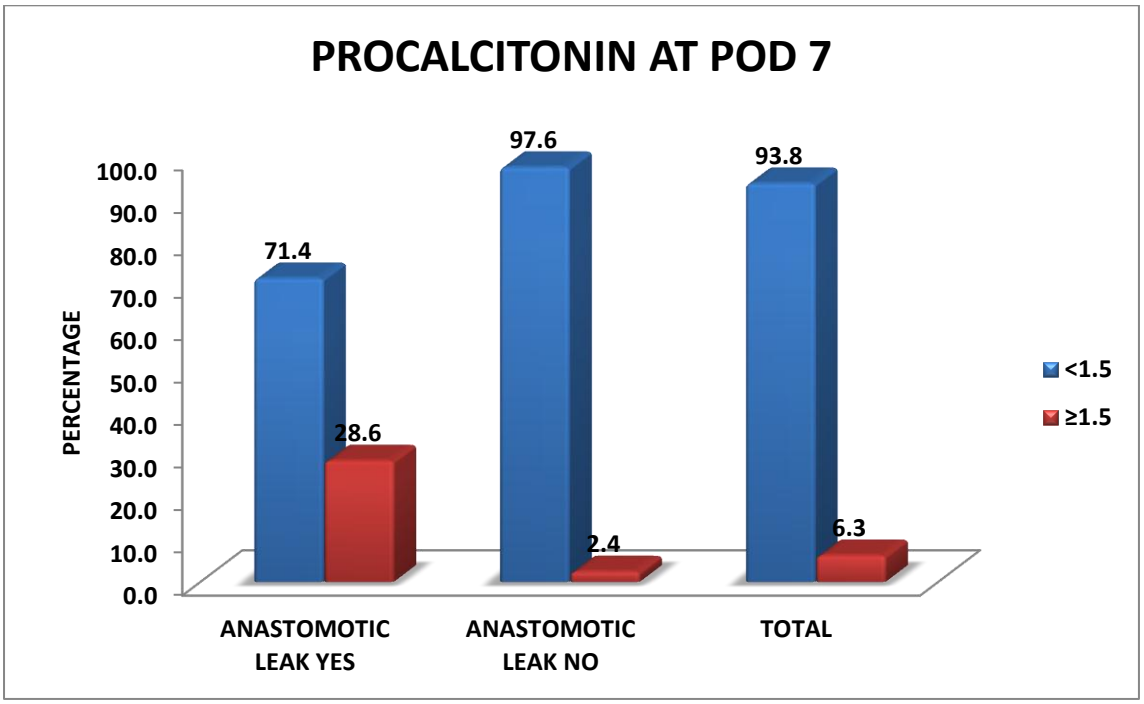

Table 15 and figure 15 shows PCT level at POD-7 according to anastomotic leak. Out of total 48 cases of study 45 cases(40 cases with no anastomotic leak and + 5 cases with anastomotic leak) had PCT value <1.5 , whereas 3 cases (1 case with no anastomotic leak + 2 cases with anastomotic leak) had PCT levels > 1.5. with significant p value.

DISCUSSION

C-Reactive protein and Procalcitonin are the important acute phase proteins which are produced in the body mainly in liver or extrahepatically at the site of injury or inflammation. Therefore it is essential to evaluate the levels of CRP and PCT at the local milieu which tends to be the specific indicator for local infection in anastomotic leaks in the surgeries of intestinal anastomosis.[72]

CRP levels in serum was used in long time to objectify infective and non infective injured tissues in body. CRP in drain fluid in one univariate analysis showed significant difference in patients with anastomotic leaks when measured on POD 3 and POD 5. [69]

Procalcitonin is produced mainly by neuroendocrine C cells of the thyroid, and sometimes shown to be secreted by different parenchymal tissues and differentiated cell types in the body. High serum levels were indicative of ongoing abdominal sepsis .In a study high PCT levels in drain fluid on Pod 5 was significant. [72]

This was the important study concerning acute phase proteins (CRP and PCT) in drain fluid and was conducted to study Procalcitonin & C-reactive protein are reliable & sensitive biomarkers of intestinal anastomotic leak in drain fluid. [56,58]

In this study 48 cases had undergone intestinal anastomosis and each one of them were followed throughout the hospital stay and investigated the values of CRP and PCT in drain fluid on POD 3,5,&7.

Here distribution of cases according to age, maximum number of cases fell in age group of 51-60 ie around 12 cases, followed by 41-50 yrs and 21-30 yrs age group ie 10 cases each . And 9 cases were in age group of 31-40 , 7 cases were >60yrs age

(Table 1). Ugras B et. al. [5] also found mean age among patient with leakage 47years and 53years among patient without leakage.

In this study , out of 48 cases 37 cases were male and 11 were female (Table 2), in the age group of 41-50 female were in higher percentage (45.5%) than males(13.5%) and with respect of 51-60 yrs age group highest percentage of males(29.7) than femles (9.1%)(Table 3). In study by Komen et al[19], out of 189 cases 100 cases were male and 89 were female.

Out of 48 cases 41 cases had no anastomotic leak whereas 7 cases had anastomotic leak(Table 4). Out of 7 anastomotic leaks 5 cases were managed conservatively where as 2 had to undergo surgery (Table 5). Ugras et. al. [5] found that out of 34 cases, 4 had anastomotic leak.

In this study , the cases with no anastomotic leak mean CRP levels at POD-3,5,7 were 1.08,0.84.0.59 whereas mean value of CRP in anastomotic leak cases were higher i.e POD-3,5,7 were 2.66,2.84 and 2.83 with significant p value 0.001, <0.001 and <0.001 respectively (Table 6).

In the cases with no anastomotic leak mean PCT levels at POD-3,5,7 were 1.17,0.98.0.67 whereas mean value of PCT in anastomotic leak cases were higher i.e POD-3,5,7 were 3.19,1.62 and 1.07 with significant p value <0.001, 0.015 and 0.046 respectively (Table 7).

In our study sensitivity and specificity of C-reactive protein increases as POD3,5,and 7 highest being 85.71% on POD5 and 97.56% on POD 7 respectively (Table 8).

We found that, sensitivity of Procalcitonin is highest and equal to on POD3 and POD 5 i.e 71.43% and low on POD 7 i.e 28.57%, and specificity of Procalcitonin is increases as POD3,5 and 7 highest being 97.56% on POD 7(Table 9).

On POD-3 out of total 48 cases of study 34 cases(30 cases with no anastomotic leak and + 4 cases with anastomotic leak) had CRP value <1.5 , whereas 14 cases (11 cases with no anastomotic leak + 3 cases with anastomotic leak) had CRP levels > 1.5(Table 10).

In this study ,on POD-5 out of total 48 cases of study 35 cases (34 cases with no anastomotic leak and + 1 cases with anastomotic leak) had CRP value <1.5 , whereas 13 cases (7 cases with no anastomotic leak + 6 cases with anastomotic leak) had CRP levels > 1.5(Table 11).

On POD-7 out of total 48 cases of study 42 cases(40 cases with no anastomotic leak and + 2 cases with anastomotic leak) had CRP value <1.5 , whereas 6 cases (1 case with no anastomotic leak + 5 cases with anastomotic leak) had CRP levels > 1.5(Table 12).

At POD-3 out of total 48 cases of study 32 cases(30 cases with no anastomotic leak and + 2 cases with anastomotic leak) had PCT value <1.5 , whereas 16 cases (11 cases with no anastomotic leak + 5 cases with anastomotic leak) had PCT levels > 1.5. with significant p value(Table 13).

It was found that at POD-5 out of total 48 cases of study 38 cases(36 cases with no anastomotic leak and + 2 cases with anastomotic leak) had PCT value <1.5 , whereas 10 cases (5 cases with no anastomotic leak + 5 cases with anastomotic leak) had PCT levels > 1.5. with significant p value(Table 14).

At POD-7 out of total 48 cases of study 45 cases(40 cases with no anastomotic leak and + 5 cases with anastomotic leak) had PCT value <1.5 , whereas 3 cases (1 case with no anastomotic leak + 2 cases with anastomotic leak) had PCT levels > 1.5. with significant p value(Table 15).

Modern surgical techniques and perioperative care have improved a lot, AL remains one of the most serious and important complications in patients after colorectal surgery. The leakage rate varies from 3% to 21% and the mortality

rate associated with symptomatic leaks is 6–22%.[73–78] which is in line of our study(14%).

This study supports the other studies where, the adequate blood supply of the anastomotic edges, the level of anastomosis, use of staples, adverse effect during the operation, lack of bowel preparation and prophylactic antibiotic therapy, blood loss and blood transfusions during operation, and patient-related risk factors including hypertension, tobacco and alcohol use, chronic obstructive pulmonary disease, obesity, and malnutrition have been associated with a higher risk of anastomotic leaking.[79-85]

The role of mechanical bowel preparation and prophylactic antibiotic therapy in preventing AL is unclear, despite some studies that describe a low incidence of AL.[84-86]

CONCLUSION

- Evaluation of C-reactive protein and Procalticonin in drain fluid on Pod3,5 and 7 were found to be associated with higher than normal values in anastomotic leakage patients .
- Sensitivity and specificity of C-reactive protein is increases as duration progresses POD3,5, and 7 highest being 85.71% on POD5 and 97.56% on POD 7 respectively.
- Positive predictive value of CRP is 83.33% on POD7

  Negative predictive value of CRP is 95.24% on POD7

  Accuracy of CRP is 93.75% on POD7.
- Sensitivity of Procalcitonin is highest and equal to on POD3 and POD 5 i.e 71.43% and low on POD 7 i.e 28.57%, and specificity of Procalcitonin increases as POD3,5 and 7 highest being 97.56% on POD 7.
- Positive predictive value of PCT is 66.67% on POD7

  Negative predictive value of PCT is 94.74% on POD5

  Accuracy of PCT is 87.50% on POD7.
- Conservative management with good nutritional support helps in management of patients with anastomotic leaks. As in this study out of 7 patients with anastomotic leaks 5 were managed conservatively and 2 had to undergo relaparotomy.

SUMMARY

In this study a total of 48 cases where analysis of drain fluid for presence of CRP and PCT on POD3,5 & 7 of intestinal anastomosis in BLDE (Deemed to be University) Shri B. M. Patil Medical College, Hospital and Research Centre, Vijayapura from October 2016-March 2018.

In our study we found that:

- Maximum number of cases fell in age group of 51-60 ie around 12 cases, followed by 41-50 yrs and 21-30 yrs age group ie 10 cases each . And 9 cases were in age group of 31-40 , 7 cases were >60yrs age.
- Out of 48 cases 37 cases were male and 11 were female
- In the age group of 41-50 female were in higher percentage (45.5%) than males(13.5%) and with respect of 51-60 yrs age group highest percentage of males(29.7) than females (9.1%)
- Out of 48 cases 41 cases had no anastomotic leak whereas 7 cases had anastomotic leak(Table 4). Out of 7 anastomotic leaks 5 cases were managed conservatively where as 2 had to undergo surgery.
- In the cases with no anastomotic leak mean CRP levels at POD-3,5,7 were 1.08,0.84.0.59 whereas mean value of CRP in anastomotic leak cases were higher i.e POD-3,5,7 were 2.66,2.84 and 2.83 with significant p value 0.001, <0.001 and <0.001 respectively.
- In the cases with no anastomotic leak mean PCT levels at POD-3,5,7 were 1.17,0.98.0.67 whereas mean value of PCT in anastomotic leak cases were higher i.e POD-3,5,7 were 3.19,1.62 and 1.07 with significant p value <0.001, 0.015 and 0.046 respectively.

- Sensitivity and specificity of C-reactive protein is increasing as POD3,5,and 7 highest being 85.71% on POD5 and 97.56% on POD 7 respectively.
- Sensitivity of Procalcitonin is highest and equal to on POD3 and POD 5 i.e 71.43% and low on POD 7 i.e 28.57%, and specificity of Procalcitonin is increasing as POD3,5 and 7 highest being 97.56% on POD 7.
- On POD-3 out of total 48 cases of study 34 cases(30 cases with no anastomotic leak and + 4 cases with anastomotic leak) had CRP value <1.5 , whereas 14 cases (11 cases with no anastomotic leak + 3 cases with anastomotic leak) had CRP levels > 1.5.
- On POD-5 out of total 48 cases of study 35 cases (34 cases with no anastomotic leak and + 1 cases with anastomotic leak) had CRP value <1.5 , whereas 13 cases (7 cases with no anastomotic leak + 6 cases with anastomotic leak) had CRP levels > 1.5.
- On POD-7 out of total 48 cases of study 42 cases(40 cases with no anastomotic leak and + 2 cases with anastomotic leak) had CRP value <1.5 , whereas 6 cases (1 case with no anastomotic leak + 5 cases with anastomotic leak) had CRP levels > 1.5.
- On POD-3 out of total 48 cases of study 32 cases(30 cases with no anastomotic leak and + 2 cases with anastomotic leak) had PCT value <1.5 , whereas 16 cases (11 cases with no anastomotic leak + 5 cases with anastomotic leak) had PCT levels > 1.5. with significant p value.
- On POD-5 out of total 48 cases of study 38 cases(36 cases with no anastomotic leak and + 2 cases with anastomotic leak) had PCT value <1.5 , whereas 10 cases (5 cases with no anastomotic leak + 5 cases with anastomotic leak) had PCT levels > 1.5. with significant p value.

- On POD-7 out of total 48 cases of study 45 cases(40 cases with no anastomotic leak and + 5 cases with anastomotic leak) had PCT value <1.5 , whereas 3 cases (1 case with no anastomotic leak + 2 cases with anastomotic leak) had PCT levels > 1.5. with significant p value.

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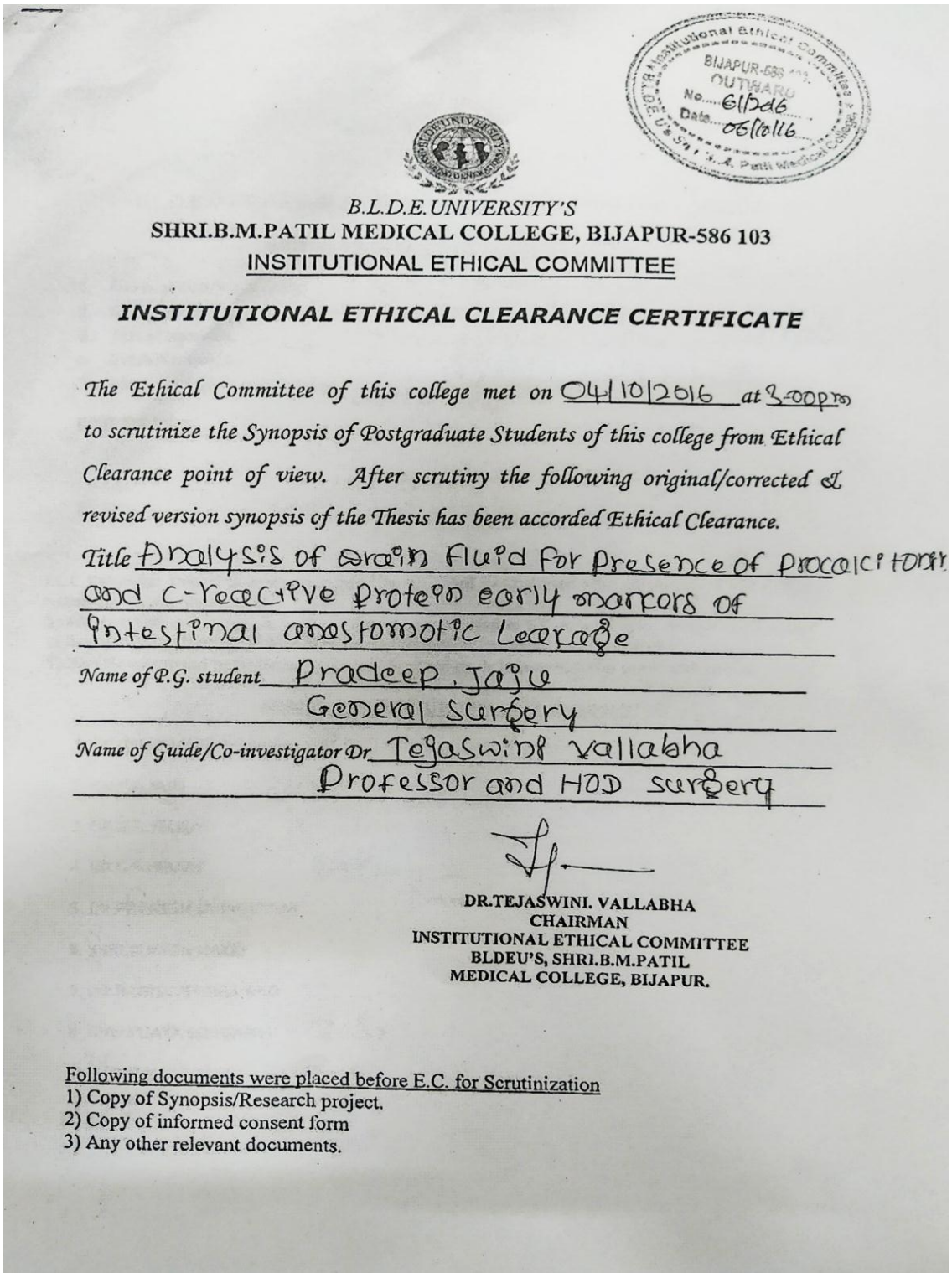
ANNEXURES

ETHICAL CLEARANCE CERTIFICATE



B.L.D.E. UNIVERSITY'S
SHRI.B.M.PATIL MEDICAL COLLEGE, BIJAPUR-586 103
INSTITUTIONAL ETHICAL COMMITTEE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 04/10/2016 *at* 3-00pm *to scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected & revised version synopsis of the Thesis has been accorded Ethical Clearance.*

Title Analysis of drain fluid for presence of procalcitonin and c-reactive protein early markers of intestinal anastomotic leakage

Name of P.G. student Pradeep. Jaju
General Surgery

Name of Guide/Co-investigator Dr Tejaswini Vallabha
Professor and HOD surgery

DR.TEJASWINI. VALLABHA
CHAIRMAN
INSTITUTIONAL ETHICAL COMMITTEE
BLDEU'S, SHRI.B.M.PATIL
MEDICAL COLLEGE, BIJAPUR.

Following documents were placed before E.C. for Scrutinization
1) Copy of Synopsis/Research project.
2) Copy of informed consent form
3) Any other relevant documents.

SAMPLE INFORMED CONSENT FORM

TITLE OF THE PROJECT	:	Analysis of drain fluid for presence of Procalcitonin and CRP as early markers of anastomotic leakage
PG GUIDE	:	**DR. TEJASWINI VALLABHA** M.S. General Surgery PROFESSOR &HOD Department of Surgery
PRINCIPAL INVESTIGATOR	:	**Dr. Pradeep.P.Jaju**

PURPOSE OF RESEARCH:

I have been informed that this study will help in analyzing, screening, & diagnosing the Intestinal anastomotic leakage. I have also been given a free choice of participation in this study. This study will help in proper management of patients having Intestinal anastomotic leakages.

PROCEDURE:

The procedure which will be followed as explained by Dr. Pradeep P. Jaju is as follows

- The surgical procedure will be decided by the surgeon, & all the patient will receive preoperative antibiotic prophylaxis & an intra-abdominal drain. Patients will be operated by laparotomy & the Intestinal anastomosis will be hand-sutured. A drain will be constructed if necessary according to surgeon's preference to obtain drain fluid, a drain will be placed at the anastomotic site

& will be left in place during the first 7 post operative days. The type of drain will be left at the surgeons' discretion.

- Drain fluid reservoirs will be emptied 2 times a day with 12 hour intervals, respecting the rules of sterility. The evening collection will be disposed off then the morning drain fluid sample will be collected for determining the levels of CRP, Procalcitonin on the post operative day 3, 5 and 7.

RISK AND DISCOMFORTS:

I understand that I may experience some pain and discomforts during the examination or during my treatment. This is mainly the result of my condition and the procedures of this study are not expected to exaggerate these feelings which are associated with the usual course of treatment.

BENEFITS:

I understand that my participation in the study Analysis of drain fluid for presence of Procalcitonin and CRP as early markers of intestinal anastomotic leakage, will help the patients for the early detection of the complications associated with it.

CONFIDENTIALITY:

I understand that the medical information produced by this study will become a part of hospital records and will be subject to the confidentiality. Information of sensitive personal nature will not be part of the medical record, but will be stored in the investigations research file.

If the data are used for publication in the medical literature or for teaching purpose, no name will be used and other identifiers such as photographs will be used only with special written permission. I understand that I may see the photograph before giving the permission.

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study to Dr. Pradeep.P,Jaju in the Department of General Surgery who will be available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of the study, which might influence my continued participation. A copy of this consent form will be given to me to keep for careful reading.

REFUSAL FOR WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary and that I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice. I also understand that Dr. Pradeep.P.Jaju may terminate my participation in the study after he has explained the reasons for doing so.

INJURY STATEMENT:

I understand that in the unlikely event of injury to me resulting directly from my participation in this study, if such injury were reported promptly, the appropriate treatment would be available to me. But, no further compensation would be provided by the hospital. I understand that by my agreements to participate in this study and not waiving any of my legal rights.

I have explained to _____the purpose of the research, the procedures required and the possible risks to the best of my ability in pts own language.

Date | Dr Tejaswini V (Guide) | Dr Pradeep P. Jaju (Investigator)

Witness signature :

1)

DATE

2)

DATE

STUDY SUBJECT CONSENT STATEMENT:

I confirm that Dr. Pradeep. P. Jaju has explained to me the purpose of research, the study procedure, that I will undergo and the possible discomforts as well as benefits that I may experience in my own language. I have been explained all the above in detail in my own language and I understand the same. Therefore I agree to give consent to participate as a subject in this research project.

_____ _____

(Participant) Date

_____ _____

(Witness to signature) Date

PROFORMA FOR CASE TAKING

SL NO: IP NO: H / M

Name: UNIT:-

Age/Sex: DOA:-

Religion: DOS:-

Occupation: DOD:-

Address:

Mobile No:

Chief complaints**:**

History of presenting complaints**:**

Past history:

Co morbidities:

PERSONAL HISTORY:

Diet: Appetite: Bowel/Bladder:

Sleep: Digestion: Habits:

GENERAL PHYSICAL EXAMINATION:

Built: Well/Moderate/Poor

Nourishment: Well/Moderate/Poor

Pallor/Icterus/Cyanosis/clubbing/pedal oedema/ lymphadenopathy

BP: PR: RR:

Temperature: SPo_2:

SYSTEMIC EXAMINATION:

Per Abdomen:

Respiratory System:

Cardio Vascular System:

Central Nervous System:

Local examination of wound:

LABORATORY TESTS

Haemoglobin% : BT: CT:

Total Count : N L E B M

Platelets :

Blood Urea :

Serum Creatinine :

HIV : HB_SAg:

Electro Cardiogram :

Urine routine :

USg abd and pelvis :

Surgery :

Operative procedure:

Clinical examination on day 3

	POD 3	POD 5	POD 7

Drain fluid analysis

1. Procalcitonin levels on POD 3

   POD 5

   POD 7

2. CRP level on POD 3

   POD 5

   POD 7

HPR : HPR no:

Anastomotic leakage: yes or no

If yes, Management:

FINAL DIAGNOSIS :

MASTER CHART

SR.NO	NAME	IPNO	AGE	SEX	DIAGNOSIS	PROCEDURE	C-REACTIVE PROTEIN			PROCALCITONIN			ANASTOMOTIC LEAK	MANAGEMENT
							POD-3	POD-5	POD-7	POD-3	POD-5	POD-7		
1	BASANGOUDA C.B	32942	60	M	INT.OBST	EXP.LAP WITH ILEAL RESECTION AND ANASTOMOSIS	2.6	1.6	1.8	2.5	1.8	1.2	YES	CONSERVATIVE MANAGEMENT
2	VITTAL	1874	66	M	INT.OBSRT	EXP.LAP WITH ILEAL RESECTION AND ANASTOMOSIS	0.6	0.2	0.4	3.7	2.9	2.3	NO	
3	HANUMANTH PUJARI	39525	50	M	PENETRATING ABDOMEN TRAUMA WITH JEJUNAL TEAR	EXP LAP WITH JEJUNOJEJUNAL ANASTOMOSIS	0.85	1.07	0.5	0.6	0.5	0.6	NO	
4	GANGAWWA G	39526	65	F	INT OBST	EXP LAP WITH ILEOILEAL ANASTOMOSIS	1.2	0.6	0.8	1.2	0.4	1. 2	NO	
5	BASAPPA IJERI	3523	55	F	INT OBST	EXP LAP WITH JEJUNOTRANSVERSE COLIC ANASTOMOSIS	1.5	1.5	0.6	0.6	0.8	0.8	NO	
6	SHABBIR.H.MULLA	7707	22	M	GASTRIC OUTLET OBST	ROEX EN Y RETROCOLIC SIDE TO END ISOPERILSTALTIC GASTROJEJUNOSTOMY WITH JEJUNOJENUOSTOMY	1	0.6	0.4	0.27	0.2	0.1	NO	
7	REKHA UPPAR	11180	28	F	PERITONITIS SEC TO HOLLOW VISCUS PERFORATION	EXP LAP WITH RESECTION OS 1ST PART OF DUODENUM WITH RETROCOLIC ISOPERILSTALTIC GASTROJEJUNOSTOMY	0.6	1.3	1.6	0.2	0.24	0.28	YES	SURGICAL MANAGEMENT
8	SHIVAPPA S.C	18367	25	M	PERITONITIS	EXP LAP WITH JEJUNAJENUNAL ANASTOMOSIS	2.2	1.6	1.1	1.4	1	0.6	NO	

9	ADIVEPPA	42229	55	M	STAGE 4 ADENOCARCINOMA STOMACH	SUBTOTAL GASSTRECTOMY WITH ROEX EN Y GASSTROJEJUNOSTOMY WITH D1 LYMPHADENECTOMY	3.5	3	2.5	6.7	2	0.5	YES	SURGICAL MANAGEMENT
10	HANAMANTH	8980	60	M	SQ.CELL CA.OESOPHAGUS	TRANHIATAL ESOPHAGECTOMY WITH FEEDING JEJUNOSTOMY WITH INTERCOASTAL DRAINAIGE	0.85	1.1	0.3	1.6	0.4	0.25	NO	
11	SIDAPPA	20833	61	M	INT OBST	EXP LAP WITH RESECTION AND END TO END ILEOILEAL ANASTOMOSIS	1	1.5	0.4	0.6	0.4	1	NO	
12	Bapugouda	29077	60	m	Int obs	Exp lap with resection and end to end ileoileal anastomosis	1.2	1.4	1	0.5	0.6	0.8	No	
13	KAREMMA S P	91	40	M	GASTRIC OUTLET OBST	EXP LAP WITH TRUNCAL VAGOTOMY WITH RETROCOLIC ISOPERILSTALTIC GASTROJEJUNOSTOMY WITH ADHESIOLYSIS	0.4	0.1	0.5	0.8	0.5	0.5	NO	
14	AMBAJI K G	30395	70	M	GASTRIC OUTLET OBST	EXP LAP WITH GASTROJEJUNOSTOMY	1.7	0. 5	0.3	0.58	0.3	0.15	NO	
15	MAHANTESH	44256	30	M	PENETRATING ABDOMEN INJURY WITH ILEAL AND JEJUNAL PERFORATION	EXP LAP WITH RESECTION OF ILEUM AND ILEOILEAL ANASTOMOSIS WITH JEJUNAL PERFORATION PRIMARY CLOSURE WITH MESENTRIC CLOSURE	1.7	0.5	0.3	2.48	1.2	0.58	NO	

16	SUNIL C SULAKHE	39998	50	M	PERITONITIS SEC TO HOLLOW VISCUS PERFORATION	EXP LAP WITH RESECTION AND END TO END ILEAOILEAL ANASTOMOSIS	0.9	1.5	0.5	0.9	2.5	0.5	NO	
17	SAHEBAGOUDA S PATIL	39050	21	M	INT OBST SEC TO ILEOILEAL INTUSSUPTIO N WITH MOBILE CAECUM	EXP LAP WITH RESECTION AND ILEOILEAL ANASTOMOSIS WITH CAECOPEXY WITH APPENDECTOMY	1	1.5	0.4	0.6	0.5	0.3	NO	
18	HANUMANTH	25850`	60	M	INT OBST	EXP LAP WITH RESECTION AND ILEOILEAL ANASTOMOSIS	1	1.5	0.6	1	0.8	0.5	NO	
19	KASTURI	26078	42	F	PERITONITIS SEC TO HOLLOW VISCUS PERFORATION	EXP LAP WITH RESECTION AND ILEOILEAL ANASTOMOSIS	1.5	0.5	0.6	0.9	2.5	0.5	NO	
20	JARABAI	28752	45	F	INT OBST	EXP LAP WITH RESECTION AND ILEOILEAL ANASTOMOSIS	0.4	1.2	1.8	0.3	0. 2	0.1	NO	
21	SHASHKALA	29731	40	F	INT OBST	EXP LAP WITH RESECTION AND ILEOILEAL ANASTOMOSIS	1.3	1.5	0.6	1.5	0.9	0.6	NO	
22	IRAPPA	30458	65	M	INT OBST	EXP LAP WITH RESECTION AND ILEOILEAL ANASTOMOSIS	1.5	1. 2	1	1.1	0.6	0.4	NO	
23	GOLLAPPA	6160	95	M	INT OBS	EXP LAP WITH RESECTION AND ILEOILEAL ANASTOMOSIS	0.5	0.3	0. 2	1.8	1.4	1	NO	

24	VEERESH	12989	38	M	INT OBST	EXP LAP WITH RESECTION AND ILEOILEAL ANASTOMOSIS	1	0.6	0.5	0.8	0.4	0.6	NO	
25	RAMAKANT	8829	54	M	PERITONITIS SEC TO HOLLOW VISCUS PERFORATION	EXP LAP WITH RESECTION AND ILEOILEAL ANASTOMOSIS	0.6	0.4	0.4	1.1	1.4	0.9	NO	
26	KASHINATH	9531	22	M	INT OBST	EXP LAP WITH RESECTION AND ILEOILEAL ANASTOMOSIS	1	0.5	0.5	1.4	1.3	0.9	NO	
27	MAHADEVAPPA	901	75	M	CAECALPERFORATION	EXP LAP WITH LOOP ILEOSTOMY WITH ILEOILEAL ANASTOMOSIS	1.5	0.6	0.4	1.6	1.4	0.9	NO	
28	CHANDRAPPA	11002	50	M	PERITONITIS SEC TO JEJUNAL PERFORATION	EXP LAP WITH RESECTION AND JEJUNOJEJUNAL ANASTOMOSIS	0.6	0.4	0.4	1.1	1.4	0.9	NO	
29	VIVEKANAND D R	19691	27	M	PERITONITIS SEC TO HOLLOW VISCUS PERFORATION	EXP LAP WITH RESECTION AND END TO END JEJUNOJEJUNAL ANASTOMOSIS	8.5	9	9.5	8	2	1.7	YES	CONSERVATIVE MANAGEMENT
30	DAYANAND	16180	53	M	PERITONITIS WITH HOLLOW VISCUS PERFORATION	EXP LAP WITH RESECTION AND ILEOILEAL ANASTOMOSIS	0.6	0.4	0.4	1.1	0.9	1.4	NO	
31	RENUKRAJ	15489	32	M	INT OBST	EXP LAP WITH RESECTION AND ILEOILEAL ANASTOMOSIS	1.5	0.5	0.5	1.3	1.4	0.5	NO	

32	NEELKANT	15493	40	M	PERITONITIS SEC TO ILEAL PERFORATION	EXP LAP WITH RESECTION AND ILEOILEAL ANASTOMOSIS	0.7	0.4	0.3	1.5	1	1.3	NO	
33	TUKARAM	20304	53	M	GASTRIC OUTLET OBSTRUCTION	EXP LAP WITH GASTROJEJUNOSTOMY WITH COLOCOLIC ANASTOMOSIS WITH APPENDECTOMY	0.6	0.3	0.2	1	1.5	0.8	NO	
34	RENUKA GANI	22149	34	M	PERITONITIS WITH HOLLOW VISCUS PERFORATION	EXP LAP WITH RESECTION AND ILEOILEAL ANASTOMOSIS	1	1.7	3	1.5	2	2.5	YES	CONSERVATIVE MANAGEMENT
35	VIVEKANAND	19691	60	M	BLUNT ABDOMEN TRAUMA	EXP LAP WITH RESECTION AND JEJUNOJEJUNAL ANASTOMOSIS WITH MESENTERIC CLOSURE	1	0.6	0.5	1	0.8	1.3	No	
36	Shreedevi	20198	50	f	Peritonitis	Exp lap with resection and end to end ileal anastomosis	1.1	1.8	0.6	1.4	1.9	0.6	yes	CONSERVATIVE MANAGEMENT
37	Dawalsab	21189	55	m	Peritonitis sec to hollow viscus perforation	Exp lap with resection and end to end ileal anastomosis	1	0.8	0.5	0.9	0.6	0.6	No	
38	Roshan	25866	25	m	Blunt abdomen trauma	Exp lap with roux en y anastomosis with feeding jejunostomy	1.3	1.5	0.8	2	1.4	0.7	Yes	CONSERVATIVE MANAGEMENT
39	Shridevi	29266	35	f	Peritonitis	Exp lap with resection and end to end ileoileal anastomosis	1.1	1.3	0.6	1.8	1.5	0.6	No	
40	Leelavati	29271	48	f	Int obs	Exp lap with resection and end to end ileoileal anastomosis	1	0.8	0.6	0.8	0.9	0.5	No	

41	Rahul	30110	29	m	Peritonitis	Exp lap with resection and end to end ileoileal anastomosis	1.5	1.3	0.6	1.1	0.8	0.6	No	
42	Prakash	30108	50	m	Peritonitis	Exp lap with resection and end to end ileoileal anastomosis	1.1	0.9	0.6	1.3	1	0.6	No	
43	Abhiram	29568	28	m	Peritonitis	Exp lap with resection of mesenteric cyst with segment of transverse colon with end to end colocolic anastomosis.	1.5	1.1	0.6	1.5	1	0.6	No	
44	Parashuram	29575	56	m	Peritonitis	Exp lap with resection and end to end ileoileal anastomosis	1	1.1	0.7	1.9	1.2	0.8	No	
45	Hanumanth	29010	45	m	Peritonitis	Exp lap with resection and end to end ileoileal anastomosis	1	1.3	0.8	1.5	1.2	0.8	No	
46	Tulsibai	23140	40	f	Int obs	Exp lap with resection and end to end ileoileal anastomosis	1.5	1	0.9	1.1	0.5	0.6	No	
47	Seetabai	21345	50	f	Peritonitis	Exp lap with resection and end to end ileoileal anastomosis	1.1	1	1.1	0.8	0.9	0.3	No	
48	Ningappa	21132	38	m	Peritonitis	Exp lap with resection and end to end ileoileal anastomosis	1.2	1	0.9	0.9	0.7	0.3	No	