The role of biomarkers in the early detection of dehiscence of intestinal and colonic anastomoses

Original Article

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ABSTRACT

Background: Anastomotic leakage is a major complication after intestinal and colorectal surgery. Diagnosis is usually established days after it has occurred, which is associated with high morbidity and mortality. Inflammatory markers have been proposed to predict the incidence of anastomotic leakage.

Objective: The aim was to evaluate the role of C-reactive protein (CRP), white cell count, gamma-glutamyl transferase, CRP/albumin ratio (CAR), neutrophil/lymphocyte ratio (NLR) and hyponatremia in early detection of anastomotic leakage (AL)in preclinical stage following open and laparoscopic colorectal and intestinal surgery.

Patients and Methods: A longitudinal prospective cohort study included patients admitted to the general surgery department. Patients were indicated for intestinal anastomosis and were eligible for inclusion. Among them, 55 were on elective settings, and 50 in emergency settings.

Results: A total of 105 patients were included. They had a mean age of 49.0±15.1 years and 61% of them were males. Twenty (19%) patients developed postoperative anastomotic leakage, among those, 6 were on the sixth postoperative day. CAR day 3 and CAR day 5 were significantly higher among the mortality patients with *P values* of 0.041 and 0.027, respectively. CRP level was significantly higher among patients with poor survival outcomes (*P value= 0.024*). CRP trajectory was significantly associated with a mortality rate as patients who had a rise greater than 50 mg/dl between day 3 and day 5 had a higher mortality rate with a *P value* of 0.007.

Conclusion: CRP trajectory, CAR and Neutrophil/lymphocyte ratio can significantly predict the incidence of anastomotic leakage. Settings of surgery (emergency) was an independent risk factor for development of postoperative leakage.

Key Words: Biomarkers, dehiscence, intestinal anastomosis, leakage.

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INTRODUCTION

Intestinal anastomosis is one of the most performed surgical procedures, especially in the emergency setting where a section of bowel is removed and then anastomosis of the ends is done[1,2].

Anastomotic leakage, defined as a defect of the intestinal wall at the anastomotic site, is a life-threatening complication. Proper understanding of the mechanism of healing is important to reduce this complication[3–5].

Despite the advances in operative and stapling techniques, the incidence of leakage remains high[6]. Once diagnosed late, it is usually associated with sepsis, and systemic manifestations leading to higher mortality among patients[7]. Early diagnosis of leakage results in improvements in morbidity and mortality rates[8].

Clinical signs of anastomotic leak are sometimes confusing and may occur late. Radiological and laboratory tools (biomarkers) can aid in diagnosing anastomotic leak at an early stage[9].

A biomarker is defined as a substance that is measured objectively as an indicator of a pathogenic process[10]. For many years, C-reactive protein (CRP) and white cell count (WCC) were used to identify septic complications[11,12]. Gamma-glutamyl transferase (GGT) and neutrophil□to□ lymphocyte ratio (NLR) are also well-known acute phase reactant[13,14].

The ratio of CRP to albumin has been used as a predictor of postoperative complications in intestinal and colorectal surgery, and the ratio has higher diagnostic accuracy than CRP alone[15].

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Recently, the presence of hyponatremia has been shown to be an indicator of peritonitis after perforation[16].

For the purpose of this study, we chose some inflammatory serum biomarkers: CRP, WCC, GGT, CAR, NLR, and hyponatremia and sought to assess their utility with respect to reliably predicting intestinal anastomotic leakage.

PATIENTS AND METHODS:

We conducted a longitudinal prospective cohort study between March 2021 and January 2022. It included 105 consecutive patients who were candidates for bowel anastomoses for various pathologies. Patients were enrolled from elective and emergency general surgery departments of a tertiary hospital. Patients included had a laparoscopic or open approach and had anastomoses using handsewn or stappling techniques. We excluded those on immunosuppressive drugs, uncontrolled diabetic patients, and severe bowel inflammatory disorders.

A written informed consent was obtained after proper orientation for all the steps of procedures, anticipated benefits and potential risks and the objectives of the study. Participation was voluntary, only those who agreed were included and the participant may discontinue participation at any time. Strict confidentiality and privacy were maintained throughout the process of data collection, entry, and analysis as declaration of Helsinki.

Detailed history was obtained from the participants including personal, demographic and medical history. They were subjected to physical examination including general and full abdominal examination.

Preoperative laboratory investigations were done including complete blood picture (CBC), kidney function test (creatinine, urea), liver function test alanine transaminase (ALT), aspartate transferase (AST), Bilirubin, and Albumin), coagulation profile, international normalized ratio (INR), PT, and PC), and serum electrolytes (sodium, potassium). Endoscopic and radiological evaluation was done according to the diagnosis.

Operative procedures: All patients were given antithrombotic and antibiotic prophylaxis, mechanical and chemical bowel preparation for elective left colonic resections, and on table lavage for emergency left colonic resections. In open approach, a midline exploratory incision was used except for those presented with strangulated hernias who were operated through incision directly over the hernias. Laparoscopic approach was applied in elective settings.

The type of resection and anastomosis was tailored according to patient's condition. The anastomosis was done either end to end, end to side or side to side. It was done either hand-sewn or using stappling devices. Blood loss, operative time, and need for postoperative ICU admission were documented for each patient.

Patients were under Enhanced Recovery after Surgery (ERAS) pathways, they were encouraged to start sips of water or clear fluids during the first postoperative day, followed by a larger amount on day 2 then the oral intake was increased gradually according to patients' tolerance.

Postoperative laboratory tests were measured 8 h after incision (day 0), and on the third (day 3) and fifth (day 5) postoperative days. CBC with differential counts (neutrophils, and lymphocytes) and relative neutrophil/ lymphocytes ratio (NLR), calculated using the following equation = neutrophil % / lymphocytes %, were measured, CRP, and liver function tests including albumin, CRP/ Albumin ratio was calculated using the following equation = CRP (mg/dl) /Albumin level (gm/dl). GGT and serum sodium (Na) levels were also assessed.

Anastomotic leak was defined as a defect within the anastomosis requiring operative intervention, or a collection adjacent to the anastomosis requiring radiological intervention diagnosed by clinical signs with radiological evidence.

All patients were instructed to follow up in the general surgery outpatient clinics on weekly visits for 30 days from the operative day, they were instructed about alarming symptoms for leakage (pain, discharge or fever).

Sample size

Source of sample size calculation was performed using power and sample size calculator program version 3.0.43. It was based on these inputs: Power of 80% significance with the level of 0.05 alpha error. Using the estimated sensitivity of TLC 95% estimated problem prevalence 60%. The total number of patients was estimated as N =105 patients.

Statistical analysis

Statistical analysis will be done using IBM SPSS Statistics version 22 (IBM CORP., Armonk, NY, USA). Numerical data were expressed as mean and standard deviation. Qualitative data were expressed as frequency and percentage. Comparison of means was conducted using student T test after normality testing. Sensitivity analysis was conducted to estimate the predictability of laboratory tests for postoperative anastomotic line leakage. A binary regression model was conducted to assess risk factors for the incidence of postoperative leakage. All tests were two-tailed. A *P value* less than 0.05 was considered significant.

RESULTS:

Our study included 105 patients who fulfilled our criteria. They had a mean age of 49.0±15.1 years, ranging from 18 to 75 years old. Males represented 61%. Thirty-seven (35.2%) patients underwent small bowel resection and anastomosis, 27 (25.7%) patients underwent right hemicolectomy, stoma closure in 10.5%, and left hemicolectomy in 26.7%.

Almost half of the included patients (52.4%) had an elective intervention, while 47.6% had an emergency operation. End-to-end anastomosis was the most reported type among the included patients (78.1%), side end represented 4.8% and 17.1% were side to side. Anastomoses were hand sewn in 67.6% and stapler made in 32.4% of cases (Table 1).

Twenty (19%) patients developed postoperative anastomotic leakage, among those, 6 were on postoperative day 6, followed by 4 on day 7, 3 on day 5,3 on day 9, 2 on day 4, and one patient on 3rd day and 10th day each (Fig. 1).

Table 1: Operative details of the included patients

	Count	Percent
Operative procedures		
Stoma closure	11	10.5
Left colectomy and sigmoidectomy	28	26.7
Right colectomy	27	25.7
Small bowel resection anastomosis	37	35.2
Total colectomy	2	1.9
Settings of surgery		
Emergency	50	47.6
Elective	55	52.4
Type of anastomosis		
End to end	82	78.1
End to side	5	4.8
Side to side	18	17.1
Mode of anastomosis		
Hand sewn	71	67.6
Stapler	34	32.4

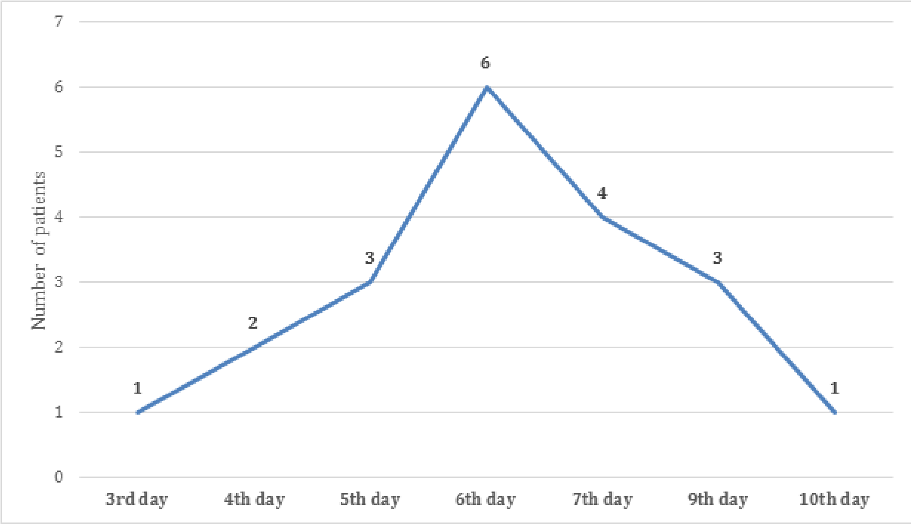

Fig. 1: Chart showing the timing of postoperative leakage.

There was no statistically significant difference regarding demographics and operative details based on the incidence of leakage among the included patients (*P values >0.05* each) except for the setting of the surgery, where emergency patients suffered from leakage more than elective setting patients with a *P value* 0.001 (Table 2).

Table 2: Comparison of demographics and operative details based on the incidence of postoperative leakage

	Leakage				
	No		Yes		
	Count	%	Count	%	*P* value
Age (Mean)	47.8	14.2	52.0	17.1	0.11
Sex					
Female	35	41.1	6	30	0.75
Male	50	58.9	14	70	
Operative procedure					
Stoma closure	10	11.8	1	5	0.7
Left hemicolectomy and sigmoidectomy	23	27.1	5	25	
Right hemicolectomy	22	25.9	5	25	
Small bowel resection anastomosis	28	32.9	9	45	
Total colectomy	2	2.4%	0	0	
Type of anastomosis					
End to end	66	77.6	16	80.0	0.93
End to side	4	4.7	1	5	
Side to side	15	17.6	3	15	
Mode of anastomosis					
Hand sewn	55	64.7	16	80.0	0.08
Stapler	30	35.3	4	20.0	
Settings of surgery					
Elective	49	57.6	6	30%	0.001
Emergency	36	42.4	14	70%	

Our results revealed that TLC greater than 10.55on the fifth postoperative day was a sensitive indicator for diagnosis of postoperative leakage of anastomotic line with *P value 0.0001*, sensitivity 93.3%, specificity 64% and area under the curve (AUC) 92.2%. As well, TLC greater than 10.7 on day 0 and greater than 10.4 on the 3rd postoperative day can significantly predict postoperative leakage (Table 3) (Fig. 2).

Table 3: Sensitivity analysis showing the predictability of WBCs count for postoperative leakage

TLC	Area	Cutoff point	Sensitivity [*n* (%)]	Specificity [*n* (%)]	*P* value	95% Confidence interval	
TLC day 0	0.633	10.7	70.0	40	0.033	0.513	0.753
TLC day 3	0.830	10.4	90.0	40	0.0001	0.731	0.928
TLC day 5	0.922	10.55	93.3	64	0.0001	0.839	1.000

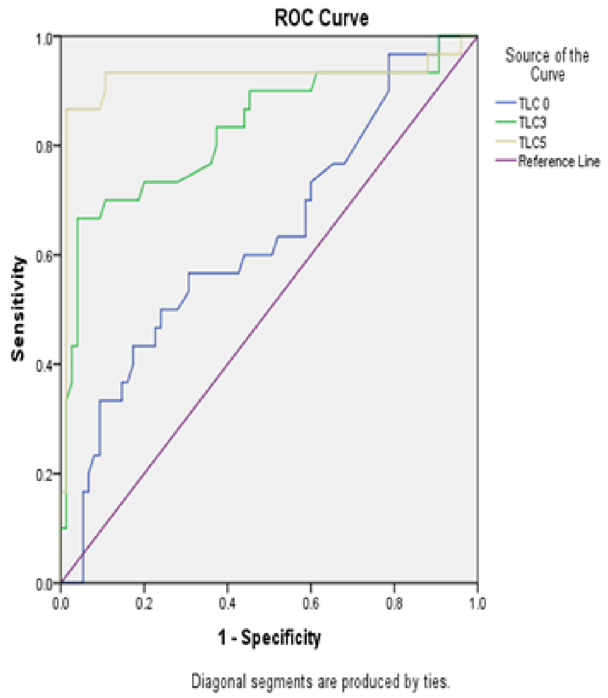

Fig. 2: Receiver operating characteristic curve showing predictability of TLC for incidence of leakage postoperatively.

Post-operative AL was significantly associated with CRP trajectory as all patients with rise greater than 50 mg/dl suffered leakage, while only 35.6% of patients who had rising CRP <50 mg/dl had postoperative AL.CRP trajectory can significantly predict the incidence of AL using the cut off 24 mg/dl rise of CRP between day 3 and day 5 with sensitivity 93.3%, specificity 92%, and AUC 98.1%.

CAR can significantly predict the incidence of postoperative leakage when using cutoff point 18.1 on day 0, 34.1 on the 3rd and 64.6 in the 5th postoperative day with *P values* 0.003, 0.0001 and 0.0001 respectively, and sensitivity ≥90% for each of the three levels. Specificity on the other hand was 26.7%, 52% and 94.7% respectively (Table 4) (Fig. 3).

Table 4: Sensitivity analysis showing the predictability of CRP/Albumin ratio for postoperative leakage

CRP/Albumin ratio (CAR)	Area	Cutoff point	Sensitivity	Specificity	*P*-value	95% Confidence Interval	
CAR day0	0.686	18.1	90%	26.7%	0.003	0.571	0.802
CAR day 3	0.910	34.1	96.7%	52%	0.0001	0.852	0.967
CAR day 5	0.995	64.6	96.7%	94.7%	0.0001	0.987	1.000

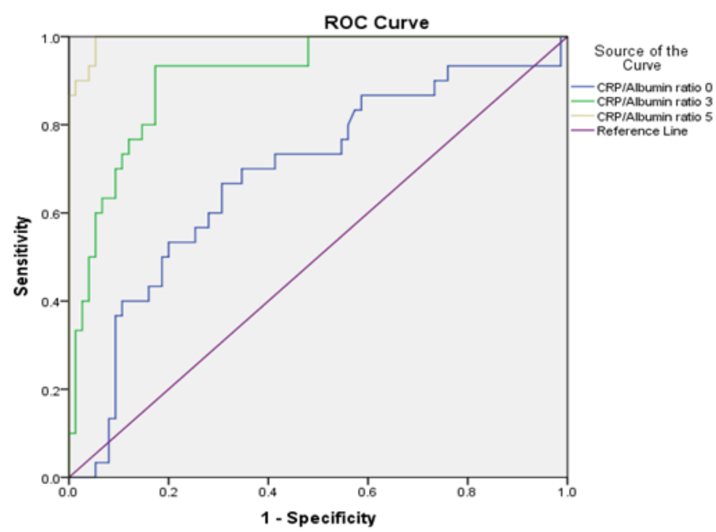

Fig. 3: ROC curve showing predictability of CRP/Albumin ratio for incidence of leakage postoperatively.

Regarding NLR, it can also significantly predict the incidence of leakage when using cutoff point 3.3 on day 0, 4.0 on the 3rd and 4.1 on the 5th postoperative day with *P-value* 0.002, 0.0001 and 0.0001 respectively, and sensitivity 90%, 96.7%, and 96.7% and specificity 32%, 53.3% and 75% respectively (Table 5) (Fig. 4).

However, Sodium and GGT levels couldn't significantly predict the incidence of postoperative leakage where *P-value* was *>0.05* on day 0, day 3 and day 5 for both biomarkers (Table 6).

By further analysis, the binary regression model showed that setting of surgery (emergency) was an independent risk factor for development of postoperative leakage with OR 5.77 (95% CI 1.2–27.5) and *P-value* 0.028 (Table 7).

This study revealed that there was a significant association between higher mortality rate and the presence of anastomotic leakage with *P values <0.05*.

CAR day 3 and CAR day 5 were significantly higher among patients who died postoperatively (*P-value 0.041* and *0.027* respectively). Besides, CRP level was significantly higher among patients with poor survival outcome with *P-value 0.024*.

CRP trajectory was associated with increased mortality as patients who had a rise >50 mg/dl between day 3 and day 5 had a significantly higher mortality rate with *P-value 0.007* (Table 8).

Table 5: Sensitivity analysis showing the predictability of neutrophil/lymphocytes ratio for postoperative leakage

Neutrophil/ lymphocyte ratio (NLR)	Area	Cutoff point	Sensitivity	Specificity	*P*-value	95% Confidence Interval	
NLR day 0	0.690	3.3	90.0%	32%	0.002	0.582	0.798
NLR day 3	0.887	4.0	96.7%	53.3%	0.0001	0.814	0.959
NLR day 5	0.960	4.1	96.7%	75%	0.0001	0.918	1.000

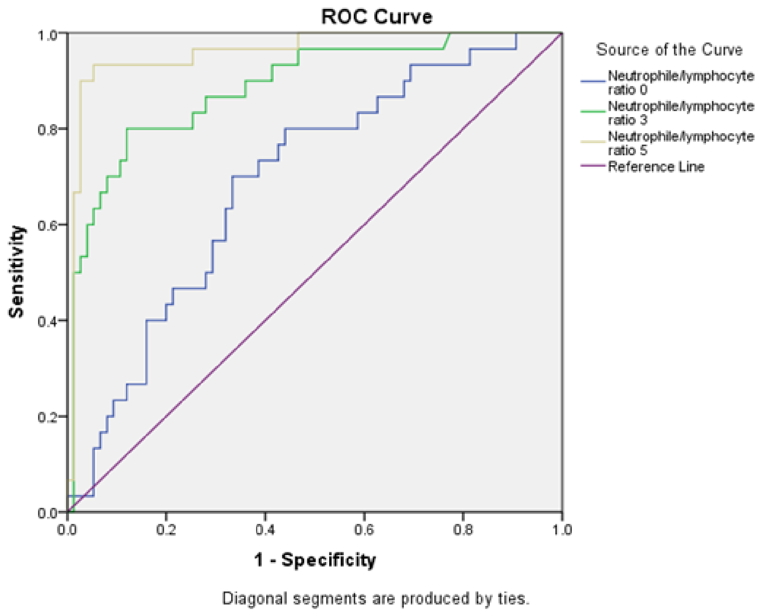

Fig. 4: ROC curve showing predictability of neutrophil/lymphocytes ratio for incidence of leakage postoperatively.

Table 6: Sensitivity analysis showing the predictability of sodium and GGT levels for postoperative leakage

	Area	Cutoff point	Sensitivity	Specificity	*P*-value	95% Confidence Interval	
Sodium day 0	0.497	135	80.0%	28%	0.960	0.377	0.617
Sodium day 3	0.379	135.4	73.3%	13.3%	0.054	0.261	0.497
Sodium day 5	0.379	135.8	80.0%	12%	0.053	0.259	0.499
GGT day 0	0.495	20.5	66.7%	44%	0.932	0.374	0.615
GGT day 3	0.499	20.5	70.0%	36%	0.986	0.374	0.624
GGT day 5	0.516	20.5	70.0%	32%	0.793	0.392	0.641

Table 7: Binary regression analysis model to assess risk factors for postoperative leakage

							95% Confidence Interval	
	B	S.E.	Wald	df	*P*-value	OR	Lower	Upper
Age	0.013	0.015	0.675	1	0.411	1.013	0.983	1.043
Females	0.137	0.458	0.090	1	0.765	1.147	0.467	2.817
Emergency surgery	1.754	0.796	4.852	1	<u>0.028</u>	5.777	1.213	27.505
Stapler	−0.787	0.870	0.818	1	0.366	0.455	0.083	2.504
Constant	−2.22	0.903	6.047	1	0.014	0.109		

Table 8: Comparison of demographics, vital sign and laboratory findings based on prevalence of postoperative mortality

	Mortality				
	Lived (Mean/SD)		Died (Mean/SD)		
	count	%	count	%	*P*-value
Age	48.4	15.2	61.2	6.1	0.05
Gender					
Female	41	41.0%	0	0.0%	0.067
Male	59	59.0%	5	100.0%	
Mode of anastomosis					
Hand sewn	66	66.0%	5	100.0%	0.11
Stapler	34	34.0%	0	0.0%	
Anastomotic Leak					
No	84	84.0%	1	20.0%	<u>0.009</u>
Yes	16	16.0%	4	80.0%	
Setting of surgery					
elective	54	54.0%	1	20.0%	0.17
emergency	46	46.0%	4	80.0%	
CRP/Albumin ratio day 0	28.02	13.9	34.3	13.2	0.20
CRP/Albumin ratio day 3	46.6	27.5	65.9	21.9	<u>0.041</u>
CRP/Albumin ratio day 5	56.1	42.4	118.7	53.9	<u>0.027</u>
Neutrophile/lymphocyte ratio day 0	6.6	6.4	7.4	3.4	0.13
Neutrophile/lymphocyte ratio day 3	7.2	8.02	9.89	5.89	0.14
Neutrophile/lymphocyte ratio day 5	7.03	7.18	12.48	6.92	0.09
Sodium day 0	138.1	4.7	137.8	4.4	0.83
Sodium day 3	138.6	4.1	138.9	2.9	0.72
Sodium day 5	139	4	143	10	0.59
GGT day 0	22.3	9.1	24.7	8.2	0.48
GGT day 3	24.5	10.8	26.8	12.9	0.80
GGT day 5	24.6	9.7	26.6	17.1	0.71
CRP day 0	83.0	36.3	81.9	30.7	0.76
CRP day 3	124.5	55.5	155.6	56.3	0.14
CRP day 5	142.4	82.1	255.7	101.1	<u>0.024</u>
CRP trajectory					
Doubling (rise > 50 mg/dl)	11	11.0%	3	60.0%	<u>0.007</u>
Fluctuating (rise then decline)	45	45.0%	1	20.0%	
Rising (rise <50 gm/dl)	44	44.0%	1	20.0%	

DISCUSSION

Anastomotic leakage (AL) is a major complication after intestinal and colorectal surgery due to its severity and high frequency[17].

Diagnosis could be delayed days after it has occurred, where the patient could be already in an advanced stage of sepsis, which is associated with a high rate of morbidity, mortality, and need for re-operation[18].

In the current work, we conducted A prospective longitudinal cohort study which included 105 patients, they were admitted to general surgery department, among them 55 were on elective settings, and 50 on emergency settings, aiming at evaluating the role of CRP, WCC, GGT, CAR, NLR, and hyponatremia in detection of early anastomotic leakage in preclinical stage following open and laparoscopic surgery.

The study participants had a mean age 49.0±15.1 years, ranging from 18 – 75 years old with males representing 61%. Twenty patients (19%) developed postoperative anastomotic line leakage, among those, 6 were on the 6th postoperative day.

These findings are considerably higher than reported in several studies that found the incidence of postoperative AL was 3.2–13.7%[19].

The higher incidence of postoperative leakage among the current cohort can be explained by the large proportion of patients who conducted their surgical interventions in emergency settings (47.6%) with relative inadequacy of perioperative preparations and associated poor general condition. Emergency settings had a significantly higher prevalence of anastomotic leakage. Besides, emergency operation was shown to be an independent risk factor for development of postoperative leakage (P value 0.028).

These findings are consistent with Kingham *et al*., and Boccola *et al*., who highlighted emergency surgical setting is an independent risk factor for development of postoperative AL[20,21].

Additionally, our results showed that the surgical technique regarding hand sewn anastomosis versus stapler did not affect the rate of development of postoperative AL. Similarly, a large meta-analysis, including 1,120 patients who underwent different types of intestinal resections, showed that there was no superiority over any modality of either stapler or hand sewn in decreasing postoperative AL[22].

Several studies have highlighted the role of CRP changes during the postoperative period as a predictor for AL with diagnostic accuracy 98.1%, offering an accurate excluding test for early discharge for patients with assuring CRP- trajectory (negative predictive value 99.3%)[23,24].

In concordance, postoperative AL was significantly associated with CRP trajectory in the present study, as all patients with rise greater than 50 mg/dl suffered leakage, while only 35.6% of patients who had rising CRP less than 50 mg/dl had postoperative AL. Hence, we can say that CRP trajectory can significantly predict the incidence of AL using the cut off 24 mg/dl rise of CRP between day 3 and day 5 with sensitivity 93.3%, specificity 92%, and AUC 98.1%.

Other research confirms the importance of CRP trajectory for the detection of AL as the study by Smith *et al*. in 2018 which reported a sensitivity 93%, and diagnostic accuracy 98.1% of CRP trajectory for the detection of AL between days 3, 4, and 5 postoperatively[23]. Also, Stephensen *et al*. reported that CRP trajectory greater than 50 mg showed a sensitivity 85%, negative predictive value 99% and overall diagnostic accuracy 97% in detection of postoperative AL[24].

Another biomarker, CRP/Albumin ratio (CAR), has been shown to significantly predict the incidence of postoperative leakage as concluded from the results of this study. Using cutoff point 18.1 on admission, 34.1 on the third and 64.6 on the fifth postoperative day CAR shows a of sensitivity 90, 96.7, and 96.7%, specificity 26.7, 52 and 94.7%, respectively.

Although less sensitivity and specificity were reported, a recent study by Paliogiannis *et al*. reported that CAR greater than 46 showed a good predictability for AL with sensitivity 76%, specificity 87% and overall diagnostic accuracy 82.5% in the fourth postoperative day[25].

Also, a recently investigated biomarker model to predict AL among patients who underwent esophagectomy showed that CAR was the key indicator of the most effective decisional model, and it was significantly higher in patients who developed leakage[26].

Other investigators demonstrated that CAR could help to identify patients with a high probability of all types of postoperative complications after colorectal surgery, including mortality[15].

Anastomotic leakage can be defined as a postoperative infection sequalae leading to disruption of anastomotic suture line, this was justified by the increase in neutrophils number and decline in lymphocytes that associate the postoperative inflammatory status[27] Assessment of neutrophil/ lymphocytes ratio (NLR) has been previously investigated as a tool for prediction of infectious perioperative complications[28,29].

In the current study, TLC greater than 10.5 on the fifth postoperative day was found to be a sensitive indicator for diagnosis of postoperative leakage of an anastomotic line with sensitivity of 93.3%, specificity 64% and AUC 92.2%. As well, TLC greater than 10.7 on admission and greater than 10.4 on the third postoperative day can significantly predict postoperative leakage.

In agreement with these results, a study assessed the association between TLC and AL, and showed that there was a statistically significant difference in the levels of serum TLC in the first and third postoperative days[30].

However, our findings disagree with Vaziri-Moghadam *et al*. and Scepanovic *et al*.who reported no significant rise in TLC among patients who developed postoperative AL. This conflict could be explained by the elective settings of surgeries conducted in the mentioned studies with baseline normal TLC among the included patients[31,32].

It has been suggested that sodium levels can be used as a biomarker since hyponatremia has been reported among postoperative patients with elevated CRP. This proposed the hypothesis that sodium is involved in acute phase reaction postoperatively[33,34]. However, in the current study, sodium level couldn't significantly predict the incidence of postoperative leakage among the study patients.

Similarly to sodium levels, GGT level could not predict the incidence of postoperative leakage among the studied population. These findings are similar to ones reported by Smith *et al*. who stated that GGT did not show any association with postoperative colorectal AL[23].

Regarding mortality among the study participants, it is worth noting that anastomotic leakage was significantly associated with a higher mortality rate. These findings are supported by several studies in literature. A study investigating the impact of AL on long-term mortality in patients alive 120 days after curative resection for colonic cancer found that AL was associated with increased long-term mortality[35]. Another study confirmed that patients who experience an AL have lower rates of survival at 30 days and as well as on long term[36].

In the current study, CAR day 3 and CAR day 5 were significantly higher among patients who died postoperatively. CRP level was significantly higher as well among patients with poor survival outcome. CRP trajectory was associated with increased mortality as patients who had a rise greater than 50 mg/dl between day 3 and day 5 had a significantly higher mortality rate with *P value* 0.007. These results were in agreement with a study in 2021 demonstrating the significant ability of CAR to detect 30-day postoperative mortality after colorectal surgery[25].

CONCLUSION

Biomarkers can significantly predict the incidence of anastomotic leakage. CRP trajectory, TLC, CAR, NLR all have high sensitivity and specificity in predicting leakage. However, Sodium and GGT levels could not significantly predict its incidence. Settings of surgery (emergency) are an independent risk factor for development of postoperative leakage. CRP trajectory is significantly associated with mortality rate as in patients who had a rise greater than 50 mg/dl.

CONFLICT OF INTEREST

There are no conflicts of interest.

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