New perspectives in the prediction of postoperative complications for high-risk ulcerative colitis patients: machine learning preliminary approach

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New perspectives in the prediction of postoperative complications for high-risk ulcerative colitis patients: machine learning preliminary approach

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Abstract. – OBJECTIVE: Patients with acute severe and medical refractory ulcerative colitis have a high risk of postoperative complications after total abdominal colectomy (TAC). The objective of this retrospective study is to use machine learning to analyze and predict short-term outcomes.

PATIENTS AND METHODS: 32 patients with ulcerative colitis were treated with total abdominal colectomy between 2011 and 2017. Biographical data, preoperative therapy, blood chemistry, nutritional status, surgical technique, blood transfusion and preoperative length of stay were the features selected for the statistical analyses and were used as input for the machine learning algorithms to predict the rate of complications.

RESULTS: Traditional statistical analysis showed an overall postoperative morbidity rate of 34% and a mortality rate of 3%. Preoperative low serum albumin levels (<2.5 g/dL) were related to a higher risk of minor infectious complications with statistical significance (*p*<0.05). Preoperative length of stay (>4 days), blood transfusions (≥1 unit) and body temperature (≥37.5°C) demonstrated a major impact on infectious morbidity with statistical significance (*p*<0.05). Patients treated with steroids and rescue therapy presented a higher risk of minor infectious complications (*p*<0.05). Evaluating only preoperative features, machine learning algorithms were able to predict minor postoperative complications with a high strike rate (84.3%), high sensitivity (87.5%) and high specificity (83.3%) during the testing phase.

CONCLUSIONS: Machine learning is demonstrated to be useful in predicting the rate of minor postoperative complications in high-risk ulcerative colitis patients, despite the small sample size. It represents a major step forward in data analysis by implementing a retrospective study from a prospective point of view.

Key Words:
Ulcerative colitis, Machine learning, Postoperative complications.

Introduction

Ulcerative colitis (UC) is a chronic inflammatory disease of the colon and rectum[1-3]. Chronic refractory UC, acute severe UC (ASUC) non-responsive to rescue therapy, toxic megacolon, perforation or massive bleeding and, more rarely, dysplasia/carcinoma, are indications for surgery.

Patients undergoing surgery for UC are exposed to the risks of wound infection, intra-abdominal abscess, sepsis, bowel obstruction, and other postoperative complications[4,5].

Age, comorbidities, preoperative medical treatment, immune impairment due to medical treatment, malnutrition, urgent status and prolonged time from admission to surgical treatment, are significant risk factors for postoperative morbidity[6].

The present study investigated with a new prediction method the short-term outcomes of total abdominal colectomy (TAC) on a cohort consisting of 32 high-risk selected patients with chro-

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nic refractory UC who were being treated with steroids, ASUC patients who were not responsive to rescue therapy or patients with an urgent status. The goal was to analyze the impact of preoperative data on the occurrence of postoperative complications in this high-risk, subgroup of patients.

In a retrospective study, a computer program based on machine learning (ML)[7] was developed to predict postoperative complications by examining data available before surgery. Results obtained by conventional statistical methods and those achieved from an ad hoc algorithm based on ML were evaluated.

Patients and Methods

Thirty-two selected patients with a high risk for perioperative complications who underwent TAC for UC in the Abdominal Surgical Unit of the F. Policlinico Gemelli – IRCCS (Rome, Italy) from September 2011 and October 2017 were retrospectively analyzed. All the data were collected from charts review. Twenty-four patients (75%) underwent TAC by the laparoscopic approach and 8 (25%) underwent open surgery. The conversion rate was 12.5% (4 patients; included in the laparotomy group for statistical analysis).

The laparoscopy specimen was extracted through a small (@ 4 cm) Pfannenstiel incision in 7 patients (29.2%), while in 17 patients (70.8%), the specimen was extracted through a minor enlargement of the trocar incision in the right flank, where an ileostomy was placed at the end of surgery.

Twenty-one patients required a semi-urgent colectomy for ASUC (according to the Truelove's criteria[8]) that did not respond to rescue therapy (steroid and biological drugs). Two patients had surgery because of an urgent status (toxic megacolon and massive bleeding). Nine patients presented with chronic refractory UC that was being treated with steroids and had not received biological drugs within 6 weeks before surgery. In our clinical practice, we usually prefer to delay surgical treatment until at least 6 weeks after biological therapy if possible.

Biographical data, preoperative therapy, pre- and postoperative blood chemistry, nutritional status (lymphocyte count and albumin), time from admission to surgery, surgical technique (laparoscopy or laparotomy), operative time, blood transfusion, postoperative complications and postoperative length of stay were recorded (Table I). The main goal of our study was to test a new prediction model of postoperative morbidity with the development of ad hoc algorithms based on ML.

Postoperative morbidity was classified as minor infectious (wound infection), major infectious (intra-abdominal abscess or sepsis) and non-infectious (bowel obstruction, thrombosis, pulmonary embolism and cardiovascular complications) complications.

Statistical Analysis

Data were first analyzed by univariate (unpaired Student's *t*-test and chi-square test) and multivariate analyses and later by a computer program

Table I. Clinical patients' characteristics.

Age, mean (SD), years	53 (± 13.8)
Gender, n (%)	
Male	17 (53)
Female	15 (47)
Length of disease before surgery, mean (SD), years	9 (± 6.8)
Time from admission to surgery, n (%)	
< 4 days	20 (62.5)
> 4 days	12 (37.5)
Preoperative therapy, n (%)	
Rescue therapy (steroids and biological drugs)	21 (65.6)
Steroids	9 (28.1)
No	2 (6.3)
Haemoglobin, mean (SD)	11,1 (± 2,3)
White Blood Cell, mean (SD)	8780 (± 3380)
Lymphocyte count, mean (SD)	1550 (± 784,7)
Serum albumin, mean (SD)	3,1 (± 0,75)
Blood transfusion, n (%)	
Yes (≥ 1)	13 (40.6)
No	19 (59.4)

based on machine learning algorithms (ML). p-values ≤ 0.05 were considered to be statistically significant.

For ML evaluation, we implemented a software using the Python programming language[9] and the SciPy ecosystem[9] and we were able to simulate a prospective study in which known data are used to fit a prediction model for the unknown ones. In particular, the goal was to predict postoperative complications by only assessing the preoperative data. The data-processing methodology is shown in Figure 1.

The Machine Learning (ML) approach allows to create a mathematical model directly from data in order to make predictions without being explicitly programmed for the given problem, and without doing any preliminary assumption on data in itself. It can be seen as an alternative approach to traditional statistics and it is closely related to computational statistics.

During the first step, called data gathering, records of the 32 patients were retrospectively identified from the hospital archive and reorganized in a dataset. The second step was data pre-processing, which consisted of the following three sub-steps:

Feature extraction: all data present in the original dataset are transformed in derived values, called *features*, in order to be more computer-readable and easy to guess. For example, complications were represented as binary variables (0: absence, 1: presence) and classified as minor infectious, major infectious and non-infectious complications.

Data normalization: in order to avoid numerical problems, data are normalized to have zero mean and unitary variance.

Feature selection: features such as biographical data (age and sex), preoperative therapy (steroids and biological drugs), preoperative blood chemistry (RBC, WBC and serum creatinine), nutritional status (lymphocyte count and albumin), surgical technique (laparoscopy or laparotomy), blood transfusion and preoperative length of stay (time from admission to TAC) are selected and used as inputs into the ML algorithms.

The last step is called *model validation,* and it is meant to assess how well the model will generalize on new independent datasets coming from the real world. The general technique consists of partitioning data into a training set and a testing set. The former is considered "known", and it is used to fit a statistical model. The latter is considered "unknown", and it is used to test predictions. In this case, we fit a multivariate classification model using Support Vector Machine (SVM) and quantitatively assess its prediction performance using the leave-one-out cross-validation (LOOCV) technique. The results of this method are expressed through the following three indicators: strike rate (percentage of correct predictions), sensitivity (true positive rate) and sensibility (true negative rate).

In particular, for each complication type, the ML software performs the following activities:

- Consider the single patient
- Create a prediction model using SVM on all patients but the one considered (*model training*)
- Predict the presence of considered complication and patient (*model testing*)
- Iterate over patients
- Iterate over complications

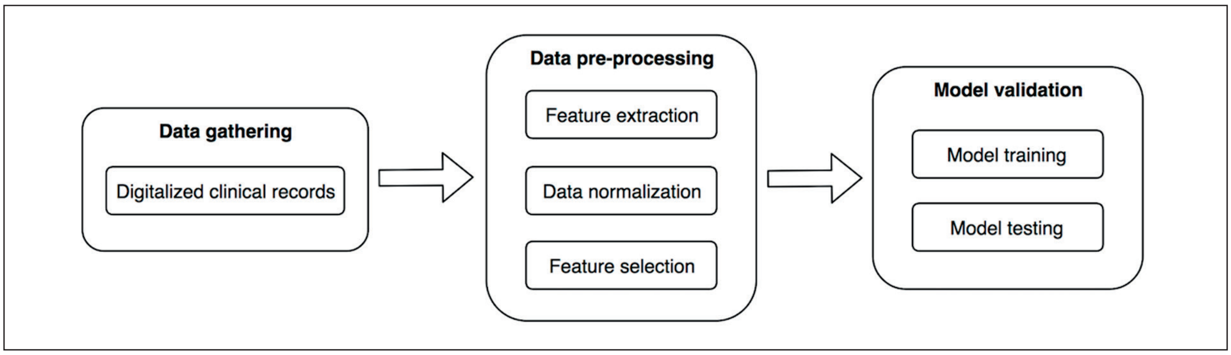

Figure 1. Data processing methodology.

- Compute the rate of correct predictions (strike rate), sensitivity and specificity. Only results with high performances in all three features (sensitivity, specificity and strike rate) can be considerable predictive and reliable.

Results

Operative time was higher in the laparoscopic group than the time in the open group (240±35 min *vs.* 190±35 min, $p<0.01$). A progressive decrease in operative time was observed in laparoscopic patients over recent years (mean: 210±20 min in the last year). Postoperative length of stay was shorter in the laparoscopic group compared to the length of stay in the laparotomy group (9±4.3 *vs.* 13±6.4 days, p=NS). A progressive decrease in hospital length of stay was observed with the laparoscopic approach (mean: 6.5±2 days in the last year).

Overall, the postoperative morbidity rate was 34% (11/32 patients). The mortality rate was 3% (1/32 patients). The results of univariate analysis are reported in Table II. Preoperative low serum

Table II. Results of different features on postoperative complications.

Features	Minor infectious complications	Major infectious complications	Non-infectious complications
Sex			
Male	6/18 (33%)	3/18 (16.6%)	1/18 (5.5%)
Female	2/14 (14%)	1/14 (7%)	2/14 (14%)
	$p = 0.23$	$p = 0.43$	p = NS
Surgical approach			
Laparoscopy	2/20 (10%)	2/20 (10%)	2/20 (10%)
Laparotomy	6/12 (50%)	2/12 (17%)	1/12 (8.5%)
	$p < 0.05$	$p = 0.59$	$p = 0.88$
Blood transfusion			
Yes	8/13 (61.5%)	3/13 (23%)	1/13 (7.5%)
No	0/19 (0%)	1/19 (5%)	2/19 (10%)
	$p < 0.01$	$p = 0.14$	$p = 0.79$
Preoperative length of stay			
> 4 days	5/12 (41.5%)	3/12 (25%)	1/12 (8%)
< 4 days	3/20 (15%)	1/20 (5%)	2/20 (10%)
	$p < 0.05$	$p = 0.36$	$p = 0.63$
White Blood Cell			
> 10.500 mmc	2/7 (28.5%)	1/7 (14%)	0/7 (0%)
< 10.500 mmc	6/25 (24%)	3/25 (12%)	3/25 (12%)
	$p = 0.36$	$p = 0.36$	$p = 0.32$
Hemoglobin			
> 10.5 g/dL	1/19 (5%)	2/19 (10.5%)	2/19 (10.5%)
< 10.5 g/dL	7/13 (54%)	2/13 (15%)	1/13 (7.5%)
	$p < 0.01$	$p = 0.80$	$p = 0.95$
Serum albumin			
> 3.5 g/dL	1/15 (6.5%)	1/15 (6.5%)	1/15 (6.5%)
2.5 – 3.5 g/dL	4/11 (36%)	2/11 (18%)	1/11 (9%)
< 2.5 g/dL	3/6 (50%)	1/6 (16.5%)	1/6 (16.5%)
	$p < 0.05$	$p = 0.42$	$p = 0.95$
Lymphocyte count			
> 900 mmc	5/23 (22%)	4/23 (17%)	2/23 (8.5%)
< 900 mmc	3/9 (33%)	0/9 (0%)	1/9 (11%)
	$p = 0.37$	$p = 0.60$	$p = 0.42$
Body temperature			
> 37.5°C	4/9 (44%)	3/9 (33%)	2/9 (22%)
< 37.5°C	4/23 (17%)	1/23 (4%)	1/23 (4%)
	$p = 0.11$	$p < 0.05$	$p = 0.12$
Preoperative therapy			
Steroids	2/9 (22.2%)	1/9 (11.1%)	0/9 (0%)
Rescue therapy	6/21 (28.5%)	3/21 (14%)	3/21 (14%)
No	0/2 (0%)	0/2 (0%)	0/2 (0%)
	$p < 0.05$	$p = 0.19$	$p = 0.33$

albumin (<2.5 g/dL) was related to a higher risk of minor infectious complications with statistical significance ($p<0.05$). Preoperative length of hospital stay (>4 days), pre- and/or intraoperative blood transfusions (≥1 unit) and body temperature (≥37.5°C) showed a major impact on infectious morbidity with statistical significance ($p<0.05$). Patients treated with steroids and those who received rescue therapy had a higher risk of minor infectious complications ($p<0.05$).

ML algorithms evaluating preoperative features (age, sex, therapy with steroids/biological drugs, hemoglobin level, WBC and serum creatinine, nutritional status, blood transfusion and preoperative length of stay) and surgical technique were able to predict minor postoperative infectious complications with a high strike rate (84.3%), high sensitivity (87.5%) and high specificity (83.3%) during the testing phase. This finding is meaningful in terms of the prediction power of the model, as the LOOCV is a robust validation technique. Training performances are always better by definition, as in this phase, the model itself is created; however, for the same reason, the training does not provide reliable insights about the prediction power. In both cases, the results are encouraging for minor infectious complications, while they were not significant for major infectious and non-infectious complications. The results obtained using the ML method are shown in Figure 2.

Discussion

Treatment of ulcerative colitis represents a very important challenge for surgeons and gastroenterologists. Patients affected by UC are often exposed to a high risk of postoperative complications due to steroids and biological therapy, malnutrition, the need for massive surgical excision and/or urgent conditions. The indications for surgery in our study were either urgent status, ASUC or chronic refractory UC with corticosteroid dependence. In this study, we only considered patients who underwent TAC with end ileostomy as the first surgical treatment, with the ileal pouch anal anastomosis (IPAA) procedure being postponed for a later date. According to most authors[1,11,12], this procedure is the best approach in high-risk patients. Bikhchandani et al[11] summarize the advantages of a 3-stage (subtotal colectomy first) *vs.* 2-stage IPAA in best nutritional status at the time of IPAA. The 3-stage approach provides the ability to taper steroids and immunosuppressant, avoids complex pelvic dissection in the setting of systemic inflammation and enables surgeons to rule out indeterminate and Crohn's colitis by an accurate pathological diagnosis of the specimen before the IPAA procedure.

In the present study, surgery was mostly performed *via* the laparoscopic approach (75%). Laparoscopy reduces surgical trauma and adhesions by facilitating the next surgical step of IPAA[13-15].

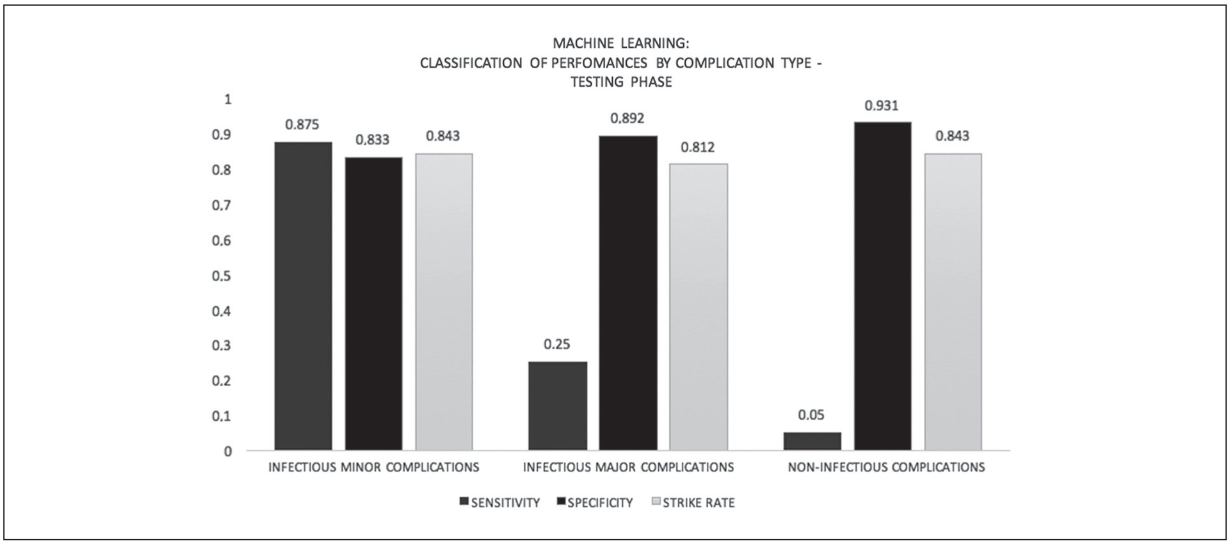

Figure 2.

Operative time was higher in the laparoscopic group with a progressive decrease in recent years (mean: 210 min in last year), most likely due to improvement of skills and confidence with laparoscopy. The hospital stay was shorter in laparoscopic patients (9 ± 4.3 *vs.* 13 ± 6.4 days, p = NS), with a decreasing trend over the last year (mean: 6.5 days in last year) as a result of improved experience.

In accordance with data in the literature[16-18], the results of this study suggest that laparoscopic TAC is a safe and valid approach in the surgical treatment of UC, even in an urgent setting with patients in critical conditions, which can reduce the global morbidity associated with UC. The laparoscopic approach proved to be highly beneficial in terms of minor infectious complications compared to laparotomy (10% *vs.* 50%, $p<0.05$), likely because of smaller surgical wounds. The two wound infections in laparoscopic patients occurred only in cases with a Pfannenstiel incision.

The difference between laparoscopy and laparotomy in terms of major infectious and non-infectious complications was not statistically significant, which may have occurred because of the low incidence of intra-abdominal abscess, sepsis, bowel obstruction, thrombosis, cardiovascular complications and pulmonary embolism in the overall sample.

ML software represents a major step forwards in data analysis. ML finds natural patterns within input and output data and develops predictive models.

In this study, *ML algorithm*s were used to simulate a prospective study in which known data are used to fit a prediction model for unknown data (morbidity was assumed as the event to guess). Our goal was to predict postoperative complications using data available before surgery on a cohort of high-risk patients. ML enables surgeons to predict the risk of complications with more accuracy prior to surgery, enabling them to potentially correct preoperative risk factors or decide to postpone surgical treatment if possible.

ML predicted minor infectious complications in surgical patients with a high strike rate (84.3%), high sensitivity (87.5%) and specificity (83.3%). Therefore, ML has been demonstrated to be useful in predicting minor infectious complications, despite of the small number of patients.

The prediction rate was lower for major infectious (strike rate: 81.2%; sensitivity: 25%; specificity: 89.2%) and non-infectious complications (strike rate: 84.3%; sensitivity: 5%; specificity: 93.1%). The rarity of those events and the small sample could explain the loss of sensitivity, sensibility and strike rate in the ML model. Nevertheless, the prediction performances of ML could improve in a larger series of high-risk surgical patients. It is possible and desirable to optimize the results by improving the ML algorithm with a wider feature selection, regularization and model averaging, which could make the model more effective in predicting also other types of complications.

None of our cases were obviously elective operations and so delaying to a better clinical condition, but to reliably predict complications before surgery could justify for example an early and prolonged use of antibiotics, most frequent medications or other specific attentions focused on the adverse event preoperative predicted.

Conclusions

ML software represents a major step forward in data analysis by implementing a retrospective study from a prospective point of view. Properly applied ML algorithms contribute to increased global understating of our patients and enable clinicians to comprehend what should be done in a clinical practice when classical statistical methods are inadequate. In the present study, the ML analysis of data predicted minor infectious complications with high accuracy, even with a small sample size.

The potential advantages of ML in health care are many and depend on the setting of the specific problem. In this case, the main ones are:

– Helps in identifying a potential postoperative complication and quantifies this risk with a probability estimation.
– Helps in better personalizing medicine in different patients.
– May support clinical trials development.

From the practical point of view, once the model has been developed and validated with the help of a Data Scientist as in this case, using it is actually very straight-forward: the clinician only needs to input patient data in the same format as required by the model (basically a new "row of the table") and he/she will receive an estimation of probability for post-operative complications.

Given that for a future single patient all the information used to fit the model are available, that information can be input in the previously fit model to receive an estimated probability for post-operative complications which can be used by clinicians as a support for decision involving the patient.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethical Approval

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

Informed Consent

The informed consents for treatment of personal and clinical data were acquired at the time of patients' admittance to the hospital and available in the clinical record archives.

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