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Assessment of Relation between Recurrence of Enterocutaneous Fistula and Preoperative C-reactive Protein Level after Complete Surgical Repair

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Authors' contributions

This work was carried out in collaboration between all authors. Author OHK designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors WSM and EMM managed the analyses of the study. Author ZAA managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Recurrence of enterocutaneous fistula after the definite surgical repair has not changed significantly. In postoperative complication of abdominal surgery, serum C-reactive protein level is used for evaluation of severity of the condition. In this study, we aim to find a relation between recurrence of enterocutaneous fistula and preoperative serum level of C-reactive protein.
Methods: A prospective study of 40 patients admitted with the diagnosis of enterocutaneous fistula (ECF) and prepared for definite surgical repair in the form of resection anastomosis of ECF. We used preoperative serum C-reactive protein as predicting factor of recurrence and independent variable for timing of surgery.

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Results: Eleven cases showed recurrence with increased level of preoperative serum level of C-reactive protein above (0.75 mg/dl) with high significant (P<0.05). There was significant different between recurrent and non-recurrent cases regarding preoperative serum level albumin and malnutrition (P<0.05).
Conclusion: C-reactive protein can be used as predicting factor for recurrence of ECF after definite surgical treatment as well as helping surgeon to take decision for proper time of operation.

Keywords: Enterocutaneous fistula; C-reactive protein; surgical repair.

1. INTRODUCTION

In one review, around 95% of ECFs were postoperative, and the ileum was the most widely recognized site of ECF [1]; 49% of fistulas were high-yield, and 51% were low-yield. The routine treatment of (ECF) in the underlying stage is constantly preservationist. Prompt surgical treatment on introduction is contraindicated, in light of the fact that the larger part of ECFs suddenly close subsequently of preservationist treatment. Surgical mediation within the sight of sepsis and poor general condition would be risky for the patient [2].

The length of traditionalist administration ought to be founded on the anatomic investigations of the fistula tract. Without the unfriendly prognostic variables (FRIEND) portrayed beforehand, the revealed achievement rate of fistula conclusion fluctuates from 30% to 74% in patients inside a time period of 4 to 12 weeks. Deciding the ideal time for surgical intercession has not been very much characterized in the writing. Be that as it may, surgery ought to be postponed until the intra-abdominal and systemic states of the patient are helpful for significant surgery. Intraperitoneal attachment release can be performed from as right on time as postoperative day 4 and cement methods are most every now and again performed at postoperative day 35 [3].

In acute phase reaction, the serum C-reactive protein level increases during inflammation due to the effect of proinflammatory cytokines. Many studies discussed post-operative rise of C-reactive protein in abdominal surgery especially colorectal surgeries. In anastomotic dehiscence or infectious complications, its level remains high during first postoperative days [4]. Many causes can lead to recurrence of ECF after definite surgical treatment like perioperative inflammatory condition in which the level of C-reactive protein is usually high. We aim to find a relation between perioperative level of C-reactive protein and recurrence of ECF in our study group.

2. METHODS

This study was carried out in the general surgery department of the Zagazig University Hospital from January 2015 to April 2017 after ethics approval of the institutional ethics committee. Forty patients with ECF were included in the study after written consent. Any connection between gastrointestinal tract and skin was considered as ECF. The diagnosis of ECF was confirmed by clinical examination and imaging studies. Senior staff evaluated all cases according to the protocol and made a decision for definite surgical treatment. Cases submitted for surgical treatment with protecting or terminal stoma were excluded from our study. Other fistulas like perianal, pancreatic, biliary and internal fistulas were not involved due to their different nature, treatment and prognosis. The first stage of ECF treatment, trailed by general strong care with fluids furthermore, electrolyte substitution, sepsis control, wholesome support and control of fistula waste by pharmacologic implies and also through protection of the skin. Deciding the ideal time for surgical treatment has not been all around characterized in the writing. Notwithstanding, surgery ought to be postponed until the intra-abdominal and systemic states of the patient are helpful for major surgery. The decision of surgical interference was individualized according to patient situation.

The data of the study group were collected. Age, sex, cause of fistula, frequency of surgical interference, site of fistula, daily 24 hours output, dehydration, electrolytes imbalance, nutritional deficiency, sepsis, laboratory investigations, type and duration of enteral and parenteral nutrition were documented and recorded. The same surgical team performed all operations with recording type of interference, indications, and duration of conservative measurement before surgery. Multidisciplinary team of ICU doctors, internists, nutritionists and other specialties shared in patient management in the perioperative period. Operations which were performed to control sepsis are not considered a

part of surgical treatment. The first stage of the study finished on patient discharge or death then patients were followed up every 3, 6, 9, 12 months.

In immediate postoperative follow up any leakage of intestinal content from the wound or drain sites is considered as recurrence of ECF and it was confirmed by image studies. In these cases we aim to find the relation between ECF recurrence and preoperative level of s-CRP (mg/dl) as a primary independent variable. S-CRP was measured one day before surgery. Secondary variables included age, sex, site of fistula (jejunal, ileal, colonic), single or multiple, high or low 24 hours output, causes of fistula, simple or complex fistula, presence or absence of sepsis, history of surgical treatment of the fistula, laboratory investigations, interval between onset of ECF and definite surgical interference and type of surgical interference.

IBM SPSS version 24 program was used for analysis of collected data using descriptive statistics such as frequency, percent, mean, and SD. Analytical statistical tests such as Anova test was used to compare continuous variables and chi square test for categorical variables depending on P value (less than 0.05) which was considered significant. The cutoff value and accuracy of s-CRP level as predictor of ECF recurrence were evaluated by using an operating characteristic curve and area under the curve. When the value of area under curve exceeds 0.8, this indicated a high accuracy as more than 80% of patient with that variable are correctly classified according to ECF recurrence.

3. RESULTS

Between January 2015 to April 2017 patients were identified with ECF. Following chart review, 40 patients fitted the review criteria of an external fistula which surgery was performed. There were 24 males (60%) and 16 females (40%). Fig. 1 shows underlying causes of ECF. The commonest cause in our series was carcinoma operations and was significantly older than other groups. The conservative treatment duration varied according general condition of cases with median range 10 to 130 days and average 77 days. Drainage of local abscess was done in 8 cases (20%) under ultrasound, CT scan or open surgery which is not considered as part of definite treatment. Fistula resection with primary anastomosis is the treatment of choice for our patients. We used hand-sewn technique in 32 (80%) and EEA staplers in 8 (20%) of cases. The duration of surgery ranged between 2hours and 4hours with significant increase in duration in diverticular cases. Meticulous dissection using electro-cautery was used to minimize bleeding and subsequently blood transfusion. Significant decline observed in the level of preoperative of C-reactive protein with increase of the interval between start of ECF and time of definite surgical treatment Table 1.

Preoperative laboratory and radiological investigations were done to exclude intra-abdominal or distant infection before surgery. Twenty four patients (60%) were referred to our hospital from outside. Sixteen patients (40%) have previous surgical interference for fistula (Fig. 2). Early surgical interference for ECF was done in 10 patients (25%) after good evaluation of our senior staff. Other 30 patients (75%) were conservatively managed for different complications like sepsis in 10 (25%), dehydration and electrolytes imbalance in 12 (30%) and malnutrition in 22 (55%) (Fig. 3).

The output of the fistula was high in 28 patients (70%). Total parenteral nutrition was used in 34 patients (85%) depending on total proteins and albumin levels. There is a significant difference between groups of patients regarding these parameters (Table 2).

The postoperative recurrence was observed in 11 cases (27.5%). Operative interference was performed in 4 patients with success of closure in 2 cases, low output in one case and death of one case. The conservative treatment in the form of TBN, good control of infection and electrolyte balance was done in the rest 7 patients. The conservative group showed success in 4 patients, stable low output ECF in 2 cases and death in one case (Fig. 4).

On other hand analysis of other factors related to recurrence of ECF as age, sex underlying pathology, site of fistula, output, sepsis, operation duration, intraoperative blood loss, type of anastomosis, TPN and electrolytes imbalance showed no significant difference between recurrent and non-recurrent groups. Preoperative level of albumin (3.2 mg/dl) and malnutrition were significantly different between both groups ($P<0.05$).

4. DISCUSSION

The conservative therapy for an enterocutaneous fistula (ECF) in the initial phase is always indicted. Since the majority of ECFs

spontaneously close as a result of conservative therapy, immediate surgical therapy on presentation is contraindicated. It is hazardous for the patient to proceed for surgical treatment in the presence of sepsis and bad general condition [5].

In surgical treatment of ECF, we aim to regain continuity of bowel lumen by resection anastomosis of the fistula. In many studies primary anastomosis showed the best result with limited recurrence. Fine dissection is very important to avoid injury of other loops of intestine especially during abdominal exploration. Recurrence rate of ECF decreases to (16%) using end-to-end anastomosis [6]. That is why we choose to follow this policy in management of our patients.

Table 1. Preoperative characters of patients and investigation

Etiology	Age Mean ±SD	Average preoperative duration Mean ±SD	Duration of surgery min Mean ±SD
CA operations	69.3±3.9*	128±56*	185±55
Bowel obstruction	45.6±2.3	105±52	165±24
IBD	42.4±4.2	111±44	175±52
Hernia	64.7±6.4	12±15	105±58
Diverticular disease	60.2±6.5	95±28	205±25*
Trauma	39.8±2.6	25±12	120±65
Laparoscopy	52.6±2.4	65±28	155±54
Total	56.2±2.1	77±44	158.57±44
P value	0.0024*	0.0038*	0.0001*

**significant difference P Value <0.05; Anova test is used*

Table 2. ECF output, conservative treatment and TPN

Etiology	Output		Conservative treatment		TPN	
	High No (%)	Low No (%)	Yes No (%)	No No (%)	Yes No (%)	No No (%)
CA operations	10 (71%)	4(29%)	14(100%)	0(0%)	14(100%)	0(0%)
Bowel obstruction	4(57%)	3(42%)	4(57%)	3(42%)	5(71%)	2(29%)
IBD	3(100%)	0(0%)	3(100%)	0(0%)	3(100%)	0(0%)
Hernia	2(50%)	2(50%)	2(50%)	2(50%)	2(50%)	2(50%)
Diverticular disease	3(100%)	0(0%)	2(67%)	1(33%)	3(100%)	0(0%)
Trauma	4(80%)	1(20%)	2(40%)	3(60%)	4(80%)	1(20%)
Laparoscopy	2(50%)	2(50%)	1(25%)	3(75%)	2(50%)	2(50%)
P value	0.0087*		0.0453*		0.0218*	

**significant difference P Value <0.05 chi square test is used*
The f- value is 58.20516. The p-value is < .00001

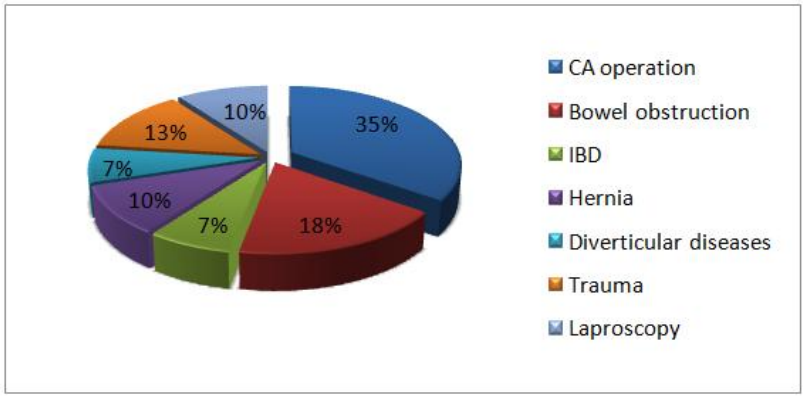

Fig. 1. Classification of the studied patients according to the underlying cause of ECF

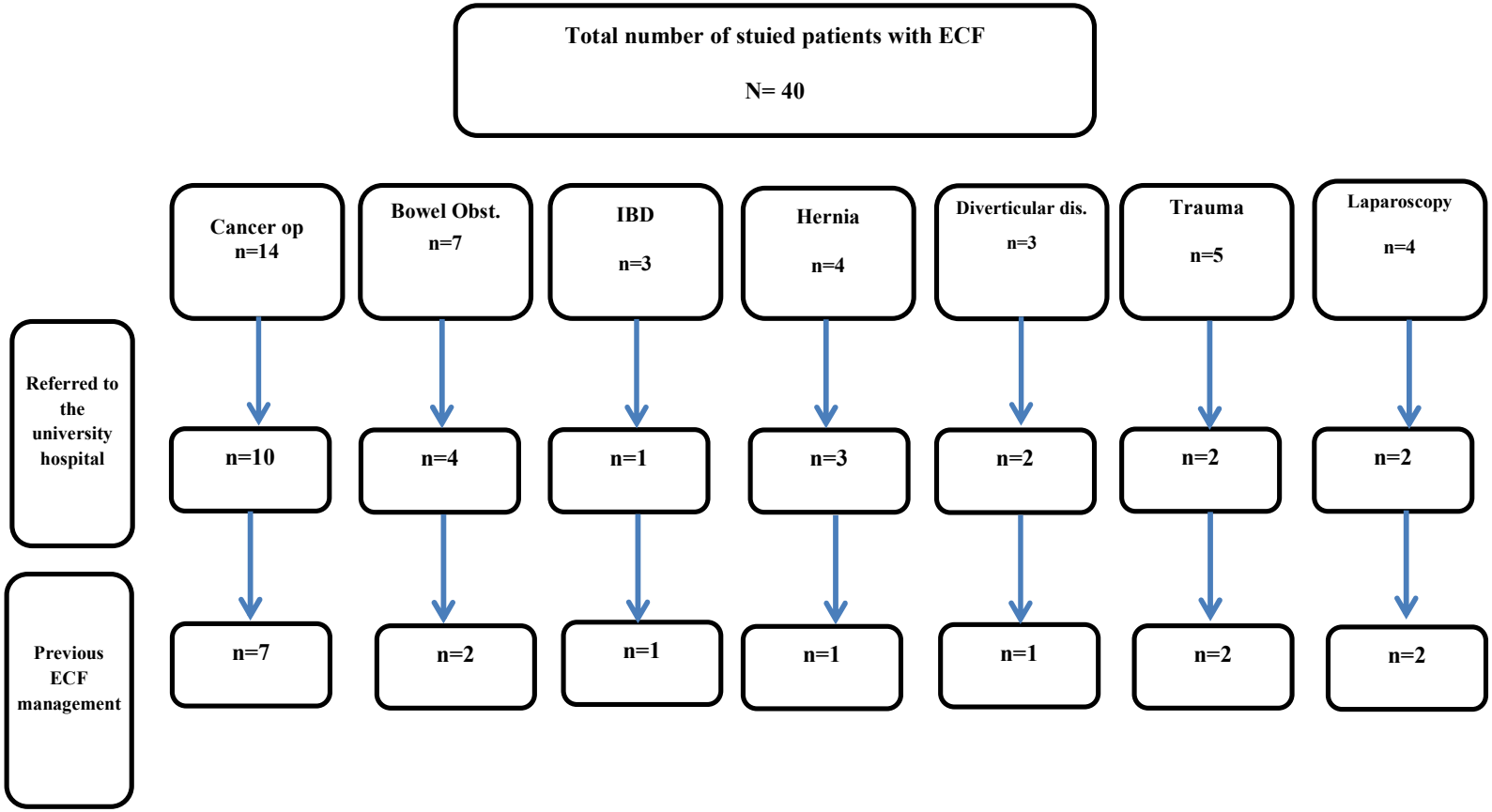

Fig. 2. Flow chart of outside referral, previous interference and surgery time

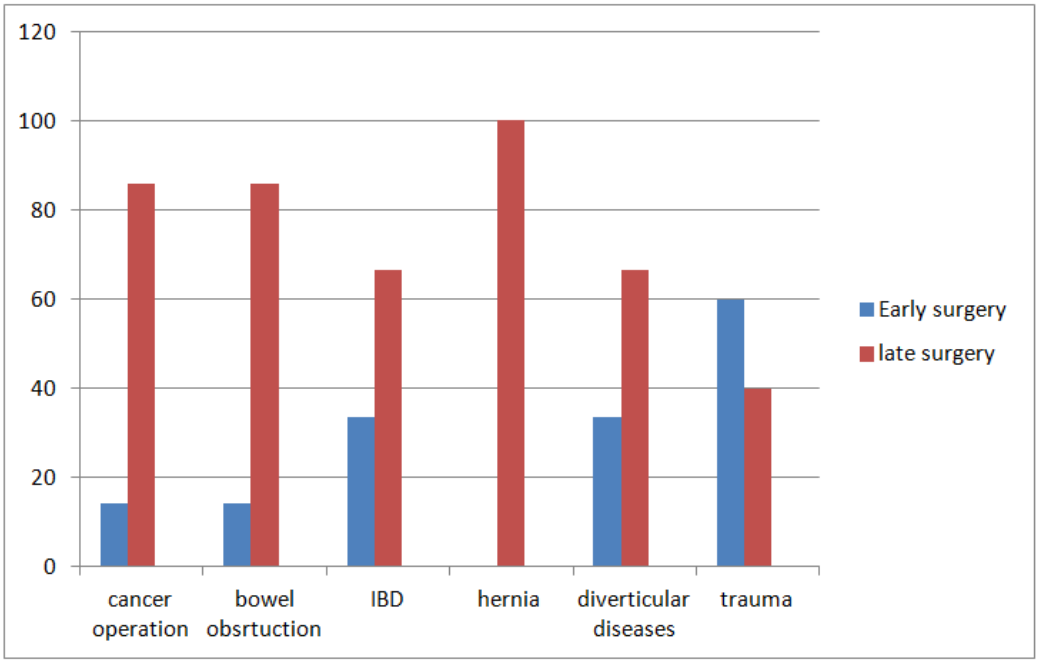

Fig. 3. Early and late surgical interference of different cases of ECF

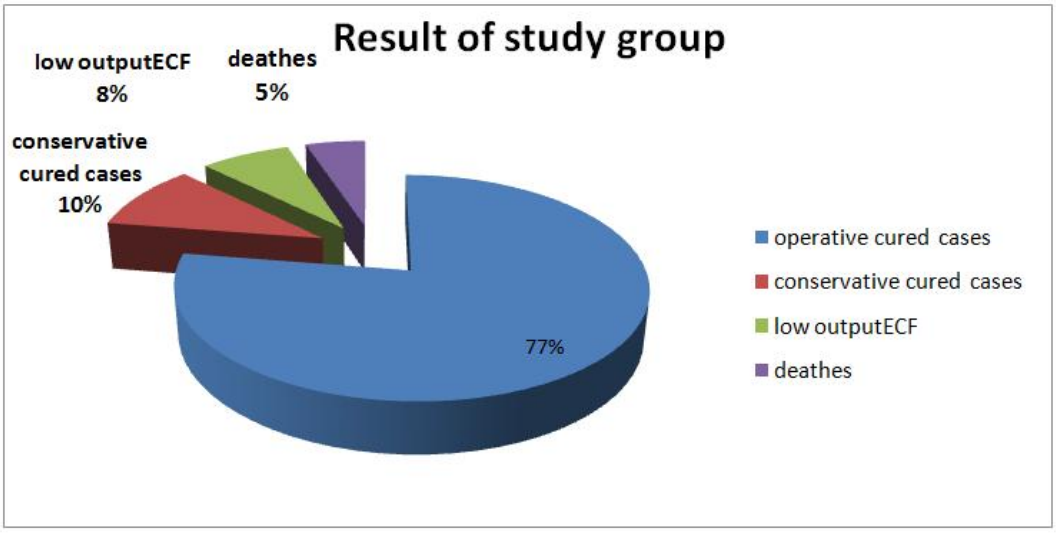

Fig. 4. Result of study group

In the literature, there is no clear point for surgical intervention. Taking decision for operation in ECF should follow guidelines including improve patient general condition and good control of sepsis. In a study Evenson and Fischer [7].

Intraperitoneal adhesion can be performed from as early as postoperative day 4 and adhesive procedures are most frequently performed at postoperative day 35. Evenson and Fischer [7] proposed waiting at least four months from the date of the previous operation. Datta et al. [8] delayed the operation for a median of nine months from the initial surgery or the occurrence of a fistula. The timing of definitive surgery should be individualized according to patient characteristics.

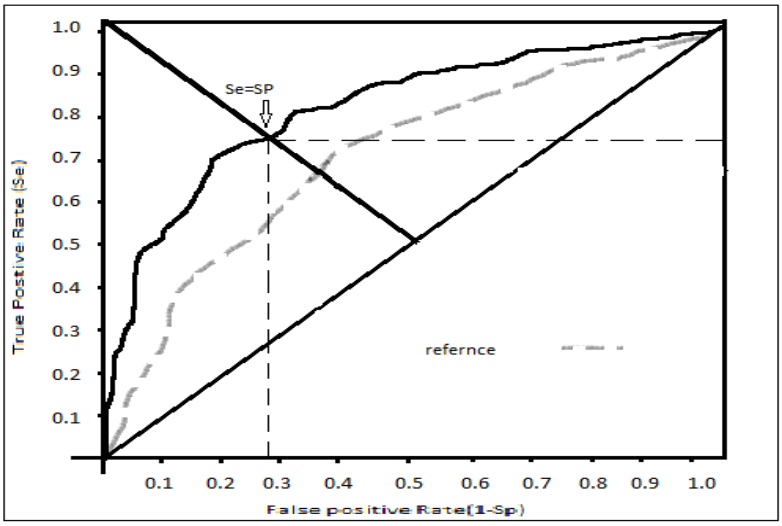

Fig. 5. Cutoff value of Serum C reactive protein when sensitivity and specificity are equal in recurrent cases after surgical treatment

Interleukin 6 and tumor necrosis factor (TNF) are inflammatory mediators that stimulate liver to produce C-reactive protein as an acute phase reactant. In operated patients, C-reactive protein remains high for few hours in response to operative stress then gradual decrease of its level to the perioperative values [9].

In our study, we aim to find the relation between recurrence of ECF after surgical treatment, preoperative level of C-reactive protein and choice of best time for surgical interference. The recurrence rate in our series was (27.5%) which is less than other study of Martinez et al. [10] (38%). The recurrent cases showed high level of preoperative C-reactive protein (3.71 mg/dl) in comparison to cured cases (2.17 mg/dl). To prove that the C-reactive protein is an independent factor in the recurrence of ECF we used multivariate analysis of this result. More than half of recurrent cases exceeded the cutoff point of C-reactive protein level in our study 0.75 mg/dl. These results support our belief that preoperative C-reactive protein level can be a useful indicator for timing of ECF surgery and decrease recurrence rate [11].

The only explanation of high level of C-reactive protein in recurrent cases is presence of hidden infection which was not clear by usual preoperative investigations or a persistence of inflammatory state after exclusion of other causes during clinical assessment. In our study, there was no significant difference between recurrent and non-recurrent cases regarding other predicting factors of recurrence except preoperative serum albumin and this is not matching studies done by Owen et al. [12] and Brenner et al. [13] as they found high incidence of ECF recurrence with prolonged preoperative interval while in Martinez et al. [10] study, blood loss was independent factor for ECF recurrence due to extensive intra-abdominal adhesions.

The totally cured cases after definite operative treatment were 77% of patients including initial and subsequent recurrence, 10% underwent conservative treatment after failed surgical management, 8% had low output fistula and for mortality rate 5%. These result were matching other studies which were done to study predicting factors of ECF recurrence [14,15,16].

5. CONCLUSION

ECF is considered as one of serious complications of gastrointestinal tract surgery. Definitive surgical treatment maybe indicated in some cases. The cornerstone of this decision is to control sepsis and inflammatory condition before surgery. In some cases there may be a hidden place for infection or continuation of the inflammatory situation without clear signs, which necessitated the presence of a possible indicator helps in making the surgical decision. Serum C-reactive protein is the common inflammatory marker used to exclude inflammatory condition. Although its level is within normal range but some cases showed high recurrence rate when the level exceeded certain value as we believed in our study. Now we can say that the perioperative serum C-

reactive protein level can be used as an objective parameter for helping to make surgical decision and reduce recurrence of ECF.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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