Is serum presepsin levels had accurate discriminative ability for patients vulnerable to develop anastomotic leakage after colorectal anastomosis? A cohort study

Mokhtar A. Bahbah[a], Marwa S. El-Melouk[b], Mysa S. Mostafa[b], Taher H. Elwan[a]

Departments of [a]General Surgery, [b]Microbiology & Immunology, Faculty of Medicine, Benha University, Benha, Egypt

Correspondence to Mokhtar A. Bahbah, MD, Department of General Surgery, Faculty of Medicine, Benha University, Benha, 13511, Egypt. Tel: 00201099038922; e-mail: mokhtar_bahbah@yahoo.com

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Objectives
Evaluation of the predictive value of serial estimations of serum presepsin (PSP), C-reactive protein (CRP), and procalcitonin (PCT) for the development of infective complications and/or anastomotic leakage (AL) after elective colorectal resection with anastomosis for N0M0 colorectal cancers.
Patients and methods
During 7-year study period, 113 patients underwent colorectal resection; postoperative (PO) morbidities were graded according to the comprehensive complication index (CCI). Five venous blood samples (T1–5) were collected at the time of induction of anesthesia, immediate, 1 day, 3 days, and 5 days after surgery for blood leukocytic count, and calculation of neutrophil-to-lymphocyte ratio and estimation of serum levels of the studied cytokines. Study outcome is the ability of serum cytokines' levels estimated in T2 sample to predict the possibility for the development of AL.
Results
Incidence of PO infective morbidities was 31%, incidence of AL was 8.85%, and PO mortality rate was 2.65%. Operative time was significantly longer; the total score of the CCI was significantly higher and PO hospital stay was significantly longer for patients who had AL. Patients who developed AL had significantly higher neutrophil-to-lymphocyte ratio in T3–5 samples than in the T1 sample. Mean serum levels of the studied cytokines were significantly higher in T2–5 samples than in T1 sample with significantly higher levels in patients who developed AL. Regression analysis defined high serum levels of PSP and PCT in the T3 sample and CRP levels in T5 sample as predictors of AL and high levels of the three biomarkers in the T3 sample could predict mortality. Automatic linear regression defined high serum PSP levels in the T3 sample and long operative time as significant predictors for high CCI and bad outcome with accuracy rates of 61 and 39%, respectively.
Conclusion
The level of serum biomarkers could predict AL, but PSP was superior to CRP and PCT. High serum PSP levels in T2 sample can accurately predict high CCI for PO complications.

Keywords:
anastomotic leakage, colorectal cancer, comprehensive complication index, infective morbidities, presepsin

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Introduction

Anastomotic leakage (AL) is the most important complication in colorectal resection (CRR) with anastomosis and mostly occurs with rectal resections reaching up to 20% after low anterior rectal resection [1]. Colorectal AL increases morbidity, hospital stay and cost of treatment, and a search to identify the risk factors for the prediction of AL is mandatory [2].

The use of biomarkers alone or in conjunction with clinical status, routine hematological and biochemical analyses and imaging to help for prediction or diagnosis of AL early during the postoperative (PO) course [3] and to ensure safe and timely patient discharge after elective CRR represents a major challenge [4]. Multiple studies have attempted to identify biomarkers to enable earlier AL diagnosis; however, no AL biomarker has yet been validated in large-scale clinical trials [3].

Procalcitonin (PCT) is the precursor structure of the calcitonin hormone with 116 amino acids and is an emerging biomarker for detecting sepsis [5]. PCT and

C-reactive protein (CRP) are significant complementary inflammatory markers and their simultaneous detection can safely reduce unnecessary antibiotic prescriptions in certain infectious syndromes [6]. Presepsin (PSP), the soluble cluster of differentiation 14 is the 13-kDa glycoprotein cleavage N-terminal fragment of CD14 [7]. PSP is expressed on monocytes and macrophages and is released into circulation after activation of a proinflammatory signal cascade on contact with infectious agents [8]. PSP is a promising biomarker for initial diagnosis and risk stratification of sepsis with a high ability to distinguish Gram-positive and Gram-negative bacterial infection [9]. Recently, PSP showed superiority against total leukocytic count (TLC), and CRP and PCT as a valuable indicator of infectious complication's detection levels after esophagectomy [10].

Objectives

Estimation of serum levels of PSP, CRP, and PCT to evaluate its predictive value for the possibility of development of infective complications and/or AL after elective CRR.

Setting

Departments of General surgery and Clinical Pathology, Faculty of Medicine, Benha University in conjunction with private centers specialized in colorectal surgery.

Design

A prospective, comparative, interventional study.

Patients and methods

The study protocol as approved by the local ethics committee considered all patients subjected to elective CRR for colorectal cancer and signed the written fully informed consent were eligible for evaluation.

Exclusion criteria

Inflammatory colorectal diseases necessitating resection, presence of stoma, chronic systemic inflammatory conditions, autoimmune disorders, maintenance on immunosuppressive therapy for any indication, ASA grade IV, endocrinopathy, liver or kidney diseases, synchronous lesions necessitating interference, lesions of N1, or M1 pathological grades.

Inclusion criteria

Colorectal cancers of N0M0 pathological grade in patients free of exclusion criteria and signed the written consent for study participation.

Preoperative data collection

Patients' demographic data including age, sex, body weight, and height for the calculation of BMI as weight divided by square of the height (kg/m^2), indication for surgery, and ASA grade were collected. Clinical systemic examinations, routine laboratory investigations, and chest plain radiograph were performed.

Operative procedure

All the procedures were performed under general inhalational anesthesia with endotracheal intubation. Open laparotomy and resection with reanastomosis were the standard procedure. All colorectal or ileorectal anastomosis were performed using staplers or hand-sewn technique according to operative conditions. Wound was drained by two suction drains. Collected intraoperative data included operative time, need for blood transfusion, and intraoperative complications.

Postoperative data collection

The incidence of PO complications other than AL was recorded; need for admission to ICU and duration of hospital stay were analyzed. PO morbidities were graded according to the comprehensive complication index (CCI), which integrates all complications encountered during the PO hospital stay according to the Clavien-Dindo classification as shown in Table 1 [11]. The overall morbidity is reflected on a scale from 0, which indicates no complication to 100 (death). Patients were asked to attend the outpatient clinic for follow-up biweekly for 1 month and at 3 months after surgery for follow-up.

Table 1 Clavien-Dindo classification and the corresponding values of the comprehensive complication index [11]

Grade of complication	Required intervention/therapy	CCI value
CDC I	Any deviation from normal PO course requiring only drugs as follows: antiemetic, antipyretics, diuretics, electrolytes, prokinetics	8.7
CDC II	Pharmacological treatment with drugs other than that required for CDC I complications, blood transfusion, total parenteral nutrition	20.9
CDC IIIa	Surgical, endoscopic, or radiological intervention not under general anesthesia	26.2
CDC IIIb	Surgical, endoscopic, or radiological intervention under general anesthesia	33.7
CDC IVa	Single-organ dysfunction, requiring intermediate or ICU management	42.4
CDC IVb	Multiorgan dysfunction, requiring intermediate or ICU management	46.2
CDC V	Death	100

CCI, comprehensive complication index; CDC, Clavien-Dindo classification.

Estimation of cytokines' serum levels

Sampling

Venous blood samples (5 ml) were collected at the time of induction of anesthesia (T1), immediate PO (T2), POD1 (T3), POD3 (T4), and POD5 (T5). Blood samples were collected from all patients under complete aseptic conditions in plain tubes and were divided into two parts:

(1) The first part was collected in an EDTA containing tube for blood leukocytic count; total and differential, and neutrophil-to-lymphocyte ratio (NLR) was calculated.
(2) The second part was allowed to clot, centrifuged at 1500*g* for 15 min and the serum samples were collected in a clean dry Eppendorf tube to be stored at −70°C until assayed.

Laboratory investigations

Serum levels of PSP, PCT, and CRP were measured using enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions and were read using a 96-well microplate ELISA reader (Dynatech. MR 7000).

(1) Human PSP level using ELISA kit (catalog no. MBS766136, MyBioSource Inc., San Diego, California, USA) by the quantitative sandwich enzyme immunoassay technique [12].
(2) Human serum PCT level was estimated using ELISA kit (catalog no. ab221828, Abcam Inc., San Francisco, Chicago, USA) by quantitative sandwich ELISA [13].
(3) Human CRP was measured with the ELISA kit (catalog no. ab99995; Abcam Inc.) by quantitative sandwich enzyme immunoassay technique [14].

Study outcome

The study outcome is the ability of serum cytokines' levels estimated immediately at the end of surgery (T2 sample) to predict the possibility for the development of AL. AL was defined as suture line disruption with intestinal content leakage or abscess formation, associated with fever or abdominal pain, and confirmed by a computed tomography scan or reoperation up to 3 months after surgery.

Sample size calculation and grouping

Pedersen *et al.* [15] and Komen *et al.* [16] detected significant difference in serum CRP levels in 41 and 19 patients who developed infective complication in comparison to those who passed smooth PO course free of infective complications. Thus, to achieve significant difference between serum cytokines' levels between patients who developed AL or not, and to get a study power of 85% with an α value of 0.05 and β value of 0.15, the sample size for group of patients who developed infective complications must be larger than 19. Patients who had AL were grouped as the AL group and the other patients who developed infective complications but did not progress to AL were collected as the no AL group. Patients who passed their PO follow-up free of complications were excluded from the statistical analyses.

Statistical analysis

The obtained data were presented as mean, SD, numbers, and percentages. Analysis of variance between parametric data was performed by the Tukey's HSD procedure for pairwise comparisons within data. Correlation between studied variables and result of blood culture was performed using Spearman's correlation analysis and predictors for positive blood culture were evaluated using the receiver-operating characteristic (ROC) curve and automatic linear modeling analysis. Statistical analysis was performed using the (Statistical analysis was done using IBM SPSS statistics for windows, Version 23.0. Armonk, NY: IBM Corp) package, 2015. A *P* value of less than 0.05 was considered significant.

Results

During the 7-year study period, 127 patients were assigned for CRR; 14 patients were excluded for not fulfilling the inclusion criteria and 113 patients were enrolled in the study. Unfortunately, 35 (31%) patients developed PO complications; 10 (8.85%) patients developed AL (AL group) and 25 (22.1%) patients had developed PO complications other than AL and were collected as the no AL group. The remaining 78 patients who completed their follow-up free of surgery-related complications were excluded from statistical analyses. Throughout the follow-up period, total mortality was three (2.65%) patients, two of AL group and one of no AL group with nonsignificantly (P=0.127) higher mortality among patients of the AL group (Fig. 1). Revision of at-admission data showed nonsignificant differences between patients of both groups (Table 2).

All surgeries were conducted uneventfully and only 11 (9.7%) patients required intraoperative blood transfusion with nonsignificant (P>0.05) difference between both groups. The mean operative time was significantly (P=0.028) longer in patients who

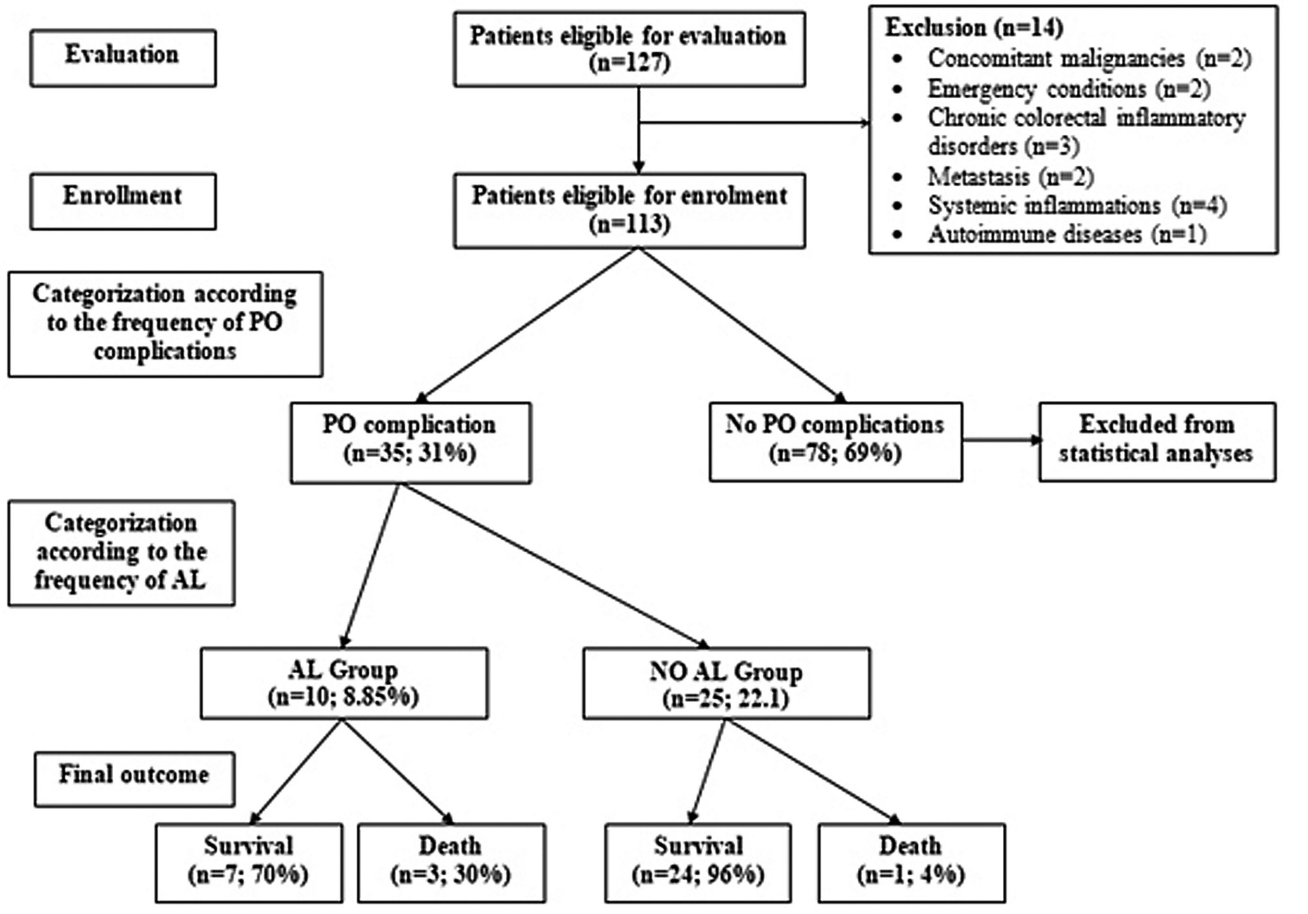
developed AL during the PO follow-up. Total CCI score of the PO course was significantly (P=0.038) higher in patients of AL versus those of no AL groups. Regarding AL data, the mean duration till the development of AL was 7.9 (±1.5) days and six patients responded to conservative treatment, while four patients required second look surgery and diverting stoma was performed. Mean duration of PO hospital stay was significantly (P=0.007) longer for patients who had AL than those of the no AL group (Table 3).

Serial TLC in blood samples of patients of both groups showed progressive increases with significant difference in comparison to TLC obtained at T1, in both groups and the count was summit in T4 sample in the no AL group but in T5 sample of patients of AL group. TLC in T1 samples showed nonsignificant differences between both groups, but the difference was significant in counts detected in T2–5 blood samples. The calculated NLR was progressively increased in samples of patients of the AL group with significantly higher ratio in T3–5 samples in comparison to T1 sample. On the contrary, NLR in patients of no AL groups was nonsignificantly higher in all samples in comparison to the T1 sample. Moreover, NLR in T3–5 samples of patients of the AL group was significantly higher in comparison to that of patients of the no AL group (Table 4).

Preoperative (T1 sample) serum levels of CRP, PCT, and PSP showed nonsignificant (P>0.05) differences between the studied patients. However, during the follow-up mean serum levels of CRP, PCT, and PSP increased progressively during the 5-day estimations, and the difference was significantly higher in comparison to preoperative levels and the preceding estimates. Follow-up estimates were significantly higher in patients of AL group in comparison to patients of the no AL group (Table 5).

Correlation analysis showed a positive significance between the calculated CCI and operative time, TLC and NLR in T4 and T3 blood samples, respectively, CRP level in T3 and T4 blood samples, PCT levels in T2, T3, and T4 blood samples, and PSP levels in T1–4 samples. Moreover, there was positive significance between incidence of AL and calculated

Figure 1



Study flowchart.

CCI, TLC, and NLR in T4 and T3 samples, and all estimated levels of studied cytokines. However, PO mortality showed positive significant correlation with calculated CCI, operative time and PCT and PSP in T3 sample (Table 6).

Regression analysis, stepwise method, defined high serum levels of PSP on POD3 (T3) blood sample (β=0.729, $P<0.001$) as a significant specific predictor for the possibility of development of AL, and followed by high serum CRP on POD5 (T4) blood sample (β=0.363, $P<0.001$) and PCT on POD3 (T3) blood sample (β=0.225, $P<0.001$) as the persistently significant predictors for the possibility of development of AL. On the other hand, high serum levels of PCT (β=0.804, $P<0.001$), PSP (β=0.496, $P=0.001$), and CRP (β=0.378, $P=0.009$) on POD3 (T3) blood sample were the persistently significant predictors for mortality.

ROC curve analysis for the serum levels of the three cytokines in POD3 (T3) blood sample) defined high serum levels of PSP and PCT as the significant specific predictors for the possibility of AL development (Table 7, Fig. 2).

Considering the CCI as a clinical score for the prediction of outcome, the automatic linear regression model for correlated variables defined high serum PSP on POD3 (T3) blood sample and long operative time as the significant predictors for high CCI and bad outcome, irrespective of the outcome with accuracy rates of 61 and 39%, respectively (Fig. 3).

Table 2 Enrollment data of patients who developed postoperative complications categorized according to the development of anastomotic leak

Data	No AL group	AL group	*P* value
n (%)	25 (22.1)	10 (8.85)	
Age (years)	67.1±5.7	65.2±4.5	0.302
Sex			
Males	17 (68)	7 (70)	0.908
Females	8 (32)	3 (30)	
Body weight (kg)	87.4±6.6	89.6±3.7	0.324
Body height (cm)	170.4±4	169.8±4.5	0.683
BMI (kg/m^2)	30.1±2.35	31.13±1.85	0.224
The American Society of Anesthesiologists Physical Status			
Grade I	5 (20)	2 (20)	0.986
Grade II	17 (68)	7 (70)	
Grade III	3 (12)	1 (10)	
Location			
Colon	18 (72)	6 (60)	0.781
Rectum	5 (20)	3 (30)	
Ileocecal	2 (8)	1 (10)	
TNM grade			
I	16 (64)	8 (80)	0.781
II	7 (28)	1 (10)	
III	2 (8)	1 (10)	

Data are presented as mean, SD, *n* (%). AL, anastomotic leakage. *P* value indicates significance of the difference, *P* value less than 0.05 indicates significant difference; *P* value more than 0.05 indicates nonsignificant difference.

Discussion

Colorectal surgery for operable cancer patients is still a major risky surgery even with proper patients' choice and preparation, as evidenced by the reported high rate of PO complications (31%), high calculated CCI, and mortality rate (2.65%). In line with these findings, Pedersen *et al.* [15] reported a septic complication rate of 32% after colorectal surgery and Vauclair *et al.* [17] detected intra-abdominal septic complication rate of 26.8; 16.9, and 9.9% after rectal resection and colectomy, respectively. Thereafter, Baeza-Murcia *et al.* [18] detected an overall morbidity and mortality rates of 42.1 and 3.2% after elective colorectal surgery with anastomosis.

Moreover, the reported rate of local anastomotic region complications was also still high (8.84%) despite the continuous progress in skill, better suture materials,

Table 3 Operative data of patients who developed postoperative complications categorized according to the development of anastomotic leak

	No AL group	AL group	*P* value
Operative time (min)	153.8±24.5	176.5±28.9	0.028
Incidence of intraoperative blood transfusion			
Yes	7 (28)	4 (40)	0.221
No	18 (72)	6 (60)	
Total CCI score	30.5±22.6	50±27.5	0.038
AL data			
Duration till the development of AL (days)	–	7.9±1.5	–
Numbers that required second-look surgery (patients)	–	4 (40)	–
Duration of PO hospital stay (days)	8.8±2.2	13±4.4	0.001

Data are presented as mean, SD, *n* (%). AL, anastomotic leakage; CCI, comprehensive complication index. *P* value indicates significance of the difference, *P* value less than 0.05 indicates significant difference; *P* value more than 0.05 indicates nonsignificant difference.

Table 4 Total leukocytic count and neutrophil–lymphocyte ratio estimated during the 5-day postoperative follow-up

Variables	Group	Time		T1	T2	T3	T4	T5
TLC	No AL	Value (±SD)		5939±1179	6678±1296	7748±1050	8587±1308	8130±1232
		Post-hoc Tukey HSD	T1 vs.		0.221	0.0058	<0.0001	0.0003
			T2 vs.			0.022	<0.0001	0.001
			T3 vs.				0.122	0.809
			T4 vs.					0.687
	AL	Value (±SD)		6478±1045	7617±924	8569±1227	9980±1150	11283±1269
		Post-hoc Tukey HSD	T1 vs.		0.531	<0.0001	<0.0001	<0.0001
			T2 vs.			0.024	0.00038	<0.0001
			T3 vs.				0.624	0.0013
			T4 vs.					0.064
			No AL	0.217	0.0155	0.041	0.0014	<0.0001
NLR	No AL	Value (±SD)		1.88±0.28	2.2±0.38	2.45±0.41	2.28±0.33	2.4±0.53
		Post-hoc Tukey HSD	T1 vs.		0.384	0.203	0.544	0.298
			T2 vs.			0.172	0.952	0.382
			T3 vs.				0.549	0.992
			T4 vs.					0.819
	AL	Value (±SD)		1.96±0.2	2.3±0.18	2.81±0.57	3.49±0.28	4.86±1.94
		Post-hoc Tukey HSD	T1 vs.		0.922	0.025	0.0049	<0.0001
			T2 vs.			0.031	0.025	<0.0001
			T3 vs.				0.047	0.0001
			T4 vs.					0.015
			No AL	0.409	0.431	0.043	<0.0001	<0.0001

Data are presented as mean and SD. AL, anastomotic leak; NLR, neutrophil–lymphocyte ratio; T1, at induction of anesthesia; T2, immediate PO; T3, 1-d PO; T4, 3-d PO; T5, 5-d PO; TLC, total leukocytic count. *P* value less than 0.05: indicates significant difference; *P* value more than 0.05: indicates nonsignificant difference.

and advances in methodology. These data and figures were better than the reported rates; 10–14% in earlier studies [19–21] and goes hand in hand with that recently reported as ranging between 7.6 and 8.6% [22,23].

These results spotlight on the necessity for an early predictor for the possibility of development of AL, which is the most disastrous PO infective complication of colorectal surgery. The current study detected positive significant correlations between CCI as a clinical evaluation score for PO complications and the incidence of AL, on one side and with serum levels of CRP, PCT, and PSP, and operative time on the other side. Moreover, the incidence of PO mortality positively correlated with operative time and high serum levels of these cytokines. However, regression analysis and ROC curve analysis showed that the high levels of studied cytokines are the best predictors for PO complications.

These findings go hand in hand with Chernyshov *et al.* [22], who documented that high negative predictive value (NPV) of CRP and PCT measurements for the diagnosis of AL may assist decision-making for early hospital discharge. Also, Yeung *et al.* [23] found that AL is associated with higher CRP levels on each POD compared with no AL after colorectal surgery. Moreover, Pachajoa *et al.* [20] reported that CRP seems superior to NLR as an early predictor of AL following colorectal surgery.

Regarding the time to estimate serum levels of these cytokines, levels estimated on POD3 showed high predictability according to ROC curve analysis. Similarly, Yao *et al.* [24] found that serum PSP estimated on POD3 can independently predict bacterial infection after major hepato-biliary-pancreatic surgery and Hernandez *et al.* [21] detected high NPV for serum CRP estimated on POD4 and considered serum CRP was the most reliable marker for excluding AL in comparison to PCT and neutrophils, and thus allows for safe hospital discharge.

Automatic linear modeling analysis defined high serum PSP on POD3 and operative time as the accurate predictors for high CCI with 1.6-fold higher accuracy rate for PSP. This finding coincided with Cikot *et al.* [25] who reported that among TLC, CRP, NLR, and PSP values, PSP had a specificity of 98.63% in determining AL and with Imai *et al.* [26], who found PSP levels were significantly higher, while PCT and CRP levels were not significantly higher in bacteremic than nonbacteremic elderly patients with sepsis criteria. Thereafter, Kaplan *et al.* [27] found PSP and PSP:

Table 5 Serum levels of studied cytokines estimated during the 5-day postoperative follow-up

Variables	Time		T1	T2	T3	T4	T5
CRP (ng/ml)							
No AL group (*n*=25)	Value (±SD)		15.6±4.9	36.6±13.8	74.4±15.1	61±15.9	45.3±18.8
	Post-hoc Tukey HSD	T1 vs.		<0.0001	<0.0001	<0.0001	<0.0001
		T2 vs.			<0.0001	<0.0001	0.0043
		T3 vs.				0.0008	<0.0001
		T4 vs.					0.0025
AL group (*n*=10)	Value (±SD)		15±4.4	48.8±19.7	83.8±18.2	111.7±19.2	135±20.8
	Post-hoc Tukey HSD	T1 vs.		<0.0001	<0.0001	<0.0001	<0.0001
		T2 vs.			<0.0001	<0.0001	<0.0001
		T3 vs.				<0.0001	<0.0001
		T4 vs.					0.00008
		No AL	0.297	0.0034	0.049	<0.0001	<0.0001
PCT (pg/ml)							
No AL group (*n*=25)	Value (±SD)		87.7±43.1	127.2±54.7	190±88.7	146.2±56.9	114.6±48.1
	Post-hoc Tukey HSD	T1 vs.		0.033	<0.0001	0.00014	0.178
		T2 vs.			0.00005	0.527	0.958
		T3 vs.				0.016	<0.0001
		T4 vs.					0.168
AL group (*n*=10)	Value (±SD)		114.9±47.2	157.6±55.9	590.6±186.4	749.7±218.8	535.6±123.8
	Post-hoc Tukey HSD	T1 vs.		<0.0001	<0.0001	<0.0001	<0.0001
		T2 vs.			0.0006	0.294	<0.0001
		T3 vs.				0.187	0.0006
		T4 vs.					0.312
		No AL	0.21	0.079	<0.0001	<0.0001	<0.0001
PSP (pg/ml)							
No AL group (*n*=25)	Value (±SD)		240.7±63.5	412.8±166	562.3±172	734.7±196.2	530.1±118.7
	Post-hoc Tukey HSD	T1 vs.		0.0003	<0.0001	<0.0001	<0.0001
		T2 vs.			0.0003	<0.0001	0.0087
		T3 vs.				0.00002	0.889
		T4 vs.					<0.0001
AL group (*n*=10)	Value (±SD)		278.2±84.7	923.7±137.5	1593.6±375	1948.3±327	1044.5±208
	Post-hoc Tukey HSD	T1 vs.		<0.0001	<0.0001	<0.0001	<0.0001
		T2 vs.			<0.0001	<0.0001	0.376
		T3 vs.				0.0001	<0.0001
		T4 vs.					<0.0001
		No AL	0.077	<0.0001	<0.0001	<0.0001	<0.0001

Data are presented as mean and SD. AL, anastomotic leak; CRP, C-reactive protein; PCT, procalcitonin; PSP, presepsin; T1, at induction of anesthesia; T2, immediate PO; T3, POD1; T4, PO3; T5, POD5. *P* value less than 0.05: indicates significant difference; *P* value more than 0.05: indicates nonsignificant difference.

albumin ratio may be novel markers superior to CRP and CRP: albumin ratio for the prediction of poor prognosis in patients with sepsis. Also, Yao *et al.* [24] reported that high serum PSP levels had greater ability to discriminate bacterial infection than high levels of serum PCT and CRP, and the NLR with very high sensitivity and specificity.

The reported high accuracy for high serum PSP for the prediction of high CCI indicated the possibility of the reliance on a combination of PSP and a complication clinical scoring system for the discrimination of patients liable for the development of septic complications especially AL. Similarly, multiple recent studies have documented a combination of clinical scoring and a biomarker for the prediction or exclusion of AL and major complications in the early period after colorectal surgery [28,29].

Interestingly, high serum PSP level in a sample obtained immediately at the end of surgery (T2) showed positive significant correlation with CCI (P=0.003) and incidence of AL (P<0.001). In line with this finding, Yao *et al.* [24] documented that PSP may help achieve faster detection of bacterial infections than other biomarkers. Also, Bösch *et al.* [30] found preoperative serum PSP level in patients undergoing emergency visceral surgery for abdominal infection exhibited the highest sensitivity, and specificity for the prediction of the development of sepsis and mortality in comparison to endotoxin, PCT, and interleukin-6 and documented that the multi-marker

Table 6 Correlations between the calculated comprehensive complication index, incidence of anastomotic leak and postoperative mortality, and clinical and laboratory variables

Variable	CCI		AL		Mortality	
	r	*P*	*r*	*P*	*r*	*P*
Outcome						
AL	0.442	<0.001	–	–	0.105	0.406
Mortality	0.827	<0.001	0.105	0.406	–	–
Age	0.161	0.201	–0.170	0.176	0.201	0.108
Operative time	0.339	0.003	0.199	0.113	0.328	0.008
CCI	–	–	0.442	<0.001	0.827	<0.001
TLC						
Immediate PO (T1 sample)	0.024	0.848	0.059	0.638	0.057	0.654
POD1 (T2 sample)	0.059	0.639	0.110	0.382	0.106	0.402
POD3 (T3 sample)	0.102	0.419	0.191	0.127	0.130	0.303
POD5 (T4 sample)	0.317	0.010	0.671	<0.001	0.169	0.180
NLR						
Immediate PO (T1 sample)	0.010	0.935	0.116	0.356	0.025	0.845
POD1 (T2 sample)	0.155	0.219	0.075	0.551	0.204	0.104
POD3 (T3 sample)	0.312	0.011	0.776	<0.001	0.052	0.679
POD5 (T4 sample)	0.161	0.201	0.523	<0.001	–0.055	0.665
CRP						
Immediate PO (T1 sample)	0.091	0.469	0.358	<0.001	0.082	0.518
POD1 (T2 sample)	0.118	0.349	0.245	0.049	0.018	0.885
POD3 (T3 sample)	0.348	0.005	0.837	<0.001	0.084	0.508
POD5 (T4 sample)	0.392	0.001	0.919	<0.001	0.105	0.403
PCT						
Immediate PO (T1 sample)	0.028	0.827	0.233	0.062	–0.050	0.691
POD1 (T2 sample)	0.300	0.015	0.782	<0.001	0.043	0.733
POD3 (T3 sample)	0.356	0.004	0.910	<0.001	0.265	0.033
POD5 (T4 sample)	0.344	0.005	0.894	<0.001	0.045	0.721
PSP						
Immediate PO (T1 sample)	0.360	0.003	0.859	<0.001	0.120	0.339
POD1 (T2 sample)	0.352	0.004	0.880	<0.001	0.077	0.545
POD3 (T3 sample)	0.363	0.003	0.920	<0.001	0.309	0.012
POD5 (T4 sample)	0.268	0.031	0.845	<0.001	0.003	0.981

AL, anastomotic leak; CCI, the calculated comprehensive complication index; CRP, C-reactive protein; NLR, neutrophil–lymphocyte ratio; PCT, procalcitonin; PO, postoperative; POD, PO day; PSP, presepsin; *r*, Pearson's coefficient; TLC, total leukocytic count. *P*: indicates the significance of the coefficient; *P* value less than 0.05: indicates significant difference; *P* value more than 0.05: indicates nonsignificant difference.

Table 7 Receiver-operating characteristic curve analysis of postoperative day 3 (T3) serum levels of presepsin, procalcitonin, and C-reactive protein as predictors for the possibility of anastomotic leak development

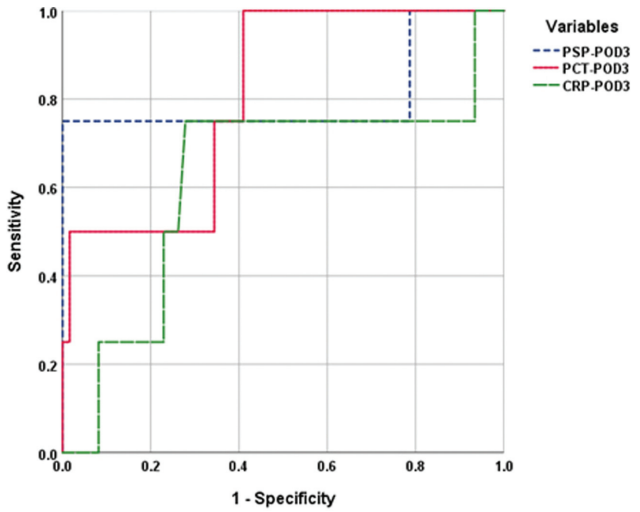
	AUC (SE)	*P* value	95% CI
PSP	0.807 (0.099)	0.041	0.613–1.00
PCT	0.803 (0.171)	0.043	0.468–1.00
CRP	0.621 (0.168)	0.421	0.291–0.951

AUC, area under the curve; CI, confidence interval; CRP, C-reactive protein; PCT, procalcitonin; PSP, presepsin. *P* value indicates significance of AUC; *P* value less than 0.05 indicates significant difference; *P* value more than 0.05 indicates nonsignificant difference.

approach included showed no additional predictive value over PSP alone.

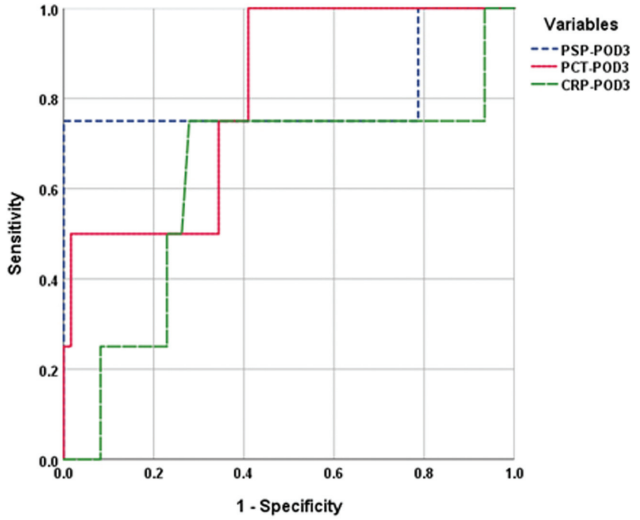
In support of the efficacy of the estimation of serum PSP and its superiority to other biomarkers as early predictors for PO bacterial infection since immediate PO, Su'a *et al.* [31] reported that high serum PCT levels on POD5 showed an NPV of 95–100% for the presence of infection, while Jin and Chen [32] found that high serum CRP was a reliable predictor for AL on POD4-7 with the highest NPV on POD6 and Pachajoa *et al.* [20] detected that using the ROC curves, the best predictive performance for high serum CRP was on POD5. Also, Tsuchida *et al.* [33] studied 1840 consecutive outpatients suspected to have bacterial infection elsewhere in the body and with at least one PSP estimation and detected a significant association between PSP level and the diagnosis of bacterial infection even when adjusted for age, sex, renal function, and biliary enzyme levels.

Figure 2



ROC curve analysis of serum levels of studied cytokines estimated on POD3 (T3) blood sample as predictors for the possibility of AL development. POD, postoperative day; ROC, receiver-operating characteristic.

Figure 3



Automatic linear regression model for correlated variables as predictors for the CCI clinical scoring. CCI, comprehensive complication index.

Conclusion

Early prediction of intra-abdominal infection after colorectal surgery that may progress to AL is mandatory to assure smooth PO course with rapid home-return and sparing the resources. Biomarkers did favorably as predictors for AL, but high serum levels of PSP were superior to CRP and PCT. Estimation of PSP in a blood sample taken immediately after the end of surgery can accurately predict high CCI for stratification of PO complications of which AL is the most disastrous.

Limitation

Evaluation of various cutoff points for serum PSP to discriminate patients liable or had AL limited this study.

Recommendation

Multicenter wider scale studies are required to assure estimation of serum PSP as an early predictor for septic PO complications and AL in patients who underwent colorectal surgery.

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Conflicts of interest

There are no conflicts of interest.

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