Received: 22 November 2021 | Accepted: 16 January 2022

DOI: 10.1002/ueg2.12206

ORIGINAL ARTICLE

UNITED EUROPEAN GASTROENTEROLOGY ueg journal WILEY

Predictive value of Milan ultrasound criteria in ulcerative colitis: A prospective observational cohort study

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Abstract

Background: Endoscopic healing is an established treatment target for ulcerative colitis (UC). We have recently validated the Milan ultrasound criteria (MUC) to assess endoscopic activity in UC; a MUC score > 6.2 is a valid cut-off to discriminate endoscopic activity (Mayo endoscopic subscore > 1).

Objective: The aim of this study was to assess the predictive value of MUC on disease course in a prospective cohort of UC patients.

Methods: UC patients regardless of disease activity and current therapy, underwent colonoscopy and bowel ultrasound (US) at baseline in a blinded fashion. Correlations between baseline MUC and Mayo endoscopic subscore were assessed using Spearman's rank correlation. UC-related negative course (defined as the need for corticosteroids, or treatment escalation, or hospitalization, or need for colectomy: a composite outcome) over a median 20 months follow-up, was investigated using the Kaplan-Meier method and Cox regression analysis.

Results: 98 UC patients were followed up for a median time of 1.6 years (IQR 0.9¬2.7). Milan ultrasound criteria and Mayo endoscopic subscore significantly correlated at baseline ($\rho = 0.653$; $p < 0.001$). 70 patients (71%) had negative disease course during the follow-up period. Milan ultrasound criteria > 6.2 at baseline was statistically significantly associated with negative disease course (HR: 3.87, 95% CI: 2.25–6.64, $p < 0.001$). Kaplan–Meier analyses drawed a statistically significantly lower cumulative probability of treatment escalation, need of corticosteroids, hospitalization and colectomy, among patients who had MUC ≤ 6.2 at baseline as compared to patients with MUC > 6.2 ($p < 0.05$ for all outcomes).

Conclusion: we have demonstrated for the first time the value of bowel US and an US score in predicting disease course in UC. Milan ultrasound criteria, a validated US-based score, predicts disease course in UC. Milan ultrasound criteria ≤ 6.2 may be the new treatment target to achieve to reduce the risk of worse outcomes.

KEYWORDS
inflammatory bowel disease, Milan ultrasound criteria, outcomes, predictive value, ulcerative colitis, ultrasound

INTRODUCTION

Ulcerative colitis is a chronic, relapsing and destructive inflammatory disorder of the colon which can lead to organ damage and impair quality of life.[1] Consensus guidelines recommend to go beyond resolution of clinical symptoms and achieve endoscopic healing.[2,3] This long-term treatment goal in UC is commonly defined by a Mayo endoscopic subscore ≤ 1,[2,3] and is associated with prolonged clinical remission, lower rates of hospitalisation and lower rates of colectomy.[4,5] However, CS is an invasive and expensive procedure, unpleasant to patients, not without risks, especially during severe flares.[6,7] Bowel ultrasound (US) is a well-tolerated, non-invasive, patient friendly, cheap, easy-to-use tool to manage UC patients in clinical practice.[8] In addition, its ability to be performed as point-of-care bowel US may drastically change frequency of the assessment of treatment response, speeding the clinical decision-making process.[9] Recently, we developed and externally validated non-invasive ultrasonography based criteria (MUC) to assess and grade endoscopic activity in UC.[10,11] We also confirmed that a MUC score > 6.2 is a valid cut-off to discriminate endoscopic activity, defined by a Mayo endoscopic subscore >1.[10,11]

Aim of this study was to prospectively assess the value of bowel US and MUC, alternatively to CS, for predicting outcomes of treatment escalation, corticosteroid use, hospitalization or colectomy in a cohort of patients with UC followed up over a median 20 months follow-up. Clinicians who followed UC patients and took clinical decisions were blinded to baseline MUC values.

Key summary

Summarise the established knowledge on this subject

- Endoscopic healing remains the long-term treatment target to achieve, as predictor of a positive long-term disease course;
- However, colonoscopy (CS) is considered the least acceptable monitoring tool among patients;
- We have recently validated non-invasive ultrasonography based criteria [Milan ultrasound criteria (MUC)] to assess and grade endoscopic activity in ulcerative colitis (UC). We have also confirmed that a MUC score > 6.2 is a valid cut-off to discriminate endoscopic activity, defined by a Mayo endoscopic subscore > 1;
- The role of MUC in predicting disease course in UC is not yet known.

What are the significant and/or new findings of this study?

- We found that patients with an ultrasound (US) activity at baseline, as defined by MUC > 6.2, had four times the risk of having a negative disease course over a median 20 months follow-up (defined as the need for corticosteroids, change of therapy, hospitalization, or need for colectomy), as compared to patients with US remission (MUC ≤ 6.2);
- MUC ≤ 6.2 may become the new treatment target to achieve in UC to reduce the risk of worse outcomes in the follow-up;
- Bowel US, a non-invasive and patient friendly procedure, may replace CS whenever mucosal biopsies are not required.

METHODS

Study design and population

This was a single-center, prospective observational study. All consecutive adult patients (18 years of age and older) with established diagnosis of UC (since at least 6 months), seen in a tertiary referral Center (Humanitas Research Hospital) between January 2016 and January 2020, requiring routine investigation by CS, were enrolled and underwent CS and bowel US, within a maximum interval of 60 days between the two exams. The treatment was kept stable in the interval between the two procedures. Colonoscopy was performed by an expert endoscopist, with at least 8 years of experience, using a standard video endoscope (Fujinon). He was blinded to the MUC value. Two independent gastroenterologists experienced in US (at least 7 years of experience) performed bowel US and measured MUC, blinded to the clinical and endoscopic scores. In order to compare the two procedures, the ileo-colonic tract visualized at bowel US was divided into five segments: ileum, cecum-ascending colon, transverse colon, descending-sigmoid colon, and rectum. Exclusion criteria were any contraindication to CS (e.g. intolerance to preparation, severe flare, pregnancy), inability to undergo procedures (CS and bowel US) within the time set by the study, concomitant participation in clinical trials, involvement limited to the rectum or any change in treatment between the two procedures. All patients, who met all the inclusion criteria and none of the exclusion criteria were included in the study. Of 1572 eligible patients, 98 UC patients were finally included. During the

screening period 1474 patients were excluded: 519 because their participation in clinical trials, 393 for disease limited to the rectum, 220 for inability or refusal to undergo CS, and 342 for inability to undergo bowel US within 60 days from the CS or inability to keep stable therapy between the two procedures. Baseline characteristics were recorded, including demographics, disease duration, extent and current medications. The disease was considered clinically active if the partial Mayo score was higher than 2.[12] The Montreal Criteria were used to define disease extent.[13]

Blood and stool samples were obtained for C-reactive protein and fecal calprotectin (FC) measurements.

All recruited patients were prospectively followed up after performing baseline bowel US, until 31 January 2021 or the date of colectomy or censoring at the time of last visit if they discontinued the study before.

They received standard clinical care,[14,15] with regular outpatient follow-up of a maximum interval of 6 months, to assess clinical outcomes. The recorded outcomes were need of corticosteroids, treatment escalation, hospitalization and need of colectomy.

Endoscopic findings

The endoscopic activity was assessed by the Mayo endoscopic subscore. Endoscopic healing was defined as a score ≤1 (12). Colonoscopy were performed after standard bowel preparation by administration of 4 L of polyethylene glycol. The endoscopist was blinded to bowel US findings.

Bowel US findings

All the patients underwent bowel US within an average interval time of 11 days (±35) from the CS. Neither preparation nor contrast were used. The two operators were blinded to patient's symptoms and endoscopic findings. Bowel US was performed after 6–8 h fasting, using an Aloka Arietta V60 with convex (5–1 MHz) and microconvex probes (4–8 MHz), according to acquisition protocol previously described.[10,11] The entire abdomen was systematically scanned starting from the right iliac fossa. The following parameters were evaluated: bowel wall thickness (BWT; normal values up to 3 mm), measured in longitudinal and transverse sections, from the interface between the mucosa and the lumen to the interface between the serosa and the muscle layer. A mean of two measurements for each section was calculated; bowel wall pattern, defined as (0) normal, multilayered,(1) predominantly hypoechogenic,(2) predominantly hyperechogenic,(3) lost; bowel wall flow (BWF), defined as absence (0) or presence(1) of blood signals at color Doppler; stricture, defined as presence of wall thickening with a narrowed lumen with or without a dilatation of a proximal loop; fistula, defined as hypoechoic tract with or without hyperechoic content; abscess, defined as a roundish anechoic lesion with an irregular wall, without signs of blood flow; presence of mesenteric lymph nodes; mesenteric hypertrophy (defined as absence [0] or presence [1]).[10] These parameters were evaluated for each intestinal segment impacted by the disease, and the worst segment taken into account.

The MUC was measured, as previously described, according to the following formula[10]:

Milan ultrasound criteria = 1.4 × BWT (mm) + 2 × BWF; where BWF = 1 if present, or BWF = 0 if absent.

Ultrasound remission was defined as a MUC score ≤ 6.2.

Clinical outcomes

Need of corticosteroids, treatment escalation, hospitalization or colectomy were recorded since the baseline assessment to 31 January 2021. Clinicians were blinded to bowel US parameters and MUC values. This was a non-interventional prospective longitudinal observational study in which the patients were followed according to good clinical practice and international guidelines.[2,3,14,15] In particular, frequency of the assessment was tailored to the patient's symptoms. Furthermore, the patients were assessed every 3 months if a new treatment was started, and every 6 months if the disease was in remission at the time of inclusion. Colonoscopy were performed before starting a new treatment and after 6 months for restaging the disease. Biomarkers, including FC and CRP, were assessed at each medical examination. A clinical flare was always confirmed by an increase of biomarkers and/or by the CS. In particular CS was always performed before changing treatment.

In detail, in case of relapse of established UC, after 2 weeks no response of optimization of 5-aminosalicylic acid therapy (oral and topical), oral corticosteroids were started. If response did not occurr within 2 weeks, a CS was performed to exclude cytomegalovirus infection and an escalation to thiopurines or biologics was planned. Treatment escalation was defined both as the need to optimize current therapy (reinduction, shortening administration intervals or dose intensification) or change to another drug with different mechanism of action. Finally, in case of acute severe colitis (defined by Truelove and Witts' criteria[16]), the patient was hospitalized. Colectomy was indicated in presence of severe, treatment-refractory colitis or high dysplasia e/o colorectal cancer complicating colitis.

Study aims

The primary objective was to investigate the predictive value of MUC at baseline on negative UC course, defined as the need for corticosteroids and/or change of therapy and/or hospitalization and/or the need for colectomy (composite endpoint).

The secondary objectives were to investigate the role of MUC at baseline in predicting a worse outcome in terms of treatment escalation, need for corticosteroids, hospitalization and colectomy, separately.

Statistical analysis

Descriptive statistics of the baseline data are presented as medians (interquartile range), or as percentages when appropriate. Correlations between baseline MUC and Mayo endoscopic subscore were assessed using Spearman's rank correlation.

In order to gain an insight into the variables that are independently associated with a patient's likelihood of experiencing negative UC course, time-to-event (survival) methods for censored observations were used because of the varying length of follow-up. For each outcome, the time to event was defined as the time from the date of baseline bowel US until the date of event (i.e. need of corticosteroids, treatment escalation, hospitalization or colectomy), or censoring at the time of discontinuation for reasons different from the event of interest, or at the end of the follow-up period. Kaplan-Meier estimates were used to draw the cumulative incidence curves, compared by log-rank tests, as well as by univariable and multivariable Cox's proportional hazards (PH) models of relevant prognostic factors. We followed a standard approach for model selection. In the univariable Cox's PH analysis, a criterion of p less than or equal to 0.10 was used to identify candidate predictors. Then, we fitted multivariable models and used backwards selection procedure to eliminate those variables not significant in the multivariable framework. We used a criterion of p less than or equal to 0.05 for determining which ones to eliminate. The hazards ratios or relative hazards (HR) derived from the Cox's PH models are presented together with their 95% confidence intervals and the respective p-values. A ratio higher than unity implies a higher probability of event (i.e. need of corticosteroids, treatment escalation, hospitalization or colectomy) compared to the reference group. p-values less than 0.05 were considered to be statistically significant.

All statistical tests are two-sided. p-values less than 0.05 were considered to be statistically significant. Stata software was used for all statistical analyses (Stata Corp.).

Ethical considerations

The study was performed according to Good Clinical Practice guidelines and was approved by our Institutional Review Board. All patients gave their informed consent for this study. Clinical trial registry website and trial number: https://praticheweb.humanitas.it; ICH1330.

All authors had access to the study data and reviewed and approved the final manuscript.

RESULTS

Study population

A total of 98 consecutive UC patients, irrespectively of disease activity and current therapy, were included in the study. All patients performed CS and bowel US at baseline. Thirty-one patients (32%) had endoscopic healing (Mayo endoscopic subscore ≤1), and 67 (68%) endoscopic activity (Mayo endoscopic subscore 2–3) at inclusion in the study. Forty-four (45%) patients had US remission (as defined by MUC ≤ 6.2), while 54 (55%) had US activity (MUC > 6.2). Baseline characteristics and clinical data of the study population are presented in Table 1. Baseline MUC correlated significantly with baseline Mayo endoscopic subscore (Figure S1, $\rho = 0.65$; $p < 0.001$). No significant correlation was observed between baseline MUC and baseline Mayo endoscopic subscore with baseline FC values (Figure S2, $\rho = 0.03$; $p = 0.82$; $\rho = 0.18$; $p = 0.11$, respectively).

A total of 185.95 person-years of observation time was analyzed (median 1.6 years per patient [IQR 0.9¬2.7]).

Association between MUC and negative disease course

In the entire study cohort, 70 patients (71%) had a negative disease course (at least one of the outcomes of interest: treatment escalation, need of corticosteroids, hospitalization or colectomy) during the follow-up period.

In Cox regression analysis, a negative disease course was predicted by MUC > 6.2 at baseline (HR: 3.87, 95% CI: 2.25–6.64, $p < 0.001$; Table 2). Twenty-one (48%) patients with MUC ≤ 6.2 at baseline and 49 (91%) with MUC > 6.2 at baseline had a negative disease course over the follow-up period (log-rank test, $p < 0.001$; Figure 1 and Table 3).

Need of treatment escalation

Sixty-three patients (64%) needed treatment escalation during the follow-up period.

Milan ultrasound criteria > 6.2 at baseline predicted increased risk of treatment escalation in Cox regression analysis (HR: 3.81, 95% CI: 2.15–6.78, $p < 0.001$; Table S1).

Seventeen (39%) patients with MUC ≤ 6.2 at baseline needed treatment escalation compared to 46 (85%) in the group with MUC > 6.2 at baseline over the follow-up period (log-rank test, $p < 0.001$; Figure 2a and Table 3).

Need of corticosteroids

Thirty-two patients (33%) needed corticosteroid therapy during the follow-up period.

TABLE 1 Characteristics of patients at inclusion in the study ($n = 98$)

Male	61 (62)
Age at diagnosis (years)	32.8 (22.1¬44.5)
Disease duration (years)	9.4 (4.6¬16.2)
Disease extent at diagnosis	
Proctitis	8 (8)
Left-sided	44 (45)
Extensive	46 (47)
Use of steroids	
Current	22 (23)
Past	60 (61)
Never	16 (16)
Use of immunosuppressants	
Current	4 (4)
Past	32 (33)
Never	62 (63)
Use of biologics	
Current[a]	24 (25)
Past	19 (19)
Never	55 (56)
Smoking	
Active	15 (16)
Past	32 (34)
Never	47 (50)
Partial mayo score (PMS)	3 (0¬5)
PMS >2	51 (53)
C-reactive protein (CRP mg/L)	4.7 (1.2¬10.1)
CRP ≥5	40 (46)
Calprotectin (μg/g)	465 (61.7¬801)
Calprotectin <50	14 (19)
Calprotectin 50–250	16 (21)
Calprotectin >250	45 (60)
Mayo endoscopic subscore at colonoscopy at inclusion	2 (1¬3)
0–1, endoscopic healing	31 (32)
2–3, endoscopic activity	67 (68)
Milan ultrasound criteria (MUC)	6.7 (4.2¬8.8)
MUC > 6.2	54 (55)

Note: Data are presented as medians (interquartile range) or percentages when appropriate.

[a]Frequencies: 13 with infliximab, 3 with adalimumab, 2 with golimumab, 5 with vedolizumab, 1 with ustekinumab.

Milan ultrasound criteria > 6.2 at baseline and male gender predicted increased risk of corticosteroid need in multivariable Cox regression analysis (HR: 2.46, 95% CI: 1.14–5.33, $p = 0.022$; HR: 2.82, 95% CI: 1.16–6.87, $p = 0.022$; respectively; Table S2**).** Eleven (25%) patients with MUC ≤ 6.2 at baseline needed corticosteroids compared to 21 (39%) in the group with MUC > 6.2 at baseline over the follow-up period (log-rank test, $p = 0.008$; Figure 2b and Table 3).

Risk of hospitalization

Nine patients (9%) were admitted for a severe flare during follow-up period.

In Cox regression analysis, there was suggestive evidence that MUC > 6.2 at baseline predicts also the risk of hospitalization (HR: 7.20, 95% CI: 0.88–58.83, $p = 0.066$) (Table S3). One (2%) patient with MUC ≤ 6.2 at baseline needed hospitalization compared to 8 (15%) in the group with MUC > 6.2 at baseline over the follow-up period (log-rank test, $p = 0.045$; Figure 2c and Table 3).

Risk of surgery

Seven patients (7%) underwent colectomy over the follow-up period: No patient with MUC ≤6.2 at baseline compared to 7 (13%) in the group with MUC > 6.2 at baseline (log-rank test, $p = 0.019$; Figure 2d and Table 3). Therefore, the respective Hazard Ratio for MUC could not be calculated (Table S4).

DISCUSSION

This study is the first to demonstrate the value of an US score in predicting patient outcomes over a long period of follow-up. Milan ultrasound criteria, which is currently the only US-based fully validated index in UC,[10,11] was shown to predict a negative course of disease, in terms of treatment escalation, need of corticosteroids, hospitalization or colectomy in a cohort of 98 patients with UC followed for a median time of 1.6 years (IQR 0.9¬2.7). The findings are striking but intuitive adding weight to calls to include a non-invasive approach, alternatively to CS, in the assessment and monitoring of inflammatory bowel disease (IBD), including UC. Clinical symptoms in UC, unlike in CD, correlate well with endoscopic findings, and their improvement together to normalization of biomarkers, such as CRP and FC, are currently considered the short-term and intermediate-term targets to achieve.[2] However, while in asymptomatic patients with FC < 50 mcg/g the chance to have endoscopic activity is <5%, and conversely patients with evident rectal bleeding and persistent increased stool frequency (≥3 stools above baseline) with FC > 250 mcg/g have less than 5% of possibility to have endoscopic healing,

TABLE 2 Influence of baseline characteristics on the risk of negative course: results of the time-to-event analysis

	Log-rank test		Univariable Cox PH model		Multivariable Cox PH model	
	Chi-squared	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Parameters						
MUC >6.2 at baseline	32.49	*<0.001*	3.87 (2.25¬6.64)	***< 0.001***	3.87 (2.25¬6.64)	***< 0.001***
Sex male versus female	3.82	*0.050*	1.59 (0.95¬2.65)	*0.074*		
Age at diagnosis (per 1-year increase)			0.99 (0.981.01)	*0.67*		
Extent at diagnosis						
Extensive	0.02	*0.88*	1.03 (0.64¬1.64)	*0.89*		
left-sided	0.97	*0.32*	1.24 (1.28¬1.98)	*0.36*		
Disease duration (per 1-year increase)			0.98 (0.96¬1.01)	*0.37*		
Active smoking	0.14	*0.70*	0.87 (0.44¬1.70)	*0.69*		

Abbreviations: CI, confidence interval; HR, hazard ratio; MUC, Milan ultrasound criteria; PH, proportional hazards.

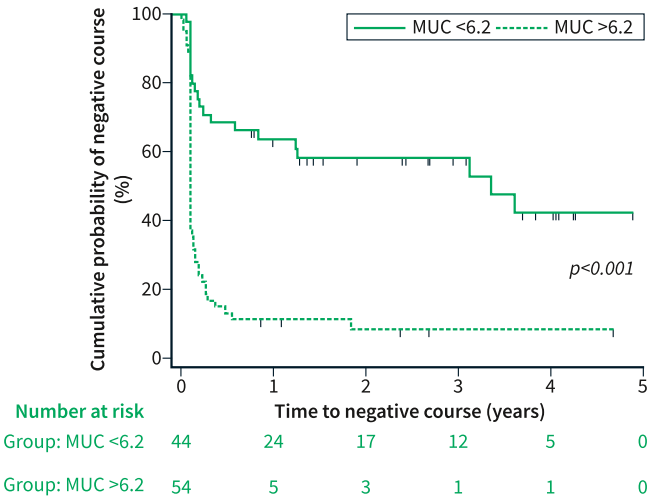

FIGURE 1 Kaplan–Meier curves for the cumulative probability of negative course in patients with Milan ultrasound criteria (MUC) ≤ 6.2 at baseline (solid line) or MUC > 6.2 at baseline (dotted line) (log-rank test, $p < 0.001$)

patients in the intermediate scenarios cannot avoid the CS.[17] Actually, endoscopic healing, as evaluated by CS to asses disease activity objectively, remains the long-term treatment target to achieve,[2] as predictor of a positive long-term disease course.[4,5] Unfortunately, only 50% patients starting a new treatment will perform a restaging CS within 2 years.[18] Surely one of the reasons is that CS is considered the least acceptable monitoring tool among patients.[19] Bowel US is patient-centered, safe, accurate, easily repeatable with assessments occurring in real-time, and most acceptable among the IBD monitoring tools,[19] able to assess treatment response in IBD, including UC patients.[8] Recently, our group determined the bowel US parameters that best identified endoscopic activity, defined by a Mayo endoscopic subscore >1, using multivariable analysis, and developed non-invasive ultrasonography based criteria (MUC) to assess and grade disease activity in UC.[10] We then validated MUC and confirmed its role in detecting UC endoscopic activity in an external, independent cohort. We also confirmed that MUC score > 6.2 is a valid cut-off to discriminate active from non-active UC.[11] In this study we found that MUC > 6.2 at baseline was able to predict a negative course, in terms of treatment escalation, need of corticosteroids, hospitalization or colectomy (HR: 3.87, 95% CI: 2.25–6.64, $p < 0.001$) during the follow-up period. Kaplan–Meier survival analyses demonstrated a significantly lower cumulative probability of each outcome among patients who had MUC ≤ 6.2 at baseline compared to patients with MUC > 6.2 at baseline ($p < 0.05$).

This study has important strengths: this is the first study ever published investigating the value of bowel US and an US score in predicting disease course in UC patients. Milan ultrasound criteria, a validated US-based score, derived by comparing bowel US parameters to CS findings, demonstrated for the first time to predict a negative course in UC, and that the cut-off of MUC ≤ 6.2 may be the new treatment target to achieve to reduce the risk of worse outcomes in the follow-up, if treat to target strategy studies will confirm it.

Our study has some limitations. Firstly, while our cohort was big enough to support the scrutiny of the selected predictors for most of the studied outcomes taking into account the rule of thumb of 10 events per predictor investigated, hospitalization and colectomy were rare events, and the "rule" is not met. For these outcomes, further studies with larger sample sizes are warranted to confirm our findings. Secondly, all the evaluated outcomes may imply some subjective decision based on patients' characteristics, multidisciplinary discussion, which is however common to all similar studies in this field. Third, since this was an observational study on consecutive patients with indication to CS, we did not stratify patients for disease activity before inclusion, however, this limitation did not impact the quality of the study population and the validity of the results. Fourth, we cannot be sure that the patient population evaluated in this study reflects all patients with UC. Our data need to be confirmed and validated in further large studies.

In conclusion, MUC is a novel non-invasive ultrasonography based tool able to predict disease course in UC patients. It may

TABLE 3 Risks of clinical outcomes in patients with UC over a median of 1.6 years of follow-up

	Negative disease course *n* (%)	Treatment escalation *n* (%)	Need for corticosteroids *n* (%)	Hospitalization *n* (%)	Colectomy *n* (%)
Total cohort (98 patients)	70 (71)	63 (64)	32 (33)	9 (9)	7 (7)
Patients with MUC ≤6.2 at baseline (n = 44)	21 (48)	17 (39)	11 (25)	1 (2)	0 (0)
Patients with MUC >6.2 at baseline (n = 54)	49 (91)	46 (85)	21 (39)	8 (15)	7 (13)

Abbreviations: MUC, Milan ultrasound criteria; UC, ulcerative colitis.

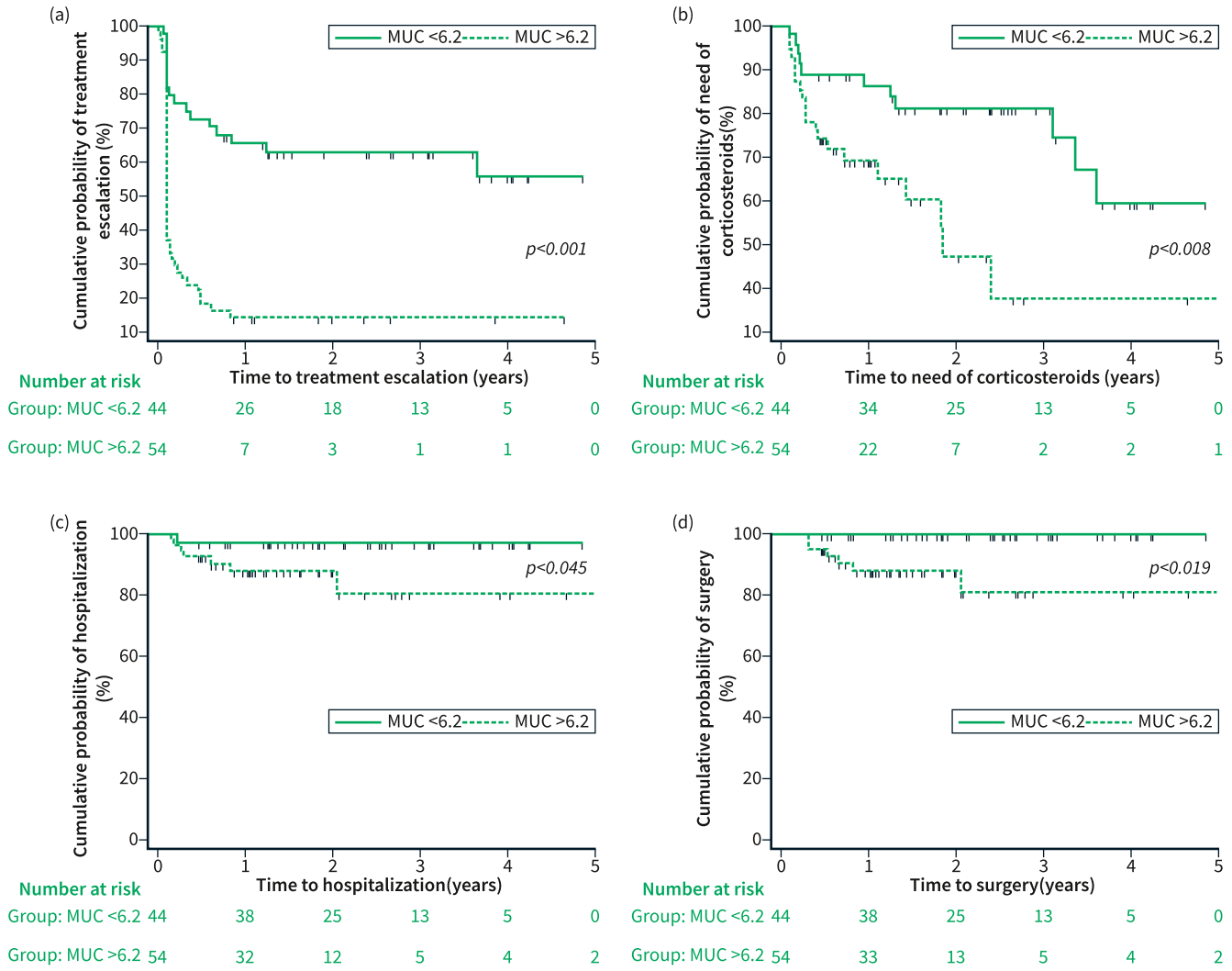

FIGURE 2 (a) Kaplan–Meier curves for the cumulative probability of treatment escalation in patients with Milan ultrasound criteria (MUC) ≤ 6.2 at baseline (solid line) or MUC > 6.2 at baseline (dotted line) (log-rank test, $p < 0.001$). (b) Kaplan–Meier curves for the cumulative probability of need of corticosteroids in patients with MUC ≤ 6.2 at baseline (solid line) or MUC > 6.2 at baseline (dotted line) (log-rank test, $p = 0.008$). (c) Kaplan–Meier curves for the cumulative probability of hospitalization in patients with MUC ≤ 6.2 at baseline (solid line) or MUC > 6.2 at baseline (dotted line) (log-rank test, $p = 0.045$). (d) Kaplan–Meier curves for the cumulative probability of colectomy in patients with MUC ≤ 6.2 at baseline (solid line) or MUC > 6.2 at baseline (dotted line) (log-rank test, $p = 0.019$)

replace CS in certain conditions in which mucosal biopsies are not required.

ACKNOWLEDGMENT

No funding was obtained for this project.

CONFLICT OF INTEREST

Mariangela Allocca received consulting fees from Nikkiso Europe, Mundipharma, Janssen, Abbvie, Ferring and Pfizer; Federica Furfaro received consulting fees form Amgen, Abbvie and lecture fees from Janssen and Pfizer; LP-B reports personal fees from Merck, Abbvie,

Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillots, Vifor, Hospira/Pfizer, Celltrion, Takeda, Biogaran, Boerhinger-Ingelheim, Lilly, HAC-Pharma, Index Pharmaceuticals, Amgen, Sandoz, Forward Pharma GmbH, Celgene, Biogen, Lycera, and Samsung Biosepsis; Gionata Fiorino received consultancy fees from Ferring, MSD, AbbVie, Takeda, Janssen, Amgen, Sandoz, Samsung Bioepis, Celltrion; Silvio Danese served as a speaker, consultant and advisory board member for Schering-Plough, Abbott (AbbVie) Laboratories, Merck, UCB Pharma, Ferring, Cellerix, Millenium Takeda, Nycomed, Pharmacosmos, Actelion, Alfa Wasserman, Genentech, Grunenthal, Pfizer, AstraZeneca, Novo Nordisk, Cosmo Pharmaceuticals, Vifor and Johnson and Johnson. Cecilia Dell'Avalle, Vincenzo Craviotto, Alessandra Zilli, Ferdinando D'Amico and Stefanos Bonovas have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Mariangela Allocca is guarantor of the article, she conceived and designed the study; Cecilia Dell'Avalle, Vincenzo Craviotto and Alessandra Zilli collected all the data; Mariangela Allocca and Federica Furfaro performed bowel US; Stefanos Bonovas and Mariangela Allocca performed the data analysis; Mariangela Allocca, Stefanos Bonovas and Gionata Fiorino drafted the manuscript; Laurent Peyrin-Biroulet and Silvio Danese critically revised the manuscript; all authors approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

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How to cite this article: Allocca M, Dell'Avalle C, Craviotto V, Furfaro F, Zilli A, D'Amico F, et al. Predictive value of Milan ultrasound criteria in ulcerative colitis: a prospective observational cohort study. United European Gastroenterol J. 2022;10(2):190–7. https://doi.org/10.1002/ueg2.12206