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Ulcerative colitis: Impact of early disease clearance on long-term outcomes - A multicenter cohort study

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Abstract

Background: Clinical remission and endoscopic mucosal healing are the main treatment targets in patients with ulcerative colitis (UC). Recently, the concept of disease clearance has been proposed as a potential target in UC.

Objective: We aimed to evaluate the impact of disease clearance on long-term outcomes in UC patients.

Methods: A multicenter retrospective cohort study was conducted at the Humanitas Research Hospital-IRCCS (Italy) and at the Nancy University Hospital (France) between 2014 and 2021. Disease clearance in UC was defined as simultaneous clinical (partial-Mayo score ≤2), endoscopic (endoscopic-Mayo score = 0), and histological (Nancy index = 0) remission, and patients were monitored over a long-time follow-up (≥12 months), to compare the occurrence of negative outcomes.

Results: A total of 494 patients with UC was included in the study (269, 54.4% males). Disease clearance was present in 109 patients (22.1%) at baseline. Median follow up was 24 months. Patients with disease clearance were associated to a significantly lower risk of UC-related hospitalization compared with the control group (5.5% vs. 23.1%; $p < 0.001$) at last observation. Similarly, a lower rate of surgeries was detected in patients with disease clearance at baseline compared with those without (1.8% vs. 10.9%; $p = 0.003$). The Kaplan Meier curves confirmed that patients with disease clearance at baseline had a lower risk of hospitalization (log-rank $p < 0.0001$) and surgery (log-rank $p < 0.00095$).

Conclusion: In UC patients with early disease clearance are at significant lower risk for hospitalization and surgery. Disease clearance should be considered as a new composite outcome.

KEYWORDS
deep remission, disease clearance, inflammatory bowel disease, ulcerative colitis

INTRODUCTION

Over the last years, specific treatment targets have been established in order to guide therapeutic decisions in patients with ulcerative colitis (UC).[1] These include a combination of symptom control and endoscopic mucosal healing, while histological remission is an additional goal and its use is limited to the definition of deep healing.[1]

Up to current, clinical targets correspond to stool frequency and rectal blood loss normalization.[2] However, discrepancies between clinical outcomes and mucosal inflammation were observed, and patients could either report symptoms while having mucosal and histological healing or become clinically asymptomatic while showing endoscopic activity.[3] Therefore, symptomatic resolution requires to be associated with objective evidence of absence of inflammation. Mucosal healing has been proposed as the optimal long-term treatment target,[4] since absence of lesions at endoscopy is associated with better long-term outcomes compared to clinical remission alone and it represents a predictor of improved disease course.[5]

Macroscopic inactivity of disease might not coincide with histological healing, and persistence of microscopic activity may lead to an increased risk of disease progression, relapses, and complications.[6,7] In parallel, studies assessing the impact of histological normalization as independent factor for relapse-free survival demonstrated that patients with microscopic healing had reduced risk of clinical negative outcomes.[8] These data indicate that targeting disease remission, solely based on clinical and endoscopic outcomes, might be insufficient to avoid disease recurrence and progression, and should therefore be integrated with histological parameters.

Based on these data, the new ambitious concept of "disease clearance" has been proposed, as the ultimate target.[9] This term defines a state of concurrent clinical, endoscopic, and histological healing.[9] The role of disease clearance as an achievable outcome in the daily clinical practice in patients with UC remain unclear. Hence, the aim of our study was to evaluate the impact of disease clearance on long-term negative outcomes in a real-life cohort.

Key summary

- Disease clearance is defined as the simultaneous clinical, endoscopic, and histological remission in patients with ulcerative colitis (UC).
- Patients with disease clearance experience a significantly lower risk of hospitalization and surgery compared with subjects without disease clearance.
- Disease clearance could represent a new treatment target in UC allowing for a greater disease control and a reduced risk of complications.

METHODS

Study population

We performed a retrospective, multicenter cohort study to evaluate the impact of disease clearance on long-term negative outcomes of UC patients. Data were collected from two centers, including the IRCCS-Humanitas Research Hospital (Rozzano, Milan, Italy) and the Nancy University Hospital (Vandoeuvre-lès-Nancy, France) between January 2014 and March 2021. Ulcerative colitis patients with established diagnosis of UC for at least 6 months were eligible for inclusion if they were ≥18-year-old and had at least one colonoscopy with biopsies within 16 weeks after any induction therapy with any drug for active disease according to routine clinical practice. Patients should have at least a follow up time of ≥12 months. Moreover, only patients with available histological reports of endoscopic biopsies and clinical data within 1 month of colonoscopy were included. At least 2 biopsies in the most severely affected area were performed in all endoscopic procedures. Pediatric patients (<18 years) or subjects with Crohn's disease or unclassified colitis were excluded.

Data collection

The following demographic and clinical characteristics were extracted from each patient's electronic medical record: sex, birth date, age at diagnosis, year of diagnosis, smoking status, UC-related medications, and clinical/endoscopic/histological data at baseline and during whole disease course. Disease clearance was defined as simultaneous clinical (partial-Mayo score ≤2, with no subscore >1), endoscopic (endoscopic-Mayo score = 0), and histological (Nancy index = 0) remission. Negative outcomes such as escalation of medical therapy, UC-related hospitalization, UC-related surgery, colorectal dysplasia/neoplasia, and death for any reason were also investigated. Escalation of medical therapy was defined as start of systemic steroids, immunosuppressants, biologics, or small molecules, dose optimization, interval optimization, switch to another drug within or outside the same drug class. Hospitalization was considered when it was superior to 3 days and admission to intensive care unit was specified. Surgical interventions included proctocolectomy, proctectomy, total, segmental, and subtotal colectomy and for each patient the number of surgeries was reported. The incidence of high- or low-grade dysplasia was investigated, distinguishing between lesions resulting from polyps or flat mucosa.

Statistical analysis

Data were analyzed using Stata (version 11) software. Categorical variables were described as frequency and percentages. Normally distributed continuous variables were presented as mean ± standard deviation (SD) while non-normally distributed variables as medians

(interquartile ranges). Comparison among quantitative variables with normal distribution was performed using the Student *t* test and the Mann-Whitney *U* test; the Wilcoxon test was adopted to compare quantitative variables with non-normal distribution. Analyses of statistical differences among categorical variables were carried out using the χ^2 or Fisher exact test, where indicated. Kaplan-Meier survival curves were created to assess the relapse-free survival time in patients who achieved disease clearance. A logistic regression model was used to identify predictive factors of long-term negative outcomes. Candidate variables were selected by bivariable model. The effect size was estimated by crude and adjusted odds ratios and their 95% confidence interval (CI). In the univariate analysis different factors were analyzed including histological healing, mucosal healing, stool frequency and rectal bleeding <3, absence of rectal bleeding, male sex, age, disease duration, smoking habits, and therapy with immunosuppressants or biologics. All statistical tests were 2-sided and $p \leq 0.05$ was considered as the statistically significant threshold.

Ethical considerations

The study was approved by the Commission Nationale de l'Informatique et des Libertés (number 1404720).

RESULTS

Baseline characteristics

Baseline characteristics are listed in Table 1. A total of 494 patients with UC was included (225, 46% female). Over 2000 patients were excluded due to lack of simultaneous clinical, endoscopic, and histological data or due to inadequate follow up. The median age at diagnosis was 41 years (range 18–86). Most patients had an extensive colitis at diagnosis (233, 47.0%). Fifty-seven percent ($n = 283$) of patients never smoked. The most frequently used drugs at baseline were oral 5-ASA

TABLE 1 Patients' characteristics stratified by disease clearance at baseline

	Overall population ($n = 494$)	Disease clearance ($n = 109$)	No disease clearance ($n = 385$)	*p* value
Median age (range)	41 (18–86)	49 (20–71)	40 (18–86)	0.02
Males	269 (54%)	57 (52%)	212 (55%)	0.608
Smoking habits				
Never smoked	283 (57%)	64 (59%)	219 (57%)	0.818
Active smoker	91 (18%)	21 (19%)	70 (18%)	
Former smoker	120 (24%)	24 (22%)	96 (25%)	
Family history of IBD	45 (9%)	8 (7%)	37 (9%)	
Median disease duration (years)	6.0 (0–45)	5 (0–36)	9 (0–45)	<0.001
Montreal classification				
E1	41 (8%)	10 (9%)	31 (8%)	0.708
E2	220 (45%)	50 (46%)	170 (44%)	0.750
E3	233 (47%)	49 (45%)	184 (48%)	0.600
Drug history				
Oral 5-ASA	473 (96%)	107 (98%)	366 (95%)	0.157
Rectal 5-ASA	168 (34%)	34 (31%)	134 (35%)	0.482
Systemic corticosteroids	394 (80%)	68 (62%)	326 (85%)	<0.001
Rectal corticosteroids	107 (22%)	17 (16%)	90 (23%)	0.080
Thiopurines	240 (49%)	55 (50%)	185 (48%)	0.657
Methotrexate	45 (9%)	11 (10%)	34 (9%)	0.686
Infliximab	274 (55%)	44 (40%)	230 (60%)	<0.001
Adalimumab	114 (23%)	30 (27%)	84 (22%)	0.212
Golimumab	65 (13%)	13 (12%)	52 (13%)	0.667
Vedolizumab	181 (37%)	18 (16%)	163 (42%)	0.011
Ustekinumab	12 (2%)	2 (2%)	10 (2%)	0.036
Tofacitinib	12 (2%)	4 (4%)	8 (2%)	0.036

Abbreviations: 5-ASA, mesalamine; E1, proctitis; E2, left-side colitis; E3, extensive colitis; IBD, inflammatory bowel disease.

(473, 96.0%), systemic steroids (394, 80.0%) infliximab (274%, 55.0%), thiopurines (240, 49.0%), and vedolizumab (181, 37.0%).

Patients' characteristics according to the induction of disease clearance

After the induction phase, disease clearance occurred in 109 patients at baseline (22.1%), with a median age of 49 years. There was an equal distribution by stratifying patients by sex (males 57, 52.3%) and smoking status (non-smokers 64, 58.7%). Disease clearance was more frequent in left sided-colitis (50, 45.9%) and pancolitis (49, 44.9%), while a minority was reported in proctitis (10, 9.2%). Instead, most of the patients without disease clearance at baseline had extensive colitis at diagnosis (184, 47.8%). Half of the patients in disease clearance at baseline were treated with thiopurines (55, 50.5%), followed by infliximab (44, 40.4%) and adalimumab (30, 27.5%). Similar results appeared in the non-disease clearance group, in which 230 patients were treated with infliximab (59.7%), 185 with thiopurines (48.0%) and 163 with vedolizumab therapy (42.3%).

Long-term negative outcomes

Median follow-up time was 24 months (range 12–77): 33.6 months in the disease clearance arm and 24.9 months in the no disease clearance group. In this time period, 98 patients (19.8%) required hospitalization or underwent surgery because of UC. Of those, 95 patients (96.9%) were hospitalized at least once (median time to event 5 months), and 44 patients (44.9%) underwent surgery. Mean hospitalization length was 4.88 $\pm$ 6.25 days. Based on the type of surgery, almost two-thirds of patients underwent total colectomy (27, 61.4%), followed by proctocolectomy (6, 13.6%), segmental colectomy (5, 11.4%), subtotal colectomy (4, 9.1%) and proctectomy (2, 4.5%). About two thirds of patients (322, 65.2%) experienced one or more strategies of dose escalation therapy, including initiation of biologics (252, 51.0%) or immunosuppressive agents (127, 25.7%), dose (32, 6.5%) or interval (110, 22.3%) optimization, and switch (52, 10.5%) or swap (96, 19.4%) to another biological drug. In addition, 25 (5.1%) cases of colorectal dysplasia (23 low-grade and 2 high-grade dysplasia) and 2 colorectal malignancies (2, 0.4%) were diagnosed. No deaths occurred during the study period.

Disease clearance and the risk of negative outcomes

In the study population, 109 patients (22%) achieved disease clearance. At last follow-up time, only 7 patients (1%) who achieved disease clearance experienced hospitalization or surgery compared to 91 patients (18.4%) who did not achieve disease clearance ($p < 0.001$). Only 6 patients who achieved disease clearance compared to 89 patients without disease clearance were hospitalized (5.5% vs. 23.1%, $p < 0.001$), and only 2 patients with disease clearance compared to 42 without disease clearance underwent surgery (1.8% vs. 10.9%, $p = 0.003$).

Using a more stringent definition of disease clearance (defined as endoscopic Mayo score = 0, Nancy score = 0, normal stool frequency and absence of rectal bleeding), 98 patients (19.8%) achieved disease clearance in the entire study population. At last follow-up time, 6 patients experienced hospitalization or surgery (6.1%), compared to 92 patients without disease clearance (23.2%, $p = 0.005$). The rate of hospitalization (90 vs. Five patients, 22.7% vs. 5.1%, $p = 0.003$) was significantly higher in those who did not achieve disease clearance, as well as the rate of surgery (43 vs. One patients, 10.9% vs. 1.0%, $p = 0.012$).

Disease clearance and complication-free survival

The survival curve analysis showed that disease clearance was associated with significant lower risk of any negative outcomes (hazard ratio (HR) 0.22, 95% CI 0.10–0.48, $p > 0.001$), hospitalization (HR 0.20, 95%CI 0.09–0.45, $p < 0.001$), and surgery (HR 0.14, 95%CI 0.03–0.59, $p = 0.007$). Using the most stringent definition of disease clearance, we still observed a significant lower risk for any complication (0.32, 0.14–0.72, $p = 0.006$), hospitalization (0.27, 95%CI 0.11–0.67, $p = 0.004$), and surgery (HR 0.12, 95%CI 0.02–0.85, $p = 0.03$). In the Kaplan-Meier survival curves, patients without disease clearance at baseline had a higher risk of any negative outcomes (Figure 1), hospitalization (Figure 2), and surgery (Figure 3) compared with those with disease clearance at 5-year (log-rank $p < 0.0001$, log-rank $p < 0.0001$, and log-rank $p < 0.00095$, respectively).

Components of disease clearance and risk for negative outcomes

The Cox-regression analysis made by splitting each measure of disease clearance (histological healing, mucosal healing, absence of rectal bleeding and normal bowel movements) showed that each one of them was significantly associated with lower risk of any negative outcome, hospitalization, and surgery (Table 2). At multivariable analysis, histological healing (Nancy score equal to 0) was the only component associated to significant lower risk of any complication, hospitalization, and surgery. The same analysis showed that normalization of bowel habit was also associated to a lower risk of hospitalization (Table 2). No impact on long-term outcomes was identified using sex, age, disease duration, smoking habits, and therapy with immunosuppressants or biologics as variables.

DISCUSSION

The concept of disease clearance as a composite target in UC is relatively new. The achievement of absence of symptoms together with endoscopic and histological absence of inflammation has never

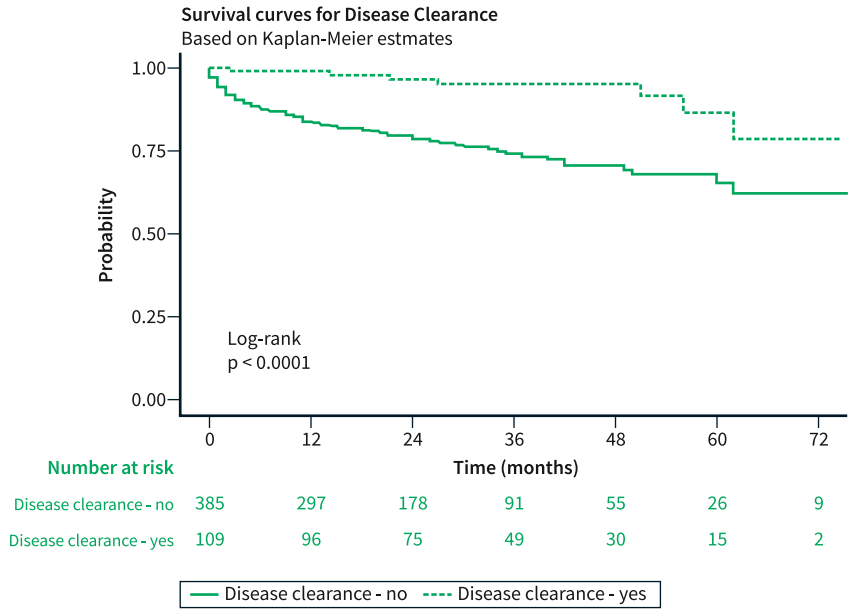

FIGURE 1 Kaplan-Meyer survival curves related to any negative outcomes in patients achieving disease clearance or not

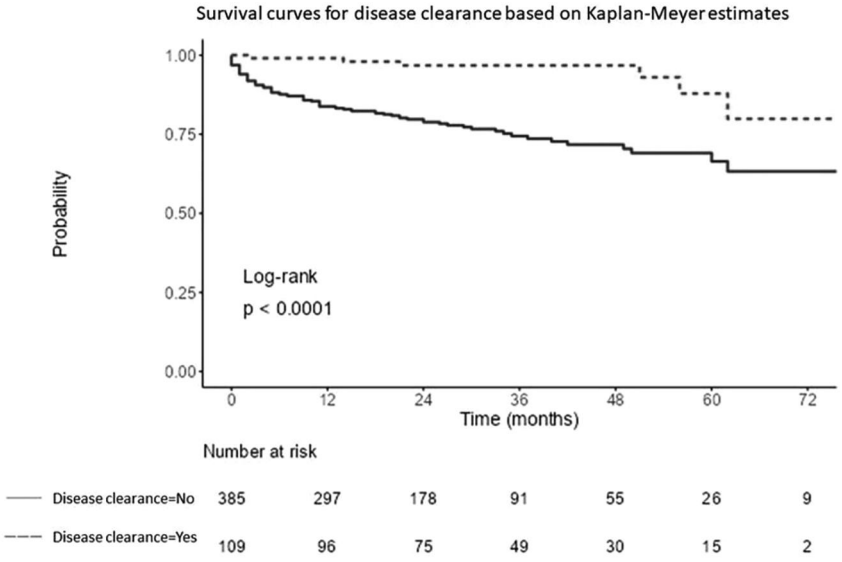

FIGURE 2 Kaplan-Meyer survival curves related to hospitalization in patients achieving disease clearance or not

been used as a primary outcome in clinical trials. We found that the achievement of disease clearance within 16 weeks of induction therapy is significantly associated with lower risk of hospitalization and surgery in the long-term, and therefore represents an important target to achieve. It could also have an important impact from an economic point of view since a reduction in the rate of surgeries and hospitalizations would result in decreased UC-associated healthcare costs. This is consistent with studies reporting that median costs for UC-related hospitalization and surgery were approximately $5000 and $30,000 respectively.[10,11] Interestingly, patients who achieved disease clearance had a shorter duration of disease than those without (5 vs. 9 years $p < 0.001$). The reason for this is not known, but it is reasonable to hypothesize that patients with a long-standing disease have a more difficult disease to treat. Moreover, early therapy initiation may have an impact on disease control and justify such finding.

Our data are in line with previous data published in the literature. Riley et al. pointed out that the presence of acute inflammatory cells was a risk factor for clinical relapse in UC patients in clinical and endoscopic remission.[12] Narang et al. reported that 32.6% of patients

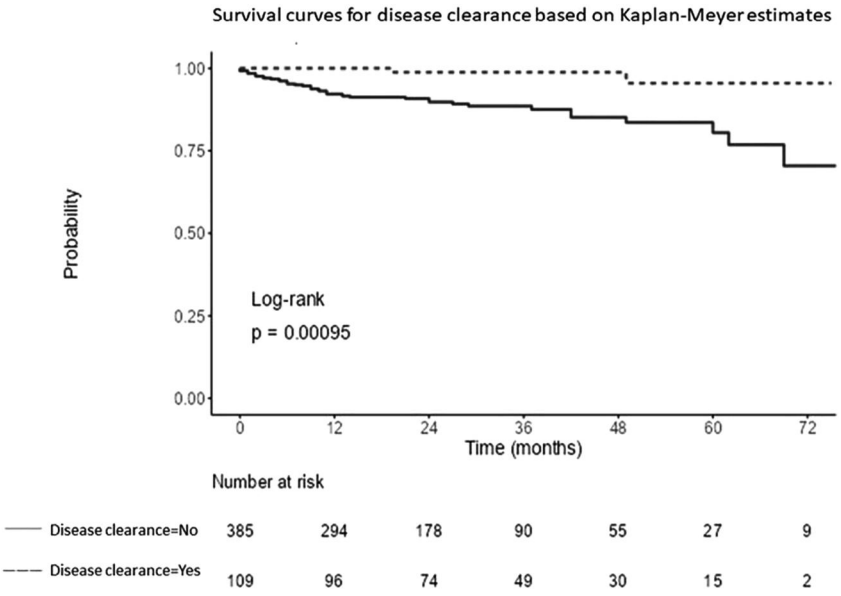

FIGURE 3 Kaplan-Meyer survival curves related to surgery in patients achieving disease clearance or not

TABLE 2 Disease clearance components and risks of negative outcomes

Any negative outcome						
	Univariable			Multivariable		
Component	HR	95% CI	*p* value	HR	95% CI	*p* value
Normal stool frequency	0.28	0.17–0.46	<0.001	-	-	-
Absence of rectal bleeding	0.35	0.23–0.53	<0.001	-	-	-
Mucosal healing	0.32	0.16–0.66	0.002	-	-	-
Histological healing	0.28	0.17–0.46	<0.001	0.48	0.26–0.90	0.022
Hospitalization						
Normal stool frequency	0.26	0.15–0.43	<0.001	0.47	0.24–0.94	0.032
Absence of rectal bleeding	0.35	0.23–0.54	<0.001	-	-	-
Mucosal healing	0.29	0.13–0.62	0.002	-	-	-
Histological healing	0.27	0.16–0.46	<0.001	0.50	0.26–0.94	0.03
Surgery						
Normal stool frequency	0.19	0.08–0.46	<0.001	-	-	-
Absence of rectal bleeding	0.40	0.22–0.75	0.004	-	-	-
Mucosal healing	0.18	0.04–0.74	0.017	-	-	-
Histological healing	0.13	0.05–0.36	<0.001	0.22	0.07–0.72	0.01

Abbreviations: CI, confidence interval; HR, hazard ratio.

in endoscopic remission had evidence of histological activity. Importantly, microscopic disease activity was associated with increased risk of negative outcomes and relapses.[13] Feagins et al. showed that the histological activity better predicted clinical flares compared with endoscopic activity.[14]

A recent meta-analysis of 17 studies that included patients with UC in clinical remission concluded that patients in both endoscopic and histological remission had a 63% lower risk of clinical relapse compared to patients with persistent microscopic activity.[15] Moreover, a higher rate of hospitalization (36.0% vs. 7.1%, $p = 0.001$) and surgery (14.0% vs. 0.0%, $p = 0.01$) was reported in patients with histological activity compared to those with quiescent microscopic disease.[16] Importantly, disease clearance represents a high hurdle to achieve, and costs and risks of the required therapies must be

considered. We found that only 22.1% of our patients had disease clearance after induction therapy. These data are not surprising, as recent randomized clinical trials showed similar results. The UNIFI trial showed that approximately 18% of patients treated with ustekinumab achieved endoscopic and histological mucosal healing (defined as Mayo endoscopic score ≤1 and neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue) after 8 weeks of induction therapy.[17] Moreover, in the VARSITY trial, the first head-to-head study comparing vedolizumab and adalimumab for the treatment of patients with UC, a higher proportion of vedolizumab-treated patients achieved disease clearance at week 52 compared to adalimumab (29.2% vs. 16.3%).[18,19] It is important to underline that the definition of disease clearance in the VARSITY trial was less stringent than in our study including an endoscopic Mayo score ≤1 and a Robarts histologic index <5.

The induction and maintenance of clinical, mucosal, and histological remission at the same time may represent a promising ultimate therapeutic goal and a starting point for identifying patients with UC with a negative predictive outcome at baseline. Prospective studies are needed for the replication and validation of our findings before our observations can be translated into recommendations for clinical practice. In this regard, the ongoing VERDICT (Determination of the Optimal Treatment Target in UC) trial is the first multicenter, prospective, randomized trial aiming to determine whether using a treatment target of corticosteroid-free symptomatic plus endoscopic plus histological remission might be superior to a treatment target of just corticosteroid-free symptomatic remission, in relation to UC-associated complications (NCT04259138).

In addition, we found that histological healing represents the most impacting component of disease clearance in regards of the risk of negative outcomes in UC. Our analyses clearly showed that histological healing is the best protective factor against hospitalization and surgery risk compared to clinical remission and mucosal healing. This is also shown by Gupta and colleagues.[7] They conducted a systematic review and meta-analysis including 2677 patients with UC in endoscopic remission. Histological activity of disease was associated with an increase in the risk of relapse (odds ratio 2.41; 95% CI, 1.91–3.04), while histological remission was associated with a better prognosis independently of endoscopy.

Although histology is the main predictor of outcomes, the endoscopic activity of disease has a relevant role on the prognosis of patients and at the same time, the clinical activity has a negative impact on daily living activities. The achievement of disease clearance could not only promote better disease control but also have a positive impact on patients' quality of life.

Our study has several strengths. Firstly, to the best of our knowledge, this is the first study to analyze negative disease outcomes of UC during a long follow-up time of at least 1 year. Secondly, it is a multi-center study, collecting data from a large cohort of patients, which confers validity and reliability to our results. Moreover, we used commonly adopted scores to define the items included in the definition of disease clearance, such as the Mayo clinical and endoscopic subscores, which are among the most used in clinical trials and clinical practice, and the Nancy index, which is a validated score for the assessment of histological disease activity.[20] Importantly, although there is no commonly accepted definition of disease clearance, we considered strict values of the aforementioned scores to determine endoscopic and histological remission (endoscopic Mayo score = 0 and Nancy index = 0).

We do acknowledge several limitations, including the retrospective nature of the study. Due to the study design, pre-treatment baseline data were not available for all patients. However, our study focuses on the long-term impact of disease clearance, so the missing data would have added little to our purpose. In addition, few cases of malignancy were reported, and no cases of death were identified, preventing us from evaluating an association between histological activity and the onset of these events. This could be explained by the duration of the follow-up, which although consistent, was not sufficient to assess outcomes that generally require more years of observation.

CONCLUSIONS

Early disease clearance in UC patients is associated with lower risk of hospitalization and surgery. Despite a minority of patients achieve disease clearance in the short-term after therapies, the long-term impact on the natural history of the disease appears to be significantly better than clinical and endoscopic remission alone. Further data are needed to understand whether targeting disease clearance may be cost-effective in the long-term. Large prospective studies aimed to confirm the positive impact of disease clearance in UC patients are needed.

AUTHOR CONTRIBUTIONS

Silvio Danese conceived the study. Ferdinando D'Amico, Virginia Solitano, and Eugenia Massarini wrote the manuscript and created the tables. Gionata Fiorino, Lucas Guillo, Mariangela Allocca, Federica Furfaro, Alessandra Zilli, Stefanos Bonovas, Fernando Magro, Laurent Peyrin-Biroulet, and Silvio Danese critically reviewed the content of the paper and supervised the project. All authors discussed the results and contributed to the final manuscript.

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CONFLICTS OF INTEREST

F D'Amico, V Solitano, E. Massarini, L Guillo, and A Zilli declare no conflict of interest. G Fiorino received consultancy fees from Ferring, Merck Sharp & Dohme (MSD), AbbVie, Takeda, Janssen, Amgen, Sandoz, Samsung Bioepis, Celltrion. M. Allocca received consulting fees from Nikkiso Europe and lecture fees from Janssen and Pfizer. F Furfaro received consulting fees form MSD and Abbvie and lecture fees from Janssen and Pfizer. S Bonovas received consulting fees from Ferring. F Magro has served as a speaker and received honoraria from Merck Sharp & Dohme, Abbvie, Vifor, Falk, Laboratorios

Vitoria, Ferring, Hospira, and Biogen. L Peyrin-Biroulet declares personal fees from Galapagos, AbbVie, Janssen, Genentech, Ferring, Tillots, Celltrion, Takeda, Pfizer, Index Pharmaceuticals, Sandoz, Celgene, Biogen, Samsung Bioepis, Inotrem, Allergan, MSD, Roche, Arena, Gilead, Amgen, Bristol Myers Squibb's, Vifor, Norgine, Mylan, Lilly, Fresenius Kabi, OSE Immunotherapeutics, Enthera, Theravance, Pandion Therapeutics, Gossamer Bio, Viatris, Thermo Fisher. Grants from AbbDvie, MSD, Takeda, Fresenius Kabi. Stock options: Clinical Trials Mobile Application. S Danese has served as a speaker, consultant and advisory board member for Schering- Plough, AbbVie, MSD, UCB Pharma, Ferring, Cellerix, Millenium Takeda, Nycomed, Pharmacosmos, Actelion, Alphawasserman, Genentech, Grunenthal, Pfizer, Astra Zeneca, Novo Nordisk, Cosmo Pharmaceuticals, Vifor and Johnson & John-son, Nikkiso Europe GMBH, Theravance.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

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REFERENCES

1. Turner D, Ricciuto A, Lewis A, D'Amico F, Dhaliwal J, Griffiths AM, et al. STRIDE-II: an update on the selecting therapeutic targets in inflammatory bowel disease (STRIDE) initiative of the international organization for the study of IBD (IOIBD): determining therapeutic goals for treat-to-target strategies in IBD. Gastroenterology. 2020;160(5):1570–83. https://doi.org/10.1053/j.gastro.2020.12.031
2. Arias MT, Vande Casteele N, Vermeire S, de Buck van Overstraeten A, Billiet T, Baert F, et al. A panel to predict long-term outcome of infliximab therapy for patients with ulcerative colitis. Clinical Gastroenterology and Hepatology. 2015;13(3):531–8. https://doi.org/10.1016/j.cgh.2014.07.055
3. Colombel JF, Keir ME, Scherl A, Zhao R, de Hertogh G, Faubion WA, et al. Discrepancies between patient-reported outcomes, and endoscopic and histological appearance in UC. Gut. 2017;66(12):2063–8. https://doi.org/10.1136/gutjnl-2016-312307
4. Neurath MF, Travis SPL. Mucosal healing in inflammatory bowel diseases: a systematic review. Gut. 2012;61(11):1619–35. https://doi.org/10.1136/gutjnl-2012-302830
5. Shah SC, Colombel JF, Sands BE, Narula N. Mucosal healing is associated with improved long-term outcomes of patients with ulcerative colitis: a systematic review and meta-analysis. Clinical Gastroenterology and Hepatology. 2016;14(9):1245–55.e8. https://doi.org/10.1016/j.cgh.2016.01.015
6. Peyrin-Biroulet L, Bressenot A, Kampman W. Histologic remission: the ultimate therapeutic goal in ulcerative colitis? Clinical Gastroenterology and Hepatology. 2014;12(6):929–34.e2. https://doi.org/10.1016/j.cgh.2013.07.022
7. Gupta A, Yu A, Peyrin-Biroulet L, Ananthakrishnan AN. Treat to target: the role of histologic healing in inflammatory bowel diseases: a systematic review and meta-analysis. Clinical Gastroenterology and Hepatology. 2020;19(9):1800–13.e4. https://doi.org/10.1016/j.cgh.2020.09.046
8. Christensen B, Hanauer SB, Erlich J, Kassim O, Gibson PR, Turner JR, et al. Histologic normalization occurs in ulcerative colitis and is associated with improved clinical outcomes. Clinical Gastroenterology and Hepatology. 2017;15(10):1557–64.e1. https://doi.org/10.1016/j.cgh.2017.02.016
9. Danese S, Roda G, Peyrin-Biroulet L. Evolving therapeutic goals in ulcerative colitis: towards disease clearance. Nature Reviews Gastroenterology and Hepatology. 2020;17(1):1–2. https://doi.org/10.1038/s41575-019-0211-1
10. Coward S, Heitman SJ, Clement F, Hubbard J, Proulx MC, Zimmer S, et al. Ulcerative colitis-associated hospitalization costs: a population-based study. Canadian Journal of Gastroenterology and Hepatology. 2015;29(7):357–62. https://doi.org/10.1155/2015/627370
11. Brookes MJ, Waller J, Cappelleri JC, Modesto I, Dibonaventura MD, Bohm N, et al. Living with ulcerative colitis study (lucy) in england: a retrospective study evaluating healthcare resource utilisation and direct healthcare costs of postoperative care in ulcerative colitis. BMJ Open Gastroenterology. 2020;7(1):e000456. https://doi.org/10.1136/bmjgast-2020-000456
12. Riley SA, Mani V, Goodman MJ, Dutt S, Herd ME. Microscopic activity in ulcerative colitis: what does it mean? Gut. 1991;32(2):174–8. https://doi.org/10.1136/gut.32.2.174
13. Narang V, Kaur R, Garg B, Mahajan R, Midha V, Sood N, et al. Association of endoscopic and histological remission with clinical course in patients of ulcerative colitis. Intestinal Research. 2018;16(1):55–61. https://doi.org/10.5217/ir.2018.16.1.55
14. Feagins LA, Melton SD, Iqbal R, Dunbar KB, Spechler SJ. Clinical implications of histologic abnormalities in colonic biopsy specimens from patients with ulcerative colitis in clinical remission. Inflammatory Bowel Diseases. 2013;19(7):1477–82. https://doi.org/10.1097/MIB.0b013e318281f4ae
15. Yoon H, Jangi S, Dulai PS, Boland BS, Prokop LJ, Jairath V, et al. Incremental benefit of achieving endoscopic and histologic remission in patients with ulcerative colitis: a systematic review and meta-analysis. Gastroenterology. 2020;159(4):1262–75.e7. https://doi.org/10.1053/j.gastro.2020.06.043
16. D'Amico F, Guillo L, Baumann C, Danese S, Peyrin-Biroulet L. Histological disease activity measured by the nancy index is associated with long-term outcomes in patients with ulcerative colitis. J Crohns Colitis. 2021;15(10):1631–40. https://doi.org/10.1093/ecco-jcc/jjab063
17. Sands BE, Sandborn WJ, Panaccione R, O'Brien CD, Zhang H, Johanns J, et al. Ustekinumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2019;381(13):1201–14. https://doi.org/10.1056/NEJMoa1900750
18. Sands BE, Peyrin-Biroulet L, Loftus EV, Danese S, Colombel J.-F, Törüner M, et al. Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis. N Engl J Med. 2019;381(13):1215–26. https://doi.org/10.1056/NEJMoa1905725
19. Danese S, Schreiber S, Loftus E, Jr., Colombel JF, Peyrin-Biroulet L, Agboton C, et al. P271 evolving targets in ulcerative colitis: defining disease clearance in the VARSITY study. Journal of Crohn's and Colitis. 2021;15(Suppl 1):S305. https://doi.org/10.1093/ecco-jcc/jjab076.396
20. Magro F, Doherty G, Peyrin-Biroulet L, Svrcek M, Borralho P, Walsh A, et al. ECCO position paper: harmonization of the approach to ulcerative colitis histopathology. J Crohns Colitis. 2020;14(11):1503–11. https://doi.org/10.1093/ecco-jcc/jjaa110

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