Drainage fluid C-reactive protein and total Leucocytic count levels as early detectors of anastomotic leakage postgastrointestinal resection

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Aim
Anastomotic leakage (AL) following gastrointestinal resection is a complication associated with significant morbidity and mortality. C-reactive protein (CRP) is produced by the liver in response to inflammatory cytokines and is used as an indicator for postoperative complications. This study investigated the role of CRP and total leukocyte count (TLC) in blood and drainage fluid in the prediction of AL following gastrointestinal resection.
Patients and methods
Serum and drainage fluid CRP and TLC in blood and drainage fluid were measured on the first, third, and fifth postoperative days (PODs) in 96 patients who underwent gastrointestinal resection.
Results
CRP in the drainage fluid was significantly elevated in patients who developed AL compared with those who did not have leak on all PODs (P=0.003, $<$0.001, and $<$0.001 on the first, third, and fifth days, respectively); however, serum CRP levels were not elevated significantly as a result of AL. We found a significant difference in the levels of the TLC in the first and third PODs and not in the level of TLC in the drain.
Conclusion
CRP in the drainage fluid was found to be a predictor of AL following gastrointestinal resection especially on the third and fifth PODs with cutoff values of 137.5 and 171.5 mg/l, respectively.

Keywords:
anastomotic leakage, C-reactive protein, total leukocyte count

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Introduction

Anastomotic leakage (AL) remains a grave complication following resection anastomosis of the intestine. Once diagnosed, it is usually associated with ascites, sepsis, and systemic manifestations. Despite the advances in operative techniques and stapling technology, the incidence of leakage still remains high [1]. Extensive research has focused on defining the preoperative risk factors governing the incidence of postoperative AL; however, late diagnosis is still problematic. Ultimately, this leads to longer hospital stay and higher mortality among patients [2].

Moreover, leakage is often difficult to recognize in critically ill patients because of the marked coexisting inflammatory process. Lack of early recognition prevents timely resuscitation and effective antimicrobial therapy, resulting in increased morbidity and mortality [3].

C-reactive protein (CRP) is a reliable, but nonspecific, marker of acute inflammation and is a popular early marker of infection following abdominal surgery [1]. Spontaneous bacterial peritonitis is now diagnosed measuring the total leukocyte count (TLC) in the ascitic fluid being diagnostic if polymorphonuclear leukocytes are more than 250/mm^3 [4].

The aim of this study is the prediction or early detection of intestinal leakage by measuring postoperative CRP and TLC levels in the blood and the drainage fluid.

Patients and methods

This study enrolled 96 patients who were attending the Kasr Alainy New Emergency Hospital (185), Cairo University, during the period between July 2018 and January 2019. The research protocol was approved by

the Research Ethics Committee of the Surgery Department, Cairo University, and informed consent was obtained from all participants.

Patients included those presenting with trauma or pathology of the gastrointestinal tract necessitating surgical intervention. This included resection of a part of the small or large bowel, with or without anastomosis, hand-sewn or stapled. Patients with malignancy or who did not have a surgical drain inserted were excluded from the study.

Clinical evaluation of patients

All patients underwent thorough history taking and meticulous clinical examination. Routine laboratory investigations in the form of complete blood picture, coagulation profile, liver and kidney functions, and electrolytes were done. Abdominal ultrasound was done routinely for all patients and selected patients underwent computed tomography abdomen according to the presentation. Patients presenting with vital instability in spite of proper resuscitation were transferred immediately to the operating theater without investigations. Those who were vitally stable were admitted to the ward where preoperative preparations were done according to the presentation. Cases with intestinal obstruction all had Ryle and catheter inserted as well as intravenous fluid administered for resuscitation and compensation of fluid loss and any electrolyte imbalance was corrected prior to surgery.

Management according to the case was done in the form of resection with diverting stoma, resection, and primary anastomosis; exteriorization with ileostomy or colostomy. The creation of diverting ileostomy or colostomy depended on the individual assessment of the surgeon. Before the closure of laparotomy incision, the abdominal cavity of the patient was routinely drained with at least one drain placed in the Douglas pouch or in the rectovesical pouch.

Postoperative care was carried out in the ward or in the ICU. Patients with clinical presentation of chest infection, urinary tract infections, or infections caused by central venous line were excluded. Leakage was suspected clinically when the patients became feverish and had tachycardia without any other obvious cause. AL was defined in the ward by the presence of purulent or fecal content at the drain site, or the surgical wound, and or by investigations in the form of abdominal US or computed tomography with contrast revealing site of leakage or abdominal collection and eventually the presence of leakage from the anastomotic line upon re-exploration.

Methods

Sample collection

In all patients, peripheral blood samples were obtained on the first, third, and fifth PODs. The CRP samples were collected in serum separator tubes, while the TLC samples were collected in EDTA tubes. Pelvic drain fluid was collected on the same days.

Sample storage

The collected samples were stored at a temperature of 4°C.

Sample analysis

Levels of CRP and TLC were measured in these samples. The CRP was analyzed using the Siemens (BN ProSpec®, Munich, Germany). The normal level of CRP is less than 3 mg/L. On the other hand the normal level of serum TLC is less than 11000 leukocyte/μL and the normal level of TLC in the drainage fluid is fewer than 500 leukocyte/μL.

Statistical collection

Demographic and clinical data were collected for each patient. This included name, age, sex, medical comorbidities, and past surgical history. The presentation of each patient, date of operation, operative details, the results of the labs withdrawn in the first, third, and fifth days and incidence of leakage were also recorded.

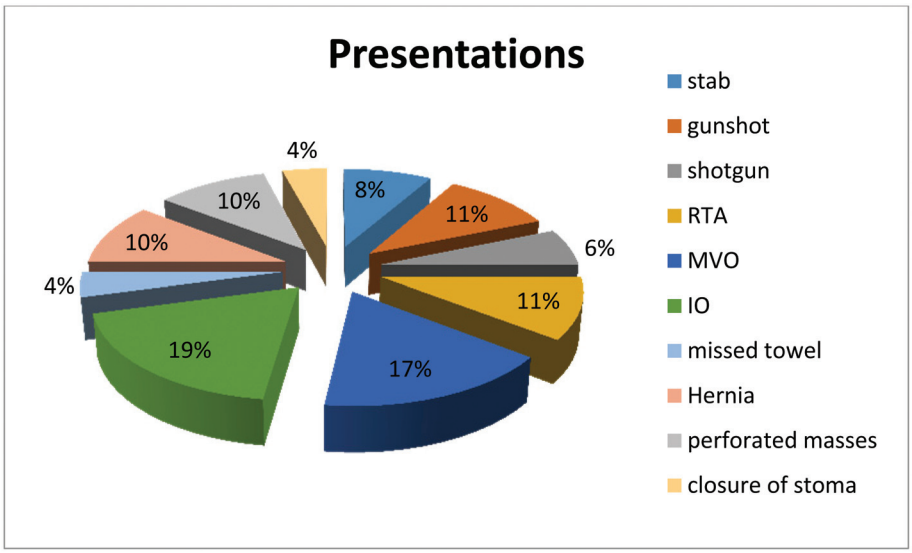
Data analysis

Data were coded and entered using the statistical package for the social sciences (SPSS) version 24 (IBM Corporation, Pyramids Heights Office Park, Building C10, Cairo, Alexandria Desert Road, KM 22. Giza Egypt). Data were summarized using mean, SD, median, minimum, and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the nonparametric Mann–Whitney test [5]. Spearman's ρ method was used to test the correlation between numerical variables. Receiver operating characteristic curve was used to determine cutoff values based on sensitivity and specificity of tests. P values less than 0.05 were considered statistically significant.

Results

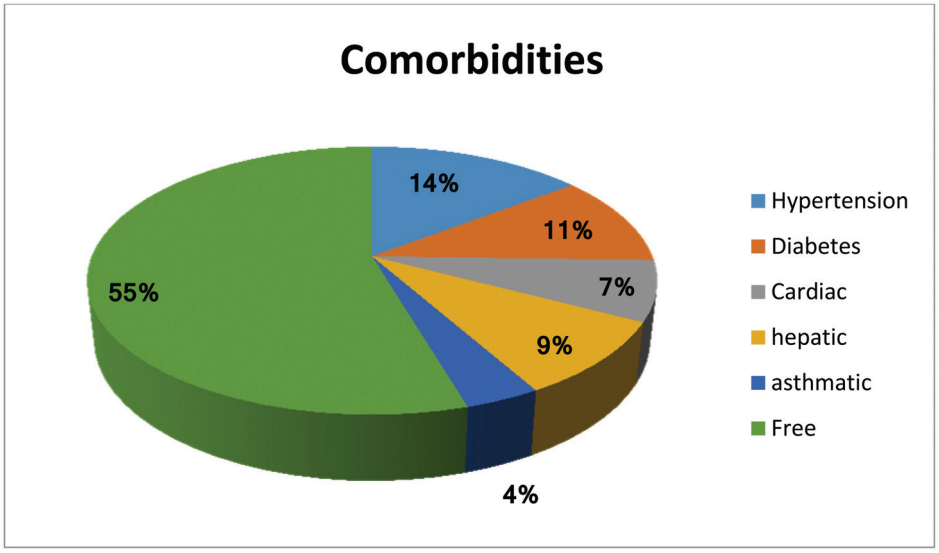
The study included 96 patients, 64 (66.7%) men and 32 (33.3%) women. Their ages ranged between 18 and 77 years with an average age of 41±14 years old. The age of the patients was not found to show any statistically

Figure 1



Pie chart showing different patient presentations.

Figure 2



Pie chart showing different comorbidities of the patients.

significant difference between non-leakage and leakage groups in our study. The patients included in the study had either traumatic or pathological presentation (Fig. 1). Among the patients included in the study, 36 (37.5%) patients had comorbidities (Fig. 2).

Eighteen out of 96 patients (18.75%) had right hemicolectomy with ileocolic anastomosis, and 78 had small bowel resection and anastomoses. Thirty (31.25%) patients had AL. Thirty-three percent of which presented with trauma, while 67% presented with pathological conditions. Leakage occurred in six patients on the first POD (20.1%), 14 (46.6%) patients on the third POD, and 10 (33.3%) patients on the fifth POD. Among the leakage group 14 (46.6%) had comorbidities, while in the nonleakage group 22 (33%) had comorbidities. Twenty-nine percent of the patients presenting with trauma had AL compared with 32% of patients with pathological conditions.

Serum CRP levels were not found to be significantly elevated in leakage compared with nonleakage patients in any of the PODs; however, CRP in the drainage fluid was significantly elevated in the leakage group on all PODs (P=0.003, <0.001 and <0.001 on the first, third, and fifth days, respectively; Table 1). On comparing the mean values of serum and drain

CRP, a statistically significant difference was found in the nonleakage group with the highest differences on POD 3 and POD 5, while in the leakage group there was no statistically significant difference in all PODs. There was positive correlation between the serum and drain CRP in the nonleakage group on all PODs (Table 3). In the leakage groups, there was negative correlation between the serum and drain CRP on the 3rd and 5th PODs, while there was positive correlation on the 1st POD.

Table 1 Comparison of the levels of serum and drain C-reactive protein between leakage and nonleakage patients

	Leakage (mean±SD)		
CRP	Yes	No	*P* value
Serum			
POD 1	138.52±80.39	172.74±69.33	0.083
POD 3	185.84±69.58	162.37±55.59	0.22
POD 5	163.82±46.79	168.70±189.76	0.121
Drain			
POD 1	157.16±78.90	103.54±55.16	0.003
POD 3	161.00±50.03	111.58±53.91	<0.001
POD 5	199.82±16.15	94.11±42.98	<0.001

CRP, C-reactive protein; POD, postoperative day.

Table 2 Comparison of the levels of serum and drain total leukocyte count between leakage and nonleakage patients

	Leakage (mean±SD)		
TLC	Yes	No	*P* value
Serum			
POD 1	14.71±6.65	12.46±7.96	0.041
POD 3	14.24±5.73	11.20±5.01	0.022
POD 5	9.27±2.10	10.07±3.86	0.74
Drain			
POD 1	17.68±23.74	16.61±17.70	0.556
POD 3	14.48±13.24	12.68±10.91	0.807
POD 5	8.17±8.78	8.29±4.17	0.235

POD, postoperative day; TLC, total leukocyte count.

Table 2 shows the changes in the mean value serum of white cell count and drain TLC among the leakage and the nonleakage groups. There is a statistically significant difference in the levels of serum TLC in the first and third PODs but not in the 5th POD. On the other hand, there was no statistically significant difference in the level of TLC in the drain in any of the PODs.

Among leakage patients, there was a statistically significant difference between serum white blood cell count and drain TLC with the highest value in the third POD. However, in the nonleakage group the first POD was the only day that had a statistically significant difference (Table 3).

Sensitivity and specificity of drainage fluid CRP measurement in the detection of AL were analyzed using the receiver operating characteristic curve and were shown in Fig. 3 with the highest sensitivity on third and fifth PODs and highest specificity recorded on the fifth POD.

Discussion

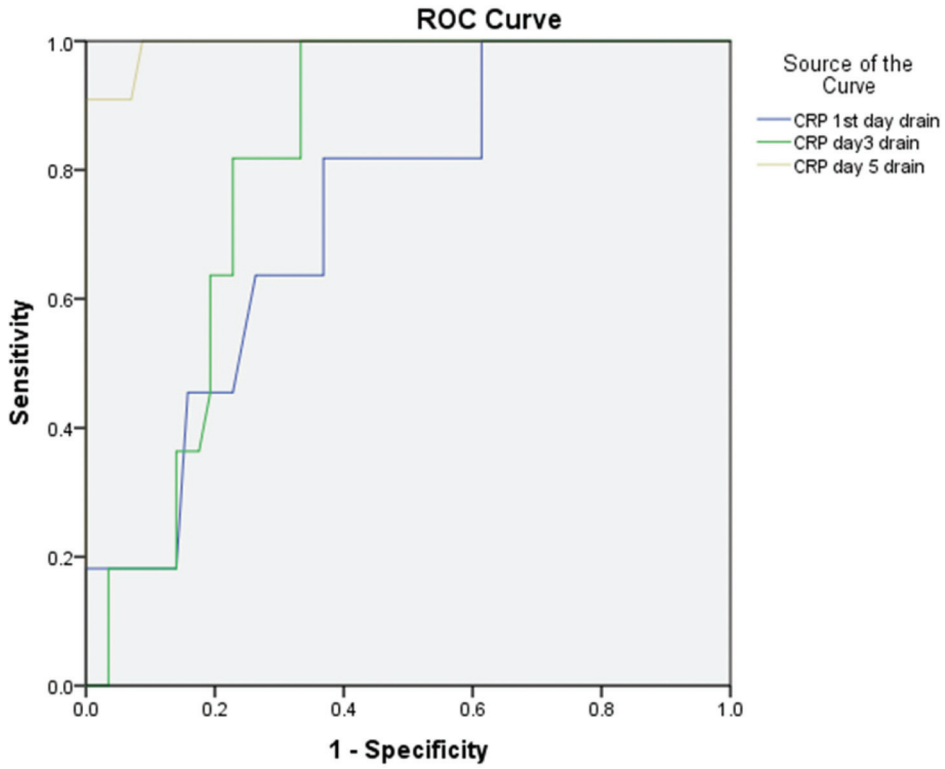
In this study, we investigated the role of CRP and TLC in both blood and drainage fluid in the prediction of AL following gastrointestinal resection. Serum CRP was not found to be significantly increased in patients with AL as compared with those without. A study by Almeida *et al.* [6] included 183 patients who had colorectal disease and

Table 3 Correlation between blood and drain levels of total leukocyte count and C-reactive protein

TLC	Serum (mean±SD)	Drain (mean±SD)	*r*	*P* value
Leakage				
POD 1	14.71±6.65	17.68±23.74	0.412	0.021
POD 3	14.24±5.73	14.48±13.24	–0.845	<0.001
POD 5	9.27±2.10	8.17±8.78	0.778	0.005
No leakage				
POD 1	12.46±7.96	16.61±17.70	0.426	<0.001
POD 3	11.20±5.01	12.68±10.91	–0.089	0.483
POD 5	10.07±3.86	8.29±4.17	0.051	0.704
CRP				
Leakage				
POD 1	138.52±80.39	157.16±78.90	0.146	0.432
POD 3	185.84±69.58	161.00±50.03	–0.298	0.149
POD 5	163.82±46.79	199.82±16.15	–0.088	0.796
No leakage				
POD 1	172.74±69.33	103.54±55.16	0.248	0.046
POD 3	162.37±55.59	111.58±53.91	0.714	<0.001
POD 5	168.70±189.76	94.11±42.98	0.447	<0.001

CRP, C-reactive protein; POD, postoperative day; TLC, total leukocyte count.

Figure 3



Receiver operating characteristic curve for detection of leakage using drain C-reactive protein.

underwent resection and primary anastomosis showed the mean serum CRP to be significantly higher in the group who developed leakage. They concluded that early and persistent elevation of serum CRP (in particular a value exceeding 140 mg/l on POD 3) after colorectal surgery had a significant association with AL. Likewise, two studies in 2012; Platt *et al.* [7], and Scepanovic *et al.* [8] supported the findings of Almeida *et al.* [6], regarding the mean serum CRP as a predictor of AL. In all three studies, the patients were carried on elective cases in which the serum CRP was not elevated preoperatively. This was in contrast to our group as our patients were not elective cases with heterogeneous presentations and CRP would have probably been elevated preoperatively. Perhaps a larger sample size and a more homogeneous population could have yielded different results. In this study, the highest levels of drain CRP occurred on the fifth POD in the leakage group, while the highest level of serum CRP was achieved on the third POD for the same group.

Another study by Vaziri-Moghaddam *et al.* [9] investigating the role of serum CRP in patients with AL also elucidated the role of CRP in its diagnosis; however, patients with preoperative infections or elevated CRP levels were excluded from the study. This was further enforced by Fernández *et al.* [10], who excluded patients with active infection, cancer patients, as well as patients who required urgent surgery; and found CRP to be useful in the diagnosis of AL.

On the other hand, our study showed a statistically significant difference in CRP values in the drain between the patients who had AL and those who did not on the first, third, and fifth PODs, P=0.003 on POD 1, and P values less than 0.001 on PODs 3 and 5. A study by Kostić *et al.* [11] aimed to use the levels of CRP in the drainage fluid as a predictor of AL after colorectal resections. The study had a longer follow-up period of up to the seventh POD in comparison to ours, which ended on the fifth POD. They had a statistically significant difference in the values of serum CRP between the leakage and nonleakage groups on the third, fifth, and seventh PODs. In both studies there was a statistically significant difference in the values of drain CRP between the leakage and the nonleakage groups on the third and fifth PODs with P values of less than 0.001. So, compatible results were found with the highest statistically significant difference on the fifth POD.

Moreover, we observed an ascending manner of elevation in the mean level of drain CRP in the leakage group compared with the nonleakage group, where there was a rise on the third POD, then a drop on the fifth POD in the latter group. Regarding the

serum CRP, there was no obvious manner of rise or decline in both groups. In contrast, Kostić *et al.* [11] observed a decline in serum and drain CRP along the PODs more evident in the group without complications. This clarifies the importance of the serial measurement of the CRP in the drain during the first week postoperatively for early prediction of leakage.

In this study, the sensitivity of measuring CRP in the drain sensitivity rose from 81 to 100% from the first to the fifth PODs, while specificity increased from 63 to 91.2%, respectively, giving us a better cutoff value to be used as an early predictor for AL from 137.5 mg/l on the third POD to 171.5 mg/l on the fifth POD. This signifies the importance of serial measurement of CRP in the drain. In the study by Kostić *et al.* [11], the sensitivity increased from 53 to 80% from the first to the seventh PODs, with a rise in specificity from 63 to 83%, respectively; however specificity decreased to 77% on the fifth PODs which was not useful in reaching a proper cutoff value to detect leakage.

In their study, the correlation analysis for CRP values in serum and drainage fluid in the group of patients without complications and those with leakage showed statistically highly significant positive correlation between the values of CRP in serum and drainage fluid for all the observed days in patients without complications, while the highest correlation in the group with leakage was observed on POD 7. In this study, there was no statistical significance when correlating serum and drain CRP in AL patients on any of the PODs; however, there was a statistically significant positive correlation in CRP values between the serum and the drain in the nonleakage group which was low on the first POD but increased on the third and fifth PODs. Hence, correlating the serum and drainage CRP values is not as important as that of measuring the CRP levels in the drain alone and could be confusing as it has a positive correlation in the nonleakage group.

When comparing TLC values between the leakage and the nonleakage groups in our study, there was a statistically significant difference on the first and third days, but not on the fifth day and this is contrary to the findings published by Scepanovic *et al.* [8] and Almeida *et al.* [6], who concluded that postoperative TLC values did not show any significant difference between the leakage and nonleakage groups until the POD 6. This could also be due to the fact that our patients were operated upon on an emergency basis with increased baseline TLC.On the other hand, TLC values in the drain did not have any significance when compared in both groups and therefore it was concluded that TLC in the drain is not useful for early detection of AL as in spontaneous bacterial peritonitis.

In 2014, a review article published by Fujita *et al.* [12] analyzed 15 studies on factors affecting leakage; age was not associated with an increased risk of AL in any study. Similarly, the age of the patients was not found to be statistically significant between nonleakage and AL patients in our study.

In this study, among the leakage group, 49% had comorbidities in comparison to 33% among the nonleakage group. Thirty-six (37.5%) patients had different comorbidities, 38.8% of which had AL, while in the medically free group only 26.6% had AL, suggesting that comorbidities and the general condition of the patient have an impact on developing leakage.

The level of the CRP in the drain of the nonleakage group was also found to be falsely high in 24 patients on the first POD, 14 of whom presented with trauma. Also, it was elevated in eight patients on the third POD and in four patients on the fifth POD who were also trauma patients. This finding shows that trauma might be associated with falsely higher levels of CRP than pathology cases, so for future studies, it might be more accurate evaluating trauma and pathology patients separately.

Conclusion

The level of CRP in the drainage fluid was found to be an accurate predictor of AL after resection and anastomosis of the bowel. Its measurement proved to be useful on the third and fifth PODs with cutoff values of 137.5 and 171.5 mg/l, respectively. Serial measurement during the first postoperative week is a better early predictor. The same could not be shown for measuring serum CRP nor for blood and drain TLC.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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