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Risk factors and outcomes of restorative proctocolectomy with ileal pouch-anal anastomosis for ulcerative colitis. Retrospective study of 75 single center cases

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Abstract. – OBJECTIVE: Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the surgical gold standard in patients with ulcerative colitis (UC). Results are generally satisfactory but there is a significant rate of patients who experience postoperative complications. The aims of our study were to identify the pre- and intraoperative risk factors and their correlation with the reported outcomes.

PATIENTS AND METHODS: A retrospective study was conducted on the medical records of all consecutive patients undergoing restorative proctocolectomy with IPAA for UC in our center from 2010 to 2021. Pre- and intraoperative factors were examined and correlated with pouchitis, endoscopic pouchitis, pouch failure, anastomotic leak, postoperative complications classified according to Clavien-Dindo score and stoma outlet obstruction. A univariate and multivariate statistical analysis was performed.

RESULTS: Out of 75 patients undergoing 3- or 2-stage IPAA surgery, the coexistence of extraintestinal clinical manifestations and preoperative topical rectal stump therapy for active proctitis were significantly associated with the occurrence of pouchitis (OR=4.4, *p*=0.03 and OR=7.6, *p*=0.01). Endoscopic pouchitis was found to be related to preoperative topical rectal therapy (OR=10.2, *p*=0.007), but not to extraintestinal manifestations of disease. Anastomotic leak was found to be significantly related to pouch failure (OR=22.7, *p*=0.007). Surgical indication for malignancy increased the risk for early complications (Clavien-Dindo >2) (OR=16.0, *p*=0.04). Young age was associated with the occurrence of outlet stoma obstruction in patients with recent IPAA surgery (OR=0.97, *p*=0.05).

CONCLUSIONS: Based on observed results, an appropriate preoperative patient assessment aimed at detecting specific risk factors is crucial to identify early or prevent worse outcomes in patients undergoing IPAA surgery.

Key Words:
Ileal pouch-anal anastomosis, Restorative proctocolectomy, Ulcerative colitis, Pouchitis, Pouch failure.

Introduction

Ulcerative colitis (UC)[1] is a chronic inflammatory disease of the digestive tract affecting the mucosa and submucosa of the rectum and colon. Correct medical treatment is important as the disease is characterized by relapses and remissions. However, in about 20% of the cases[2,3], UC patients will end up with surgery. Surgical gold standard for these patients is proctocolectomy with ileal pouch-anal anastomosis (IPAA)[4,5]. Since its inception in 1978 as S-shaped IPAA with hand-sewn anastomosis[6], moving in 1980 to J-pouch with stapled anastomosis[7], there have been many developments in the surgical approach to this type of surgery[8], until the inception of trans-anal procedure[9], laparoscopic single-incision technique[10] and robotic surgery[11]. In general, patients are satisfied after IPAA surgery and can maintain a high quality of life. However, a substantial rate of patients experiences short- or long-term complications[12] and, among these, pouchitis is certainly the most frequent and often the most disabling occurrence[13,14]. The aim of our study is to investigate pre- and intraoperative risk factors to identify early or prevent the above complications in patients undergoing IPAA surgery.

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Patients and Methods

A retrospective study was performed on all consecutive patients affected of UC that underwent the procedure of ileal pouch-anal anastomosis in the Abdominal Surgery Unit at the A. Gemelli University Hospital from 2010 to 2021. The data for the study were gathered through the medical records and post-operatory phone follow-up, subject to consent obtained from patients.

All of them underwent colectomy, proctectomy and IPAA. Surgery was performed through either open or laparoscopic technique and the anastomosis was either done with hand-sewn, stapled, or trans-anally approach. The configuration of the ileal pouch was J-shaped, the length was about 15-18 cm. Protective loop ileostomy was always performed. Only patients undergoing an IPAA in our center had been included in the study. All patients had been diagnosed of UC and followed-up after the interventions by surgeon and gastroenterologist. Patients who did not perform endoscopy to evaluate the pouch were excluded from the study.

Collected data included pre- and intraoperative factors as well as perioperative and long-term outcomes.

Preoperative patient data included demographics, body mass index (BMI), smoking history, American Society of Anesthesiologists (ASA) score, indication to surgery (Acute Severe Ulcerative Colitis - ASUC, toxic megacolon, refractory to medical therapy colitis, malignancy, and dysplasia), preoperative topical therapy of the rectal stump and extra-intestinal manifestations. The malignancy included different category such as adenocarcinoma and neuroendocrine carcinoma. Topical rectal stump therapy was given during acute phase of proctitis.

Intraoperative data analyzed were open or laparoscopic surgical technique, types of surgical procedures (2-stage or 3-stage IPAA), approach of IPAA surgery (hand-sewn, stapled or transanal), and Geboes score. All the IPAA were J-shaped. After proctectomy, the rectal stump was analyzed at the Institute of Pathological Anatomy and the Geboes score[15], a histological score, was used to classify the severity of the inflammation in UC.

Postoperative data after the performing of ileal pouch-anal anastomosis included the onset of pouchitis, endoscopic pouchitis, pouch failure, pouch leak, early and late complications, and stoma outlet obstruction.

Pouchitis is a clinical presentation with typical symptoms (increased number and looser consistency of stool discharges, rectal bleeding and/or urgency) associated to endoscopic relief of pouchitis during a symptomatic episode.

The diagnosis of pouchitis, in agreement with the literature, was defined only when modified Pouchitis Disease Activitiy Index (mPDAI)[16] was ≥ 5, identified by postoperative pouchscopy routinely experienced by all the patients of the study.

Pouch failure has been defined as a severe pouch disfunction that leads to pouch deconstruction or otherwise the maintenance of a definitive ileostomy.

Pouch leak is a defect of the anastomosis or most rarely of pouch sutures causing either pouchitis or pouch failure. Early complications consisted in the perioperative outcomes during the first 30 days after surgery, such as wound surgical infections, hemorrhage, perforation, pouch dehiscence/leak and pelvic abscesses, classified using the Clavien-Dindo score.

Late complications occurred 30 days after IPAA surgery, as pouch stenosis, pouch fistulas, pouchitis, pouch failure and stoma outlet obstruction (intestinal occlusion due to ostomy failure function before recanalization).

The primary endpoint was to evaluate the surgical risk factors of pouchitis after IPAA surgery and restored bowel transit.

The secondary endpoints were to associate risk factors to the onset of endoscopic pouchitis, pouch failure, leak from the pouch, stoma outlet obstruction and early complications.

Statistical Analysis

Continuous data were summarized with means and standard deviation (SD), while categorical data were presented with absolute frequencies and percentages.

Logistic regression models were used to assess the relationships between binary outcomes (onset of pouchitis, endoscopic pouchitis, pouch failure, leak from the pouch, early complications, and stoma outlet obstruction) and possible risk factors. Each predictor was initially tested in a univariable logistic regression model. Only predictors significant at a p-value of 0.10 entered the multivariable model. The final model was derived after the application of a stepwise elimination procedure.

Results were reported in terms of ORs (odds ratios). Accuracy rate, sensitivity and specificity were computed according to the Youden crite-

rion. The areas under the receiver operating characteristic curve (AUCs), along with the confidence intervals (CIs) by bootstrapping, were used to assess the prediction ability of the final models. A *p*-value less than or equal to 0.05 was considered as statistically significant.

Statistical analyses were conducted using SPSS software (version 24.0, IBM Corp., Armonk, NY, USA) and R software (version 4.1.3 with package stats for binary logistic regression model).

Results

Patient's Demographic and Clinical Characteristics

Seventy-five patients (29 females and 46 males, average age 44 ± 15.6 years) were enrolled from 2010 to 2021 with a median follow up of 42.4 months. All patients underwent restorative proctocolectomy with ileal pouch-anal anastomosis. Age was not significantly different between males and females (46 ± 16.7 *vs.* 40.8 ± 13.2, p=0.139, respectively). The average BMI was 21.9 ± 3.8. Six out of 75 individuals were smokers (8%). Forty-two patients (56%) got operated due to an acute fulminant colitis, twenty-three (30.7%) for refractoriness to medical treatment, four (5.3%) for malignancy and six (8%) because of dysplasia. Only 17 patients (22.7%) had some extra-intestinal manifestations. Two patients (2.7%) had a megacolon. The colectomy was performed laparoscopically in 62 patients (82.7%) and with open approach in 13 patients (17.3%). Proctectomy with restorative IPAA was done laparoscopically in 47 patients (72.3%) and with laparotomy in 18 patients (27.7%). Sixty-five patients (86.7%) performed a 3-stage procedure, ten (13.3%) performed a 2-stage IPAA. The ileostomy closure was performed in 68 patients (90.7%), while the decision to leave a definitive ileostomy was done for 2 patients (2.7%). Five patients (6.7%) out of the total are still on the waiting list to perform the final step.

Stapled anastomosis was the most used technique (70 patients, 93.3%). Two IPAA were performed trans-anally (2.7%), three hand-sewn (4%).

Out of the 65 patients that had 3-stages procedure, 45 (69.2%) were treated with local rectal therapy after the colectomy. Geboes score showed 68 patients (90.7%) with a result >3 and 7 patients (9.3%) <3.

The average interval of time between the colectomy and the proctectomy with IPAA was 11.4 months, while the interval of time between the pouch surgery and the restoration of bowel integrity was 5.5 months.

Primary Endopoint: Pouchitis

Overall, 68 patients were suitable for the primary endpoint. The multivariable logistic regression model revealed that extra-intestinal manifestations (OR=4.4; p=0.03) and topical rectal therapy (OR=7.6; p=0.01) were significant risk factors for the onset of pouchitis. The receiver operating characteristic (ROC) curve optimal cut-off value (from the Youden criterion) was 0.16. The model with the chosen cut-off provided an accuracy of 62.7%, a sensitivity of 100% and a specificity of 43.6% (Figure 1).

Secondary Endpoints

Sixty-eight patients were eligible for endoscopic pouchitis outcome evaluation. The results of the multivariable logistic regression analysis highlighted that topical rectal therapy was a significant predictor of this outcome (OR=10.2; p=0.007). The ROC curve provided an accuracy of 66.1%, a sensitivity of 91.3% and a specificity of 50% to identify patients with or without endoscopic pouchitis (Figure 2).

Pouch failure, pouch leak, stoma outlet obstruction and early complications outcomes were assessed on 75 patients. The univariable logistic regression models showed that

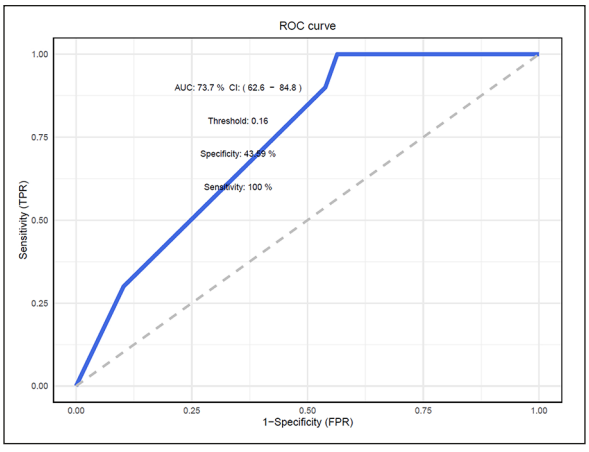

Figure 1. ROC curve from the multivariable logistic regression analysis with pouchitis as dependent variable and extra-intestinal manifestations and topical rectal therapy as independent variables. ROC: Receiver Operating Characteristic; AUC: Area Under the Curve; CI: Confidence Interval; TPR: True Positive Rate; FPR: False Positive Rate.

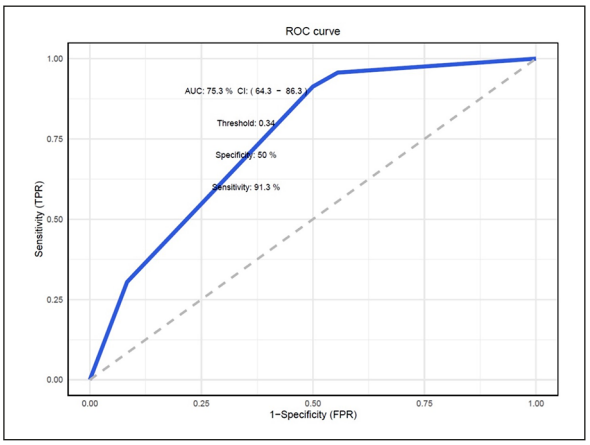

Figure 2. ROC curve from the multivariable logistic regression analysis with endoscopic pouchitis as dependent variable and topical rectal therapy as independent variable.

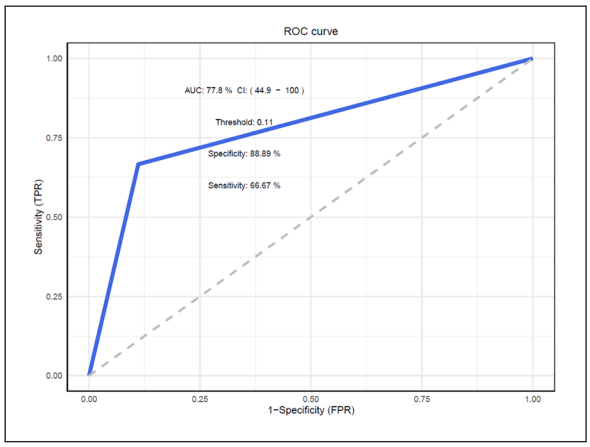

Figure 3. ROC curve from the multivariable logistic regression analysis with early complications as dependent variable and malignancy as independent variable.

the anastomotic leak is a risk factor of pouch failure (OR=22.7; p=0.007). Age resulted to be a risk factor for the occurrence of stoma outlet obstruction (OR=0.97, p=0.05). No risk factors have been identified for pouch leakage outcome. The variable malignancy resulted to be a risk factor for the outcome early complications (OR=16.0, p=0.04). The ROC curve displayed an accuracy of 88.0%, a sensitivity of 66.7% and a specificity of 88.9% to identify patients with or without this outcome (Figure 3).

Risk factors and related outcomes, odds ratios (ORs) and p-values of univariable and multivariable models are reported in Tables I-III.

Table I. Risk factors and related outcomes.

	Pouchitis n = 26 (38.2)	Endoscopic pouchitis n = 31 (45.6)	Pouch failure n = 4 (5.3)	Stoma outlet obstruction n = 20 (26.7)	Leak n = 4 (5.3)	Clavien-dindo score > 2 n = 3 (4)
Sex	9 (34.6)	11 (35.5)	1 (25)	9 (45)	0	2 (66.7)
Age	42	44	46	38	43	42
Smoker	0	0	0	2 (10)	1 (25)	0
BMI	21.5	22	22.1	22	22.8	22.2
ASA 2	23 (88.5)	29 (93.5)	3 (75)	19 (95)	4 (100)	2 (66.7)
ASA 3	3 (11.5)	2 (6.5)	1 (25)	1 (5)	0	1 (33.3)
ASUC	12 (46.2)	14 (45.2)	3 (75)	10 (50)	3 (75)	1 (33.4)
Refractory UC	8 (30.8)	9 (29)	0	7 (35)	0	1 (33.3)
Dysplasia	3 (11.5)	5 (16.1)	1 (25)	2 (10)	1 (25)	1 (33.3)
Malignancy	3 (11.5)	3 (9.7)	0	1 (5)	0	0
NEC	0	0	0	0	0	0
Megacolon	0	1 (3.2)	0	0	0	0
2-stage IPAA	6 (23.1)	7 (22.6)	1 (25)	3 (15)	1 (25)	1 (33.3)
3-stage IPAA	20 (76.9)	24 (77.4)	3 (75)	17 (85)	3 (75)	2 (66.7)
LPS IPAA	15 (57.7)	23 (74.2)	2 (50)	17 (85)	3 (75)	3 (100)
Stapled IPAA	25 (96.1)	30 (96.8)	3 (75)	18 (90)	4 (100)	3 (100)
Transanal IPAA	0	0	0	1 (5)	0	0
EIM	9 (34.6)	11 (35.5)	1 (25)	6 (30)	0	0
Topical rectal stump therapy	18 (69.2)	21 (67.7)	3 (75)	14 (70)	3 (75)	1 (33.3)
Geboes score ≥ 3	25 (96.2)	27 (87.1)	4 (100)	20 (100)	4 (100)	3 (100)
Leak	1 (3.8)	1 (3.2)	2 (50)			

All values expressed as means or n [%]. BMI: Body Mass Index; ASA score: American Society of Anesthesiologists score; ASUC: Acute Severe Ulcerative Colitis; UC: Ulcerative Colitis; NEC: Neuro-Endocrine Carcinoma; IPAA: ileal pouch-anal anastomosis; LPS: laparoscopy; EIM: Extra-Intestinal Manifestations.

Table II. ORs [95% Confidence Interval] and p-values from univariable and multivariable analysis of statistically significant risk factors related to all outcomes.

			Univariable analysis		Multivariable analysis	
Outcome	**Risk factor**	**N (%)**	**OR [95% CI]**	***p*-value**	**OR [95% CI]**	***p*-value**
Pouchitis	Malignancy	3 (11.5)	3.9 [0.9-17.2]	0.07		
	2-stage IPAA	6 (23.1)	3.9 [0.9-17.2]	0.07		
	3-stage IPAA	20 (76.9)	0.3 [0.1-1.1]	0.07		
	EIM	9 (34.6)	2.6 [0.8-8.3]	0.10	4.4 [1.1-16.9]	**0.03**
	Topical rectal stump therapy	18 (69.2)	7.7 [1.6-37.8]	0.01	7.6 [1.6-36.1]	**0.01**
Endoscopic pouchitis	Malignancy	3 (9.7)	5.5 [1.0-28.7]	0.04		
	2-stage IPAA	7 (22.6)	5.5 [1.0-28.7]	0.04		
	3-stage IPAA	24 (77.4)	0.2 [0.03-0.96]	0.04		
	Topical rectal stump therapy	21 (67.7)	10.5 [2.1-51.5]	0.004	10.2 [2.0-52.4]	**0.007**
Pouch Failure	Leak	2 (50)	22.7 [2.3-220.6]	**0.007**		
Stoma outlet obstruction	Age	38	0.96 [0.93-1.0]	0.05	0.97 [0.93-1.0]	**0.05**
	ASA 2	19 (95)	0.1 [0.01-1.1]	0.06		
	ASA 3	1 (5)	0.06 [0.005-0.6]	0.07		
Clavien-Dindo score > 2	Malignancy	0	16.0 [1.3-197.0]	0.03	16.0 [1.3-203.9]	**0.04**
	2-stage IPAA	1 (33.3)	16.0 [1.3-197.0]	0.03		
	3-stage IPAA	2 (66.7)	0.06 [0.005-0.8]	0.03		

Discussion

Pouchitis is the most frequently observed complication after IPAA surgery[17,18]. In our statistical analysis a significant association between extra-intestinal manifestations and pouchitis was found, confirming features of systemic disease[19-21]. We used to grade the rectal stump inflammatory activity after the subtotal colectomy with Geboes histological score. Recently a simplified score has been proposed, with comparable results[22]. Most patients in all different groups had a Geboes score ≥3. However, it has recently been proven that active inflammation in the rectal stump was linked to pouchitis[23]. Pouchitis rate was significantly higher in group with rectal stump inflammation. Nevertheless, in our study the topical rectal therapy and not the Geboes score was significantly related to the outcome of pouchitis. The more patients did this type of treatment, the more numerous they were with pouchitis. Therapy refractory pouchitis were only seen in patients with an active proctitis. However, inflammation in the rectal stump was not significantly associated with overall postoperative complications or anastomotic leakage.

Symptoms alone are not reliable for the diagnosis of pouchitis, therefore endoscopy is required. Symptoms, endoscopy, and histology did not correlate with each other; two or more factors

Table III. β-coefficients, ORs [95% Confidence Interval] and *p*-values related to statistically significant results from multivariable models.

	Multivariable analysis			
Outcome	**Risk factor**	**β**	**OR [95% CI]**	***p*-value**
Pouchitis	Intercept	-2.5		0.001
	Extra-intestinal manifestations	1.5	4.4 [1.1-16.9]	**0.03**
	Topical rectal therapy	2.0	7.6 [1.6-36.1]	**0.01**
Endoscopic pouchitis	Intercept	-2.4		0.003
	Topical rectal therapy	2.3	10.2 [2.0-52.4]	**0.007**
Stoma outlet obstruction	Intercept	0.5		0.54
	Age	-0.03	0.97 [0.93-1.0]	**0.05**
Clavien-dindo score > 2	Intercept	-4.1		< 0.001
	Malignancy	2.8	16.0 [1.3-203.9]	**0.04**

are necessary to make an accurate diagnosis. Pouchitis Disease Activity Index (PDAI) score was basically used to diagnose pouchitis[24,25]. However, in our study we used mPDAI, a simplified score validated in 2003 with 97% of sensitivity and 100% of specificity. In some cases, it is possible to have a positive endoscopic activity of pouchitis without clinical symptoms. In those patients the risk to develop future symptomatic pouchitis is higher[26]. Nevertheless, there are still no specific guidelines for pouch surveillance or a "treat to target" recommendation. In patients who have had preoperative topical rectal therapy, we observed a high inflammation of pouch mucosa when performing the endoscopy at the follow-up. The pouchscopy is often used to follow-up the patients even though they do not have any symptoms. Thus, we found more patients with endoscopic pouchitis than clinical pouchitis using the mPDAI score. Although endoscopy tends to overestimate the diagnosis, it could be helpful to follow-up these patients in a strict way to avoid any worsening of the inflammation and eventually pouchitis-related complications.

Pouch failure is defined as the need of excision of the pouch or maintenance of a definitive stoma after its creation. There was 5.3% of pouch failure in our study, comparable to the 5-10% of the literature. In a retrospective Danish study women seems to be at higher risk of failure than men; low hospital volume and non-diversion were also associated with a higher risk of pouch failure[27]. Hand-sewn IPAA is another related risk factor to the onset of pouch failure as a consequence of leakage[28]. In our experience, anastomotic leakage seems to predispose to an increased risk of pouch failure, probably attributing a surgical genesis to this complication.

Preventing anastomosis leakage may avoid, reduce, or delay at the very least the incidence of pouch failure. Our overall pouch leakage rate (5.3%) is in the lower end of the literature's range (5-19%). In literature, high BMI and ASA score were independent risk factors impacting the leakage[29]. However, in our study none of these factors increased the onset of pouch leak. Neither the choice of surgical approach (laparoscopy or laparotomy) seems to predispose to the risk of leakage. Although a clear consensus of best timing IPAA construction is still not available, the staged approach remains the favorite strategy, especially the 3-stage one because of significant low anastomotic leak compared to other staged procedures[30]. This was similar to our study, where most of the pouch (86.7%) were accomplished in a 3-stage procedure and only 4.6% of them had an anastomotic leak. However, none of the mentioned factors resulted significant in our study.

Stoma outlet obstruction is another common complication after IPAA surgery. In our study, small bowel occlusion rate was 26.7%, although most of the cases were functional and temporary as described in literature. Two-stage procedure was found to be a significant and independent risk factor of occlusion after IPAA surgery with loop ileostomy, maybe because of loop ileostomy tightening and angulation by abdominal wall or its rotation[31]. In a multicenter retrospective study[32], stoma outlet obstruction was significantly higher in patients with a distance from the ileal pouch to the ileostomy of less than 30 cm, probably due to major risk of internal herniation and angulation of loop ileostomy, and in patients undergoing laparoscopic surgery, possibly because of earlier recovery of bowel peristalsis and hence increased mobility of the bowel. Long distance between the superior mesenteric artery root and bottom of external anal sphincter increased the risk of occlusion, advising to reduce surgically mesenteric tension as possible[33]. However, in our research, only the age was a significant risk factor. The younger was the patient the higher was the chance to get a bowel obstruction, maybe because the tougher and thicker abdominal wall of the young patients. Although no statistically significant difference was found between the abdominal wall of patients with and without outlet obstruction before ileostomy closure, the thickness of the abdominal rectum muscle may be a risk factor of obstruction[34]. Therefore, it might be imaginable in the future to reserve a diverting loop ileostomy only to older patients or the youngers with high risk IPAA, trying to avoid ileostomy in those with "safe" IPAA.

We defined early complications the occurrence of a Clavien-Dindo score >2 within the first 30 days after IPAA surgery. In our experience, 3-stage procedure was performed more commonly than 2-stage, however it wasn't significantly associated to this outcome. Indeed, in other studies[35,36] has been showed no difference in term of early complications between 2- and 3-stage procedure. Open or laparoscopic approach did not influence the result either. Hand-sewn or stapled IPAA did not significantly affect post-operative complications[37,38]. In the hands of experienced high-volume surgeons, low early morbidity is

emphasized[39]. However, the age at the time of surgery and the amount of blood loss during intervention seems to influence the onset of early complication[40]. In our multivariate analysis the only significant factor influencing the occurrence of early complications was the malignancy as indication to surgery.

Limitations

The present study suffers from limitations due to its retrospective nature. However, the reported evidence could give a relevant contribution to clinical practice in the management of patients with ulcerative colitis undergoing surgery.

Conclusions

In patients undergoing IPAA surgery and affected by extraintestinal clinical manifestations and preoperative acute proctitis with need for topical therapy, a close follow-up is indicated to identify and treat early onset of pouchitis. Further studies are required to clarify the indication for medical/microbiological prophylaxis aimed to prevent the occurrence of endoscopic pouchitis. Anastomotic leak is associated with an increased risk of pouch failure and surgical indication for neoplasia with the onset of major early complications, both events more frequent in 2-stage procedures. The younger the patients, the greater the risk of observing stoma outlet obstruction, therefore modified 2-stage surgery might be suggested in selected individuals.

The risk factors we identified as statistically significant in our study deserve particular attention in the aim to prevent bad outcomes either in the short and long term.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

Mauro Giambusso, Paola Caprino, Franco Sacchetti and Luigi Sofo contributed to the study conception and design. Material preparation, data collection and analysis were performed by Mauro Giambusso, Franco Sacchetti, Simona Panunzi and Ilaria Piergentili. The first draft of the manuscript was written by Mauro Giambusso and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data Availability

The datasets generated during and/or analyzed during the current study are not publicly available because obtained consulting clinical records but are available from the corresponding author on reasonable request.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Ethics Approval

All the study was based on hospital data obtained consulting clinical records; therefore, ethical disclosure was not necessary.

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