Identifying the discriminative value of leukocytes, CRP and Procalcitonin serum level in detecting the anastomosis leakage after gastrointestinal surgery

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Received: 25-12-2022; Received: 13-01-2023; Accepted: 17-02-2023

Abstract

Background: Anastomosis leakage is a pivotal post colorectal surgery, threatening patient survival. Unspecific clinical presentations prolong the diagnostic process, potentially reducing the effectiveness of interventions. This situation has highlighted the need for a biomarker that enables early prediction of anastomosis leakage (AL). Previous studies suggest the potential utility of serum levels of white blood cells (WBC), C-reactive protein (CRP), and procalcitonin (PCT) as biomarkers for early detection of AL. Consequently, the present study was conducted with the aim of investigating the potential correlation of these markers with the occurrence of AL.

Methods: Patients who were referred to the hospitals of Tehran University of Medical Sciences from November 2018 to January 2020 were evaluated for inclusion in the study. After obtaining informed consents, 277 cases were enrolled in the study. Serum levels of WBC, CRP, and PCT were measured preoperatively and up to five days post-operation. A statistical correlation analysis was conducted using SPSS software (version 24).

Results: Among the 277 cases, 14 exhibited AL. The highest sensitivity and specificity for AL were observed for CRP on the second and third post-operative days. PCT, however, showed higher utility on the fourth post-operative day with 57% sensitivity, 56% specificity (p-value = 0.001 for the second day and 0.002 on the third day), and a negative predictive value of 96%. These values changed to 36%, 64%, and 95% respectively on the fifth post-operative day, which remains within the acceptable range (p-value = 0.018).

Conclusions: Both CRP and PCT have potential utility as diagnostic biomarkers for the presence of AL and can significantly accelerate the diagnosis period. For the highest sensitivity and specificity, CRP should be used on the second and third post-operative days. The optimal utility for PCT, however, is on the fourth post-operative day.

Citation: Sobhanian E., Moghimi Z., Yaghoobi Notash A., Ahmadi Amoli H., Sadeghian E. **Identifying the discriminative value of leukocytes, CRP and Procalcitonin serum level in detecting the anastomosis leakage after gastrointestinal surgery.** *Acad J Surg*, 2023; 6(1): 1-6.

Keywords: Anastomosis leakage, gastrointestinal surgery, procalcitonin (PCT), CRP

Introduction

Anastomosis leakage (AL) following colorectal surgery significantly impacts patient outcomes [1]. This complication is a notable cause of increased 30-day mortality rates after colorectal surgeries [2], and early diagnosis and intervention can significantly alter clinical outcomes [3].

The clinical manifestations of AL are vague, ranging from ileus and abdominal pain to a simple lack of post-operative progress. This complexity prolongs the diagnosis period [4] and underscores the need for a biomarker for early diagnosis.

Various potential biomarkers could indicate the occurrence of AL. The most investigated are established sepsis biomarkers, including serum procalcitonin (PCT), C-reactive protein (CRP), leukocytosis, tumor necrosis factor-α (TNF-α) levels of drain fluid, and interleukin-6 (IL-6) [5]. Most studies have found that WBC, CRP, and PCT have acceptable sensitivity regarding AL, and increased PCT serum levels significantly correlate with early diagnosis [6].

However, controversies exist regarding the clinical accuracy of these markers. Various clinical conditions caused by organ dysfunctions, such as

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end-stage renal diseases, congestive heart failure, chronic obstructive pulmonary disease, and others, can significantly elevate most of these biomarkers [7]. Due to the possible presence of these confounding underlying diseases in many patients, defining an exact pattern for the alterations of these biomarkers is necessary for clinical application [8].

Therefore, this study aims to illustrate the patterns of alterations in PCT and CRP serum levels post-operatively that could accelerate AL diagnosis.

Methodology

Patients undergoing elective gastrointestinal anastomosis surgery in hospitals affiliated with Tehran University of Medical Sciences from November 2018 to January 2020 were considered for inclusion in the study. Those aged above 18 who were not referred to these centers due to medical emergencies were included. Written informed consents were obtained, and 277 cases that underwent elective gastrointestinal anastomosis were enrolled in the study. Due to ethical considerations, all tests were conducted free of charge, and patients were allowed to exit the study whenever desired. All patients underwent a standardized surgical and anesthetic protocol, and surgical complications, including surgical site infection, AL, operative site edema, and ileus, were monitored. The study protocol was approved by the ethics committee of Tehran University of Medical Sciences.

For this study, serum PCT and CRP levels and complete blood count (CBC) were measured once preoperatively and up to five days post-operation. All lab data were obtained using local hospital lab kits. The reference range for PCT was less than 0.046 ng/ml for healthy adults. For CRP, the reference range used was lower than 5 mg/l.

Clinical and paraclinical manifestations of AL were recorded, including leukocytosis, raised CRP, raised PCT, fever, ileus, and changes in the volume of drainage discharges. When indicating anastomosis leakage, a CT scan or operative exploration was conducted afterward, and patients were discharged when meeting the routine discharge protocol of the related hospitals (no signs of sepsis, return of bowel movement, food intake recovery, and regaining movement).

PCT serum level was compared between those with and without anastomosis leakage, and statistical analysis was conducted using independent samples t-test. When required, the chi-squared analysis was applied.

The receiver operating characteristic (ROC) curve and the value of the area under the curve were used to analyze the accuracy of the different variables as predictors of AL. For statistically significant variables at the univariate analysis, a ROC curve analysis was performed. The Youden's J statistic was applied to determine the cutoff value (sensitivity + specificity - 1). A p-value of < 0.05 was accepted for statistical significance (2-tailed test).

The SPSS package version 24 for Windows was utilized for conducting the statistical analysis.

Results

A total of 277 cases were enrolled in the study, which included 89 cancer ileostomy cases, 9 FAP cases, 5 transverse colon cases, 6 secum polyp cases, 3 ulcerative colitis cases, 2 diverticulitis cases, and 2 closing Hartman colostomy cases. Table 1 presents the preoperative demographic characteristics of the cases and the distribution of the anastomosis types.

Among all, 14 cases exhibited anastomosis leakage (AL) during the study (5.07%). The mean age of cases that did not manifest leakage was 58 years, and those presenting with anastomosis leakage averaged 54 years of age. Cases and controls were matched regarding age and gender, and no significant difference was present regarding these two variables.

No significant difference was observed regarding the correlation between age and gender with anastomosis leakage. Also, the presence of various AL rates in various disease types was statistically insignificant (p-value = 0.357).

Table 1: Preoperative demographics and surgical data

Anastomosis type	Leakage		P-value
	No	Yes	
Ileocolic	91	2	
Coloanal	67	6	
Colocolic	25	0	
Gastrojejenostomy	15	2	0.22
Ileorectal	11	3	
Entroentral	53	1	
Total	262	14	
Mean age (years)	58	54	

Table 2: The percent of AL occurrence in various anastomoses

Anastomose Type	Leakage		P value
	No	Yes	
Ileocolic	91	2	0.022
Coloanal	67	6	
Colocolic	25	0	
Gastrojejenostomy	15	2	
Ileorectal	11	3	
Entroentral	53	1	
Total	262	14	

Table 3: The mean value (SD) of PCT, CRP, and WBC on post-operative days 1 to 5 for patients with and without AL

Biomarker	Post-operative day	Leakage	Number	Mean	SD	P-value
PCT, ng/ml	0	No	261	0.05	0.03	0.001
		Yes	14	0.03	0.01	
	1	No	261	2.29	4.18	0.383
		Yes	14	4.16	8.85	
	2	No	261	2.07	3.35	0.651
		Yes	14	1.66	1.52	
	3	No	262	1.22	1.59	0.304
		Yes	14	1.65	1.82	
	4	No	262	0.78	1.13	0.09
		Yes	14	1.85	2.45	
	5	No	262	0.57	0.94	0.186
		Yes	14	2.05	3.16	
CRP, mg/l	0	No	261	8.53	11.37	0.606
		Yes	14	5.79	4.51	
	1	No	262	42.24	17.32	0.040
		Yes	14	60.43	31.15	
	2	No	262	47.85	13.93	<0.001
		Yes	14	78.86	40.62	
	3	No	262	48.72	13.96	0.002
		Yes	14	70.93	35.04	
	4	No	262	46.46	15.35	0.018
		Yes	14	69.21	47.45	
	5	No	262	40.48	14.53	0.018
		Yes	14	64.07	50.36	
WBC	0	NO	262	6.48	2.07	0.236
		YES	14	5.70	1.86	
	1	NO	262	12.31	4.10	0.122
		YES	14	13.56	3.49	
	2	NO	262	10.59	3.94	0.833
		YES	14	10.03	1.80	
	3	NO	262	9.59	3.61	0.862
		YES	14	8.75	3.15	
	4	NO	262	8.32	3.25	0.766
		YES	14	8.41	4.04	
	5	NO	262	7.71	3.48	0.046
		YES	14	9.65	3.92	

When comparing the percentage of AL in various anastomosis types using the Chi-squared statistical test, significant differences were detected (Table 2).

PCT and CRP levels immediately increased post-operatively and were significantly higher in the group with AL on the first, second, and third post-operative days for both markers. CRP levels remained significantly higher on the fourth and fifth

Table 4: AUC and ROC for CRP

Area Under the Curve					
Test Result Variable(s)	Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
CRP1	.663	.064	.040	.538	.788
CRP2	.836	.049	.000	.739	.933
CRP3	.745	.051	.002	.645	.846
CRP4	.687	.080	.018	.530	.844
CRP5	.687	.092	.018	.506	.868

Table 5: AUC and ROC for Procalcitonin

Area Under the Curve					
Test Result Variable(s)	Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
PROCL1	.571	.074	.374	.426	.715
PROCL2	.537	.069	.638	.402	.673
PROCL3	.583	.078	.294	.430	.737
PROCL4	.636	.074	.086	.492	.781
PROCL5	.607	.085	.179	.440	.774

post-operative days. Table 3 presents an overview of the results regarding all measured biomarkers.

Moreover, the CRP serum level showed 100% sensitivity up to five days post-operation. However, the measured specificity was 1.5% on the first post-operative day and later altered to 0.3%, 0%, 0%, and 3% respectively from day 2 to day 5 post-operation. Negative predictive values were 100% from day 1 to day 5 (Table 4).

PCT serum level showed 92.8% sensitivity on the first post-operative day that later decreased to 71.4%, 57%, 57%, and 36% respectively. Regarding the specificity alterations from day 1 to 5 post-operation, numbers were as follows: 31.4%, 30%, 38.5%, 56%, and 64.5%. Positive predictive values decreased from 6.7% to 5% in 3 days and again raised to 6.7% on the fourth post-operative day. The last calculation yielded 5% on the fifth post-operative day. Also, the numbers for negative predictive values were 98.7%, 95%, 94.5%, 96%, and 95% respectively (Table 5)

Discussion

This study aimed to identify the PCT and CRP in diagnosing anastomosis leakage after colorectal surgeries. These serum markers have long been used as biomarkers in determining the activation of infectious processes [9], but only recently has a significant correlation been noted between their serum level increase and post colorectal surgery AL.

CRP, PCT, leukocytosis, and gamma glutamyl transferase have been the subject of debate in recent studies regarding the determination of sensitive and specific biomarkers for early detection of anastomosis leakage post colorectal surgeries, as early diagnosis significantly enhances clinical outcomes [10].

In this study, the mean leukocyte level was raised in the group manifesting AL on the first postoperative day and later decreased, reaching within the normal limit in three days. Previous works have confirmed the rise of CRP, leukocytes, and neutrophils 48 hours post-operation and a later decrease in their serum level. However, these markers were not confirmed to be sufficient for clinical diagnosis due to the general activation of immune responses post-operation [11].

The mean CRP level was also raised in the first 24 post-operative hours and later decreased, normalizing within five days. The peak CRP level was measured up to five days post-operation and was significantly higher in the group manifesting AL compared to the group without AL presentation. A 100% sensitivity was calculated for CRP in detecting AL, however, low specificity might distort the interpretations. The acceptable negative predictive value for CRP and PCT regarding the occurrence of AL was also previously researched, and potential usage in discharge protocols was recommended [12]. Ultimately, the overall highest sensitivity and specificity for CRP were on the second and third post-operative days respectively (higher than 60.5

on the second day and higher than 59.5 on the third day).

Regarding PCT, no significant correlation was detected between the mean PCT levels and AL. A recent comprehensive meta-analysis suggested PCT to be a useful test for ruling out AL, but not sufficient for diagnosis alone [13]. This finding aligns with our results. A higher correlation was previously indicated between PCT and AL in the third to fifth post-operative days [3], though this was not consistent with our work and no remarkable difference was detected between PCT and CRP in the mentioned days. Moreover, in our study, raised PCT was mostly detected in the first 48 hours post-operation and later decreased in the cases not manifesting AL or post-operative infection. Our results indicate that PCT is most sensitive on the first post-operative day, though the specificity increases until the fifth day post-operation. Ultimately, the low measure of positive predictive value regarding PCT can distort its potential utility as a diagnostic biomarker, which has been the subject of major debates in past related studies [14].

Leukocytosis was also noted to correlate with AL in some studies [15]. However, due to its late occurrence, it was not considered as an early detection biomarker [16]. This observation aligns with our results, suggesting only a significant difference on the fifth post-operative day. Therefore, due to the complicated nature of AL manifestations and a lack of clear clinical profile [17], leukocytosis is neither sensitive nor specific enough for leading to an early AL diagnosis. Previously established high specificity and negative predictive value, however, have made this biomarker useful for excluding AL [18].

It should be mentioned that in our study, pelvic ALs were noted to lead to less PCT increase compared to abdominal and large intestinal ALs. This might be due to the higher sterility of the pelvis. Further research is required to clarify the significance of this observation.

Conclusion

In conclusion, the results suggest a significant potential for both PCT and CRP in diagnosing AL. However, further research is required to define an accurate cutoff point for these biomarkers. To achieve the highest sensitivity and specificity, CRP should be used on the second and third post-operative days. The optimal utility for PCT, however, is on the fourth post-operative day. Simultaneous monitoring of both CRP and PCT can increase the likelihood of early diagnosis and is therefore recommended to be included in the monitoring protocol for the high-risk period for AL (up to five days post-operation).

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