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ORIGINAL ARTICLE

Impact of elective surgery on tumor necrosis factor-α, interleukin-6 and quality of life in uncomplicated diverticular disease

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Abstract

Aim: Growing evidence suggests that immune/inflammatory pathways play a crucial role in the persistence of symptoms in diverticular disease (DD). We hypothesize that chronic diverticulitis triggers a self-sustained inflammatory status which can be detected by measuring the levels of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). The aim of this study was to investigate the systemic levels of TNF-α and IL-6 before and after elective surgery in patients with DD, and their relationship with the gastrointestinal quality of life index (GIQLI) score.

Method: This prospective multicentric study enrolled patients from the Diverticular Disease Registry (DDR-Trial, NCT04907383). All adult patients diagnosed with symptomatic uncomplicated diverticular disease (SUDD), uncomplicated recurrent diverticulitis (URD) and smouldering diverticulitis (SmD) between 1st December 2022 and 31st December 2023 were included in this study. Exclusion criteria were as follows: no surgery, a concurrent chronic immunomodulated systemic disease, a SARS-CoV-2-positive test in the previous 12 months, a history of cancer in the previous 5 years, patients treated with immunomodulators, an American Society of Anesthesiologists category of class IV, and complicated acute diverticulitis.

Results: Seventy-two patients were included: 52 (72%) with URD, 11 (15%) with SUDD, and nine (13%) with SmD. The median postsurgery – presurgery (Δ)IL-6 and ΔTNF-α levels were −16.8 and −17.3 pg/mL, respectively ($p < 0.001$ for both; Wilcoxon test). Spearman correlation revealed a significant, negative association between the ΔGIQLI and the ΔIL-6, as well as the ΔTNF-α ($p < 0.001$ for both). Greater reduction in the levels of IL-6 and TNF-α following surgery are associated with higher GIQLI scores postoperatively.

Conclusion: Patients with chronic diverticulitis may experience persistent systemic inflammation driven by a colonic trigger. Surgical removal of this trigger appears to enhance GIQLI outcomes reducing IL-6 and TNF-α across surgery.

KEYWORDS
diverticulitis, IL-6, quality of life, surgery, TNF-α

INTRODUCTION

Diverticular disease (DD) is one of the most common benign gastrointestinal pathologies in civilized countries, yet it remains one of the least understood conditions, lacking standardized protocols [1–3]. Some patients develop acute complicated diverticulitis, often requiring surgery, while others develop chronic inflammation [4–6]. Symptomatic uncomplicated diverticular disease (SUDD), uncomplicated recurrent diverticulitis (URD) and smouldering diverticulitis (SmD) are prevalent, yet complex, gastrointestinal disorders characterized by chronic, low-grade inflammation and the absence of clear diagnostic and treatment guidelines. They affect millions of patients globally, with a rising incidence linked to aging populations and dietary changes. Patients with any of these entities experience recurring abdominal pain, altered bowel habits and quality-of-life impairment, which places a significant burden on healthcare systems until surgery is performed [6–10]. Despite its prevalence, the clinical management of DD remains challenging because of its overlapping symptoms with other gastrointestinal disorders and the absence of biomarkers for prognosis or disease severity [5, 11].

Growing evidence suggests that immune and inflammatory pathways play a crucial role in the pathogenesis and persistence of symptoms in DD. Specifically, inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6) and interleukin-10 (IL-10), are potential indicators of disease activity, as they are integral mediators of inflammation [12–14]. All these molecules have been related to several unfavourable scenarios, such as cachexia, septic shock, graft rejection, graft-versus-host disease, autoimmune diseases and arteriosclerosis [14–16]. However, the utility of these markers in predicting disease course and severity in DD has not been systematically evaluated, creating a significant gap in clinical knowledge and practice.

Current approaches for managing SUDD, URD and SmD rely primarily on symptomatic relief during an acute flare, with limited emphasis on understanding the underlying immune mechanisms. Mesalamine was initially introduced for the management of DD because of its anti-inflammatory properties and the original hypothesis of constant inflammation in DD; however, a recent meta-analysis revealed no benefit of mesalamine over placebo and therefore current guidelines do not recommend it [2, 17, 18].

We hypothesize that chronic diverticulitis triggers a self-sustained inflammatory status, which could be detected through proinflammatory biomarkers, such as TNF-α and IL-6, even during non-acute phases. Therefore, the levels of these biomarkers could be reduced after elective surgery. In this study, the systemic levels of TNF-α and IL-6 were measured before and after elective surgery in patients with DD, and the relationship between the levels of TNF-α and IL-6 and quality of life, evaluated using the gastrointestinal quality of life index (GIQLI) score, were determined.

What does this paper add to the literature?

The findings highlight the potential mechanistic role of inflammation in symptom persistence in diverticular disease and support the therapeutic value of surgery, not only for symptom relief but also for addressing systemic inflammation, strengthening the rationale for surgical intervention in certain cases.

METHOD

This prospective multicentric study enrolled patients from the Diverticular Disease Registry (DDR Trial, NCT04907383). All samples were collected according to the Helsinki Declaration and STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines after participants signed informed consent. All adult patients diagnosed with SUDD, URD and SmD between 1st December 2022 and 31st December 2023 in participating hospitals were included in this study. Exclusion criteria were as follows: no surgery, a concurrent chronic immunomodulated systemic disease (arthritis, lupus erythematosus, inflammatory bowel disease, etc.), a SARS-CoV-2-positive test in the previous 12 months, a history of cancer during the last 5 years, patients treated with immunomodulators, an American Society of Anesthesiologists (ASA) category of class IV, and complicated acute diverticulitis. Participants were asked to be available at 6 and 12 months of follow-up for periodic laboratory tests and a GIQLI score survey. The venous drafts needed for this study were collected and stored in two laboratories for 12 months. All patients underwent mechanical bowel preparation combined with preoperative oral antibiotics. No antibiotic was administered routinely postoperatively, and no maintenance medication was recommended. The surgical technique was standardized: a laparoscopic sigmoidectomy/left colectomy was performed, making sure that all visible diverticula were resected. No ostomy was needed for these patients.

The levels of TNF-α and IL-6 (normal values: IL-6, <5.9 pg/mL; TNF-α, 6–12.4 pg/mL) were tested in a preoperative non-acute phase (defined as a low white blood cell count and a low C-reactive protein level) and 6 months after surgery. Interleukin-6 and TNF-α were used according to a prospective national study and a meta-analysis, which suggested an association between those factors and the risk of diverticulitis [12–16]. The enrolment proceeded in four north Italian hospitals. For each enrolled individual, a complete medical history and physical record was collected, focusing on age, sex, body mass index (BMI), ASA class, Charlson Comorbidity Index (CCI), medications, previous surgeries, clinical symptoms, number of flares, preoperative GIQLI, preoperative CT scans, MRI, preoperative World Society of Emergency Surgery (WSES) classification for diverticulitis, diagnostic procedures, white blood cell count and C-reactive protein level. Additional

laboratory details can be found in Appendix 1. All laboratory tests were performed using the same protocols in each hospital, while data analysis was conducted only in one hospital to reduce interpretation bias.

Categorical variables were reported as frequencies (percent), while continuous variables were reported as mean ± SD or median (interquartile range), according to their distribution. Missing values (only present for time to first flatus/stool and CCI) were excluded from the descriptive analyses. The chi-square test for categorical variables and the independent samples *t*-test or Mann–Whitney *U* test for continuous variables were used, as appropriate, for comparison between groups. Pre- and postsurgery values of IL-6, TNF-α and GIQLI were compared using a Wilcoxon test. A generalized linear mixed model (GLMM) was used to assess the relationship between the variance of the GIQLI and the variance of IL-6/TNF-α values. All tests were two-sided; a significant difference was considered with an alpha level of <0.05.

RESULTS

After applying the exclusion criteria, 72 patients were included in the study (the flowchart of cohort development is depicted in Figure 1). Among them, 42 (58%) were male, the median (range) age was 50 (20–81) years and the mean BMI was 26.9 ± 5.8 kg/m^2. Preoperative characteristics are given in Table 1. Most patients presented with URD ($n = 52$, 72%), followed by SUDD ($n = 11$, 15%). In patients with URD, the number of past episodes varied greatly, with eight (11%) patients having one episode, 23 (32%) patients having two episodes, 15 (21%) patients having three episodes and six (8%) patients having four episodes. Most patients were ASA class I ($n = 35$, 49%). The mean CCI was 1.3 ± 1.2.

The intra- and postoperative details of the study cohort are shown in Table 2. The mean operative time was 132 ± 31 min, and all surgeries were performed laparoscopically with no conversion to open surgery. In addition, 30-day complications occurred in seven (10%) patients, with two (3%) being ileus requiring a nasogastric tube and five (7%) being anastomotic bleeding that did not require any intervention. The mean number of days to first flatus and stool were 2 ± 1 days and 3 ± 1.8 days, respectively, while the mean length

TABLE 1 Baseline details of the study cohort ($n = 72$).

Characteristic	Value
Sex	
Male	42 (58)
Female	30 (42)
Age, years, median (range)	50 (20–81)
BMI (kg/m^2)	26.9 ± 5.8
Diverticulitis type	
Smouldering diverticulitis	9 (13)
Symptomatic uncomplicated DD	11 (15)
Uncomplicated recurrent diverticulitis	52 (72)
Episodes in uncomplicated recurrent diverticulitis	
1	8 (11)
2	23 (32)
3	15 (21)
4	6 (8)
ASA class	
I	35 (49)
II	25 (35)
III	12 (17)
Charlson comorbidity index	1.3 ± 1.2
Presurgery GIQLI	89.0 ± 11.2
Presurgery IL-6	23.0 (5.7–37.6)
Presurgery TNF-α	30.6 (21.4–38.2)

Note: values are given as *n* (%), mean ± SD or median (IQR), unless indicated otherwise.

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; DD, diverticular disease; GIQLI, gastrointestinal quality-of-life index; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α.

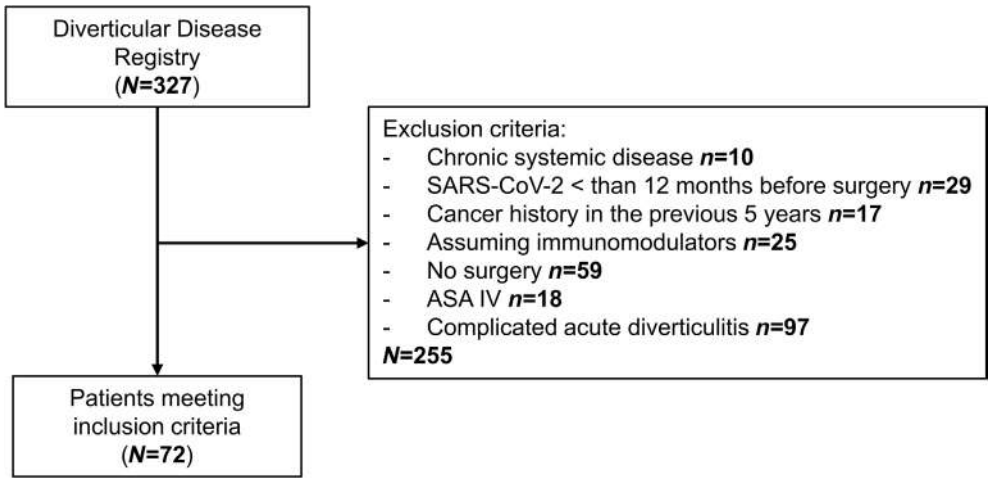

FIGURE 1 Flowchart of cohort development. ASA, American Society of Anesthesiologists.

of hospital stay (LOS) was 4 ± 3.1 days. The mean GIQLI score pre- and postsurgery was 89 ± 11.2 and 117 ± 11.6, respectively.

Figure 2 illustrates the IL-6 values in the preoperative setting and 6 months after surgery: a median reduction in IL-6, of 16.8 pg/mL, 6 months after surgery, was found ($p < 0.001$, Wilcoxon test). Similarly, Figure 3 illustrates the TNF-α values in the preoperative setting and 6 months after surgery: a median reduction in TNF-α, of 17.3 pg/mL, 6 months after surgery, was found ($p < 0.001$, Wilcoxon test). A subgroup analysis is shown in Table S1, revealing different median values of IL-6 and TNF-α between each subtype of DD, with SmD having the highest median values of both IL-6 and TNF-α.

Spearman correlation revealed a significant, negative association between the postsurgery – presurgery (Δ)GIQLI value and the ΔIL-6 value, as well as between the (Δ)GIQLI value and the ΔTNF-α value (p-values < 0.001, Figure 4). Greater reductions in IL-6 and TNF-α levels following surgery are associated with higher GIQLI scores postoperatively.

TABLE 2 Intra- and postoperative details of the study cohort ($n = 72$).

Characteristic	Value
Operative time (min)	132 ± 31
Conversion rate	0 (0)
Estimated blood loss (mL)	30 ± 17
30-Day complications	7 (10)
Anastomotic bleeding	5 (7)
Ileus	2 (3)
Clavien–Dindo ≥3	0 (0)
30-Day reoperation	0 (0)
First flatus (days)	2 ± 1.0
First passage of stool (days)	3 ± 1.8
Length of hospital stay (days)	4 ± 3.1
Postsurgery GIQLI	117.0 ± 11.6
Postsurgery IL-6	3.1 (1.7–6.1)
Postsurgery TNF-α	11.4 (7.9–15.5)

Note: values are given as *n* (%), mean ± SD or median (IQR).

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; DD, diverticular disease; GIQLI, gastrointestinal quality of life index; IL-6, interleukin-6; TNF, tumor necrosis factor.

DISCUSSION

This prospective multicentre study investigated the systemic levels of TNF-α and IL-6 before and after elective surgery in patients with DD, as well as the relationship of TNF-α and IL-6 levels with the GIQLI score. After elective surgery, a significant reduction in the levels of TNF-α and IL-6 was found, as well as a substantial improvement in the GIQLI score, possibly because of a decrease in the chronic systemic inflammation status caused by SUDD, URD and SmD.

From a biological point of view, chronic colonic inflammation could be as impactful as an acute event. It is well known that DD, particularly chronic non-complicated diverticulitis, does not have standardized treatment paradigms. Indication for surgery is therefore given on a case-by-case approach that is tailored to the symptoms and quality of life of the patient and their risk for future urgent surgery. After an acute phase of diverticulitis, persistent colonic inflammation and thickening can usually be detected at a CT scan

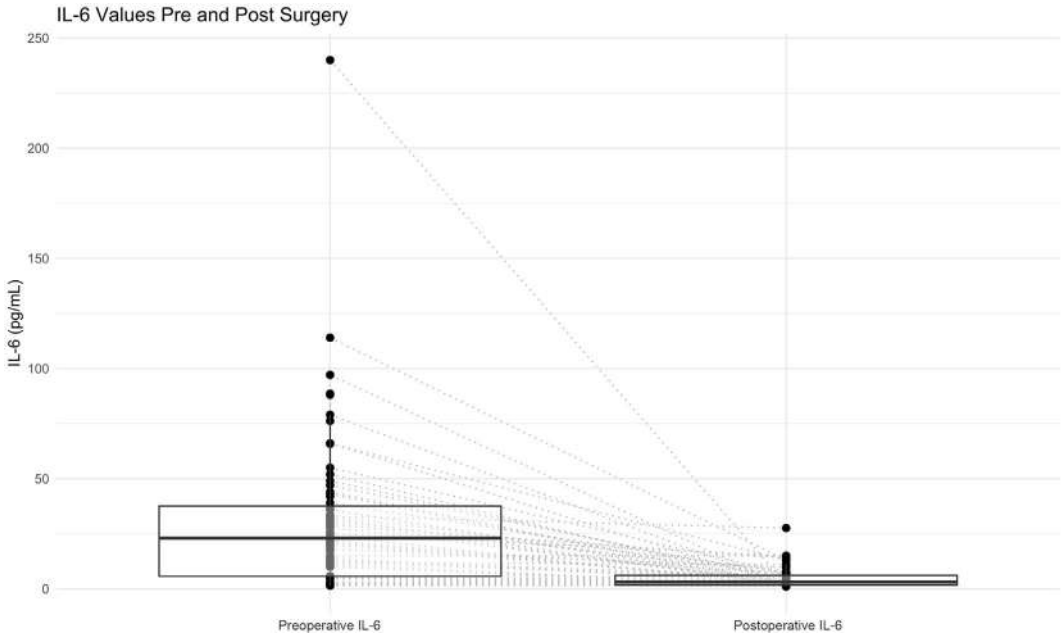

FIGURE 2 Box plot displaying interleukin-6 (IL-6) levels before and after surgery. Each data point represents an individual measurement. The dashed lines connect paired pre- and postoperative values, illustrating the change in IL-6 levels for each patient. A significant decrease in IL-6 levels is observed postoperatively, as indicated by the narrowing distribution and the individual trajectories ($p < 0.001$).

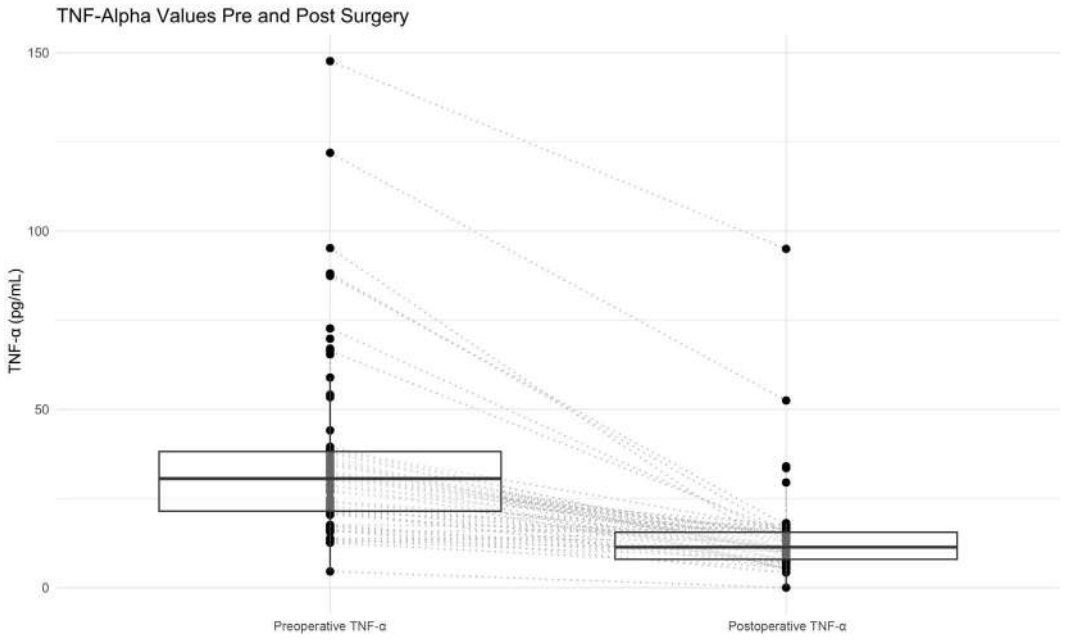

FIGURE 3 Box plot displaying tumor necrosis factor-α (TNF-α) levels before and after surgery. Each data point represents an individual measurement. The dashed lines connect paired pre- and postoperative values, illustrating the change in TNF-α levels for each patient. A significant decrease in TNF-α levels is observed postoperatively, as indicated by the narrowing distribution and the individual trajectories ($p < 0.001$).

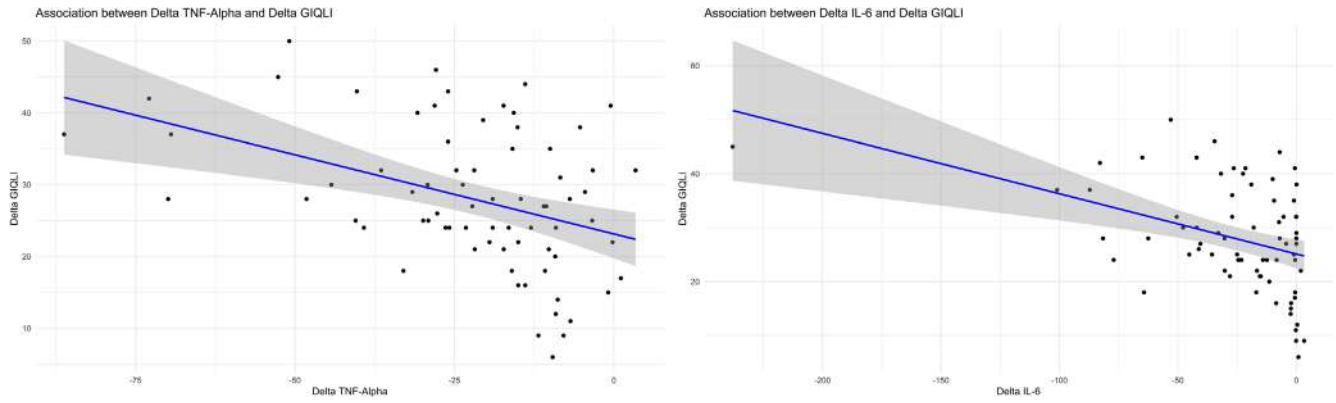

FIGURE 4 Scatterplot depicting the association between postoperative minus preoperative (Δ)interleukin-6 (IL-6) and Δtumor necrosis factor-α (TNF-α) values with the ΔGIQLI value. The blue line represents the linear regression model fit, and the shaded area indicates the 95% CI for the regression. As the ΔIL-6 and ΔTNF-α values become more negative (indicating a larger reduction in IL-6 and TNF-α levels postoperatively), the ΔGIQLI tends to decrease, suggesting a potential relationship between inflammatory markers and gastrointestinal quality-of-life outcomes.

or by endoscopy. Although several biomarkers (C-reactive protein, white blood cells, procalcitonin) are used for assessing the presence of acute-phase DD, there is a paucity of data regarding biomarkers for assessment of chronic DD. Therefore, it is reasonable to think that chronic colonic inflammation in DD might alter the levels of pro-inflammatory markers, such as TNF-α and IL-6.

Notably, in the present study the levels of TNF-α and IL-6 were increased preoperatively, despite the presence of normal levels of white blood cells and C-reactive protein, corroborating the hypothesis of this study. As expected, increasingly higher levels of both IL-6 and TNF-α were found in SUDD, URD and SmD. Additionally, the Wilcoxon test from this cohort revealed a significant reduction in the TNF-α and IL-6 levels 6 months after elective surgery. This might be due to the surgical removal of the colon, which is the suspected trigger of the inflammation status. Other possible causes for this improvement include a diet change after surgery (although this is not supported by the literature) and a simultaneous improvement in the anxiety caused by this disease [19–21].

Concordant to these findings, Tursi et al. described a reduction in the biomarker levels after starting medication treatment for uncomplicated DD; however, long-term quality-of-life outcomes were not reported [13]. In our study, the median GIQLI score 6 months

after surgery was also improved. This increase was inversely related to the serum levels of both TNF-α and IL-6 in the Spearman's rank correlation analysis, supporting the results of a recent meta-analysis by Kertzman et al. in which it was suggested that elective surgery might improve long-term quality of life compared to a conservative approach with medical treatment [22].

If validated in larger and comparative studies, these biomarkers could be used as prognostic and diagnostic tools to understand who needs surgery most, offering a foundation for future clinical guidelines, more effective disease management and a reduced cost for the National Health System and for patients.

Several limitations need to be discussed for this study. First, the lack of a non-surgical control group introduces well-known bias. However, the preoperative blood tests were collected in a symptom-free period, partially accounting for a non-surgical group. Second, URD, SUDD and SmD might have different levels of inflammation in the bowel, which could influence the IL-6 and TNF-α levels in the serum. Third, the GIQLI score is not validated for all the spectrums of DD; however, we believe it is the most appropriate for this study. Fourth, the presurgery IL-6 and TNF-α levels might be elevated because of another undiagnosed chronic disease. However, the white blood cell count and the C-reactive protein level were within typical values. Lastly, the population of this study only included patients in four hospitals in northern Italy, limiting the generalization of the findings.

CONCLUSION

The levels of IL-6 and TNF-α were significantly reduced 6 months after surgery for patients with URD, SUDD and SmD. The GIQLI score demonstrated an inverse relationship with IL-6 and TNF-α levels, indicating improved quality of life following surgery. These findings suggest that patients with chronic diverticulitis may experience persistent systemic inflammation driven by a colonic trigger. Surgical removal of this trigger appears to enhance GIQLI outcomes. If validated by future comparative and larger studies, these biomarkers might be used as a prognostic and diagnostic tool to understand who needs surgery most, offering a foundation for future clinical guidelines and more effective disease management.

AUTHOR CONTRIBUTIONS

R.S., G.M., F.R., and J.C. drafted the manuscript. R.S., P.A., and V.P.D. conducted the statistical analysis. C.S., R.D., and V.L. contributed to the appendix and parts of the methods section. All other authors reviewed and approved the final version of the manuscript.

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No funding was received for this study.

CONFLICT OF INTEREST STATEMENT

All authors have nothing to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This retrospective study was conducted in accordance with the principles outlined in the Declaration of Helsinki. Informed consent was obtained from all subjects. All data were anonymized prior to analysis to ensure confidentiality and privacy. No identifiable personal information was used in any part of the study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX 1

METHODS

Tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) levels were measured using two different immunoassay platforms. The tumor necrosis factor-α (TNF-α) was measured using the Human TNF-α ELISA Kit (Thermo Fisher Scientific, KHC3011), a solid-phase enzyme-linked immunosorbent assay (ELISA) performed on 96-well microtitre plates. The assay uses two monoclonal antibodies (MAbs) directed against distinct epitopes of TNF-α. Calibrators and samples react with the capture monoclonal antibody (MAb 1) coated on the wells of microtitre plates and with a monoclonal antibody (MAb 2) labelled with horseradish peroxidase (HRP). After a 120 minutes incubation at room temperature (20–25°C) with an orbital shaker (450 round per minute) which allows the formation of a sandwich (coated MAb 1 – TNF-α – MAb 2 – HRP), the microtitre plate is washed five times with a phosphate-buffered saline solution containing 0.05% Tween-20 at 20–25°C to remove unbound enzyme-labelled antibody. Finally, the plates are tapped upside down on absorbent paper to remove any residual wash buffer. Bound enzyme-labelled antibody is measured through a chromogenic reaction, as follows. Chromogenic solution (TMB) is added and the microtitre plate is incubated for 15 minutes at 20–25°C. The reaction is stopped with the addition of a stop solution, and the microtitre plate is then read at the appropriate wavelength, at 450 and 490 nm (reference filter 620 or 650 nm), within 30 minutes and then the results are calculated. Substrate turnover is determined according to the change of colour by measuring the absorbance, which is proportional to the TNF-α concentration. A calibration curve is plotted and the TNF-α concentration in samples is determined by interpolation from the calibration curve. Use of the ELISA reader (linearity up to 3 absorbance units) and a sophisticated data-reduction method (polychromatic data reduction) result in a high sensitivity in the low range and in an extended calibration range. IL-6 was measured using the Elecsys IL-6 assay (Roche Diagnostics) on the cobas e analyzer, an automated electrochemiluminescence immunoassay (ECLIA). The platform performs all steps automatically, including reagent handling, incubation, and detection. The assay duration is approximately 18 minutes, and all incubation steps occur at 37°C within the instrument. Results were calculated automatically by the system using a master calibration curve, with no manual washing or shaking required.