

## Elective Laparoscopic Sigmoidectomy Reduces IL-6 Serum Levels in Uncomplicated Recurrent Diverticulitis

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### Rezumat

#### *Sigmoidectomia laparoscopică elective reduce nivelurile serice de IL-6 în diverticulita recurentă necomplicată*

**Introducere:** Deși diverticulita recurentă pare a fi o boală cronică recidivantă din punct de vedere clinic, nu există suficiente date privind markerii inflamatori care să permită monitorizarea diverticulitei recurente în faza de remisie. Ipoteza noastră este că markerii inflamatori serici pot fi crescuți în fazele clinice de remisie ale diverticulitei și că vor scădea după sigmoidectomia laparoscopică elective pentru diverticulită recurentă necomplicată. De asemenea, considerăm că o scădere a nivelurilor de IL-6 după intervenție ar putea fi asociată cu o îmbunătățire a calității vieții.

**Material și metode:** Acest studiu epidemiologic își propune să evalueze nivelurile serice de IL-6 și calitatea vieții preoperator și la 6 luni postoperator într-un lot de 30 de pacienți la care s-a practicat sigmoidectomie laparoscopică elective pentru diverticulită recurentă necomplicată.

**Rezultate:** Nivelul mediu preoperator de IL-6 a fost de  $9,5 \pm 9,2$  pg/ml (interval 0-5), în timp ce la șase luni după operație nivelul mediu de IL-6 a fost de  $4,5 \pm 3,5$  ( $p=0,0085$ ). Calitatea vieții pre-

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operatorie măsurată prin chestionarul GIQLI a fost de  $98 \pm 11,3$ , crescând semnificativ după intervenție la  $112 \pm 9,8$  ( $p=0,043$ ).

*Concluzii:* Am observat o scădere a nivelului seric de IL-6 după sigmoidectomia laparoscopică electivă, care poate fi atribuită eliminării chirurgicale a sursei de inflamație la pacienții cu diverticulită recurentă necomplicată. De asemenea, chestionarul GIQLI a arătat o îmbunătățire semnificativă a calității vieții după intervenție.

**Cuvinte cheie:** sigmoidectomie, boală diverticulară, diverticulită recurentă, IL-6, laparoscopie, GIQLI

## Abstract

*Introduction:* Although recurrent diverticulitis appears to be a chronic relapsing disease from a clinical standpoint, there are no sufficient data about inflammatory markers that allow monitoring recurrent diverticulitis in the quiescent phase. Our hypothesis is that serum inflammatory markers may be increased during clinical quiescent phases of diverticulitis and will drop after elective laparoscopic sigmoidectomy for uncomplicated recurrent diverticulitis. We also believe that a drop in IL-6 levels across surgery could be related to an improved quality of life.

*Material and Methods:* This epidemiological study aims to evaluate IL-6 serum levels and quality of life preoperatively and 6 months after surgery in 30 patients undergoing elective laparoscopic sigmoidectomy for uncomplicated recurrent diverticulitis.

*Results:* The mean preoperative IL-6 level was  $9.5 \pm 9.2$  pg/ml (range 0-5), while at six months after surgery the mean IL-6 was  $4.5 \pm 3.5$ . ( $p=0.0085$ ). Preoperative QoL measured with the GIQLI questionnaire was  $98 \pm 11.3$  and raised significantly after surgery to  $112 \pm 9.8$  ( $p=0.043$ ).

*Conclusions:* We found a serum IL-6 reduction after elective laparoscopic sigmoidectomy that can be attributed to the surgical removal of the source of inflammation in patients suffering from uncomplicated recurrent diverticulitis. Similarly, the GIQLI questionnaire showed a significantly improved QoL after surgery.

**Key words:** sigmoidectomy, diverticular disease, recurrent diverticulitis, IL-6, laparoscopy, GIQLI

## Introduction

Uncomplicated recurrent diverticulitis (URD) is one of the most frequent clinical presentations of diverticular disease (1). It has been defined as the recurrence of acute diverticulitis without septic complications or colonic perforation alternating with periods of complete absence of colonic symptoms (2).

During the acute phases of recurrent diverticulitis, the extent of the intensity of inflammation can be assessed through laboratory blood tests. Several authors reported an

increased white blood cell count (WBC) and C-reactive protein (CRP) in patients with acute diverticulitis as well as altered mean platelet volume, neutrophil count, platelet count (PLT), procalcitonin, and calculation of neutrophil count/lymphocyte and PLT/lymphocyte ratios (3).

Conversely, it is rather complex to evaluate the chronic modifications of the immune system during the non-acute phases of the disease. Recent studies inquired the serum TNF-alpha (4,5,6), and IL-6 levels (7) during quiescent phases as a predictive factor related

to the recurrence of diverticulitis without reaching valid conclusions. Ma et al. found that the plasma level of inflammatory markers was increased in patients who developed diverticulitis compared to a normal population (8). Although recurrent diverticulitis appears to be a chronic relapsing disease from a clinical standpoint, there are still insufficient data about inflammatory markers that allow monitoring recurrent diverticulitis in its quiescent phase.

However, cell-mediated immunity plays a maintenance-activation role even during the non-acute phases of the disease, being detectable through the serum analysis for biomarkers such as IL-6. Therefore, it is conceivable that serum inflammatory markers could be increased during the clinical quiescent phases of diverticulitis as a consequence of the chronic activation of the cell-mediated immunity. Consequently, removing the trigger pro-inflammatory factor through an elective laparoscopic sigmoidectomy in patients suffering from uncomplicated recurrent diverticulitis could result in a reduction of pro-inflammatory chronic biomarkers as well as in an improved quality of life (QoL).

## Material and Methods

### *Type of Study and Population*

This epidemiological study aims to evaluate IL-6 serum levels pre-operatively and at 6 months after surgery in patients undergoing elective laparoscopic sigmoidectomy. The indication for elective surgery was tailored case by case according to patients' desires to improve QoL and after providing informed consent. QoL was measured by the GIQLI score (9).

IL-6 was dosed in blood samples prospectively collected from 30 consecutive patients referred to Desio Hospital for uncomplicated recurrent diverticulitis and undergoing elective laparoscopic sigmoidectomy between June 1<sup>st</sup> and December 31<sup>st</sup>, 2022, enrolled in the Diverticular Disease Registry (DDR Trial) ClinicalTrials.gov (NCT04907383) (10).

Institutional Review Board approval was obtained by Milano Area 3 Ethics Committee (approval number 233-22042021). The study was conducted according to the Declaration of Helsinki following the STROBE guidelines.

Patients had to be older than 18 years, with a 1-3 American Society of Anesthesiologists (ASA) class (11), with a CT and/or endoscopic proven diverticular disease. To reduce the false positive bias, we did not include patients affected by chronic systemic diseases (such as rheumatic disease, inflammatory bowel diseases), having a recent SARS Cov-2 infection (< two months), or concomitant cancer. We did not include patients with immune system disease nor under immunomodulators that could lower plasma levels of IL-6 with a consequent decrease of the inflammatory response. We did not include patients with an underlying diagnosis of inflammatory bowel disease or with a diagnosis of cancer in the previous 5 years. All patients underwent pre-operative colonoscopy before surgery.

For each patient sex, age, body mass index (BMI), ASA classification, number of previous episodes of symptomatic non-complicated diverticulitis [according to the WSES definition (12)], development of post-surgical complications [rated with Clavien-Dindo classification (13)], postoperative hospital length of stay (LOS) were collected.

Preoperative IL-6 was sampled during a non-acute disease phase proved by a normal WBC count and PCR level at the time of the blood sample. Post-operative IL-6 was sampled during an outpatient examination at six months after elective surgery. The GIQLI score was calculated preoperatively and at six months post-operatively.

The surgical procedure included a non-cancerous sigmoid resection extended beyond the recto-sigmoid hinge and a tension-free colorectal anastomosis. Sigmoid arterial branches or distal inferior mesenteric artery was resected distally. Proximal colon resections were based on diverticular disease length. Usually, a transanal T-T mechanical anastomosis was performed.

## Statistical Analysis

Categorical variables were expressed in numbers and percentages. Numerical variables were expressed in means  $\pm$  standard deviation, median and interquartile range (IQR) according to their distribution. Statistical analysis was performed with SPSS software. The Primary end-point (IL-6) was evaluated using Fisher's exact test (one-sided).

## Results

Patient characteristics, intra- and post-operative details are shown in *Table 1*.

Overall, 30 patients were included in this study, 10 male (33.3%) and 20 female (66.7%) with a median age of 68 [45-86] years. Most patients had mild comorbidities: 19 patients (63.3%) were ASA 2, and 13 (23.3%) were ASA 1. All patients underwent elective laparoscopic sigmoidectomy after at least one episode of acute uncomplicated diverticulitis. Surgery was performed after one episode of acute diverticulitis in 11 patients (36.7%), two episodes in 8 patients (26.6%), three in 7 patients (23.3%), four and five episodes in 2 patients each (6.7%). The mean operative time was  $160 \pm 54$  minutes. The postoperative course was uneventful in 23 patients (76.6%), whilst complications occurred in 7 patients (23.3%); all were minor complications except for 1 (3.3%) anastomotic bleeding treated endoscopically (Clavien-Dindo classification 3b). No patient received ileostomy. The mean postoperative hospital LOS was 7.1 days (SD  $\pm$  5.5).

In postoperative recovery, patients received planned paracetamol and ketorolac i.v. if needed.

The mean preoperative (non-acute phase) IL-6 was  $9.5 \pm 9.2$  pg/ml (range 0-5), while at six months after surgery the mean IL-6 was  $4.5 \pm 3.5$ . The postoperative reduction of IL-6 levels was statistically significant ( $4.9 \pm 8.4$ ,  $p=0.0085$ ), while there was no difference in WBC and CPR levels at six months compared to baseline. Preoperative QoL measured with the GIQLI questionnaire was  $98 \pm 11.3$  and

**Table 1.** Patient characteristics

Sex	Male = 10 Female = 20	33.3% 66.7%
Age	68 (45-86) (13)	
BMI	$25.8 \pm 4.2$	
ASA	ASA 1 = 13 ASA 2 = 19 ASA 3 = 8	10% 63.3% 26.7%
Number of episodes	One episode = 11 Two episodes = 8 Three episodes = 7 Four episodes = 2 Five episodes = 2	36.7% 26.6% 23.3% 6.7% 6.7%
Operative time (min)	$160.3 \pm 53.7$	
Clavien - Dindo	0 = 23 1 = 4 2 = 2 3B = 1	76.7% 13.3% 6.7% 3.3%
Post-Operative days	$7.1 \pm 5.5$	

All values refer to number of patients except BMI and Age. ASA indicates American Society of Anesthesiologists; BMI indicates body mass index.

raised significantly after surgery to  $112 \pm 9.8$  ( $p=0.043$ ) (*Table 2*).

## Discussion

Our study found an increased level of IL-6 in 30 consecutive patients scheduled for elective laparoscopic sigmoidectomy for URD during the non-acute phases of the disease. The serum level of IL-6 significantly dropped after six months after elective laparoscopic sigmoidectomy. In addition, GIQLI scores significantly improved after surgery.

Different factors seem to be related to the transition from asymptomatic to symptomatic diverticular disease: alterations of neurotransmission and colon motility (14), changes in the colic commensal flora, and genetic factors and inflammation (15).

**Table 2.** IL-6 and GIQLY trend across surgery

	Pre-operative	6 months after surgery	P value
IL-6	$9.5 \pm 9.2$	$4.5 \pm 3.5$	$P = 0.0085$
WBC	$7800 \pm 1100$	$6900 \pm 900$	$P = 0.245$
CRP	$3.5 \pm 1.1$	$4.2 \pm 0.9$	$P = 0.165$
GIQLY	$98 \pm 11.3$	$112 \pm 9.8$	$P = 0.043$

In particular, a chronic mild inflammatory process has been described in symptomatic patients and is consequently associated with the thickening of the bowel wall, immune cells in the colonic mucosa, and an increased number of reactive lymph nodes (16). Some authors observed various histological colonic alterations resembling the clinic patterns of chronic inflammatory bowel disease in patients affected by recurrence diverticulitis (6,17,18).

Therefore, it is reasonable that uncomplicated recurrent diverticulitis leaves traces of itself also during the non-acute phases (19). During the acute phases, it is possible to determine the extent of the ongoing inflammation through laboratory blood tests such as WBC and CRP. On the contrary, there are no standard lab tests to monitor the level of the underlying inflammation during the non-acute stages of the disease. Therefore, it becomes necessary to measure inflammatory mediators that are not dosed in the usual clinical practice. In particular, IL-6 plays a key role in the development of immune derangement caused by chronic inflammation. Therefore, its upregulation during the quiescent phases of URD could be related to a pro-inflammatory state (7). Recent evidence has shown that patients with higher serum IL-6 concentrations have a higher risk of developing diverticulitis than patients with normal IL-6 levels (8).

However, to our knowledge, there is no literature about the IL-6 level in patients with URD disease in a non-acute phase. From this point of view, the preoperative IL-6 level measured in a non-acute phase and reported in our study is a new finding. Indeed, IL-6 concentration was found to be increased in patients scheduled for surgery for URD, supporting our initial hypothesis. The significant reduction at six months after surgery of IL-6 concentration indicates an inflammatory systemic status reduction consequent to the sigmoidectomy. Moreover, the QoL measured with the GIQLI questionnaire was impaired in patients with URD. Parallel with the

reduction in IL-6, QoL significantly improved six months after surgery.

Previous literature focused on a different mediator of inflammation: tumor necrosis factor-alpha (TNF- $\alpha$ ). Tursi et al. described the overexpression of TNF- $\alpha$  in patients affected by symptomatic uncomplicated diverticular disease; they interestingly reported a significant dropping in TNF- $\alpha$  level after six months of medical therapy (20).

Further studies should analyze a possible synergy between IL-6 and TNF- $\alpha$  in depicting the pro-inflammatory state present in the URD and the capability of surgery to mitigate this immunological dysregulation should be the core of a larger ad hoc prospective study.

Highlighting a reduction in the levels of inflammatory markers after an elective laparoscopic sigmoidectomy could strengthen the indication for surgical treatment in patients with URD that today is mainly based on a clinical feature (21) and impaired QoL.

This study has several limitations. It takes into consideration only one pro-inflammatory mediator within such a vast panorama available of inflammatory mediators for chronic diseases. Also, it did not provide a control group made of non-operated similar patients, therefore the impact of a placebo response is actually unknown. Additionally, the small sample size and the relatively short follow-up could generate biases in the analyses performed.

However, this study will pave the way for future analysis with a pre-fashioned sample size calculation based on the findings reported. In particular IL-6, TNF alfa, and high sensitivity C reactive protein will be paired up as possible bio-markers of the inflammatory response and as predictive factors for the decrease in chronic inflammation after surgery.

## Conclusions

We found a serum IL-6 reduction after elective laparoscopic sigmoidectomy that can be attributed to the surgical removal of the

source of inflammation in patients suffering from URD. Similarly, the GIQLI questionnaire showed a significantly improved QoL after surgery. Further studies are necessary to evaluate whether IL-6 could be a marker for patients who will most benefit from surgery.

### *Conflicts of Interest and Source of Funding*

The authors declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest and that no financial support was received for the research, authorship, and/or publication of this article.

### *Ethics Statements*

This study was approved by Milano Area 3 Ethics Committee (approval number 233-22042021).

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