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Early Prediction of Anastomotic Leakage Following Colorectal Surgery by Measuring Haematological and Biochemical Markers

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Abstract

Background: Post-operative anastomotic leakage (AL) is a common and severe complication following colorectal surgery that leads to high morbidity and mortality. Early prediction and risk stratification is very essential in reducing clinical consequences of AL. Therefore, this study aimed to determine the relation of hematological and biochemical markers with AL among the patients underwent colorectal surgery.

Objectives: The aim of the study was to assess the predictive value of haematological and biochemical markers for anastomotic leakage after colorectal surgery.

Methods: This prospective analytical type of study was conducted at the Department of Surgery, Dhaka Medical College & Hospital, and Dhaka for a period of one year from November 2020 to October 2021. A total of 70 patients who underwent colorectal surgery were included by convenient, consecutive sampling as study patients according to inclusion and exclusion criteria. Each patient was subjected to detail clinical evaluation along with history taking a standard guideline was followed during post-operative management. A semi-structured questionnaire and collected data were analysed by using the statistical software SPSS 27.

Results: Mean age of the study patients was 63.6±7.09 (SD) years with a male predominance (88.1% male and 11.9% female). At 4th postoperative day, WBC, NLR, PLR and CRP were higher in patients with AL and serum albumin was lower in patients with AL ($p<.05$). In predicting AL, NLR, WBC, CRP, PLR and serum albumin showed a sensitivity of 63.3%, 72.7%, 81.8%, 72.7%, 72.7% accordingly. The specificity were 74.6%, 78%, 71.2%, 71.2%, 66.1% accordingly and the respective cut-off value were 8.7, 9.1/109l, 9.98 gm/l, 205, 3.03 gm/dl.

Conclusions: According to present study findings, NLR, WBC, CRP, PLR and serum albumin might play a valuable role in predicting AL among the patients underwent colorectal surgery. But before validating this finding, further extensive study is recommended.

Keywords: Anastomotic leakage; Colorectal Surgery; Haematological; Biochemical

Introduction

Colorectal surgeries are performed due to colon cancer, rectal cancer, complicated diverticular disease, colonic perforation, colonic volvulus, familial adenomatous polyposis, appendicular tumour, ulcerative colitis and colostomy owner. Colorectal surgeries include right hemicolectomy, transverse colectomy, left hemicolectomy, sigmoid colectomy, subtotal/total colectomy, anterior resection, colocolic anastomosis, and Hartman reversal [1]. Complications after intestinal resection and anastomosis include bleeding, stricture, and anastomotic leakage [2]. Anastomotic leakage is defined as the presence of pus or enteric contents within the drains, presence of abdominal or pelvic collections in the area of anastomosis on postoperative imaging, leakage of contrast through the anastomosis during an enema or evident anastomotic dehiscence at reoperation for postoperative peritonitis [3]. It is one of the most dreaded complications following colorectal surgery, with rates of 3-27% depending on specific risk factors [4]. It typically becomes clinically apparent between the 5th and 8th postoperative days. If diagnosed late, anastomotic leakage (AL) can progress to overwhelming sepsis, multiple organ dysfunction, and death [2,4,5]. Delayed diagnosis and subsequent delay in antibiotic administration from the onset of septic shock have been associated with a decrease in survival of 7.6 percent per hour. [6] Long-term consequences of significant AL may include increased risk of colorectal cancer recurrence, reduced quality of life, and decreased long-term survival. Thus, an early prediction of AL before clinical symptoms become apparent is of utmost importance [7-9]. Fever, pain, tachycardia, peritoneal purulent or faecal drain, and dynamic ileus have commonly been suggested as clinical signs of AL. The mean time to clinical diagnosis was 6-12 days after surgery [10-14]. Several biochemical and hematological markers have been proposed to be associated with AL, such as leukocyte count, C-reactive protein (CRP), serum procalcitonin (PCT) levels, hypoalbuminemia, neutrophil-lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), and derived neutrophil-lymphocyte ratio (dNLR). Patients with anastomotic leakage (AL) had significantly greater mean WBC and neutrophil values but lower mean lymphocyte values on the 4th POD [15-19]. In addition, the mean NLR, dNLR, and PLR values were consistently greater in patients who developed AL. Among the blood cell indexes of inflammation evaluated, NLR on the 4th postoperative day showed the best ability to predict AL with a cut-off value of 7.1. Nevertheless, its potential usefulness in daily practice needs to be further evaluated in prospective studies. CRP is a nonspecific acute-phase protein [19]. In some retrospective studies, it was observed that from the second postoperative day onwards, mean serum CRP was found to be significantly higher (>140 mg/L) in the group who developed AL, and this marker remained elevated until the diagnosis of the complication. Again, its potential usefulness in daily practice needs to be further evaluated in prospective studies [16,20]. Preoperative hypoalbuminemia, a well-known indicator for malnutrition, is one of the most prevalent risk factors associated with postoperative complications in colorectal surgery, including anastomotic leakage. In a retrospective study, it was found that postoperative serum albumin levels in AL were significantly lower than those in nonanastomotic leakage (NAL) on POD 0, POD 1, POD 3, and POD 7 [21-23]. As this was a retrospective study and there is no other study regarding this predictor, it demands a prospective study before clinical implication [24]. Compared with the other biochemical and hematological markers, procalcitonin was found to be the most reliable biomarker for the early diagnosis of anastomotic leak. However, stressing the issue of increased costs, as determination of serum PCT concentration is 4-20-fold more expensive than the estimation of CRP level, we do not include it in our study [25]. Therefore, in the present study, we investigated the role of postoperative leukocyte count, NLR, PLR, CRP, and serum albumin as early predictive markers of anastomotic leakage following colorectal surgery (CRS).

Methods

This prospective analytical type of study was conducted at the Department of Surgery, Dhaka Medical College & Hospital, and Dhaka for a period of one year from November 2020 to October 2021. A total of 70 patients who underwent colorectal surgery were included by convenient, consecutive sampling as study patients according to inclusion and exclusion criteria. Each patient was subjected to detail clinical evaluation along with history taking. All patients underwent relevant investigations when needed. White blood cell (WBC) count, Neutrophil lymphocyte ratio (NLR), Platelet lymphocyte ratio (PLR), C-reactive protein (CRP) and Serum albumin level were measured pre-operatively and at 1st and 4th post-operative day (POD). A standard guideline was followed during post-operative management. A semi-structured questionnaire and collected data were analysed by using the statistical software SPSS 27.

Results

Male patients were significantly more likely to have AL than female patients (63.6% vs 36.4%, p=0.040), and the mean age of the patients was significantly higher among AL than non-AL patients (68.3±1.79 vs 62.8±6.01, p=0.004). Patients with AL had a significantly lower mean BMI value (16.6±0.90 vs 21.2±3.51, p= 0.002) and more than 10% weight loss in the preceding 6

months (81.8 vs 27.1, p=0.001) (Table 1). The majority of the patients had a normal BMI (62.9%), followed by 21.4% who were underweight and 11.4% and 4.3% who were overweight and obese, respectively. Among the AL patients, the majority had a fitness grade of III (54.5%) compared to non-AL patients (18.6%). Moreover, among AL and non-AL patients, 36.4% and 57.6% had a fitness grade of II, respectively.

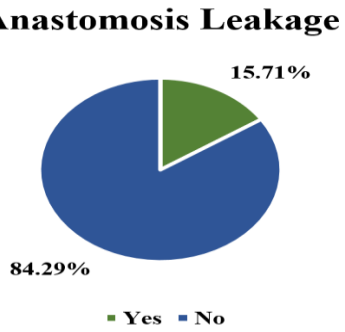

***Figure 1**: Incidence of anastomotic leakage among the study patients (n=70). Among the 70 patients, 11 (15.7%) patients were reported to have anastomotic leakage.*

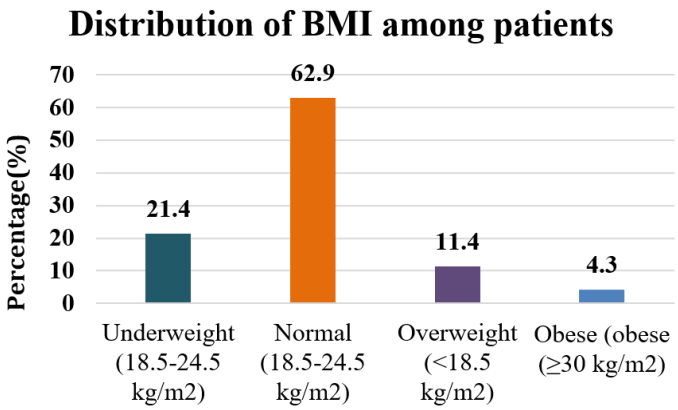

***Figure 2**: Distribution of nutritional status according to BMI among the patients (n=70).*

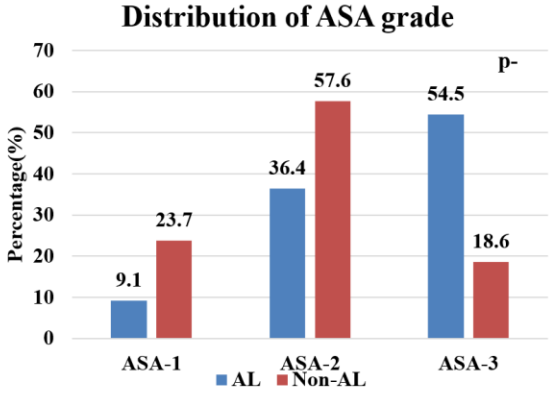

***Figure 3:** Distribution of ASA fitness grade among the AL and non-AL patients (n=70)*

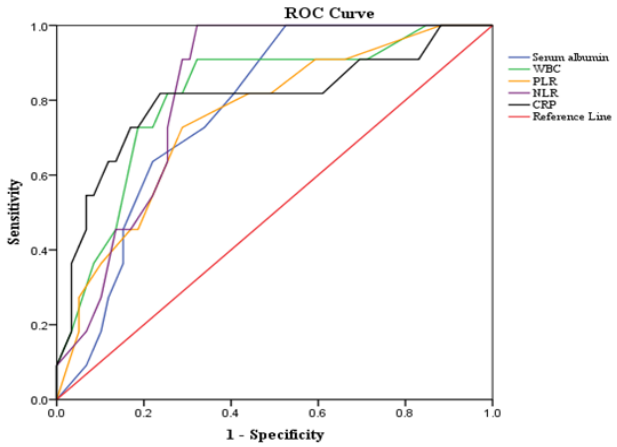

***Figure 4**: ROC curves of WBC, NLR, PLR and CRP in predicting anastomotic leakage (n=70).*

There was a significantly higher fitness grade among AL than non-AL patients (p=0.037). Among the patients, the surgery type played a significant role in the increased risk of AL (p=0.007), and transverse colectomy and total colectomy increased the risk of AL (27.3%) compared with other surgery types. As shown in Table 4.3, no significant differences were found preoperatively between patients with and without anastomotic leakage in the median values of WBCs count, NLR and PLR. On the first postoperative day, the PLR was significantly higher (AL-213 vs non-AL-190, p<0.001). However, the greatest significant differences were registered on the 4th postoperative day. On that day, patients with AL had significantly greater WBC (12 vs 6.36, p=0.014) and NLR (9.34 vs 5.6, p < 0.0001) values, PLR (213 vs 190, p-0.031). AL-with anastomotic leakage, non-AL-without anastomotic leakage, NLR-neutrophil to lymphocyte ratio, PLR-platelet to lymphocyte ratio, WBC-white blood cell count. As shown in Table 4, no significant differences were found preoperatively between patients with and without anastomotic leakage in the median values of C-reactive protein and serum albumin (p>0.05). On the first postoperative day, the serum albumin level was significantly lower (AL-2.9 vs non-AL-3.4, p<0.001). However, the greatest significant differences were registered on the 4th postoperative day. On that day, patients with AL had significantly greater CRP (17.6 vs 8.48, p<0.001) and significantly lower serum albumin level (AL-2.8 vs non-AL-3.1, p=0.005). AL-with anastomotic leakage, non-AL-without anastomotic leakage, CRP-C-reactive protein While assessing the reports of 1st and 4th postoperative day among the AL patients it was observed that the WBC,PLR,NLR was significantly higher and serum albumin level was significantly lower at the 4th postoperative day(p<0.05). There was no significant rise in the CRP level on the 4th postoperative day compared to the 1st postoperative day. POD-Postoperative day, AL with anastomotic leakage, NLR-neutrophil to lymphocyte ratio, PLR platelet to

lymphocyte ratio, CRP-C-reactive protein, WBC-white blood cell count. A ROC curve analysis was performed for the indexes that showed statistically significant differences between the two groups of patients on the 4th postoperative day (Table 6, Figure 4). NLR at a cut-off point of 8.7 showed the best AUC (0.827, 95% CI 0.73–0.93) with a sensitivity and specificity of 63.3% and 74.6%, respectively, followed by the WBC (0.814, 95% CI 0.68–0.95) at a cut-off point of 9.1 and CRP (0.802, 95% CI 0.63–0.97) .The AUC of PLR (0.75, 95% CI 0.60-0.90) and serum albumin (0.775, 95% CI 0.63–0.97) showed a relatively poor result compared to WBC and NLR and CRP.

***Table 1**: Distribution of demographic and clinical features of the patients with and without AL (n=70).*

Variables	All patient (n=70) n(%)	AL (n=11) n(%)	Non-AL (n=59) n(%)	p value*
Gender				
Male	59(84.3)	7(63.6)	52(88.1)	0.040
Female	11(15.7)	4(36.4)	7(11.9)	
Age				
Mean±SD	63.6±7.09	68.3±1.79	62.8±6.01	0.004
BMI(kg/m^2)				
Mean±SD	20.8±3.69	16.6±0.90	21.2±3.51	0.002
Weight loss in preceding 6 months (>10%)				
Yes	25(35.7)	9(81.8)	16(27.1)	0.001
No	45(64.3)	2(18.2)	43(72.9)	
Indication of surgery				
Malignant pathology	64(91.4)	9(81.8)	55(93.2)	
Benign pathology	6(8.6)	2(18.2)	4(6.8)	
Diabetes mellitus				
Yes	9(12.9)	2(18.2)	7(11.9)	0.566
No	61(87.1)	9(81.8)	52(88.1)	

***Table 2:** Distribution of type of surgery among the patients with and without AL (n=70)*

Variables	AL (n=11) n(%)	Non-AL (n=59) n(%)	p value*
Surgery type			
Right hemicolectomy	1(9.1)	22(37.3)	0.007
Left hemicolectomy	2(18.2)	18(30.5)	
Transverse colectomy	3(27.3)	4(6.8)	
Anterior resection	-	-	
Subtotal/Total colectomy	3(27.3)	6(10.2)	
Others	2(18.2)	9(15.3)	

***Table 3:** Comparisons of the median values of the hematological markars studied preoperatively and on the 1st and 4th postoperative days in patients with and without anastomotic leakage (n=70)*

Hematological markars	Patients (n=70)	Preoperative day Median(IQR)	1st postoperative day Median(IQR)	4th postoperative day Median(IQR)
WBC (/10^{9}L)	Non-AL	6.37(5.78-6.70)	9.87(9.0-10.4)	6.36(6.0-7.34)
	AL	6.40(5.78-6.70)	10.4(9.8-11.0)	12.0(10.0-14.0)
	p value*	0.879	0.308	0.014
NLR	Non-AL	2.2(2.0-2.8)	8(7.0-9.0)	5.6(4.3-6.3)
	AL	2.8(1.0-3.0)	9.0(8.0-9.0)	9.34(8.4-9.8)
	p value*	0.727	0.195	<0.001
PLR	Non-AL	176(159-183)	200(190-220)	190(180-200)
	AL	178(177-200)	210(200-260)	213(210-240)
	p value*	0.509	<0.001	0.031
P value obtained by Mann–Whitney U test				

***Table 4**: Comparisons of the median values of the biochemical markers studied preoperatively and on the 1st and 4th postoperative days in patients with and without anastomotic leakage (n=70).*

Biochemical markers	Patients (n=70)	Preoperative day Median(IQR)	1st postoperative day Median (IQR)	4th postoperative day Median (IQR)
CRP (mg/l)	Non-AL	0.60(0.32-0.93)	9.0(7.8-10)	8.48(7.6-8.9)
	AL	0.88(0.40-1.60)	13.6(12.3-15.4)	17.6(15.8-19)
	p value*	0.241	0.587	<0.001
Serum albumin (g/dl)	Non-AL	3.6(3.4-3.9)	3.4(3.4-3.5)	3.1(2.9-3.3)
	AL	3.8(3.5-3.9)	2.9(2.5-3.2)	2.8(2.3-2.9)
	p value*	0.354	<0.001	0.005
**p value obtained by Mann–Whitney U test*				

***Table 5**: Comparisons of the median values of the indexes studied on the 1st and 4th postoperative days in patients with AL (n=11).*

Hematological and biochemical markers	1st POD Median(IQR)	4th POD Median(IQR)	p value*
CRP(mg/l)	13.6(12.3-15.4)	17.6(15.8-19)	0.893
WBC(/10^9L)	10.4(9.8-11.0)	12.0(10.0-14.0)	<0.001
NLR	9.0(8.0-9.0)	9.34(8.4-9.8)	<0.001
PLR	210(200-260)	213(210-240)	<0.001
Serum albumin(g/dL)	2.9(2.5-3.2)	2.8(2.3-2.9)	<0.001
**p value obtained by Wilcoxon signed-rank test*			

***Table 6:** Receiver's operating curve (ROC) of the indexes under evaluation as predictive markers of anastomotic leakage*

Marker	AUC	95%CI	p value	Cutoff	Sensitivity	Specificity
WBC	0.814	(0.68-0.95)	0.001	≥ 9.11	72.7	78
NLR	0.827	(0.73-0.93)	0.001	≥ 8.7	63.3	74.6
PLR	0.754	(0.60-0.90)	0.008	≥ 205	72.7	71.2
CRP	0.802	(0.63-0.97)	0.002	≥ 9.98	81.8	76.3
Serum albumin	0.775	(0.66-0.89)	0.060	≤ 3.03	72.7	66.1

Receiver's operating curve (ROC) of the indexes under evaluation as predictive markers of anastomotic leakage is tabulated. AUC-area under the curve, CI-confidence interval, NLR-neutrophil to lymphocyte ratio, PLR platelet to lymphocyte ratio, CRP-C-reactive protein, WBC-white blood cell count. Significance at 0.05.

Discussion

In this study, 11 (15.7%) patients were reported to have anastomotic leakage. Male patients were significantly more likely to have AL than female patients (63.6% vs 36.4%, p=0.040), and the mean age of the patients was significantly higher among AL than non-AL patients (68.3±1.79 vs 62.8±6.01, p=0.004). Patients with AL had a significantly lower mean BMI value (16.6±0.90 vs 21.2±3.51, p= 0.002) and more than 10% weight loss in the preceding 6 months (81.8 vs 27.1, p=0.001). Patient age and sex were identified as AL risk factors in this study, which was also reported in a systemic review paper that identified male sex, age >60 years, and underweight as factors responsible for an increased risk of AL. Although the exact reason for this is unknown, it is thought that the narrower male pelvis and androgenic hormonal effects on the intestinal microvascular blood supply may play roles in AL development in male patients [26]. Adequate nutrition is an important factor for intestinal healing, as it contributes to collagen synthesis and immune responses [27]. Various studies have shown that patients who are malnourished (including obese patients) have preoperative weight loss. And an increased risk of AL [28,29]. Among the AL patients, it was observed that American Society of Anaesthesiologists (ASA) fitness grade III or above was more common (54.5%) than in non-AL patients (18.6%), and there was a significantly higher fitness grade among AL than non-AL patients (p=0.037), emphasizing that ASA grade is also an important independent AL risk factor. Moreover, multiple studies have also shown that the American Society of Anaesthesiologists (ASA) fitness score is also an independent AL risk factor. Patients with scores greater than grade III are associated with a 2.5-fold increased AL risk. Currently, there is no consensus as to whether metabolic diseases, such as diabetes mellitus increase the risk of AL, which corresponds to our findings [30-32]. A study conducted among Dutch patients undergoing colonic cancer resection with the creation of an anastomosis reported that surgical resection types

such as transverse resection, left colectomy and subtotal colectomy were independent risk factors for AL ($p<0.001$), which is in partial agreement with our study, as we have reported that transverse and subtotal colectomy and not left colectomy were risk factors ($p>0.05$) [30]. To our knowledge, simple blood count indexes, together with the NLR, have been demonstrated to have prognostic potential in several chronic pathologies and a potential role in predicting outcomes in surgical procedures. NLR is the most studied index for this purpose. Josse et al [33-35]. Retrospectively investigated its role in predicting complications in 583 patients who underwent surgical resection for suspected or confirmed colorectal cancer. The authors found that a preoperative NLR greater than or equal to 2.3 was significantly associated with a major perioperative complication rate, and we observed a similar finding in our study, where patients with AL had a median value of 2.8, which was more than 2.3 on the preoperative day, and the value increased gradually until the 4th postoperative day, hence providing evidence that the NLR is indeed a good index to study for determining postoperative complications [36]. Moreover, it was observed in the present study that the NLR at a cut-off point of 8.7 showed the best AUC (0.827, 95% CI 0.73–0.93), with a sensitivity and specificity of 63.3% and 74.6%, compared to the other markers considered in this study. These findings contradicted another recent study, performed in 44 patients, which reported a poor AUC (0.697) in predicting AL at an NLR cut-off value of 8.7, with sensitivity and specificity of 52% and 88%, respectively. [37] PLR in this study showed a gradual increase from preoperative day to 4th postoperative day in AL patients and was significantly higher at 1st and 4th postoperative day in AL patient than Non AL patient which corresponds to the finding in a study conducted among 1432 patients where PLR was significantly higher in AL patients in all the evaluations performed, with the statistical significance increasing from the preoperative to the 4th postoperative day. Additionally, in this case, the AUC on the 4th postoperative day was poor (AUC-0.632, sensitivity-74.5 and specificity-49.9) compared to our study (AUC-0.754, sensitivity-72.7 and specificity-71.2), but the finding deserves further evaluation in future studies [37]. Walker et al. published their results on the predictive roles of CRP in 136 patients retrospectively enrolled. Median CRP values were found to be significantly higher in patients with AL than in those with non-AL on postoperative days 2 through 5. ROC analysis evidenced that the cut-off for CRP (10.5 mg/dL) with the highest sensitivity (100%) and specificity (56.5%) was on postoperative day 5 as opposed to the cut-off value of CRP (9.98 mg/dL) with sensitivity 81.8 and specificity 76.3 in our study at the 4th postoperative day [37]. Another study reported that CRP was significantly higher in patients with anastomotic leakage, and the AUC for CRP was 0.869, and the AUC of CRP was 0.80 in this study, both indicating CRP as a good diagnostic marker in the early detection of AL [38]. In 200 CRC (colorectal cancer) patients undergoing curative laparoscopic surgery, univariate analysis showed that lower average levels of serum albumin on POD1 and POD3 ($p=0.0074$) and higher average levels of serum WBC and CRP on POD1 (postoperative day-POD) and POD3 (WBC; $p=0.0159$, CRP; $p=0.0159$) were also significant predictors affecting anastomotic leakage, which is similar to our findings regarding serum albumin and WBC [39].

Conclusions

This study observed a significant relationship of the white blood cell count, neutrophil lymphocyte ratio, platelet lymphocyte ratio, C-reactive protein level and serum albumin level with anastomosis leakage (AL). These relations might be used in predicting AL among patients who underwent colorectal surgery. All of these parameters showed a recommendable area under the curve in the receiver's operating curve for the prediction of AL. Nevertheless, further larger studies are recommended before validating this study.

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