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The clinical and economical impact of postoperative ileus in patients undergoing colorectal surgery

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Abstract

Background: Colorectal surgery is associated with postoperative ileus (POI). Despite its widespread manifestation, the influence of POI on recovery, quality of life (QoL), and costs is largely unknown. The aim of this study was to assess whether the inflammatory processes found in experimental studies are also evident in patients undergoing colorectal surgery. In addition, the impact of POI on short and long-term QoL and costs was investigated.

Methods: We analyzed the outcomes of the SANICS-II trial, including prospective evaluation of inflammatory parameters in blood samples, costs from a societal perspective and QoL, using validated questionnaires. Outcomes were compared between patients with and without POI, and in particular patients with POI as unique complication.

Key Results: A total of 265 patients (POI, n = 66 vs non-POI, n = 199) were included and 38/66 had POI as only complication. CRP levels were significantly increased on postoperative day (POD) 1, 2, 3, and 4 in patients with POI. Furthermore, plasma levels of cytokines IL-6, IL-8 and IL-10 were significantly increased the first 2 days after resection. Patients with POI had a higher overall complication rate and a reduced QoL 3 months postoperatively, even in the only POI group. Moreover, mean societal cost per patient with POI was 38%-47% higher at 3 months postoperatively.

Conclusions & Inferences: Supporting findings from experimental studies, inflammatory parameters were increased in patients with only POI and comparable with all patients with POI. These results demonstrate the impact and large contribution of POI in postoperative inflammation, costs and QoL in patients undergoing colorectal surgery.

KEYWORDS

inflammation, postoperative ileus, quality of life, societal costs

1 | INTRODUCTION

Colorectal surgery is associated with a substantial complication rate. In particular, postoperative ileus (POI) is affecting 10%-40% of patients undergoing a colorectal resection and is an important clinical determinant of short-term morbidity.¹ POI is often seen as an inevitable complication of abdominal surgery, and attempts have been made to reduce the incidence by enhanced recovery after surgery protocols, less opioid use and studies investigating the use of chewing gum.² Still, POI is leading to discomfort, impaired recovery, a prolonged length of hospital stay, reoperation and readmission.^{3,4} Notably, an association exists between POI and anastomotic leakage, further indicating the impact of POI on postoperative morbidity.⁵

Complications after colorectal surgery have impact on the quality of life (QoL) and are associated with a substantial increase in costs.^{6,7} However, it is unknown what the significance of POI is in these costs and quality of life, in the short and long term after patients have been discharged. Furthermore, clinically relevant therapeutic strategies for POI are lacking, although the underlying mechanism of POI has been unraveled in rodent models.⁸ Such models point out that POI is triggered by local inflammatory infiltrates and is associated with systemic inflammatory markers. Manipulation of the intestine induces activation of macrophages, mast cells, and enteric glial cells.⁹⁻¹¹ Vagus nerve stimulation has been shown in experimental models to be effective in reducing the inflammatory process underlying POI.¹² Also, stimulation of the vagus nerve via lipid-enriched nutrition was effective in several experimental models, although such an effect of lipid-enriched nutrition was not observed in a large double-blind randomized controlled trial (SANICS-II trial).¹³ However, despite the insight into molecular cues to POI development, little progress is made in translating these experimental findings to a clinical practice. The reason for this discrepancy between the experimental data and the implementation into clinical practice may be twofold; on the one hand there is a lack of consensus amongst physicians toward the clinical features of POI, its impact, and its management, resulting in few high quality clinical studies also in a surgical setting.¹⁴ On the other hand, it is uncertain whether the mechanisms found in rodent models can be completely translated into the clinical setting.¹⁵⁻¹⁸ The aim of the current study is to address whether inflammatory processes such as those found in experimental studies, occur in patients undergoing colorectal surgery. In addition, the impact of POI on short and long-term QoL and costs was investigated.

2 | MATERIALS AND METHODS

This is a sub-study from a previous international multicenter double-blind randomized controlled trial (SANICS-II trial) in three Dutch hospitals and three Danish hospitals.¹³ The trial was designed to compare lipid-rich nutrition administered just before, during,

Key Points

- Current status and key question(s) being addressed in the research paper: Postoperative ileus (POI) is a common complication in patients, however, translation of experimentally found mechanisms and resolutions to the clinical setting remain challenging.
- Results of the current paper: This study found that patients with POI had a higher inflammatory response, more complications, an increased length of stay, a decreased quality of life and more healthcare costs.
- Importance of these results: This study confirms the association of POI with inflammation and demonstrates the burden of POI on patients, the healthcare system, and society.

and after colorectal resection to standard care (no nutrition). The original study was approved by the Medical Ethics Committee of the Catharina Hospital (Eindhoven, The Netherlands) and was reported according to the CONSORT guidelines. The principles of Good Clinical Practice and the Declaration of Helsinki were followed. The trial was registered with ClinicalTrials.gov (number NCT02175979) and trialregister.nl (number NTR4670). Further details regarding the trial design and outcomes have previously been reported.^{13,19}

2.1 | Population and setting

In the SANICS-II trial described earlier, 280 patients were randomized, 15 of whom were excluded after random allocation because they fulfilled one or more exclusion criteria. All 265 patients analyzed in the original trial were considered for inclusion in the current study. Briefly, inclusion criteria were age 18 years or older and undergoing elective segmental colorectal resection with primary anastomosis. The exclusion criteria were a previous gastric or esophageal resection, peritoneal metastases, a pre-existing or the creation of an ileostomy, and the use of glucocorticosteroids or medication that disrupted acetylcholine metabolism (eg, selective serotonin reuptake inhibitors or anticonvulsants). All patients provided written informed consent. Patients were randomly assigned to the intervention or control group and stratification was applied to ensure an equal distribution between colonic and rectal surgery and between laparoscopic and open procedures. In the present study, patients were stratified into two groups including those with and without POI. First, in order to assess the true influence of POI, an analysis was performed in a selected group of patients in which patients with POI as unique complication ($n = 38/66$) were compared with patients that did not develop any complications after surgery ($n = 144/199$). Second, the total study population ($n = 265$) was

analyzed to investigate the contribution of POI to other complications, inflammation, QoL and costs.

2.2 | Clinical outcomes

Postoperative ileus is the primary outcome in the original trial and is measured clinically. POI was scored by the definition as described by Vather et al.²⁰ Patients had to meet the following criteria at postoperative day (POD) 4 after colorectal surgery: lack of flatus or stool passage and inability to tolerate a regular oral diet. We also included late POI which is established when the symptoms of POI (lack of flatus or stool passage and inability to tolerate an oral diet) are first experienced after POD 4. Patients were instructed to register presence of nausea or vomiting, passage of flatus and defecation, and consumption of a regular oral diet in a diary daily. All surgical complications within 30 days postoperatively were registered and graded according to the Clavien-Dindo Classification of Surgical Complications.²¹ Secondary outcomes included length of stay, readmissions, health-related QoL, and costs and the inflammatory response.

2.3 | Measurement of the inflammatory response

Blood samples were collected from all patients at four predefined time points. Samples were taken the day before surgery and 4, 24, and 48 hours after onset of surgery. All the blood samples were immediately put on ice, centrifuged at 4°C and 3000 g for 12 minutes and the plasma was stored at -80°C until further analysis. To determine the most important inflammatory cytokines, a Human Inflammatory Cytokines Kit was used to measure cytokine levels of IL-1 β , IL-6, IL-10, IL-8, IL12p70, and TNF- α by cytometric bead array (BD Biosciences) according to manufacturer's instructions. CRP (C-reactive protein) measurement was part of the standardized care and the outcomes were retrieved from the medical chart. As such, CRP was only measured postoperatively, on postoperative day (POD) 1, 2, 3, and 4. CRP levels were determined by an immunoturbidimetric assay (Roche/Hitachi cobas C system, Roche).

Data on costs and QoL were collected by means of questionnaires for the period between August 2014 and August 2017, at three time points namely preoperatively, at 3 months and at 6 months postoperatively. Patients who completed the questionnaires at least at two time points were included for this analysis.

2.4 | Costs

The Institute for Medical Technology Assessment (iMTA) Medical consumption questionnaire (iMCQ) was used to measure the healthcare costs; these include hospitalizations, medical procedures, medications, outpatient clinic visits etc. The iMTA productivity cost questionnaire (iPCQ) was used to measure the costs due to

productivity losses in two domains (a) paid work due to absenteeism and presentism and (b) unpaid work.²² The costs were expressed and analyzed in Euros. The updated Dutch manual for Costing Analysis in Health Care Research was used for valuation of the health care costs.²³ Costs were divided into three categories: (a) healthcare sector costs; (b) costs for patient and family; and (c) productivity costs. Healthcare costs consisted of medication costs, consultations with healthcare professionals, use of diagnostic methods and the frequency of inpatient stay and outpatient treatment. The identified health services consumed by the patient were multiplied with their corresponding unit prices. Total costs were estimated by summing the individual services. Medication costs were based on the price per dosage of the drug in the Netherlands. Patient and family costs included the use of formal (paid care) and informal care (unpaid care). The costs for unpaid care were valued using the proxy good method, which values the time spent on informal care at the labor market price of a close market substitute. Productivity costs included productivity losses due to absence from work and were valued using friction cost method. The friction cost method which takes into account production losses confined to the period needed to replace the sick employee (85 days).²³

2.5 | Quality of life and utilities

Quality of life was assessed using the five level, five dimensional EQ-5D-5L, which is a standardized measure of health status developed by the Euroqol group. EQ-5D-5L consists of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension was scored on a five-point scale which represented "no problems," "slight problems," "moderate problems," "severe problems," and "extreme problems". Utilities were derived from EQ-5D-5L using Dutch tariffs.²⁴ The five dimensions can be summed into a health state. Utility values can be calculated for these health states, using preferences elicited from a general population, the so called Dutch algorithm. Here, utility is used to measure a single value between 0 and 1 that reflects the health-related quality of life of the patient.

In colorectal cancer patients, QoL was further assessed using the European Organization for the Research and Treatment of Cancer Quality of life Questionnaire Cancer Core-30 (EORTC QLQ C-30). The scale ranges from 0 to 100, with higher scores indicating higher level of functioning for Global Quality of Life, Physical, Role, Emotional, Cognitive and Social Functioning and Fatigue. For financial problems, higher scores indicate increased difficulty.

2.6 | Statistical methods

All statistical data were analyzed using SPSS V.25 (IBM). Graphics were conducted with GraphPad Prism version 7 (GraphPad Software) Cost data are presented as means with 95% confidence interval and unpaired t test was used to compare the cost means.²⁵ To compare continuous data between groups, the data were tested

for normal distribution (with skewness and kurtosis). Consequently, the Mann-Whitney U test was used for utility and inflammatory parameters, and the data were presented as medians. Analyses of inflammatory parameters were predefined in the protocol and chosen according to literature.^{11,15,26} Inflammatory parameters were treated as independent samples, CRP and cytokine measurements were compared per time point for the chosen conditions and no multiple comparisons have been applied. Univariate logistic regression was used to identify risk factors on POI. A multivariable logistic regression model was developed using factors identified as significant in univariate analyses and clinically relevant factors, including the following variables: American Society of Anesthesiologists (ASA) grade, colon or rectal surgery, open or laparoscopic surgical approach, duration of surgery, intraoperative blood loss and opioid use postoperatively. A two-tailed *P* value <.05 was considered significant.

3 | RESULTS

A total of 265 patients were included in this study. Patients with only POI (*n* = 38) were compared to patients without developing any complication (*n* = 144). Furthermore, 66 patients in total met the criteria of POI, and 199 patients did not have POI. In the group of patients with only POI, 17/38 were operated laparoscopically (45%), and in the group without complications laparoscopic surgery was performed in 95/144 patients (66%). Demographics and clinical characteristics are outlined in Table 1. Multivariate logistic regression analysis showed that ASA-III grade (OR: 4.08 CI: 0.64-6.80 *P* = .002), smoking (OR: 4.13 CI: 1.40-11.84 *P* = .008) and duration of surgery in minutes (OR: 1.01 CI: 1.00-1.02 *P* = .018) were associated with POI.

To evaluate the systemic inflammatory response to surgery, CRP was routinely measured postoperatively and was significantly increased on postoperative day (POD) 1, POD2, POD3, and POD4 in patients with only POI compared to patients without complications (*P* = .016, *P* < .001, *P* = .001, *P* = .047, respectively) (Figure 1A). On predefined time points for every patient plasma cytokine measurements were performed. As expected, preoperative cytokine levels were not different in patients with or without POI. Four hours after start of surgery, a trend toward higher IL-6 for patients with only POI was shown (*P* = .054). Moreover, at 24-48 hours after surgery, cytokine levels showed an increase in patients with POI as only complication. The most pronounced difference between only POI and patients without complications was shown in IL-6 levels (24 hours: *P* = .027; 48 hours: *P* = .016). Furthermore, patients who only developed POI as complication had elevated levels of IL-8 at 24 hours (*P* = .047) and 48 hours (*P* = .015) compared to patients without complications. Also, levels of IL-10 were significantly elevated in patients with only POI compared to no complications at 48 hours: *P* = .012 (Figure 1B-D). IL-1 β , TNF- α , and IL-12p70 were not different between groups; however, concentrations in most samples were below detection limit (Figure 1E-G).

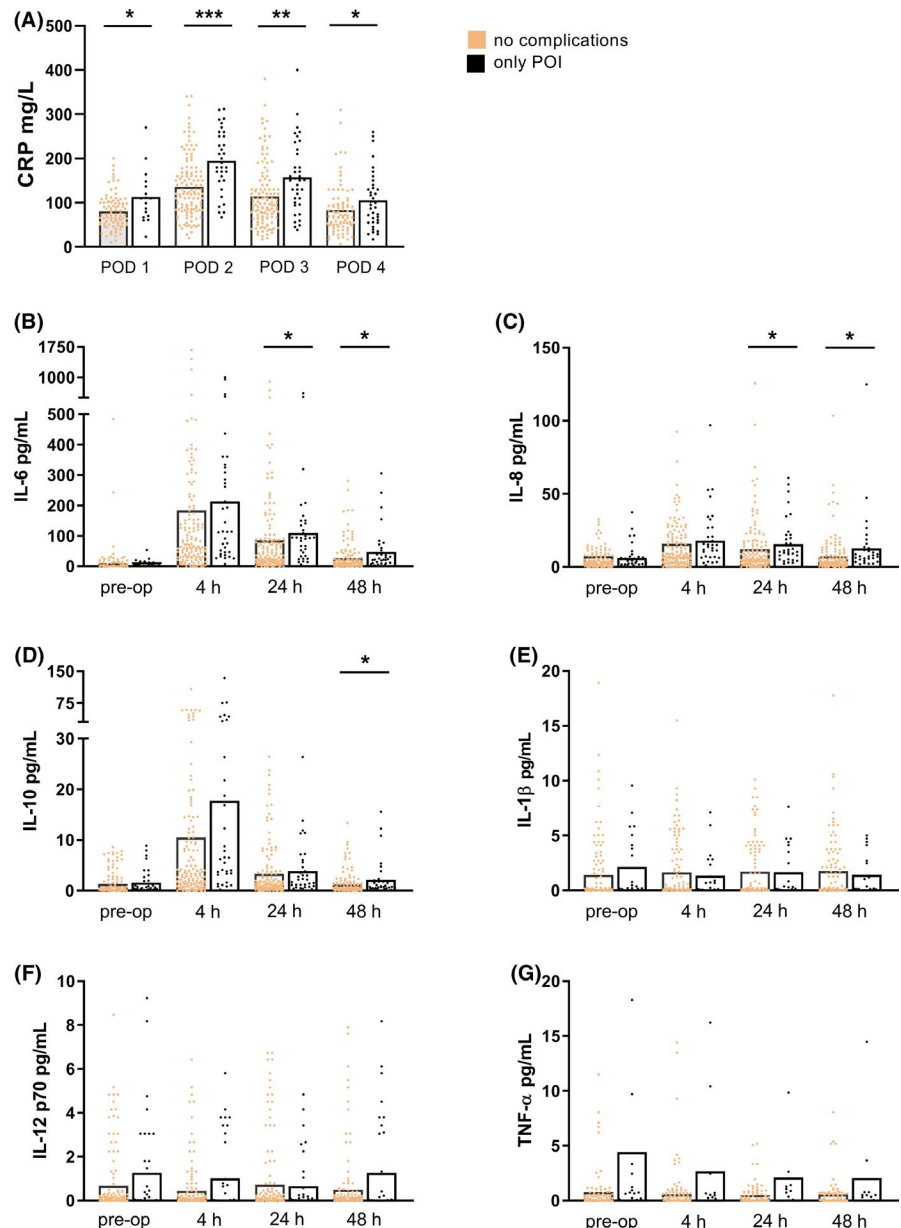
TABLE 1 Demographic characteristics

	No complications (n = 144)	only POI (n = 38)	P-value
Age (y)	67 [63-72]	67 [61-76]	.839
Male	84 (58)	21 (55)	.733
Female	60 (42)	17 (45)	
Body Mass Index (kg/m ²)	25.3 [22.3-27.7]	26.7 [23.7-30.0]	.159
ASA grade			
I	34 (24)	4 (11)	.005
II	98 (68)	24 (63)	
III	12 (8)	10 (26)	
Smoking	13 (9)	9 (24)	.023
Alcohol	115 (78)	21 (55)	.002
Diabetes Mellitus	14 (10)	6 (16)	.379
Previous abdominal surgery	46 (32)	18 (47)	.077
Malignancy	135 (94)	35 (92)	.716
Neo-adjuvant treatment	18 (13)	8 (21)	.180
Surgical approach			
Laparoscopic	95 (66)	17 (45)	.017
Open	49 (34)	21 (55)	
Type of resection			
Colon	118 (82)	27 (71)	.138
Rectum	26 (28)	11 (29)	
Deviating colostomy	19 (13)	12 (32)	.007
Duration of surgery (min)	140 [118-170]	168 [120-225]	.020
Intraoperative blood loss (mL)	100 [40-200]	150 [100-325]	<.001
Perioperative nutrition (intervention)	72 (50)	19 (50)	1.000
Opioid use postoperatively	119 (83)	36 (95)	.062

Note: The data are n (%) or the median [interquartile range].
Abbreviation: ASA, American Society of Anesthesiologists.

Results of the analysis of the total study population, including patients that had other complications as well, were comparable with the results of the only POI and no complications groups. CRP was significantly increased on POD 2, 3 and 4 in patients with POI compared to patients without POI (POD2: *P* < .001; POD3: *P* < .001; POD4: *P* = .003) (Figure 2A). Subsequently, levels of IL-6 (24 hours: *P* = .017 and at 48 hours: *P* = .003), IL-8 (48 hours: *P* = .001) and IL-10 (24 hours: *P* = .036 and 48 hours: *P* = .003) were elevated significantly in patients who developed POI compared to patients without POI (Figure 2B-G). A summary of the inflammatory markers is shown in Table S1.

FIGURE 1 Analysis showing perioperative circulating CRP and cytokine levels in patients with only postoperative ileus (POI) ($n = 38$) against patients without complications ($n = 144$). Every single dot represents a patient, the bar indicates the mean. CRP was significantly elevated on postoperative day (POD) 1, 2, 3 and 4 in patients with only POI. IL-6 and IL-8 showed a significant increase 24 and 48 h after surgery, IL-10 after 48 h (Mann-Whitney U test). * $P < .05$, ** $P < .01$, and *** $P < .001$



3.1 | Costs and QoL assessments

In total 259/265 (98%) patients completed the questionnaires at baseline, 85% (224/265) of the questionnaires were completed postoperatively at 3 months and 82% (216/265) at 6 months postoperatively. Thirty-two patients with missing questionnaires at two time points were excluded from the analysis. This resulted in a total of 233 (88%) patients to be included in the analysis, of which 53 patients were reported with POI and 180 patients without POI. Of these, 32 patients had POI as only complication and 133 had an uncomplicated recovery. Furthermore, 15 patients with a non-malignant disease were excluded from the EORTC analysis.

3.2 | Costs

Costs were calculated from a societal perspective meaning that all the monetary benefits were included regardless of who pays the

costs and who gain the benefits. At 3 months postoperatively, mean societal cost per patient was 38% higher for patients with POI as the only postoperative complication compared to patients without complications (€10 647 vs €6606; $P = .022$; Table 2). Moreover, analyses of all patients with POI showed 47% higher mean societal costs than for all patients without POI (€14 529 vs €7702; $P < .001$; Table 2).

3.3 | Quality of life

Median utility score was significantly lower 3 months postoperatively in patients with only POI (0.85 IQR 0.76-0.98), compared to patients without complications (0.89 IQR 0.83-1; $P = .023$). This effect was even more remarkable in all patients with POI at 3 months, who scored significantly lower on health-related QoL than patients without POI (utility score 0.85 IQR 0.75-0.91 vs 0.89 IQR 0.81-1; $P = .002$). This difference was also apparent at 6 months

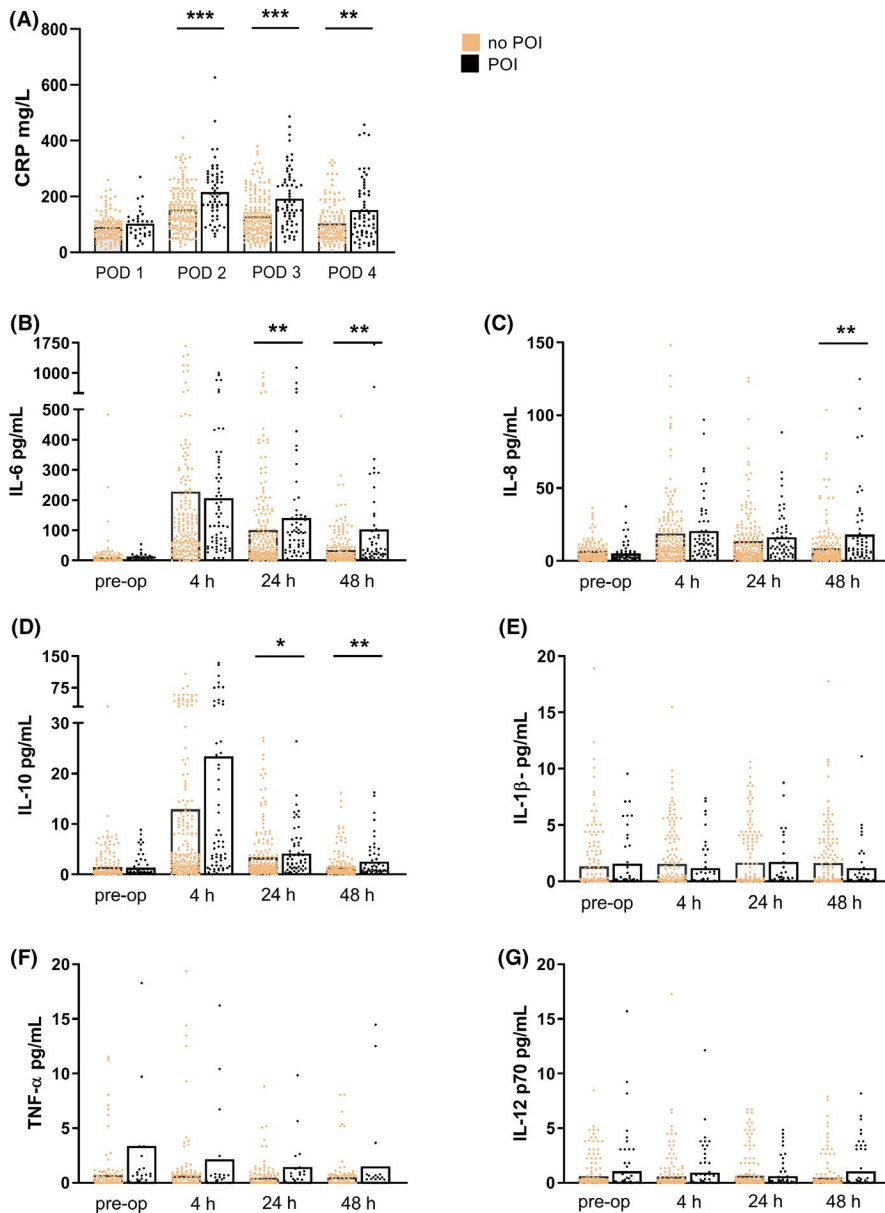


FIGURE 2 Perioperative circulating CRP and cytokine levels in patients with (n = 66) and without postoperative ileus (POI) (n = 199), every single dot represents a patient, the bar indicates the mean. CRP was significantly elevated on postoperative day (POD) 2, 3, and 4 in patients with POI. IL-6 and IL-10 showed a significant increase 24 and 48 h after surgery, IL-8 after 48 h (Mann-Whitney U test). * $P < .05$, ** $P < .01$, and *** $P < .001$

postoperatively; the utility score in patients with POI was 0.84 IQR 0.75-0.92 compared to 0.89 IQR 0.82-1 in those without POI ($P = .017$; Table 2).

Considering the EQ-5D-5L health profile levels (no problems = level 1 and problems = levels 2 to 5) patients with POI as only complication were more likely to experience at least some problems relative to patients without complications. This effect was mostly shown in the dimensions mobility, usual activity and pain. Patients with only POI experienced more mobility problems (47%) than patients without complications (27%) at 3 months and even more at 6 months (66% vs 32%). The same was shown in usual activity: at 3 months 66% of patients with only POI vs 37% of patients without complications experienced problems and at 6 months 56% vs 38% experienced problems in usual activity, respectively. Pain did still impact QoL at 3 months in 63% (only POI) vs 48% (no complications). Accordingly, in the total analysis, half of the patients with a period of POI experienced problems in mobility at 3 months (49% POI vs 32%

no POI) and at 6 months this increased until 60% in POI patients and 36% in patients without POI. This trend was also shown in problems in usual activity: 68% (POI) vs 43% (no POI) at 3 months, and at 6 months 60% (POI) vs 43% (no POI). Pain did still impact QoL at 3 months in 66% of all the patients with POI, while in 49% of patients without POI. (Table S2).

The EORTC QLQ-C30 indicates the level of functioning in patients. At 3 months, patients with POI as only complication had significantly lower scores in Physical functioning and Role functioning than patients without complications. At 6 months, patients with only POI still had lower scores on Physical functioning (Figure 3). When other complications were included, patients with POI had lower scores on Global quality of life, Physical functioning, and Role functioning at 3 months, and still experienced lower scores on Global quality of life and Role functioning, and also in Emotional functioning at 6 months, compared to patients without POI (Figure 3).

TABLE 2 Costs and utilities in patients undergoing colorectal surgery

	Selection of patients		All patients		P-value	P-value
	No complications (n = 133)	POI only (n = 32)	No POI (n = 180)	POI (n = 53)		
Cost (€)						
Baseline	4274 (1401)	2986-5562	5052 (1457)	3752-6354	7549 (3290)	4605-10 494
3 mo	6606 (4595)	5200-8013	7702 (5631)	6458-8946	14 529 (10 968)	10 246-18 813
6 mo	3353 (1354)	2469-4238	3765 (1497)	2910-4620	3856 (2456)	2407-5305
Utility						
Baseline	0.91	0.88-1	0.91	0.88-1	0.89	0.81-1
3 mo	0.89	0.83-1	0.89	0.81-1	0.85	0.75-0.91
6 mo	0.89	0.84-1	0.89	0.82-1	0.84	0.75-0.92

3.4 | Complications, length of stay and readmission

The observation of elevated inflammatory biomarkers in patients suffering from POI, was also associated with a higher complication rate. Patients with POI experienced more complications than patients without POI; 42% (28/66) of the patients with POI had one or more accompanying complications, compared to 28% (55/199) of the patients without POI that had a complication ($P = .025$). Multivariate logistic regression analysis showed that ASA-III grade (OR: 4.53 CI: 1.61-12.75 $P = .004$) and duration of surgery in minutes (OR: 1.01 CI: 1.00-1.01 $P < .001$) were associated with POI in the total study population. Corrected for ASA-grade, smoking and duration of surgery, patients with POI remained at risk to have one or more accompanying complications (OR: 2.31 CI: 1.25-4.27 $P = .007$). In addition, POI patients had a significantly higher number of complications (Table 3) and more severe complications, graded by the Clavien-Dindo classification: 17% (11/66) of the patients with POI had a Clavien-Dindo grade 3b or higher complication vs 8% (15/199) of patients without POI ($P = .031$). This means that patients with POI experienced another complication more often, either for which an intervention under general anesthesia was required, or leading to ICU admission or to death. In more detail, 14/66 POI patients also developed anastomotic leakage, against 9/199 of non-POI patients ($P < .001$), and 9 vs 4 patients developed pneumonia, respectively ($P = .001$). No change was found in the rate of wound infection (4 vs 11 patients; $P = 1.00$). Length of stay, readmissions within 30 days of discharge and reoperations were all significantly increased in patients with POI (Table 3). Length of stay was significantly associated with POI when corrected for other complications, ASA-grade, rectal surgery, and duration of surgery (OR: 1.51 CI: 1.34-1.70 $P < .001$). In addition, patients with POI as only complication were on average admitted 4 days longer than patients with an uncomplicated recovery. The length of stay of patients without complications was median 4 days (IQR: 3-6 days) and was for only POI patients median 8 days (IQR: 7-12 days, $P < .001$). Furthermore, 5% (2/38) of patients with only POI underwent additional surgical laparoscopy because of clinical deterioration with no new findings, and 13% (5/38) of only POI patients was readmitted to the hospital within 30 days after discharge.

3.5 | Laparoscopic and open surgery

It is recognized that the surgical approach, open or laparoscopic surgery, has effect on surgical outcomes. In this study, both open and laparoscopic cases were included. Therefore, additional analyses were performed on the total study population. In patients undergoing open surgery 30% (34/112) developed POI. In the group undergoing laparoscopic procedure 21% (32/153) developed POI ($P = .079$). Length of stay was 6 days longer in the POI group compared to the non-POI group, and when stratified for open and laparoscopic approach, patients were admitted 5 days longer when they received open surgery and developed POI (6 days IQR 5-7 no POI; vs 11 days IQR 8-15 POI) and 4 days longer when patients had

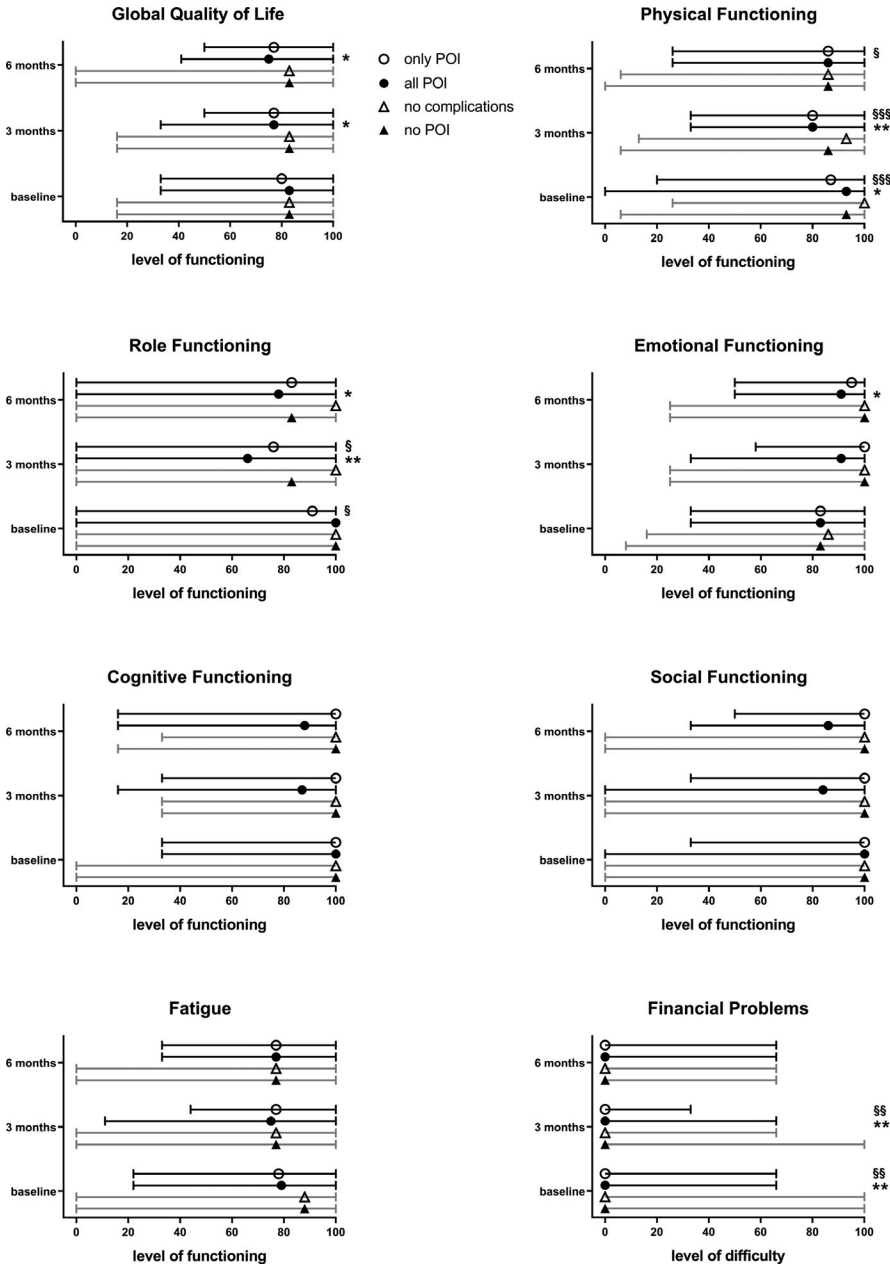


FIGURE 3 EORTC-QLQ-C30 level of functioning in categories measured at baseline, 3 and 6 mo after surgery in patients with POI as unique complication vs patients with no complications and all POI vs non-POI patients. Higher scores indicate higher levels of functioning except for financial difficulties. Data are medians (dots) and ranges. §*P* < .05, \$\$\$*P* < .01 and \$\$\$*P* < .001 for only POI (▲) vs no complications (△). **P* < .05 and ***P* < .01 for all POI (●) vs no POI (○)

laparoscopic surgery and developed POI (4 days IQR 3-5 no POI; vs 8 days IQR 7-12 POI).

There was no difference in open or laparoscopic surgery in patients with POI and other complications; that is, patients who had an open procedure and had POI did not develop more complications than laparoscopic operated patients.

In addition, patients without complications were admitted 1 day longer when they received open surgery compared to laparoscopic surgery (5 days IQR 5-7 open surgery; vs 4 days IQR 3-5 laparoscopic surgery). Moreover, patients were also admitted 1 day longer when they had POI as only complication and had open surgery than laparoscopic surgery (9 days IQR 8-14 open surgery; vs 8 days IQR 7-12 laparoscopic surgery).

Next, there was a clear difference in level of inflammation between patients that had laparoscopic surgery and open surgery.

Inflammation was significantly lower in patients that had a laparoscopic procedure 4, 24 and 48 hours after surgery for IL-6, IL-8, and IL-10. Of note, this significant difference was already apparent before surgery (0 hours). For CRP inflammation was only lower on POD1 for laparoscopic surgery compared to open surgery (Table S3). Interestingly, as demonstrated earlier, while IL-6 levels are significantly higher in patients with only POI compared to patients without complications 24 and 48 hours after surgery and similar higher levels of IL-6 in laparoscopic vs open surgery, in case of stratifying the POI patients and the patients without complications for laparoscopic and open surgery, results are not significant. For IL-6, between laparoscopic and open surgery, levels increase. CRP levels are more consistent; levels of CRP do not differ much between open or laparoscopic surgery, and significant higher levels of CRP remain in POI patients compared to no complications.

TABLE 3 Complications

	No POI (n = 199)	POI (n = 66)	P-value
Any complication (besides POI)	55 (28%)	28 (42%)	.025
Number of complications besides POI			
0	144 (72%)	38 (58%)	.002
1	44 (22%)	13 (20%)	
2	9 (6%)	10 (15%)	
3	1 (0.5%)	3 (5%)	
4	1 (0.5%)	1 (1.5%)	
6	0	1 (1.5%)	
Reoperations	11 (8%)	13 (20%)	.001
Length of stay (median; days)	5 [4-6]	11 [8-15]	<.001
Readmissions (within 30 d)	13 (9%)	11 (17%)	.013

Note: The data are n (%) or the median [interquartile range].

4 | DISCUSSION

We report here that patients having colorectal surgery resulting in POI as a complication, had a higher level of circulating inflammatory biomarkers, an increased length of stay, a decreased quality of life and more healthcare costs compared to patients with uncomplicated recovery. This study provides novel information because data were analyzed in patients with POI as a unique complication, where most studies allow for a mix of postoperative events possibly leading to bias. Moreover, these results were consistent in the total study population in which patients with other complications were included. Patients with POI were more at risk to develop other and more severe complications. The results of this study regarding the rise of inflammatory markers are in agreement with those of animal studies showing that increased levels of inflammatory cytokines and chemokines are detectable systemically next to a localized inflammation in the gut following its manipulation during surgery.^{5,27,28} Furthermore, we demonstrate that POI is a strong driving factor in upregulating the inflammatory response after surgery, irrespective of the surgical open or laparoscopic approach.

Recently, a study of Boersema et al²⁶ showed an association between systemic cytokines and postoperative complications in patients, and IL-6, also elevated in our study, had the best diagnostic value in predicting infectious complications. Of note, patients with POI had higher levels of IL-6 and CRP in that study, however not significantly because of a small sample size. We observed elevated levels of IL-10 in our study as well, and those were similarly reported by others to occur in the early phase of POI in patients, being significantly increased in patients with longer recovery from POI in abdominal surgery.²⁹ Remarkably, in animal models IL-1 β has been suggested to play an important role in POI pathology¹⁰; however, systemic levels of IL-1 β were very low and no differences were shown between patients with and without POI, which was also reported by Boersema et al.²⁶

Another important finding in this study is the confirmation of data from experimental studies that inflammation is elevated early after manipulation of the intestine. An increased inflammatory response early after surgery may be causal for development of POI.¹¹ The analysis of patients with POI as only complication showing increased inflammation supports this, as soon as 24 hours after onset of surgery CRP and IL-6 have risen significantly. Besides, in the total study population, co-existing complications could also contribute, many of these complications present later in the postoperative period. For instance, the interval between surgery and anastomotic leakage was median 7 days in patients with POI that developed anastomotic leakage in this study, which is in line with earlier studies where a median interval of 6-12 days was reported for anastomotic leakage and 8 days for all infectious complications.³⁰⁻³³ Importantly, POI is associated with anastomotic leakage, although the causal relation of anastomotic leakage and POI is to be determined.⁵ Irrespective, reducing early inflammatory activation could be considered to reduce both POI and anastomotic leakage in patients at risk. From another point of view, higher cytokine levels, regardless of its cause, indicate poorer outcomes: Patients develop POI and are at significant risk of developing other adverse outcomes. This was shown in this study with POI patients having another complication in 42%, while non-POI patients developed a complication in 28%, with an odds ratio of 2.31. Therefore, POI may be an early marker of complications or maybe even a marker of poor outcomes in the setting of other complications.

In animal studies, interventions have been explored aiming to reduce the early inflammatory responses that lie at the basis of POI. For instance, prucalopride, a5-Ht4 receptor agonist, and vagus nerve stimulation, either electrical or via lipid-enriched nutrition inhibits inflammation in an early stage and can prevent experimental POI.^{18,34,35} Interestingly, two recent clinical pilot studies by Stakenborg et al showed promising results in patients. Preoperative administration of prucalopride resulted in decreased local IL-6 and IL-8 expression and improved clinical recovery in a small cohort of patients.^{18,36} In another pilot study in which abdominal vagus nerve stimulation was investigated in patients that underwent colorectal surgery was shown that nerve stimulation could reduce levels of cytokines induced by ex vivo lipopolysaccharide (LPS) stimulation of whole blood. This suggests a systemic modulatory effect on immune cells, and there is great potential for future studies in this field. However, it remains uncertain whether the interventions that were effective in animal studies have an effect on POI clinically, especially since enteral nutrition was not able to reduce POI in a clinical trial performed by our group.¹³

Many different risk factors for POI have been described.³⁷⁻³⁹ In this study, ASA-grade and duration of surgery were independent risk factors. It is notable that patients with POI as only complication did smoke and used alcohol more often. Furthermore, these patients had more open surgery, more intraoperative blood loss and received a colostomy more often. Of note, some of the patients that reported lower levels of QoL preoperatively, in particularly physical functioning, developed POI as only complication.

Patients with POI experienced reduced QoL in different modalities. This effect was not limited to the direct postoperative period, but remained evident 3 and 6 months after surgery, emphasizing the long-term impact of the burden of POI in patients. The current results are in line with a prospective study where the impact of postoperative complications after colorectal cancer surgery on long-term QoL was investigated,⁶ though specific selection of patients with POI had not yet been applied. Besides, POI was associated with additional complications, which evidently affects the QoL of these patients. In the present study, QoL was still reduced after 3 months in the selected group of patients with POI as unique complication. This is remarkable and shows that POI which usually resolves in a couple of days in the hospital and is often considered a minor complication has great impact on patients' lives, even months after discharge. It is likely that in the total population anastomotic leakage and pneumonia contribute to an increased length of stay and costs, and a reduced QoL in patients with POI even 6 months after surgery. Since patients with POI are at significant risk of developing other complications, POI leaves its mark on society. Furthermore, an earlier study showed a relationship between POI and other complications and a higher mortality rate in patients with POI and additional complications.⁴ The latter is one of the few studies that analyzed POI as unique complication, however only reports on 30 day-mortality for the POI only group, which was equal to patients without POI (1%). In the past, few studies have calculated costs for patients with POI, and some did not report if patients had other complications as well. A retrospective cohort study of Iyer et al in the United States showed a mean difference of \$8000 for patients with POI vs without POI in hospitalization costs.³ Another retrospective study of Asgeirsson et al⁴⁰ of 184 patients that underwent a colectomy showed similar results (US \$16 612 vs \$8316), obtaining their cost data through a hospital accounting system. In a more recent study, POI patients were found to be more expensive even after adjustment for major complications and length of stay.⁴¹ In the current study, data were prospectively collected and all the relevant costs from the broadest perspective were included in an economic evaluation, thereby measuring the impact on society.²³ Interestingly, data on complications in colorectal surgery showed that 31% of the total hospital costs were spent on complications.⁷ Conversely, we show that patients with POI have a higher chance of developing other complications which is accompanied with a 9% rise in costs and decline in Global QoL. The data from our study emphasize the societal impact (both QoL and costs) of POI and the necessity to keep searching for applicable therapeutics and reduce costs.⁴²

The strengths of this study are that data were prospectively collected as part of a RCT with a clear definition of POI as primary outcome, a high response rate regarding cost and QoL data and almost complete data on inflammatory markers. Analyses were done on both a selected group of patients that only developed POI, and the whole study population, representing the general population undergoing colorectal surgery to substantiate the results. This study has also

limitations. First, systemic cytokine levels were determined, whereas cytokine levels locally in the bowel wall may be a better reflection of a local inflammatory response associated with POI. Second, costs and QoL were assessed by self-reported questionnaires which may result in recall bias, although the overall completion rate was 88%. The cost elements for all participating centers (of which some are located in Denmark) reflect the reference prices from the Netherlands which may have influenced the total cost estimates.

In conclusion, POI has a significant negative impact on quality of life, increases length of stay and is associated with a higher overall complication rate. The differences between the selected group of patients with POI as unique complication (n = 38) and the total group of patients with POI who developed other complications as well (n = 66) are relatively small, demonstrating the impact of POI and the large contribution of POI in postoperative inflammation, length of stay, costs, and QoL in the general population of patients undergoing colorectal surgery. This study confirms the association of POI with inflammation and this supports that therapeutic strategies need to be developed aimed at reducing the inflammatory response to reduce the burden of POI following colorectal surgery.

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CONFLICT OF INTERESTS

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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