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Review Article

Risk factors and timing for colectomy in chronically active refractory ulcerative colitis: A systematic review

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ABSTRACT

Background: In patients with chronic refractory ulcerative colitis (UC) the precise timing for indication to colectomy is unclear.
Aims: We performed a systematic review of the literature on the risk factors for colectomy in patients with chronic refractory UC in the biologic era.
Methods: PubMed Central/Medline and Embase were systemically searched for records published between January 2000 and December 2017. Current evidence was summarized and filtered by expert opinion.
Results: 70 studies were included in the qualitative synthesis. Several factors were found to be associated with a higher or reduced risk for colectomy, including variables at baseline – such as progression from proctitis/left-sided to extensive colitis, extensive colitis at diagnosis, high baseline C Reactive Protein or erythrocyte sedimentation rate, male gender, and younger age at diagnosis – previous medical history, and factors arising during therapy with biologics, including the absence of clinical response after induction with infliximab or adalimumab, and the lack of mucosal healing during therapy with anti-TNFs.
Conclusions: Two main points may help physicians to decide when the surgical option may be considered in patients with chronic refractory UC: (1) a first risk stratification can be obtained by analyzing factors at baseline and medical history, including the previous exposure to anti-TNFs; (2) during therapy with biologics, the early assessment (after 12–16 weeks of treatment) of clinical and endoscopic response is a strong predictor of the subsequent risk of colectomy.

1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) mostly affecting the young and middle-aged. The clinical presentation at onset is variable, and the subsequent course may be difficult to predict, ranging from a quiescent condition to a chronically active refractory disease leading to surgery or complications such as cancer [1]. Colectomy has been traditionally considered as a cure for the disease, because it eliminates the organ involved by the inflammatory process [2]. However, this concept has been repeatedly criticized, as several studies reported high rates of complications which may negatively affect the quality of life of patients with ileal pouch anal anastomosis, including fecal incontinence, pouchitis, cuffitis, irritable pouch syndrome, missed or de novo Crohn's disease, reduced fecundity in females, and erectile dysfunction in males [3]. In the last years, the introduction of potent biologics aiming at altering the course of moderate to severe phenotypes of UC led to investigate whether these drugs really have changed the rates of hospitalization, cancer occurrence, and – ultimately – surgery, which should be considered the main clinical outcome in UC. Unfortunately, data on these aspects are remarkably heterogeneous and difficult to summarize due to confounding factors and organizational differences between the health-care systems of different countries [4]. Some reports indicated that surgery rates at 1 and 5 years in the biologic era (2001–2008) are lower

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than those recorded in the past [5–7]. Nonetheless, surgery will still be required in approximately 20–40% of individuals with UC [8], and recent cohorts of incident patients [9] showed that the risk of surgery is not so lower today as compared with the pre-biological era. Waiting for more rigorous data from literature to better clarify this issue, gastroenterologists must everyday unravel the various therapeutic options available for UC. Absolute indications for surgery include uncontrolled hemorrhage, perforation, toxic megacolon, colorectal carcinoma or high-grade dysplasia, and medically-refractory acute severe ulcerative colitis [2,10]. Chronically active refractory UC can be defined as the persistence of disease activity despite optimal medication regimen, or corticosteroid dependent/resistant disease, in outpatients – a setting to be distinguished by medically-refractory acute severe ulcerative colitis – and represents another relevant context in which surgery should be considered. Anyway, the precise timing for indication to surgery is unclear, particularly today, as several medical therapeutic options exist and may delay surgery — sometimes inappropriately. As a consequence, the threshold for surgery in UC is variable in this clinical setting, and it mostly depends on the characteristics of each IBD center, including personal beliefs as well as the experience of the gastroenterological and surgical team.

In an attempt to provide actual evidence-based indications on the correct timing for colectomy in patients with chronic refractory UC – even in the rapidly evolving current scenario of therapeutics available for this disease – a panel of eight gastroenterologists met to perform a systematic review of the literature on the risk factors for colectomy, focusing on studies conducted during biologic era only, i.e. published after the introduction of biologics for the treatment of UC (year 2000). Current evidence was resumed and filtered by expert opinion in order to propose therapeutic flow charts that may support gastroenterologists dealing with IBD in the everyday clinical practice.

2. Materials and methods

A panel of 4 Italian experts in IBD management (A.O, A.A., P.G., and M.V.) and 4 young gastroenterologists (F.S.M, C.F., M.M, and F.C.) held a roundtable discussion in November 2017. Panelists were then prompted to express their opinion about the modality of bibliographic search and the specific setting to analyze. The discussion was summarized in an intermediate report. The focus of the bibliographic search and literature review was divided among F.S.M, C.F., M.M, and F.C., who subsequently produced a preliminary report of the evidence. The panel joined a second roundtable meeting in January 2018 to discuss these preliminary results. The heterogeneity of the studies was judged to be too high to conduct a reliable meta-analysis, so a narrative review was chosen as the proper modality of data presentation and drafting of the manuscript.

2.1. Information sources and search strategies

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed [11]. Primary sources of the reviewed studies, including English sources only, were PubMed Central/Medline and Embase, which were searched systemically for records published since January 2000 to December 2017, thus covering a period mostly subsequent to the introduction of biological therapy. The full strings used for bibliographic search in PubMed Central/Medline and Embase are reported in Supplementary files 1 and 2, respectively. Database searches were supplemented with literature searches of reference lists from potentially eligible articles by 4 panel members (F.S.M., C.F., M.M., and F.C.) to find additional studies.

2.2. Eligibility criteria

Papers selected for the analysis fulfilled the following criteria: (1) retrospective or prospective or ambidirectional studies including patients with steroid-dependant or steroid-refractory or chronically active UC (outpatient setting); (2) the outcome of interest was the rate of colectomy; (3) the risk factors for colectomy were clearly specified. Studies reported solely as abstracts, narrative reviews, editorials, case reports, meta-analysis, as well as those with a sample size inferior to 30 and those dealing only with acute severe UC patients (inpatients), were not included in the qualitative synthesis.

2.3. Searches

Among the 2948 records that were identified through electronic search strategies, 1154 duplicates were excluded. Afterward, the 4 young gastroenterologists independently evaluated the titles and abstracts, removed irrelevant studies, and selected 133 potentially relevant reports that were identified and retrieved for detailed full text evaluation. Among these, 70 studies [12–81] comprising 206,862 UC patients met the inclusion criteria and were included in the qualitative synthesis (Fig. 1).

2.4. Data collection process and synthesis

Four panel members (F.S.M., C.F., M.M., and F.C.) independently extracted the data of interest and the study-level variables, and entered them into a structured database. In particular, the outcomes of interest were the risk factors associated with colectomy in UC patients. For each risk factor, the corresponding measure of effect/association (odds ratio or hazard ratio according to the specific design of the study) was extracted. Furthermore, they were categorized into one of the following subgroups: (1) risk factors dealing with patients' characteristics at baseline (at diagnosis or before biological treatment initiation); (2) risk factors dealing with previous therapies; (3) risk factors arising during therapy with biologics; (4) other risk factors. Study-level variables included the name of the first author, publication year, study design (distinguishing between observational case-control or cohort studies, and randomized controlled trials), time direction of data collection (distinguishing between retrospective or prospective or ambidirectional studies), sample size, and number of patients who underwent colectomy.

Discrepancies among reviewers about qualitative and quantitative data collection were infrequent (overall interobserver variation <10%).

3. Results

3.1. Characteristics of the studies included in the qualitative synthesis

The main characteristics of the 70 studies included in the qualitative synthesis are shown in Supplementary Table 1. Sixty-five (92.8%) were observational cohort studies. About the time direction of data collection, most of them (82.8%) were retrospective, 3 (4.3%) were ambidirectional, and 9 (12.9%) were prospective. With the exception of two papers, all papers were published from 2006 onward. Median sample size per study was 248, with a wide range (30–58,681), while the median number of patients who underwent colectomy per study was 38 (4–4037). Finally, the median number of risk factors for colectomy extracted per study was 2 (range 1–7).

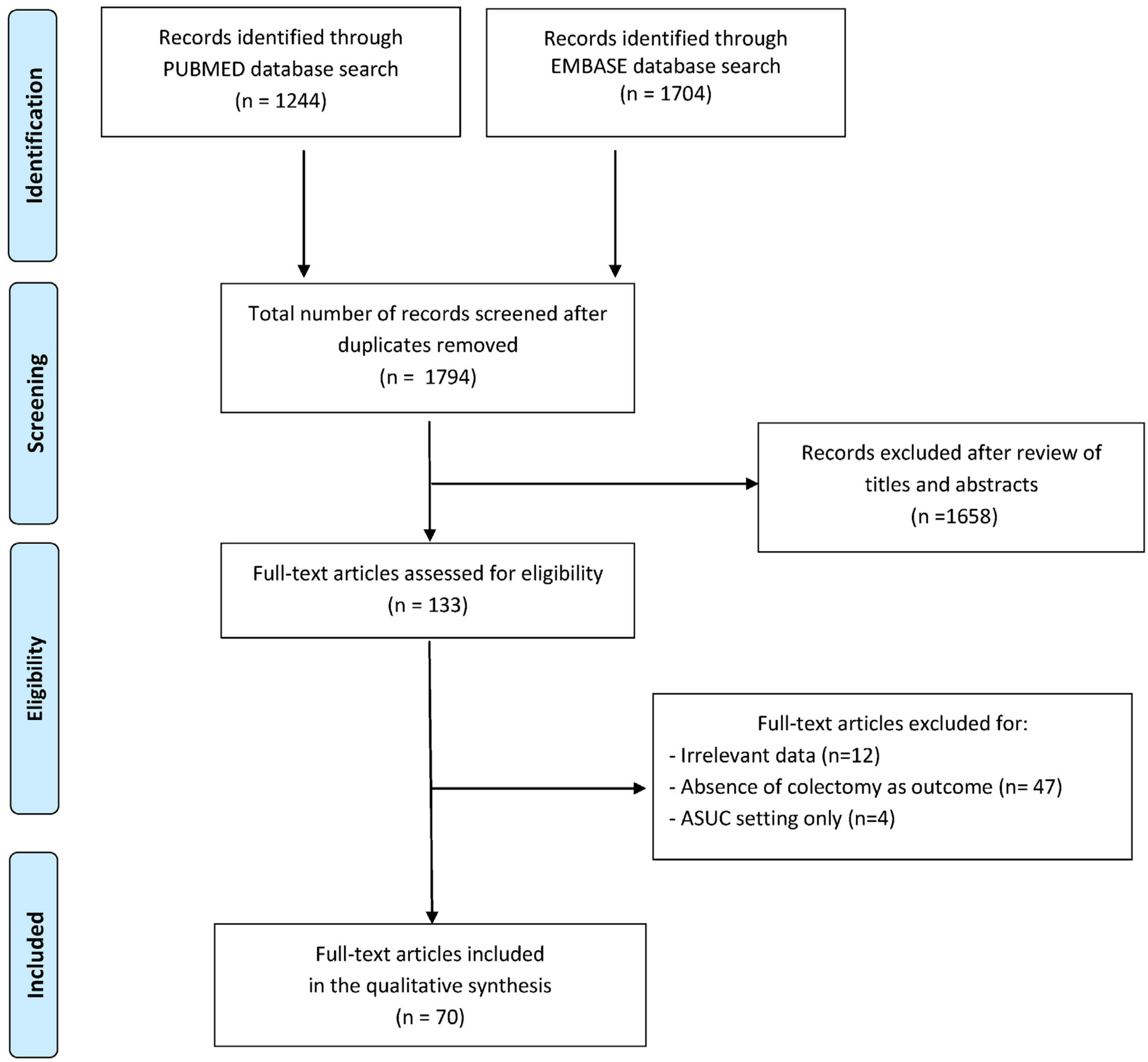

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the search process.

3.2. *Risk factors for colectomy: baseline characteristics and previous therapies (Table 1)*

Several factors at baseline were associated with the risk of colectomy among UC patients. In particular, progression from proctitis/left-sided to extensive colitis, extensive colitis, high baseline C Reactive Protein or erythrocyte sedimentation rate, male gender, younger age at diagnosis, and moderate or severe disease activity emerged more frequently as risk factors, while current smoking was the most frequently reported protective factor. About previous therapies, the need for systemic steroids or cyclosporine A was repeatedly associated with the risk of colectomy, as well as the previous exposure to anti-TNFs (OR/HR 2.5-5.4).

3.3. *Risk factors for colectomy arising during therapy with biologics (Table 2)*

The absence of a clinical response after induction with infliximab (IFX) was the most frequently reported risk factor for colectomy arising during therapy with biologics. Other risk factors included the lack of mucosal healing during IFX therapy, high C reactive protein values after induction, anti-TNF use, the need of intensification of IFX maintenance therapy, and the absence of clinical response to adalimumab after 12 weeks. Other factors were reported to be protective against the risk of colectomy, including the achievement of a short-term response after dose escalation with an anti-TNF, the use of combination therapy, the presence of an endoscopic response or mucosal healing after induction with an anti-TNF, a short-term clinical response to golimumab, the achievement of steroid sparing, and IFX serum level higher than 2.5 mg/mL at week 14 of therapy.

Other risk or protective factors for colectomy are shown in Table 3.

4. Discussion

This systematic review aimed at summarizing the current evidence on the risk factors for colectomy in patients with chronic refractory UC in order to provide proper indications on the correct timing for colectomy in this setting — a common clinical dilemma for all physicians dealing with IBD, since it is not addressed by specific data from the literature. This crucial decision is even more difficult today if we consider how biologics have changed the current management and prognosis of UC [5–7]. This is the reason

Table 1
Risk factors for colectomy: baseline characteristics and previous therapies.

Risk factor [references]	OR	HR	Pts. who underwent colectomy	No. of studies
Baseline characteristics				
Progression from proctitis/left-sided to extensive colitis [40,44,64]	NR	3.9–21.9	75	3
Extensive colitis [21,22,28,32,38,44,46,48,51,53,58,59,61,63,64,70,73]	2.6–15.2	1.5–7.7	1108	17
High baseline C Reactive Protein/erythrocyte sedimentation rate [19,34,42,50,62,73,75]	3.0–4.8	5–1–14.5	148	7
Extra-intestinal manifestations [38,66]	7.9	1.5	155	2
Chronically active disease [53,61]	NR	7.1	95	2
Male gender [31,35,59,61,69,72]	1.5–2.0	1.4–4.9	1449	6
Disease activity at histology [18]		3.3	25	1
Endoscopic Mayo score 3 [49,65]		2.8–3.1	29	2
Low albumin [34,75]	3.0	7.5	57	2
Younger age at diagnosis [43,59,69,73,74]		1.4–2.8	343	5
Glycan ratio m/z 2378/1914 (>median) [49]		2.7	NR	1
Living in a non-university county [26]	2.7		28	1
Diagnostic delay of more than 6 months [64]		2.5	NR	1
Moderate or severe clinical activity [26,54,61]	2.3	2.1–NR	71	3
Congestive heart failure [31]		2.1	649	1
Anemia at diagnosis [31]		1.7	649	1
Being diagnosed in biologics era [31,69]	0.8	1.5	649	2
Charlson index of 2 [69]	1.5		NR	1
Hospitalization in the year preceding the index episode [31]		1.2	649	1
Longer duration of disease (per year) [74]	1.04		94	1
Current smoking [15,38,58,70]	0.3–NR	0.6–NR	203	4
Previous appendectomy [15,29]	NR	0.4	109	2
Asian race [47]	0.3		NR	1
Disease duration >2 years before start of IFX [78]	0.3		21	1
NOD2 mutations [17]	NR		12	1
–				
Previous therapies				
Previous need for Cyclosporine A [37,41,50,66,71]		2.5–9.7	64	5
No or partial response to the first course of systemic steroids [12]		8.4	7	1
Previous need for systemic steroids [13,18,42,45,48,53,59,64,72,73]	2.9–5.0	1.2–6–9	565	10
Previous exposure to anti-TNFs/IFX [20,56,59]	2.5–5.4		150	3
Previous use of MTX [32]	5.3		NR	1
Need for an IM within 33 months from diagnosis [66]		4.9	NR	1
History of steroid dependency/resistance [44]	4.7		183	1
Previous need for thiopurines [59,72]	2.6	3.0	123	2
Thiopurine naive status [65]		0.3	29	1

In case of multiple studies reporting the same risk factors, OR/HR value is expressed as minimum and maximum value, and the number of patients who underwent colectomy as the sum derived by the single studies. Confidence intervals are not provided because several risk factors were found in multiple studies, so often it was not possible to report single confidence intervals. *Abbreviations*: IM: immunosuppressant; IFX: Infliximab; MTX: methotrexate; NR: not reported.

Table 2
Risk factors for colectomy arising during therapy with biologics.

Risk factor [references]	OR	HR	Pts. who underwent colectomy	No. of studies
Lack of mucosal healing during IFX therapy [79]	18.0		14	1
No clinical response after induction with IFX [24,28,33,34,39,42,50,68,71]	7.4–10.3	7.0–10.8	274	10
High C reactive protein after induction [65]		5.7	NR	1
Anti-TNF use [48]		3.4	120	1
Need of intensification of IFX maintenance therapy [16,76]		3.3–3.4	33	2
Higher hemoglobin levels after 3 months of anti-TNF therapy [35]	0.9		22	1
Short-term response after dose escalation with anti-TNF [55,77]	NR	0.5	22	2
Combination therapy [16,60,76]	0.3–NR	0.3	154	3
Endoscopic response or mucosal healing after induction with anti-TNF [14,34]		0.25–NR	95	2
Short term clinical response to GOL [60]		0.21	15	1
Steroid sparing [67]		0.1	12	1
IFX serum level higher than 2.5 mg/mL at week 14 (protective) [34]	NR		NR	1
No clinical response to ADA at week 12 [25,41,55]	NR		22	3

In case of multiple studies reporting the same risk factors, OR/HR value is expressed as minimum and maximum value, and the number of patients who underwent colectomy as the sum derived by the single studies. Confidence intervals are not provided because several risk factors were found in multiple studies, so often it was not possible to report single confidence intervals. *Abbreviations*: ADA: Adalimumab; GOL: Golimumab; IFX: Infliximab; NR: not reported.

Table 3
Other risk factors for colectomy.

Risk factor [references]	OR	HR	Pts. who underwent colectomy	No. of studies
Leukocytapheresis prior to IFX [16]	3.0		NR	1
IFX indication due to severe steroid-resistant flare-up [16]		2.5	27	1
Clostridium difficile infection [23]	2.4		34	1
Use of 5-ASA [18,72]		0.3–0.4	25	2

In case of multiple studies reporting the same risk factors, OR/HR value is expressed as minimum and maximum value, and the number of patients who underwent colectomy as the sum derived by the single studies. Confidence intervals are not provided because several risk factors were found in multiple studies, so often it was not possible to report single confidence intervals. *Abbreviations*: 5-ASA: 5-aminosalycilates; IFX: Infliximab; NR: not reported.

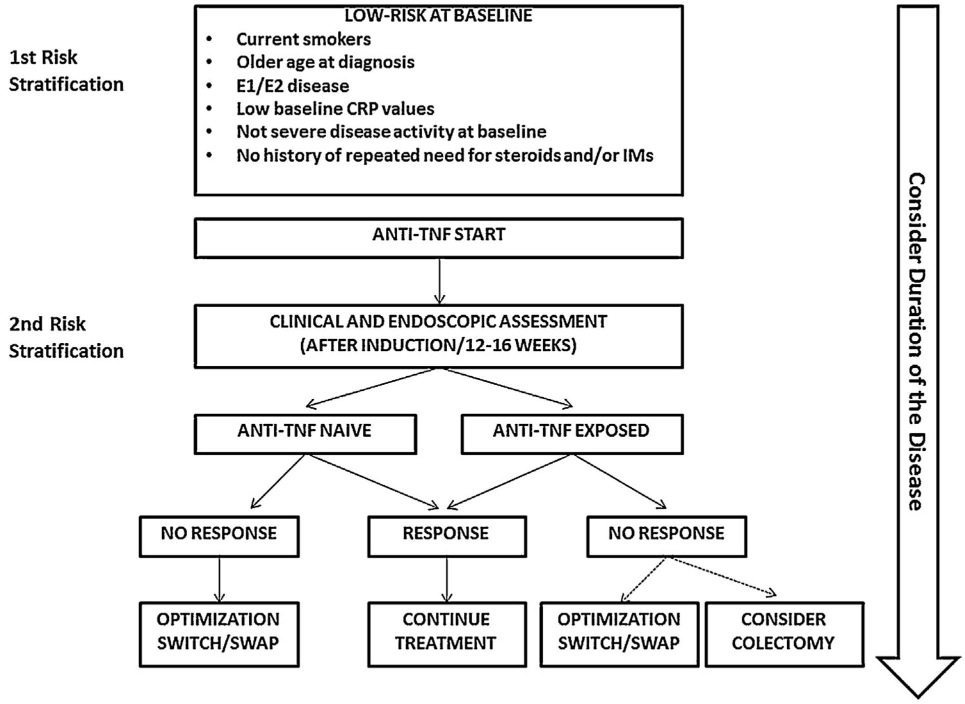

Fig. 2. Therapeutic flow chart 1: baseline low-risk patients.

underlying the choice of focusing our search on studies performed only in the biologic era.

Regarding baseline characteristics, smoking habit, male gender, C reactive protein values, severity of symptoms at diagnosis, endoscopic severity, extent of the disease, and the presence of extraintestinal manifestations were frequently associated with a higher or lower risk of colectomy among UC patients. Similarly, need for previous systemic steroids or IMs – including cyclosporine – was repeatedly associated with a higher risk of colectomy: as a consequence, a “rich” drug history should be considered as a marker for a more severe disease requiring systemic immunomodulation during its course or rescue therapy with cyclosporine. In this line, a previous exposure to anti-TNFs was also associated with a higher risk of colectomy, this being not surprising, as all clinical outcomes were reported to be worse in patients with previous failure(s) to anti-TNFs [82]. Furthermore, one of the most interesting points of this systematic analysis lies in the identification of several factors arising during biological therapy which affected the risk of colectomy. In particular, it is relevant to underline how clinical and endoscopic outcomes – particularly mucosal healing – appeared to be able to predict the risk of colectomy even when assessed early after the initiation of biological therapy, for example after induction or after 12 weeks. This capability to predict the risk of colectomy suggests that the early evaluation of these outcomes may guide the therapeutic decision process in a patient on biological therapy, so that useless or harmful overtreatments with biologics could be avoided in favor of surgery in some UC patients.

On the basis of all the above data, we depicted two distinct ideal clinical scenarios based on a first stratification of the colectomy risk based on factors at baseline and previous medical history. Of note, even if our search included the term “vedolizumab”, no study reported data on the use of this biologic and colectomy rates, so the current evidence is based almost exclusively on anti-TNFs, and consequently they were considered the first-line therapy in this setting. In the first flow chart (baseline low-risk patients — Fig. 2), we suggest distinguishing between patients naïve or exposed to anti-TNFs, being the threshold for colectomy higher among naïve patients. In the second flow chart (baseline high-risk patients — Fig. 3), colectomy may be discussed with the patient in case of clinical and/or endoscopic non-response to an anti-TNF even after the first failure, and, in general, multiple lines of biological treatments should be avoided. In any case, clinical and endoscopic response to biologics should be always assessed early, after induction or within 12–16 weeks from the initiation of the treatment, because the risk of colectomy was associated with primary non-responses, while secondary loss of response was not consistently found to be predictive for surgery. Furthermore, another relevant point to take always into account when assessing the timing of colectomy should be the duration of the disease, because it affects the risk of colorectal cancer [83]; even if this review was not able to consider systematically this important variable, we strongly underline as expert opinion that the longer is the duration of the disease, the earlier the colectomy should be considered in case of chronically active refractory UC.

This systematic review has strengths and limitations. The rigorous methodology allowed to retrieve a satisfyingly high number of studies, and only “independent” risk factors were considered in data collection, i.e. those identified as significantly associated with colectomy in multivariate analysis, unless only univariable analysis was available. The main limitations are inherent to the overall quality and design of the studies included in this review, as most of them are retrospective, observational only, with variable sample sizes, and the total number of patients who underwent colectomy – which could be considered a kind of proxy of the study quality – was not always reported. Time of follow-up was highly variable among studies, and in some cohorts it was not possible to distinguish between inpatients and outpatients, as the results were presented altogether. Anyway, this latter issue occurred in a minority of studies. Given all these limitations, we should emphasize that our treatment flow charts are purposely generic, as the available evidence is not qualitatively or quantitatively sufficient to provide precise temporal indications.

In conclusion, this systematic review highlighted two main points that may help physicians to decide when it is appropriate

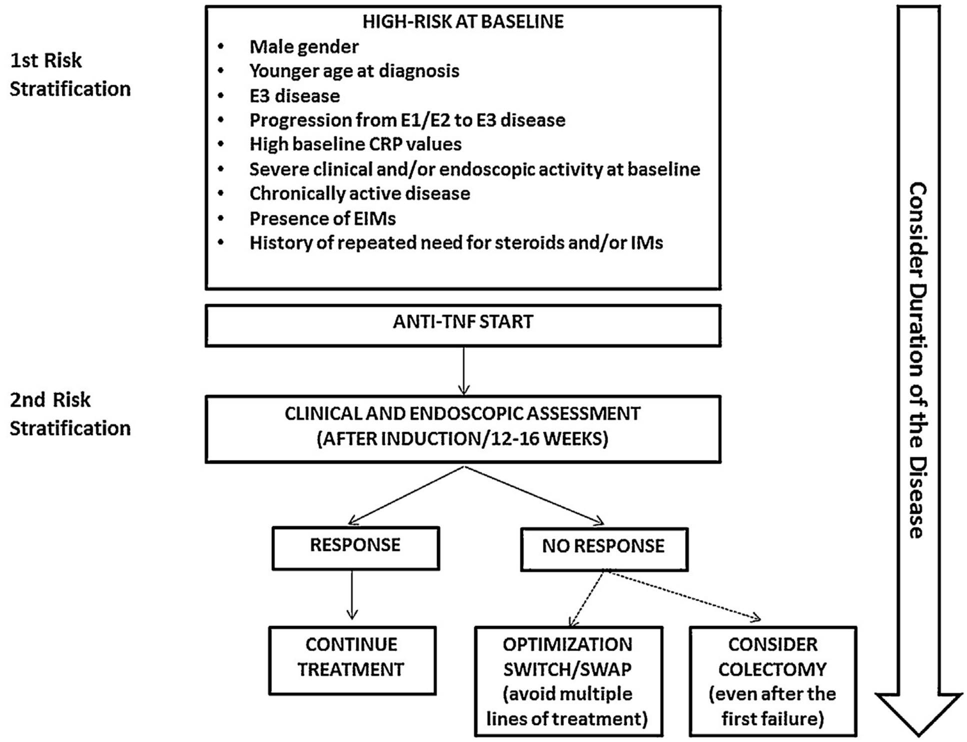

Fig. 3. Therapeutic flow chart 2: baseline high-risk patients.

to discuss and propose the surgical option in patients with chronic refractory UC: (1) the analysis of baseline characteristics and medical history, including previous exposure to anti-TNFs, may be useful as a first risk stratification to classify UC patients as low- or high-risk for colectomy; (2) during therapy with biologics, the early assessment of clinical and endoscopic response should be used to better predict the subsequent risk of colectomy. These findings should be intertwined with the always valid assumption that the final decision must be taken on a case by case basis.

Conflict of interest

Fabio Salvatore Macaluso served as advisory board member for MSD and Abbvie, and received lecture grants from MSD, Takeda Pharmaceuticals and Zambon. Carla Felice served as advisory board and received honoraria for consultancy from MSD and AbbVie. Marta Mazza served as advisory board member for MSD, and received lecture grants from Takeda Pharmaceuticals. Alessandro Armuzzi served as consultant or advisory member for AbbVie, Allergan, Amgen, Biogen, Celgene, Celltrion, Ferring, Hospira, Janssen, Lilly, MSD, Mundipharma, Pfizer, Samsung Bioepis, Sofar and Takeda, has received lecture fees from AbbVie, AstraZeneca, Chiesi, Ferring, Hospira, Janssen, Medtronic, MSD, Mitsubishi Tanabe, Mundipharma, Nikkiso, Otsuka, Pfizer, Samsung Bioepis, Takeda, Tigenix, and Zambon, and has received research funding from MSD and Takeda. Paolo Gionchetti received honoraria or consultation fees from Janssen, Abbvie, Pfizer, Celgene, Takeda, Ferring, MSD, Alfa Wasserman, and Amgen, and participated in a company sponsored speaker's bureau for Abbvie, Janssen, Takeda, Ferring, Msd, Sofar, and Chiesi. Maurizio Vecchi participated into advisory board, received lecture fees or support for research from: MSD, Hospira, Mundipaharma, Takeda, Abbvie, Chiesi, Zambon, Amgen, Biogen, Jannsen, Pfizer, Sofar, Giuliani. Ambrogio Orlando served as advisory board member for AbbVie, MSD, Takeda Pharmaceuticals, Janssen, Pfizer, and received lecture grants from AbbVie, MSD, Sofar, Chiesi, and Takeda Pharmaceuticals.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.dld.2019.01.018.

References

[1] Ungaro R, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel JF. Ulcerative colitis. Lancet 2017;389:1756–70.
[2] Øresland T, Bemelman WA, Sampietro GM, Spinelli A, Windsor A, Ferrante M, et al. European evidence based consensus on surgery for ulcerative colitis. J Crohns Colitis 2015;9:4–25.
[3] Dayan B, Turner D. Role of surgery in severe ulcerative colitis in the era of medical rescue therapy. World J Gastroenterol 2012;18:3833–8.
[4] Annese V, Duricova D, Gower-Rousseau C, Jess T, Langholz E. Impact of new treatments on hospitalisation, surgery, infection, and mortality in IBD: a focus paper by the epidemiology committee of ECCO. Crohns Colitis 2016;10:216–25.
[5] Jakobsen C, Paerregaard A, Munkholm P, Wewer V. Pediatric inflammatory bowel disease: increasing incidence, decreasing surgery rate, and compromised nutritional status: a prospective population based cohort study 2007-2009. Inflamm Bowel Dis 2011;17:2541–50.
[6] Vind I, Riis L, Jess T, et al. Increasing incidences of inflammatory bowel disease and decreasing surgery rates in Copenhagen City and County, 2003–2005: a population-based study from the Danish Crohn colitis database. Am J Gastroenterol 2006;101:1274–82.
[7] Vester-Andersen MK, Prosberg MV, Jess T, Andersson M, Bengtsson BG, Blixt T, et al. Disease course and surgery rates in inflammatory bowel disease: a population-based, 7-year follow-up study in the era of immunomodulating therapy. Am J Gastroenterol 2014;109:705–14.
[8] Singh S, Al-Darmaki A, Frolkis AD, Seow CH, Leung Y, Novak KL, et al. Postoperative mortality among patients with inflammatory bowel diseases: a systematic review and meta-analysis of population-based studies. Gastroenterology 2015;149:928–37.
[9] Burisch J, Pedersen N, Čuković-Čavka S, Brinar M, Kaimakliotis I, Duricova D, et al. Eastwest gradient in the incidence of inflammatory bowel disease in Europe: the ECCO-EpiCom inception cohort. Gut 2014;63:588–97.

[10] Laine L, Kaltenbach T, Barkun A, McQuaid K, Subramanian V, Soetikno R. SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease. Gastroenterology 2015;148:639–51, e28.
[11] Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015;349:7647.
[12] Ardizzone S, Cassinotti A, Duca P, et al. Mucosal healing predicts late outcomes after the first course of corticosteroids for newly diagnosed ulcerative colitis. Clin Gastroenterol Hepatol 2011;9:483––489.
[13] Charpentier C, Salleron J, Savoye G, et al. Natural history of elderly-onset inflammatory bowel disease: a population-based cohort study. Gut 2014;63:423–32.
[14] Colombel JF, Rutgeerts P, Reinisch W, et al. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. Gastroenterology 2011;141:1194–201.
[15] Cosnes J, Carbonnel F, Beaugerie L, et al. Effects of appendicectomy on the course of ulcerative colitis. Gut 2002;51:803–7.
[16] Fernández-Salazar L, Muñoz F, Barrio J, et al. Infliximab in ulcerative colitis: real-life analysis of factors predicting treatment discontinuation due to lack of response or colectomy: ECIA (ACAD Colitis and Infliximab Study). Scand J Gastroenterol 2016;51:186–95.
[17] Freire P, Cardoso R, Figueiredo P, et al. NOD2 gene mutations in ulcerative colitis: useless or misunderstood? Int J Colorectal Dis 2014;29:653–61.
[18] Hefti MM, Chessin DB, Harpaz NH, et al. Severity of inflammation as a predictor of colectomy in patients with chronic ulcerative colitis. Dis Colon Rectum 2009;52:193–7.
[19] Henriksen M, Jahnsen J, Lygren I, et al. C-reactive protein: a predictive factor and marker of inflammation in inflammatory bowel disease. Results from a prospective population-based study. Gut 2008;57:1518–23.
[20] Herzog D, Fournier N, Buehr P, et al. Prevalence of intestinal complications in inflammatory bowel disease: a comparison between paediatric-onset and adult-onset patients. Eur J Gastroenterol Hepatol 2017;29:926–31.
[21] Ho GT, Chiam P, Drummond H, et al. The efficacy of corticosteroid therapy in inflammatory bowel disease: analysis of a 5-year UK inception cohort. Aliment Pharmacol Ther 2006;24:319–30.
[22] Hoie O, Wolters FL, Riis L, et al. Low colectomy rates in ulcerative colitis in an unselected European cohort followed for 10 years. Gastroenterology 2007;132:507–15.
[23] Jodorkovsky D, Young Y, Abreu MT. Clinical outcomes of patients with ulcerative colitis and co-existing *Clostridium difficile* infection. Dig Dis Sci 2010;55:415–20.
[24] Park SH, Yang SK, Hong SM, et al. Severe disease activity and cytomegalovirus colitis are predictive of a nonresponse to infliximab in patients with ulcerative colitis. Dig Dis Sci 2013;58:3592–9.
[25] Christensen KR, Steenholdt C, Brynskov J. Clinical outcome of adalimumab therapy in patients with ulcerative colitis previously treated with infliximab: a Danish single-center cohort study. Scand J Gastroenterol 2015;50:1018–24.
[26] Rönnblom A, Holmström T, Tanghöj H, et al. Low colectomy rate five years after diagnosis of ulcerative colitis. Results from a prospective population-based cohort in Sweden (ICURE) diagnosed during 2005-2009. Scand J Gastroenterol 2016;51:1339–44.
[27] Italian Group for the Study of Inflammatory Bowel Disease, Armuzzi A, Biancone L, Daperno M, et al. Adalimumab in active ulcerative colitis: a "real-life" observational study. Dig Liver Dis 2013;45:738–43.
[28] Angelison L, Almer S, Eriksson A, et al. Long-term outcome of infliximab treatment in chronic active ulcerative colitis: a Swedish multicentre study of 250 patients. Aliment Pharmacol Ther 2017;45:519–32.
[29] Radford-Smith GL, Edwards JE, Purdie DM, et al. Protective role of appendicectomy on onset and severity of ulcerative colitis and Crohn's disease. Gut 2002;51:808–13.
[30] Taxonera C, Estellés J, Fernández-Blanco I, et al. Adalimumab induction and maintenance therapy for patients with ulcerative colitis previously treated with infliximab. Aliment Pharmacol Ther 2011;33:340–8.
[31] Abou Khalil M, Boutros M, Nedjar H, et al. Incidence rates and predictors of colectomy for ulcerative colitis in the era of biologics: results from a provincial database. J Gastrointest Surg 2018;22:124–32.
[32] Manser CN, Borovicka J, Seibold F, et al. Risk factors for complications in patients with ulcerative colitis. United Eur Gastroenterol J 2016;4:281–7.
[33] Buhl S, Steenholdt C, Rasmussen M, et al. Outcomes After Primary Infliximab Treatment Failure in Inflammatory Bowel Disease. Inflamm Bowel Dis 2017;23:1210–7.
[34] Arias MT, Vande Casteele N, Vermeire S, et al. A panel to predict long-term outcome of infliximab therapy for patients with ulcerative colitis. Clin Gastroenterol Hepatol 2015;13:531–8.
[35] Subramaniam K, Richardson A, Dodd J, et al. Early predictors of colectomy and long-term maintenance of remission in ulcerative colitis patients treated using anti-tumour necrosis factor therapy. Intern Med J 2014;44:464–70.
[36] Colombel JF, Rutgeerts P, Reinisch W, et al. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. Gastroenterology 2011;141:1194–201.
[37] Williet N, Pillot C, Oussalah A, et al. Incidence of and impact of medications on colectomy in newly diagnosed ulcerative colitis in the era of biologics. Inflamm Bowel Dis 2012;18:1641–6.
[38] Safroneeva E, Vavricka SR, Fournier N, et al. Prevalence and risk factors for therapy escalation in ulcerative Colitis in the Swiss IBD Cohort Study. Inflamm Bowel Dis 2015;21:1348–58.
[39] Taxonera C, Barreiro-de Acosta M, Calvo M, et al. Infliximab dose escalation as an effective strategy for managing secondary loss of response in ulcerative colitis. Dig Dis Sci 2015;60:3075–84.
[40] Etchevers MJ, Aceituno M, García-Bosch O, et al. Risk factors and characteristics of extent progression in ulcerative colitis. Inflamm Bowel Dis 2009;15:1320–5.
[41] García-Bosch O, Gisbert JP, Cañas-Ventura A, et al. Observational study on the efficacy of adalimumab for the treatment of ulcerative colitis and predictors of outcome. J Crohns Colitis 2013;7:717–22.
[42] Ferrante M, Vermeire S, Fidder H, et al. Long-term outcome after infliximab for refractory ulcerative colitis. J Crohns Colitis 2008;2:219–25.
[43] Jakobovits SL, Jewell DP, Travis SP. Infliximab for the treatment of ulcerative colitis: outcomes in Oxfordfrom 2000 to 2006. Aliment Pharmacol Ther 2007;25:1055–60.
[44] Kalkan İH, Dağlı Ü, Kekilli M, et al. Clinical course and predictors of total colectomy in ulcerative colitis; a referral center experience from Turkey. Turk J Gastroenterol 2015;26:25–30.
[45] Khan NH, Almukhtar RM, Cole EB, et al. Early corticosteroids requirement after the diagnosis of ulcerative colitis diagnosis can predict a more severe long-term course of the disease — a nationwide study of 1035 patients. Aliment Pharmacol Ther 2014;40:374–81.
[46] Lakatos PL, Vegh Z, Lovasz BD, et al. Is current smoking still an important environmental factor in inflammatory bowel diseases? Results from a population-based incident cohort. Inflamm Bowel Dis 2013;19:1010–7.
[47] Li D, Collins B, Velayos FS, et al. Racial and ethnic differences in health care utilization and outcomes among ulcerative colitis patients in an integrated health-care organization. Dig Dis Sci 2014;59:287–94.
[48] Manetti N, Bagnoli S, Rogai F, et al. Disease course and colectomy rate of ulcerative colitis: a follow-up cohort study of a referral center in Tuscany. Inflamm Bowel Dis 2016;22:1945–53.
[49] Miyahara K, Nouso K, Saito S, et al. Serum glycan markers for evaluation of disease activity and prediction of clinical course in patients with ulcerative colitis. PLoS One 2013;8:e74861.
[50] Oussalah A, Evesque L, Laharie D, et al. A multicenter experience with infliximab for ulcerative colitis: outcomes and predictors of response, optimization, colectomy, and hospitalization. Am J Gastroenterol 2010;105:2617–25.
[51] Romberg-Camps MJ, Dagnelie PC, Kester AD, et al. Influence of phenotype at diagnosis and of other potential prognostic factors on the course of inflammatory bowel disease. Am J Gastroenterol 2009;104:371–83.
[52] Rungoe C, Langholz E, Andersson M, et al. Changes in medical treatment and surgery rates in inflammatory bowel disease: a nationwide cohort study 1979-2011. Gut 2014;63:1607–16.
[53] Sahami S, Konté K, Buskens CJ, et al. Risk factors for proximal disease extension and colectomy in left-sided ulcerative colitis. United Eur Gastroenterol J 2017;5:554–62.
[54] Shiga H, Takagi S, Inoue R, et al. What determines the later clinical course of patients who do not undergo colectomy at the first attack? A Japanese cohort study on ulcerative colitis. Digestion 2010;81:104–12.
[55] Taxonera C, Iglesias E, Muñoz F, et al. Adalimumab maintenance treatment in ulcerative colitis: outcomes by prior anti-TNF use and efficacy of dose escalation. Dig Dis Sci 2017;62:481–90.
[56] Iborra M, Pérez-Gisbert J, Bosca-Watts MM, et al. Effectiveness of adalimumab for the treatment of ulcerative colitis in clinical practice: comparison between anti-tumour necrosis factor-naéve and non-naéve patients. J Gastroenterol 2017;52:788–99.
[57] Ananthakrishnan AN, Issa M, Beaulieu DB, et al. History of medical hospitalization predicts future need for colectomy in patients with ulcerative colitis. Inflamm Bowel Dis 2009;15:176–81.
[58] van der Heide F, Dijkstra A, Weersma RK, et al. Effects of active and passive smoking on disease course of Crohn's disease and ulcerative colitis. Inflamm Bowel Dis 2009;15:1199–207.
[59] Al-Darmaki A, Hubbard J, Seow CH, et al. Clinical predictors of the risk of early colectomy in ulcerative colitis: a population-based study. Inflamm Bowel Dis 2017;23:1272–7.
[60] Taxonera C, Rodríguez C, Bertoletti F, et al. Clinical outcomes of golimumab as first, second or third anti-TNF agent in patients with moderate-to-severe ulcerative colitis. Inflamm Bowel Dis 2017;23:1394–402.
[61] Portela F, Magro F, Lago P, et al. Ulcerative colitis in a Southern European country: a national perspective. Inflamm Bowel Dis 2010;16:822–9.
[62] Niewiadomski O, Studd C, Hair C, et al. Prospective population-based cohort of inflammatory bowel disease in the biologics era: disease course and predictors of severity. J Gastroenterol Hepatol 2015;30:1346–53.
[63] Kevans D, Waterman M, Milgrom R, et al. Serological markers associated with disease behavior and response to anti-tumor necrosis factor therapy in ulcerative colitis. J Gastroenterol Hepatol 2015;30:64–70.
[64] Burisch J, Ungaro R, Vind I, et al. Proximal disease extension in patients with limited ulcerative colitis: a Danish population-based inception cohort. J Crohns Colitis 2017;11:1200–4.
[65] Armuzzi A, Pugliese D, Danese S, et al. Long-term combination therapy with infliximab plus azathioprine predicts sustained steroid-free clinical benefit in steroid-dependent ulcerative colitis. Inflamm Bowel Dis 2014;20:1368–74.
[66] Cañas-Ventura A, Márquez L, Ricart E, et al. Risk of colectomy in patients with ulcerative colitis under thiopurine treatment. J Crohns Colitis 2014;8:1287–93.
[67] Armuzzi A, Pugliese D, Danese S, et al. Infliximab in steroid-dependent ulcerative colitis: effectiveness and predictors of clinical and endoscopic remission. Inflamm Bowel Dis 2013;19:1065–72.

[68] Oussalah A, Evesque L, Laharie D, et al. A multicenter experience with infliximab for ulcerative colitis: outcomes and predictors of response, optimization, colectomy, and hospitalization. Am J Gastroenterol 2010;105:2617–25.
[69] Kin C, Kate Bundorf M. As infliximab use for ulcerative colitis has increased, so has the rate of surgical resection. J Gastrointest Surg 2017;21:1159–65.
[70] Szamosi T, Banai J, Lakatos L, et al. Early azathioprine/biological therapy is associated with decreased risk for first surgery and delays time to surgery but not reoperation in both smokers and nonsmokers with Crohn's disease, while smoking decreases the risk of colectomy in ulcerative colitis. Eur J Gastroenterol Hepatol 2010;22:872–9.
[71] García-Bosch O, Aceituno M, Ordás I, et al. Long-term follow-up of patients treated with infliximab for ulcerative colitis: predictive factors of response — an observational study. Dig Dis Sci 2016;61:2051–9.
[72] Chhaya V, Saxena S, Cecil E, et al. The impact of timing and duration of thiopurine treatment on colectomy in ulcerative colitis: a national population-based study of incident cases between 1989 and 2009. Aliment Pharmacol Ther 2015;41:87–98.
[73] Solberg IC, Høivik ML, Cvancarova M, et al. Risk matrix model for prediction of colectomy in a population-based study of ulcerative colitis patients (the IBSEN study). Scand J Gastroenterol 2015;50:1456–62.
[74] Murthy SK, Greenberg GR, Croitoru K, et al. Extent of early clinical response to infliximab predicts long-term treatment success in active ulcerative colitis. Inflamm Bowel Dis 2015;21:2090–6.
[75] Papamichael K, Rivals-Lerebours O, Billiet T, et al. Long-term outcome of patients with ulcerative colitis and primary non-response to infliximab. J Crohns Colitis 2016;10:1015–23.
[76] Fernández-Salazar L, Barrio J, Muñoz F, et al. Frequency, predictors, and consequences of maintenance infliximab therapy intensification in ulcerative colitis. Rev Esp Enferm Dig 2015;107:527–33.
[77] Cesarini M, Katsanos K, Papamichael K, et al. Dose optimization is effective in ulcerative colitis patients losing response to infliximab: a collaborative multicentre retrospective study. Dig Liver Dis 2014;46:135–9.
[78] Rostholder E, Ahmed A, Cheifetz AS, et al. Outcomes after escalation of infliximab therapy in ambulatory patients with moderately active ulcerative colitis. Aliment Pharmacol Ther 2012;35:562–7.
[79] Laharie D, Filippi J, Roblin X, et al. Impact of mucosal healing on long-term outcomes in ulcerative colitis treated with infliximab: a multicenter experience. Aliment Pharmacol Ther 2013;37:998–1004.
[80] Myrelid P, Landerholm K, Nordenvall C, et al. Appendectomy and the risk of colectomy in ulcerative colitis: a national cohort study. Am J Gastroenterol 2017;112:1311–9.
[81] Parian A, Limketkai B, Koh J, et al. Appendectomy does not decrease the risk of future colectomy in UC: results from a large cohort and meta-analysis. Gut 2017;66:1390–7.
[82] Gisbert JP, Marin AC, McNicholl AG, Chaparro M. Systematic review with meta-analysis: the efficacy of a second anti-TNF in patients with inflammatory bowel disease whose previous anti-TNF treatment has failed. Aliment Pharmacol Ther 2015;41:613–23.
[83] Maida M, Macaluso FS, Ianiro G, et al. Screening of colorectal cancer: present and future. Expert Rev Anticancer Ther 2017;17:1131–46.