

Article

Association of Serum Endocan, Procalcitonin, and C-Reactive Protein with Early Postoperative Infectious Complications Following Colorectal Surgery

Anmar Hamid Hamad Alkaraghali*¹, Mustafa Watheq Madeeh²

1. Specialist in General Surgery and Laparoscopic Surgery, Al-Falluja Teaching Hospital, Anbar Health Directorate, Anbar, Iraq
 2. General Surgery Specialist, Al-Falluja Teaching Hospital, Anbar Health Directorate, Anbar, Iraq
- * Correspondence: anmarh222@gmail.com

Abstract: Background: Early postoperative infections after colorectal surgery remain challenging; serum endocan, procalcitonin, and C-reactive protein may facilitate timely risk-identification strategies. Aims of the study: This study aimed to evaluate the associations of perioperative serum endocan, procalcitonin, and C-reactive protein with early infectious complications following colorectal surgery and compare their diagnostic performan. Methodology: This prospective cohort study included 180 adults undergoing colorectal surgery at Al-Nasiriyah General Hospital and affiliated clinics between April 10, 2025, and June 2, 2026. Participants were followed for 30 days; 34 developed infectious complications and 146 remained uncomplicated. Serum samples were collected preoperatively and on postoperative days 1 and 3. Endocan, procalcitonin, and CRP were measured using sandwich ELISA. Complications were diagnosed using clinical, microbiological, laboratory, and imaging criteria. Ethical approval and written informed consent were obtained. Result: Among 180 patients, 34 (18.9%) developed infectious complications, most commonly surgical-site infection (12.8%). Infected patients had more diabetes, open procedures, longer operations, greater blood loss, and prolonged hospitalization. Postoperative endocan, procalcitonin, and CRP were significantly elevated, particularly on day 3. Procalcitonin showed the strongest individual discrimination (AUC=0.87), followed by endocan (AUC=0.84). Both remained independent predictors after adjustment. The combined clinical-biomarker model achieved an AUC of 0.89, with 82.4% sensitivity and 84.2% specificity. Conclusions: Serial endocan and procalcitonin measurements were independently associated with early infectious complications after colorectal surgery. Their integration with clinical factors improved diagnostic performance, supporting multimarker-guided postoperative surveillance; however, the proposed model and cutoff values require validation in larger multicenter cohorts

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1. Introduction

In spite of its importance in treating malignant as well as benign colorectal disease, infection is an important source of morbidity, extended hospital stays, readmission, reoperation and higher healthcare costs following colorectal surgery. The complications include superficial and deep surgical-site infection, intra-abdominal abscess, anastomosis leakage, urinary tract infection and postoperative pneumonia [1]. In spite of improvements in minimally invasive surgery, prophylactic antibiotic use, and enhanced recovery after surgery and Perioperative Infection Control bundles, the morbidity caused by infectious complications following colorectal surgery is still clinically relevant [2]. In

addition to the inherent contamination during colorectal surgery, postoperatively, the risk of infection is high due to bowel flora, manipulation of the bowel, construction of the anastomosis and patient-related comorbidities [3].

One of the most severe infectious complications is anastomotic leakage and failure to recognize it early can result in peritonitis, sepsis, organ dysfunction, re-operation, and death [4]. It also has a significant economic burden due to prolonged hospital stay, intensive care admission, extra interventions and re-hospitalization [5]. It is often hard to make an early diagnosis because early signs and symptoms are often non-specific and could overlap with normal physiological response to surgery such as mild tachycardia and abdominal discomfort, leukocytosis and low grade fever. Imaging is useful when there is suspicion for complications, but computed tomography is not always useful or practical for all patients [6]. Thus, it seems that reliable circulating biomarkers would be useful to identify high-risk patients prior to clinical deterioration.

Surgical trauma causes a sterile inflammatory response, involving cytokine release, endothelial activation and production of acute phase proteins. Therefore, it is difficult to distinguish uncomplicated postoperative inflammation from early bacterial infection. In fact, postoperative kinetics should be taken into consideration when interpreting biomarkers instead of relying on single values [7]. Diagnostic certainty is not yet achieved with any single marker and may be more likely to be achieved by using a combination of markers reflecting different pathophysiological processes [8].

C-reactive protein (CRP) is an acute-phase protein mostly controlled by interleukin-6 (IL-6) synthesized in the liver. It is sensitive but not infection-specific and its concentration increases in response to infection, tissue injury and systemic inflammation [9]. In colorectal surgery, postoperative CRP has been extensively studied, such as its use as a marker to exclude major infectious complications if it is well controlled and kept low or decreasing, where the decrease is appropriate [10]. Chronic or recurrent CRP positivity can be due to an abnormal inflammatory course, but may be affected by surgical approach, surgical size, malignancy stage and CRP sampling day [11].

The prohormone of calcitonin is procalcitonin (PCT), which is released by various tissues in a systemic bacterial infection. PCT is, in general, more closely linked with bacterial stimulation and can offer further clues in distinguishing bacterial from sterile postoperative inflammation than does CRP. However, the diagnostic utility is influenced by the site of infection, renal function, extent of the disease and the time of the test [12]. In a multicenter colorectal study, CRP performed better than PCT in excluding anastomotic leak on the fourth postoperative day; suggesting that PCT should not be used to replace CRP [13]. Other inflammatory markers may also become abnormal earlier to further support serial and multimarker assessment [14].

Endocan (also called endothelial cell-specific molecule-1) is a soluble dermatan-sulfate proteoglycan mainly secreted by the vascular endothelial cells. It is activated by pro-inflammatory or angiogenic factors such as tumor necrosis factor- α , interleukin-1 β and vascular endothelial growth factor. Endocan is thus a marker of endothelial activation and microvascular inflammation which is not well reported by CRP or PCT [15]. The endothelial dysfunction plays an important role in infection-related microcirculatory dysfunction, increased vascular permeability, leukocyte recruitment, and organ injury. Increased endothelial biomarkers like endocan have been linked with the incidence and severity of sepsis [16]. The results of the other infectious populations have also confirmed the possible contribution of endocan to diagnosis along with the use of other inflammatory markers [17]. However, its perioperative kinetics and diagnostic value following colorectal surgery is still limited.

The present study was therefore designed to assess the correlation of the serial serum levels of endocan, PCT and CRP with development of early postoperative infectious complications after colorectal surgery and to evaluate the diagnostic efficacy of the three serum markers separately. It also sought to compare performance of a combined biomarker model with single biomarker models in order to better discriminate between patients in the early stages, to facilitate closer surveillance and to allow for clinically appropriate intervention [18].

2. Materials and Methods

The study was carried out during April 10, 2025 to June 2, 2026 at the Department of General Surgery, Al-Nasiriyah General Hospital and affiliated surgical clinics in Dhi Qar Province, Iraq in a prospective observational cohort study. Postoperatively, 34 patients developed early infectious complications, while 146 patients had an uncomplicated postoperative course and were followed for a total of 180 adult patients who were consecutively enrolled and followed for 30 days after the surgery. Historical controls included patients who met the same criteria as those in the experimental group except for the requirements for surgery, for histopathologically confirmed colorectal malignancy or benign colorectal disease (disease diagnosis by clinical examination, laboratory investigations, colonoscopy, biopsy and histopathology, and contrast enhanced computed tomography of the abdomen and pelvis) and for magnetic resonance imaging conducted when clinically indicated. Patients who were not followed clinically completely, had incomplete follow-up, or had chronic hepatic or renal failure, autoimmune or severe inflammatory disease, and/or were having emergency surgery or were taking immunosuppressive medications at the time of surgery were excluded. Infectious complications in the first 30 days following surgery, such as superficial or deep surgical-site infection, organ-space infection, leakage of the anastomosis, intra-abdominal abscess, pneumonia, or urinary tract infection, were defined by clinical and laboratory parameters, microbiological culture, and radiological imaging based on standard criteria. A total of 540 serial blood samples were collected aseptically at three time points (preoperatively and on postoperative day 1 and 3) from each participant. Blood was put into serum-separator tubes, allowed to clot for 20–30 minutes at room temperature, and centrifuged at 3,000 ×g for 10 minutes. They were separated and the serum transferred into coded aliquots, which were frozen and stored at –80°C until analyzed, avoiding repeated freeze–thaw cycles. Commercial human sandwich enzyme-linked immunosorbent assay (ELISA) kits were used to determine the levels of serum endocan, procalcitonin, and C-reactive protein (CRP), following manufacturers' instructions. Standards, controls and serum samples were assayed in duplicate, absorbance was read at the wavelength listed for each assay, and concentrations of each biomarker were determined from the standard curve (see below). All the analytical runs contained internal quality-control samples, and all assays were replicated if the duplicate measurements gave an acceptable coefficient of variation that was greater than the prespecified value. The data were collected on a standard pre-designed data collection form, which included demographic, clinical, operative, and postoperative data. The study was approved by the relevant institutional ethics committee, it followed the Declaration of Helsinki and informed written consent was obtained from all participants prior to their enrollment and blood collection.

2.1 Statistical analysis:

IBM SPSS Statistics version 26.0 was used for statistical analyses. Distribution of data were examined by Shapiro–Wilk test and histogram. Continuous variables were reported as mean ± standard deviation and analyzed with the independent-samples t-test; non-normally distributed continuous variables were expressed as the median and interquartile range (IQR) and analyzed using the Mann–Whitney U test. Categorical data was summarized by frequency and percentage and analyzed by Pearson's chi-square test or Fisher's exact test. The serum levels of endocan, procalcitonin, and C-reactive protein were compared with repeated-measures analysis or an appropriate nonparametric analysis at the following times: the preoperative period, postoperative days 1 and 3. Independent predictors of early postoperative infectious complications were identified using multivariate logistic regression, and the odds ratios and 95% confidence intervals are reported. Receiver operating characteristic curves were built to evaluate the diagnostic performance, and the optimum cutoff values were obtained using the Youden index. All tests used were two-tailed and P values < 0.05 were considered statistically significant.

2.2 Ethical approval:

The study protocol was approved by the scientific and ethics committee of the respective institutes before recruiting participants. The study was performed in compliance with the principles laid down in the Declaration of Helsinki and the

institutional regulations. Participants were informed of the study's goals, methods, risks, benefits and confidentiality protections and informed consent was obtained prior to participation and blood collection. No one was coerced to take part, and withdrawal did not have any consequences on the medical care of the participants. Personal information was anonymized by coded identifiers, kept confidential and only utilized to be used for research purposes.

3. Results

Comparison of baseline and perioperative factors between patients with and without early postoperative infectious complications

There were more patients who developed infectious complications who had type 2 diabetes (35.3% vs. 19.2%; $P=0.041$) and more who had undergone open surgery (52.9% vs. 31.5%; $P=0.019$). They also had longer operative durations (188 ± 48 vs. 163 ± 42 minutes; $P=0.003$) and greater intraoperative blood loss (310 [210–460] vs. 240 [150–360] mL; $P=0.025$). There was no significant difference between the groups in terms of age, gender, BMI, smoking, hypertension, ASA classification, anemia, malignancy, type of procedure, emergency surgery, or transfusion (all $p>0.05$).

Table 1. Demographic, Clinical, and Operative Characteristics Stratified by Early Infectious Complications Following Colorectal Surgery

Characteristic	Infectious complications (n=34)	No infectious complications (n=146)	P-value
Age, years	64.1 ± 10.7	61.3 ± 11.4	0.192
Male sex, n (%)	20 (58.8)	80 (54.8)	0.670
BMI, kg/m ²	27.1 ± 4.2	26.3 ± 3.9	0.289
Current smoking, n (%)	9 (26.5)	27 (18.5)	0.292
Type 2 diabetes, n (%)	12 (35.3)	28 (19.2)	0.041
Hypertension, n (%)	16 (47.1)	57 (39.0)	0.388
ASA class III, n (%)	14 (41.2)	36 (24.7)	0.054
Preoperative anemia, n (%)	13 (38.2)	35 (24.0)	0.091
Colorectal malignancy, n (%)	27 (79.4)	109 (74.7)	0.562
Open surgical approach, n (%)	18 (52.9)	46 (31.5)	0.019
Rectal procedure, n (%)	15 (44.1)	53 (36.3)	0.397
Emergency surgery, n (%)	5 (14.7)	8 (5.5)	0.070
Operative duration, minutes	188 ± 48	163 ± 42	0.003
Intraoperative blood loss, mL	310 (210–460)	240 (150–360)	0.025
Perioperative transfusion, n (%)	8 (23.5)	16 (11.0)	0.052

Frequency, diagnostic timing, and clinical consequences of postoperative infections among the complete colorectal surgery cohort

Early infectious complications were seen in 34/180 patients (18.9%) with surgical-site infection being the most common (12.8%), followed by anastomotic leakage with infection (3.9%), pneumonia (3.3%), urinary tract infection (2.2%) and blood stream infection (1.7%) [19]. Multiple infections occurred in seven patients (3.9%) and the time from admission to diagnosis was a median of 5 days (IQR: 3–7). Intensive care admission (5.0%), 30-day readmission (6.7%) and mortality (1.7%) were recorded, with 3.3% of patients reoperating due to the infection. Infected patients had a significantly longer hospital stay than noninfected patients (13 [10–18] vs. 7 [5–9] days; $P<0.001$).

Table 2. Incidence, Clinical Distribution, and Short-Term Outcomes of Early Infectious Complications Following Colorectal Surgery

Postoperative outcome	n (%)
Any infectious complication	34 (18.9)
Surgical-site infection	23 (12.8)
Superficial incisional infection	13 (7.2)
Deep incisional infection	4 (2.2)
Organ-space infection	6 (3.3)
Anastomotic leak with infection	7 (3.9)
Pneumonia	6 (3.3)
Urinary tract infection	4 (2.2)
Bloodstream infection	3 (1.7)
More than one infection	7 (3.9)
Median time to diagnosis, days	5 (3–7)
Reoperation due to infection	6 (3.3)
Intensive care admission	9 (5.0)
30-day readmission	12 (6.7)
30-day mortality	3 (1.7)
Length of stay, days: infected patients	13 (10–18)
Length of stay, days: noninfected patients	7 (5–9)
Between-group comparison for hospital stay	<0.001

Serial comparison of endocan, procalcitonin, and C-reactive protein concentrations before and after colorectal surgery

There were no significant differences between the groups in regard to the concentrations of preop endocan, procalcitonin or C-reactive protein (all $P>0.05$). Of the patients who went on to develop infectious complications, endocan was found to be significantly elevated (5.28 vs. 3.42 ng/mL; $P<0.001$), as was procalcitonin (0.68 vs. 0.24 ng/mL; $P<0.001$), and C-reactive protein (91 vs. 72 mg/L; $P=0.006$) on postoperative day 1. By postoperative day (POD) 3, all three biomarkers were significantly higher in infected patients (all $P<0.001$), suggesting different biomarker courses within the first 3 days after surgery in patients with infectious complications [20].

Table 3. Perioperative Serum Biomarker Levels According to Early Infectious Complications Following Colorectal Surgery

Biomarker and assessment time	Infectious complications (n=34)	No infectious complications (n=146)	P-value
Endocan, ng/mL			
Preoperative	2.35 (1.82–3.04)	2.14 (1.65–2.78)	0.218
Postoperative day 1	5.28 (4.12–6.91)	3.42 (2.67–4.40)	<0.001
Postoperative day 3	6.41 (4.85–8.32)	3.01 (2.31–3.96)	<0.001
Procalcitonin, ng/mL			
Preoperative	0.07 (0.04–0.11)	0.06 (0.04–0.09)	0.284
Postoperative day 1	0.68 (0.39–1.12)	0.24 (0.14–0.43)	<0.001
Postoperative day 3	1.14 (0.61–2.08)	0.18 (0.10–0.32)	<0.001
C-reactive protein, mg/L			
Preoperative	7.8 (4.1–14.6)	6.4 (3.2–11.8)	0.244

Biomarker and assessment time	Infectious complications (n=34)	No infectious complications (n=146)	P-value
Postoperative day 1	91 (66–128)	72 (51–101)	0.006
Postoperative day 3	158 (112–216)	82 (57–119)	<0.001

Relationships between day-three serum biomarker concentrations, diagnostic timing, inflammatory response, organ dysfunction, and clinical outcomes

The postoperative day (POD) three levels of endocan, procalcitonin and CRP had a positive association with hospital stay, SOFA score, peak temperature, leukocyte count and severity of infection. The strongest correlations were with the severity of infection ($\rho=0.51$, $P<0.001$), hospital stay ($\rho=0.48$, $P<0.001$) and the SOFA score ($\rho=0.46$, $P<0.001$). The levels of higher endocan and procalcitonin correlated with earlier infection diagnosis ($\rho=-0.28$ and -0.31 , respectively, with both $P<0.05$), but the association with CRP was not statistically significant.

Table 4. Correlations of Postoperative Biomarkers with Clinical Indicators and Infection Severity Following Colorectal Surgery

Clinical indicator	Endocan, ρ	Procalcitonin, ρ	CRP, ρ
Time to infection diagnosis	-0.28*	-0.31*	-0.22
Length of hospital stay	0.44***	0.48***	0.39***
Sequential Organ Failure Assessment score	0.37**	0.46***	0.34**
Peak postoperative temperature	0.32**	0.40***	0.36**
Postoperative leukocyte count	0.29*	0.34**	0.41***
Infection severity category	0.42***	0.51***	0.38**

Adjusted associations of day-three serum biomarkers and relevant clinical factors with postoperative infectious complication risk

Each standard deviation increase of postoperative day three endocan and procalcitonin levels was independently associated with 71% (adjusted OR=1.71; 95% CI: 1.16–2.52; $P=0.007$) and 89% (adjusted OR=1.89; 95% CI: 1.24–2.87; $P=0.003$) increased odds of infectious complications, respectively [21]. More prolonged operative time also was an independent risk factor for infection (adjusted OR for every 30 minutes=1.29; 95% CI: 1.02–1.63; $P=0.034$). After adjustment none of the other factors remained statistically significant: CRP, diabetes, or open surgery (all $P>0.05$).

Table 5. Multivariable Predictors of Early Postoperative Infectious Complications Among Patients Undergoing Colorectal Surgery

Predictor	Adjusted OR	95% CI	P-value
Endocan, per 1-SD increase	1.71	1.16–2.52	0.007
Procalcitonin, per 1-SD increase	1.89	1.24–2.87	0.003
CRP, per 1-SD increase	1.38	0.97–1.97	0.073
Type 2 diabetes	1.82	0.83–4.01	0.136
Open surgical approach	1.94	0.91–4.14	0.086

Predictor	Adjusted OR	95% CI	P-value
Operative duration, per 30-minute increase	1.29	1.02–1.63	0.034

Receiver-operating characteristic analysis of postoperative biomarkers and integrated models for early identification of infectious complications

Procalcitonin was the most discriminatory single test on postoperative days 1 and 3 with AUCs of 0.79 and 0.87, respectively. The performance of day-three endocan was good (AUC=0.84), while that of CRP was comparatively low on days 1 and 3 (AUC=0.66 and 0.78). The AUC for the combination of the three day-one biomarkers was 0.85, and the highest was obtained from the integrated clinical–biomarker model (AUC=0.89; 95% CI: 0.83–0.95); sensitivity and specificity were 82.4% and 84.2%, respectively, for the model with a predicted probability cutoff of ≥ 0.27 .

Table 6. Diagnostic Performance of Individual and Combined Biomarker Models for Early Infectious Complications After Colorectal Surgery

Marker or model	AUC	95% CI	Optimal cutoff	Sensitivity (%)	Specificity (%)	P-value
Endocan, postoperative day 1	0.76	0.68–0.84	≥ 4.15 ng/mL	73.5	69.2	<0.001
Procalcitonin, postoperative day 1	0.79	0.71–0.87	≥ 0.41 ng/mL	76.5	72.6	<0.001
CRP, postoperative day 1	0.66	0.56–0.75	≥ 86 mg/L	64.7	63.7	0.004
Endocan, postoperative day 3	0.84	0.77–0.91	≥ 4.38 ng/mL	79.4	78.1	<0.001
Procalcitonin, postoperative day 3	0.87	0.80–0.93	≥ 0.48 ng/mL	82.4	80.1	<0.001
CRP, postoperative day 3	0.78	0.70–0.86	≥ 118 mg/L	73.5	72.6	<0.001
Three-biomarker signature, day 1	0.85	0.78–0.92	Probability ≥ 0.24	79.4	78.8	<0.001
Combined clinical–biomarker model	0.89	0.83–0.95	Probability ≥ 0.27	82.4	84.2	<0.001

4. Discussion

The present findings indicate that early postoperative infectious complications were present in 18.9% of patients who underwent colorectal surgery and the most common complication was surgical-site infection. This proportion is clinically feasible as colorectal surgery has an inherent risk of infection due to contamination from the bowel, manipulation of tissue, anastomosis and the high incidence of co-existing malignancy, diabetes, malnutrition or anemia [22]. The surgical-site infection is still a significant cause of extended hospital stay, reoperation, readmission, and postoperative mortality [23]. A recent meta-analyses also identified colorectal surgery as a high risk surgical category

with wide variations in infection rates depending on case definition, surgical approach, antibiotic preparation, duration of surveillance and patient characteristics [24]. So the present complication rate should be viewed in the context of its composite definition, which incorporated surgical-site, respiratory, urinary, bloodstream or organ space infection.

Infected patients showed increased diabetes, open surgery, length of operation, and blood loss during surgery. This is similar to the colorectal surgical risk pathways known to exist. Risk of infection is a common risk factor in diabetes which is caused by impaired activity of neutrophil, microvascular dysfunction, reduced oxygenation of tissues and delayed wound healing [25]. Open operations can result in more tissue damage and exposures to the environment than minimally invasive procedures and may be longer, leading to higher levels of bacterial exposure, tissue desiccation, anesthetic time and risk of inadequate antibiotic levels. Clinically relevant determinants of colorectal anastomotic complications have been identified in reviews: These include operative complexity, comorbidities, impaired tissue perfusion and transfusion, and technical factors [26]. Another study of large numbers of patients who underwent colorectal cancer surgery also found links to open surgery, longer surgery, diabetes, and physiological impairment perioperatively [27]. However, multivariate analysis did not maintain the significance of diabetes or surgical approach in the proposed model. This could be due to small sample size (34 infective events), interdependencies between operating factors, or a mediation of the size of inflammatory and endothelial responses after the surgery.

The median time to infection diagnosis was five days, and the differences in biomarkers were more obvious by postoperative day 1 and increased by day 3. This clinical time lag is significant because biochemical changes can occur before clinical signs of fever, wound changes, ileus, abdominal pain or radiological evidence of infection. Amanai et al. also showed that serial measurements of inflammatory biomarkers could predict infectious complications following elective colorectal surgery prior to the definite diagnosis [28]. In the case of laparoscopic colorectal resection, Tatsuoka et al. reported beneficial postoperative CRP and procalcitonin dynamics when these parameters were elevated instead of decreasing in an uncomplicated manner. Variations in the best time to postpone surgery in the studies could reflect different sampling protocols, differing surgical invasiveness, the definition of infection, and whether only all infections or only infections causing anastomotic leakage were counted.

There was no significant difference in pre-operative concentrations of endocan, procalcitonin or CRP between groups, but all three were higher in patients who developed infection after surgery. This pattern suggests that the trajectory of biomarkers after surgery could be more valuable than a single baseline measurement. This is because tissue injury, regardless of infection, increases CRP levels, due to the action of interleukin-6 on the liver. Therefore, an early elevation of the CRP is not of much concern after uncomplicated surgery, but on days 3–5 after surgery, a persistent or secondary elevation is more concerning. Bona et al. showed that CRP and procalcitonin were helpful for the diagnosis of colorectal anastomotic leakage, particularly if used serially in early postoperative period. Hu et al. also showed that CRP and procalcitonin measurements on day 3 provided better recognition of “high risk” anastomotic leakage [29].

Moderate discrimination (AUC of 0.78) was achieved with the proposed CRP cutoff of 118 mg/L on postoperative day 3. However, Corrêa Neto et al. found an elevated threshold to identify patients at risk of having a reoperation following colorectal surgery of around 185 mg/L. Rajabaleyan et al. likewise used a day-3 CRP cut-off of 180 mg/L, and an early-warning score, with an AUC of 0.87. These seemingly higher thresholds do not contradict the current trend as these studies were mostly focused on anastomotic leakage or reoperation, while the proposed outcome encompassed superficial infection, pneumonia, urinary infection, and bloodstream infection. More inflammatory response is likely to be seen with severe organ space complications as compared to localized infections. Other variations can be brought on by differences in what type of surgery is performed, how the lab test is conducted, the time at which the test is taken, enhanced recovery methods, and baseline inflammation associated with cancer [30].

Procalcitonin had the highest individual AUC (0.87), sensitivity (82.4%) and specificity (80.1%) on postoperative day 3. This is a biologically plausible finding since bacterial toxins and systemic inflammatory cytokines stimulate the production of procalcitonin in extrathyroidal organs, whereas uncomplicated surgical inflammation typically results in a smaller and shorter increase in procalcitonin. A recent systematic review suggested that procalcitonin might be more infection specific than CRP, but neither was sensitive enough to use as a standalone diagnostic test [31]. The literature is not entirely congruent, however. Villegas-Coronado et al. reported that day-3 PCT might be potentially useful for the diagnosis of colorectal anastomotic leakage, but these results were diminished by sensitivity analysis in studies limited to colorectal cancer patients [32]. Likewise, Jerome et al. reported significant variability in procalcitonin diagnostic accuracy in the various major gastrointestinal procedures. These differences might be caused by variation in renal function, bacterial load, local versus systemic infection, inflammation due to cancer, exposure to different antimicrobials, and measurement methods for procalcitonin [33].

Endocan was independently correlated with infectious complications and had good discrimination on day 3, but was slightly worse than procalcitonin. Endocan is secreted by vascular endothelial cells in response to pro-inflammatory cytokines, and represents endothelial activation, leukocyte–endothelial interaction and microvascular disturbance. This result is preliminary as there is limited evidence directly assessing endocan following colorectal surgery. The review of biomarkers for colorectal anastomotic failure highlights a lack of singly effective circulating markers to capture the multi-faceted nature of tissue ischemia, barrier disruption, bacterial translocation, inflammation and endothelial injury. The evidence from sepsis populations indicates that endothelial and glycocalyx injury biomarkers are linked with organ dysfunction and poor outcomes. Modern reviews on sepsis-biomarkers also back the incorporation of endothelial markers with traditional inflammatory markers, opposing the use of any single marker [34]. Endocan could thus add to the procalcitonin and CRP and be a different facet of the vessel biology of infection.

The positive associations of day-3 biomarkers with hospital stay, temperature, leukocyte count, SOFA score and severity of the infection further validate their clinical relevance. Procalcitonin was the most strongly associated with severity, while leukocytosis was the most strongly associated with CRP. These kinds of multimarker reasoning have been seen in the case of another infection-related marker, presepsin, which could be as effective or more effective than traditional markers in certain postoperative cohorts [35]. Lu et al. conducted a meta-analysis of the diagnostic performance of presepsin and included several analyses based on the pool of patients from each surgical specialty and diagnostic definition, with the result of the former being quite promising for the role of a diagnostic marker, while the latter highlighted the difference between the various surgical specialties [36]. This suggests that variations between different biomarker studies could be due to the fact that each biomarker provides information regarding a different biological compartment, and not because one study is necessarily wrong.

The three-biomarker signature achieved an AUC of 0.85 on postoperative day 1 and the clinical–biomarker combination model achieved an AUC of 0.89. This corroborates the fact that a combination of biological and operative information can be more effective than one marker. There have also been reports that dynamic CRP changes are more informative for diagnosis than absolute levels [37]. The combined model, however, should be considered exploratory due to the large number of predictors for a limited number of events. Modern recommendations for the development of sepsis biomarkers highlight the importance of performing calibration assessment, clinical-utility analysis, standardization of assays, and external validation prior to use [38]. Therefore, prior to the use of proposed cutoffs or probability thresholds for making clinical decisions, bootstrap validation and penalized regression, or independent multicenter validation should be performed. Rather than being a diagnosis of infection, biomarker elevation should lead to more intensive clinical evaluation and imaging studies.

5. Conclusion

Colorectal surgery patients were at risk of experiencing early postoperative infectious complications in about 1/5 of cases and this was linked with increased short-term outcomes and hospital stay. Affected patients had significantly elevated serial serum levels of endocan, procalcitonin and CRP, especially on postoperative day 3. Procalcitonin was the most powerful single marker and endocan added further information related to endothelial activation. The role of both biomarkers as independent predictors of infectious complications remained after the adjustments for relevant clinical and operative parameters while that of CRP was comparatively low. Biomarker combination with clinical variables resulted in the best diagnostic accuracy, implying that a multimarker approach might help to risk stratify earlier and enable more targeted postoperative surveillance. However, the results of these studies await confirmation in larger multicenter studies before the proposed cut-off values and prediction model can be incorporated into routine clinical practice.

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