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High body mass index is associated with increased risk of treatment failure and surgery in biologic-treated patients with ulcerative colitis

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Summary

Background: Though pharmacokinetic studies suggest accelerated biologic drug clearance with increasing body weight, evidence of obesity's impact on clinical outcomes in biologic-treated patients with ulcerative colitis (UC) is inconsistent.

Aim: To evaluate the impact of obesity on real world response to biological therapy in patients with UC.

Methods: In a single-centre retrospective cohort study between 2011-2016 of biologic-treated patients with UC, we evaluated treatment response by baseline body mass index (BMI). Primary outcome was treatment failure (composite outcome of IBD-related surgery/hospitalisation or treatment modification including dose escalation, treatment discontinuation or addition of corticosteroids); secondary outcomes were risk of IBD-related surgery/hospitalisation and endoscopic remission. We conducted multivariate Cox proportional hazard analyses to evaluate the independent impact of BMI on clinical outcomes. Stratified analysis by weight-based regimens (infliximab) or fixed-dose regimens (adalimumab, golimumab, vedolizumab, certolizumab pegol) was performed.

Results: We included 160 biologic-treated UC patients (50% males, 55% on infliximab) with median (IQR) age 36 y (26-52) and BMI 24.3 kg/m^2 (21.4-28.7). On multivariate analysis, each 1 kg/m^2 increase in BMI was associated with 4% increase in the risk of treatment failure (adjusted hazard ratio [aHR], 1.04 [95% CI, 1.00-1.08]) and 8% increase in the risk of surgery/hospitalisation (aHR, 1.08 [1.02-1.14]). The effect on treatment failure was seen in patients on weight-based dosing regimens or fixed-dose therapies.

Conclusion: BMI is independently associated with increased risk of treatment failure in biologic-treated patients with UC, independent of dosing regimen.

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1 | INTRODUCTION

The prevalence of obesity and IBD is increasing in parallel; approximately 15%-40% of patients with IBD are obese and up to 66% are overweight.[1-4] Obesity has been associated with increased risk of developing Crohn's disease, but not ulcerative colitis (UC).[5,6] Obesity has been variably associated with IBD phenotype, with some studies suggesting milder disease and others suggesting lower prevalence of remission in cross-sectional studies.[7,8] Longitudinal studies have suggested that obesity is associated with inferior quality of life, higher burden of hospitalisation and healthcare utilisation, and higher risk of relapse; among patients who undergo surgery, obesity has been associated with increased risk of short-term complications.[2-4,8]

Population pharmacokinetic studies of biologic agents have consistently shown that higher body weight is associated with increased drug clearance and lower trough concentrations.[9-11] However, clinical studies of obesity's impact on response to biologic agents in patients with IBD have been sparse and conflicting. In their cohort of 261 infliximab-treated patients, Billiet and colleagues observed that each unit increase in BMI was associated with 6% higher risk of treatment failure only on univariate analysis, but not on multivariate analysis.[12] In contrast, Bultman and colleagues observed that obesity (BMI $\geq$30 kg/m^2) is associated with increased need for adalimumab dose escalation.[13] Most of the studies have been performed in patients with Crohn's disease, with only a single, 24-patient study in infliximab-treated patients with UC.[14] Given higher drug clearance and faecal wasting in patients with severe UC compared to Crohn's disease, obesity may be more relevant in biologic-treated patients with UC.[15,16]

Hence, we conducted a retrospective cohort study to evaluate the impact of obesity on response to biologic therapy in patients with UC. We hypothesised that higher BMI is associated with an increased risk of treatment failure in biologic-treated patients with UC, particularly in a subset of patients treated with fixed-dose regimens.

2 | METHODS

2.1 | Study design

We performed a retrospective cohort study in biologic-treated patients with UC seen and followed at University of California San Diego (UCSD). Patients were included if they had UC, were new users of a biologic agent (anti-tumour necrosis factor-α [TNF] agent such as infliximab, adalimumab or golimumab, or anti-integrin agent, vedolizumab) between January 1, 2011 and December 31, 2016, were followed at UCSD for at least 6 months, and had a BMI recorded within 3 months of start of biologic therapy. Patients were excluded if they: (1) had Crohn's disease or indeterminate colitis, (2) were not treated with biologic agents, (3) were followed at UCSD for <6 months, (4) were underweight with BMI <18.5 kg/m^2 at time of cohort entry, (5) were pregnant or (6) had already undergone colectomy prior to starting biologic therapy. Prevalent users of biologic agents (ie patients who were already on a biologic agent at time of study start date) were also excluded to minimise immortal time bias. This study was approved by the UCSD Institutional Review Board (IRB #160967).

2.2 | Data abstraction

A single reviewer (SK) abstracted data through medical record review using a piloted data abstraction form, with constant feedback from a second gastroenterologist reviewer (SS). Besides exposure and outcomes (as detailed below), data on the following variables were abstracted: (1) patient characteristics—age, sex, smoking status and BMI at time of starting new biologic therapy, (2) disease characteristics—disease extent, disease duration, endoscopic disease activity at time of starting biologic agent classified by Mayo endoscopy score, laboratory variables including haemoglobin, erythrocyte sedimentation rate, albumin and C-reactive protein at time of starting biologic agent, prior hospitalisation within 1 year of cohort entry, (3) treatment characteristics—current index biologic agent, prior use of immunomodulators and other biologic agents, prior use of corticosteroids within the past 1 year, concurrent therapy with immunomodulators and/or corticosteroids and (4) outcomes—date of IBD-related surgery, hospitalisation, dose escalation, treatment discontinuation and addition of corticosteroids and endoscopic re-assessment after starting biologic therapy.

2.3 | Exposure

The primary predictor variable was BMI as a continuous variable. We evaluated the association between each 1 kg/m^2 increase in BMI and clinical outcomes.

2.4 | Outcomes

Primary outcome of interest was time to treatment failure, a composite outcome of IBD-related surgery, hospitalisation, or treatment modification (including index biologic dose escalation, drug discontinuation or addition/continuation of corticosteroids after 3 months of starting index biologic therapy). Secondary outcomes of interest were: time to IBD-related surgery (ileal pouch anal anastomosis, ileorectal anastomosis or colectomy with end ileostomy), time to IBD-related hospitalisation (primary discharge diagnosis of UC flare), or achieving endoscopic remission (Mayo endoscopy sub-score of 0 or 1, based on review of endoscopy reports performed by study IBD specialists) within 1 year of starting biologic therapy. Patients were followed from time of starting new biologic therapy until occurrence of study outcome or definitive colectomy surgery (all other outcomes were considered independent of other), loss to follow-up, treatment interruption for >6 months or study completion (December 12, 2016).

Additionally, we performed post-hoc analysis evaluating the association between biologic trough concentration and BMI. At our centre, routine proactive therapeutic drug monitoring (TDM) is not

performed for all patients with quiescent IBD; instead, providers variably perform reactive TDM in patients failing therapy, and in selected patients with quiescent disease.

2.5 | Statistical analysis

We performed univariate time-to-event analysis or logistic regression (for endoscopic remission outcome) to evaluate the association between BMI and clinical outcomes. To evaluate the independent effect of BMI on response to biologic therapy, we performed multivariate Cox proportional hazard analyses with a combination of backward variable selection ($P < 0.15$ in univariate analysis among age, sex, BMI, disease duration, disease extent, C-reactive protein, prior and concomitant use of steroids and/or immunomodulators) and inclusion of clinically relevant variables (albumin [≥3.5 g/dL vs <3.5 g/dL], prior anti-TNF failure for all outcomes; in addition, for hospitalisation outcome, prior hospitalisation within 1 year of cohort entry). Proportional hazard assumption was met based on graphical evaluation and examining weighted residuals.[17] Association between biologic trough concentration and BMI was examined using Pearson's correlation coefficient.

To evaluate whether BMI may differentially impact response to weight-based dosing regimens vs fixed-dose therapies, we performed stratified analysis by type of index biologic agent, evaluating the impact of BMI on clinical outcomes in each stratum. Our sample was a convenient consecutive sample, starting from the time the IBD centre was established at our hospital. No formal sample size assessment was performed.

All hypothesis testing was performed using a 2-sided P value with a statistical significance threshold <0.05. All statistical analyses were performed with Stata MP (StataCorp. 2015. College Station, TX: StataCorp LP).

3 | RESULTS

3.1 | Patient characteristics

Table 1 shows the baseline characteristics of 160 patients with UC who formed the study cohort. Median age of cohort was 36.0 y (IQR, 26.0-51.8), with 80 males and 80 females. Median BMI was 24.3 kg/m^2 (IQR, 21.4-28.7), and 18.1% were obese (class I obese, with BMI 30.0-34.9 kg/m^2: 8.7%; class II obesity with BMI 35.0-39.9 kg/m^2: 3.1%; class III obesity with BMI ≥40.0 kg/m^2: 6.3%). Approximately 61% patients had pancolitis, and 53% had severely active endoscopic disease. Approximately 73% patients were biologic-naïve at time of cohort entry, 55.0% treated with infliximab (weight-based therapy) and 18.8% were treated with vedolizumab. About 53% and 52% were concomitantly on immunomodulators and corticosteroids, respectively, and 81% had used corticosteroids in the last 1 year prior to initiation of biologic therapy. Over a median follow-up of 2 years after starting biologic therapy, 110 patients experienced treatment failure, 23 patients underwent surgery and 41 patients experienced IBD-related hospitalization. All patients with "treatment failure" underwent treatment modification as the primary reason for treatment failure; within treatment modification, initiation of corticosteroids was the most common intervention. These have been detailed in Table S1.

3.2 | Primary outcome

On multivariate analysis, each 1 kg/m^2 increase in BMI was associated with a 4% higher risk of treatment failure (aHR, 1.04; 95% CI, 1.00-1.08, $P = 0.029$). This effect was similar in patients treated with weight-based therapy (aHR, 1.05; 95% CI, 1.00-1.10, $P = 0.050$) and in patients treated with fixed-dose therapy (aHR, 1.05; 95% CI, 0.99-1.10, $P = 0.106$) (Figure 1). Besides BMI, low albumin and shorter disease duration were associated with treatment failure (Table 2).

3.3 | Secondary outcomes

3.3.1 | IBD-related surgery and/or hospitalisation

On multivariate analysis, each 1 kg/m^2 increase in BMI was associated with 8% risk of IBD-related surgery or hospitalisation (aHR, 1.08; 95% CI, 1.02-1.14, $P = 0.008$). This negative effect was similar in patients treated with weight-based therapy (aHR, 1.10; 95% CI, 1.03-1.19, $P = 0.006$) or in patients treated with fixed-dose therapy (aHR, 1.09; 95% CI, 0.99-1.20, $P = 0.059$) (Figure 1). Besides BMI, prior hospitalisation within 1 year of cohort entry was also associated with 2.3 times higher risk of IBD-related surgery or hospitalisation (aHR, 2.26; 95% CI, 1.01-5.05, $P = 0.047$) (Table 3).

3.3.2 | Endoscopic remission

Although not significant, each 1 kg/m^2 increase in BMI was associated with 6% lower risk of achieving endoscopic remission (aOR, 0.94; 95% CI, 0.87-1.01, $P = 0.070$), though it did not meet statistical significance. This negative effect was significant only in patients treated with weight-based therapy (aOR, 0.91; 95% CI, 0.83-0.99, $P = 0.035$), but not in patients treated with fixed-dose therapies (aOR, 0.96; 95% CI, 0.85-1.10, $P = 0.571$) (Figure 1). Besides BMI, patients with longer disease duration were significantly more likely to achieve endoscopic remission (aOR, 1.12; 95% CI, 1.04-1.21, $P = 0.003$) (Table 4).

3.3.3 | Biologic trough concentration and body mass index

Overall, trough concentration during maintenance therapy was available for 51/88 patients treated with infliximab and 14/31 patients treated with adalimumab. A significant negative correlation was observed between BMI and adalimumab trough concentration (Pearson's correlation coefficient = −.58, $P = 0.03$); none of the patients had undetectable adalimumab trough concentration. In contrast, we did not observe any significant association between BMI and infliximab trough

TABLE 1 Baseline characteristics of biologic-treated patients with ulcerative colitis included in cohort

Baseline characteristics	Normal BMI (18.5-24.9 kg/m^2)	Overweight (25.0-29.9 kg/m^2)	Obese (≥30 kg/m^2)
Number of patients	90 (56.3%)	41 (25.6%)	29 (18.1%)
Patient characteristics			
Age at cohort entry, in years (median, IQR)	31.0 (24.0-45.8)	43.0 (31.5-53.0)	40.0 (29.0-54.5)
Gender-Males/Females	36/54	28/13	16/13
Follow-up, mo (median, IQR)	22.0 (14.5-36.7)	28.5 (19.6-34.3)	20.8 (14.1-31.7)
Body mass index (kg/m^2) (median, IQR)	21.6 (20.4-23.2)	27.4 (26.0-28.7)	35.2 (32.2-40.9)
Smoking status (%)			
Current smokers	4 (4.4)	2 (4.9)	2 (6.9)
Recent past smoker (<1 y from cohort entry)	1 (1.1)	0 (0)	1 (3.4)
Former smokers	14 (15.6)	16 (39.0)	9 (31.0)
Never smoker	71 (78.9)	23 (56.1)	17 (58.6)
Disease characteristics			
Disease duration at cohort entry, in years (median, IQR)	4.0 (1.0-8.0)	5.0 (2.0-11.5)	4.0 (1.0-7.5)
Disease extent, N (%)			
Extensive colitis	59 (65.6)	19 (46.3)	20 (69.0)
Left-sided colitis	30 (33.3)	22 (53.7)	9 (31.0)
Proctitis	1 (1.1)	0 (0)	0 (0)
Disease severity[a] (%)			
Mayo score 0	0 (0)	1 (4.3)	0 (0)
Mayo score 1	10 (18.5)	0 (0)	0 (0)
Mayo score 2	13 (24.1)	6 (26.1)	8 (53.3)
Mayo score 3	31 (57.4)	16 (69.6)	7 (46.7)
Prior IBD hospitalisation <1 y from cohort entry (%)	33/90 (36.7)	8/41 (19.5)	3/29 (10.3)
Treatment characteristics			
Anti-TNF taken at cohort entry (%)			
Infliximab	49 (54.4)	23 (56.1)	16 (55.2)
Adalimumab	19 (21.1)	5 (12.2)	7 (24.1)
Golimumab	6 (6.7)	4 (9.8)	0 (0)
Certolizumab pegol	0 (0.0)	1 (2.4)	0 (0)
Vedolizumab	16 (17.8)	8 (19.5)	6 (20.7)
# of prior anti-TNF failures			
0	71 (78.9)	29 (70.7)	17 (58.6)
1	16 (17.8)	8 (19.5)	10 (34.5)
2	2 (2.2)	4 (9.8)	2 (6.9)
3	1 (1.1)	0 (0)	0 (0)
Prior steroid use <1 y from cohort entry (%)	74 (82.2)	34 (82.9)	22 (75.9)
Steroid use at cohort entry (%)	46 (51.1)	22 (53.7)	15 (51.7)
Prior use of immunomodulators (%)	47 (52.2)	20 (48.8)	18 (62.1)
Immunomodulator use at cohort entry (%)			
Azathioprine	30 (63.8)	17 (65.4)	7 (43.75)
Mercaptopurine	11 (23.4)	8 (30.8)	7 (43.75)
Methotrexate	6 (12.8)	1 (3.8)	2 (12.5)
C-reactive protein, g/L (median, IQR)	0.002 (0.001-0.013)	0.007 (0.003-0.027)	0.003 (0.002-0.006)
Albumin, g/L (median, IQR)	40.0 (37.0-43.0)	41.0 (37.0-42.3)	41.0 (39.0-44.0)

(Continues)

TABLE 1 (Continued)

Baseline characteristics	Normal BMI (18.5-24.9 kg/m^2)	Overweight (25.0-29.9 kg/m^2)	Obese (≥30 kg/m^2)
Haemoglobin, g/L (mean, SD)	120 (21)	125 (22)	126 (20)
Erythrocyte sedimentation rate, mm/hr (median, IQR)	15.5 (6.0-30.0)	18.5 (6.0-42.3)	11.0 (7.0-18.8)

BMI, body mass index; IQR, interquartile range; IBD, inflammatory bowel disease; TNF, tumour necrosis factor.
[a]Data available for 92/160 patients (54 patients with normal BMI, 23 overweight patients and 15 obese patients).

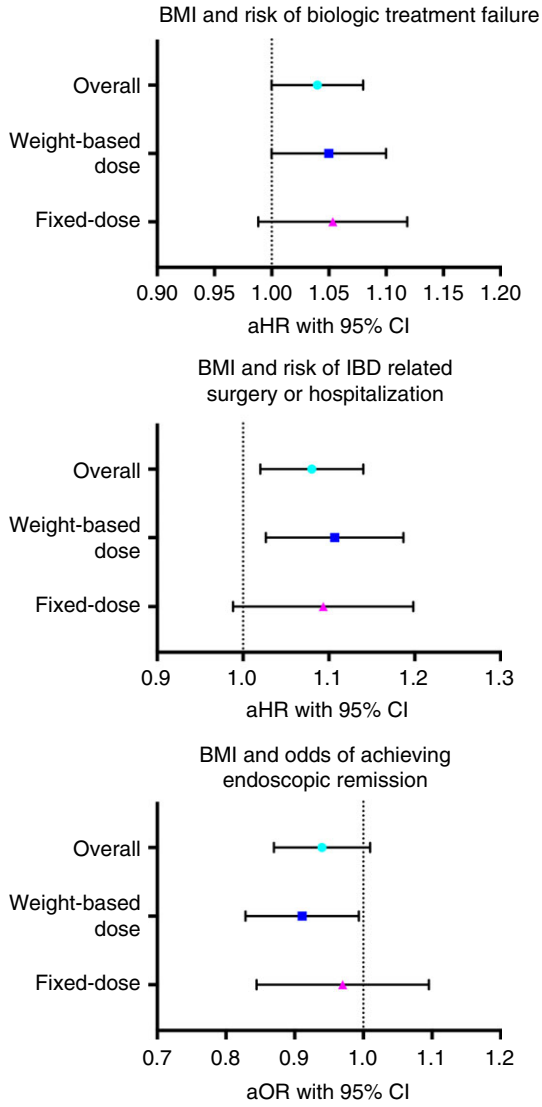

FIGURE 1 Association between BMI and risk of treatment failure, risk of IBD-related surgery or hospitalisation, and odds of achieving endoscopic remission

concentration (Pearson's correlation coefficient = .11, P = 0.46); 10/51 patients had undetectable infliximab concentration.

4 | DISCUSSION

In this retrospective study on the impact of BMI on treatment response and outcomes in 160 biologic-treated patients with UC, we made several key observations. First, we found that higher BMI is independently associated with an increased risk of treatment failure and IBD-related surgery and/or hospitalisation, with each unit increase in BMI being associated with a 4%-8% higher risk of adverse outcomes. This effect of BMI is independent of biologic dosing regimen, observed in patients treated with either weight-based dosed infliximab or other fixed-dose therapies. Second, we also observed that higher BMI may be independently associated with failure to achieve endoscopic remission, though this outcome did not reach statistical significance. Our findings suggest that obesity is a negative prognostic factor in biologic-treated patients with UC and a treatment effect modifier that must be considered in clinical trial design and clinical practice.

TABLE 2 Multivariate Cox proportional hazard analysis examining factors associated with treatment failure in biologic-treated patients with ulcerative colitis

Variables	Hazard ratio	95% CI	*P* value
Body mass index (per 1 kg/m^2 increase)	1.043	1.004-1.082	0.029
Prior prednisone use (yes vs no)	1.852	0.93-3.67	0.078
Concomitant immunomodulators (yes vs no)	0.652	0.415-1.024	0.063
Albumin (<3.5 g/dL vs ≥3.5 g/dL)	1.733	1.028-2.924	0.045
Disease duration (per 1 y)	0.951	0.912-0.991	0.018
Prior anti-TNF failure (yes vs no)	0.753	0.463-1.223	0.25

CI, confidence interval; TNF, tumour necrosis factor.

TABLE 3 Multivariate Cox proportional hazard analysis examining factors associated with IBD-related surgery or hospitalisation in biologic-treated patients with ulcerative colitis

Variables	Hazard ratio	95% CI	*P* value
Body mass index (per 1 kg/m^2 increase)	1.078	1.020-1.138	0.008
Prior prednisone use (yes vs no)	1.894	0.559-6.419	0.305
Concomitant immunomodulators (yes vs no)	1.006	0.481-2.104	0.988
Albumin (<3.5 g/dL vs ≥3.5 g/dL)	1.318	0.548-3.165	0.537
Disease duration (per 1 y)	0.999	0.934-1.068	0.974
Prior anti-TNF failure (yes vs no)	0.675	0.290-1.571	0.362
Prior hospitalisation (yes vs no)	2.261	1.012-5.053	0.047

CI, confidence interval; TNF, tumour necrosis factor.

TABLE 4 Multivariate logistic regression analysis examining factors associated with achieving endoscopic remission in biologic-treated patients with ulcerative colitis

Variables	Odds ratio	95% CI	*P* value
Body mass index (per 1 kg/m^2 increase)	0.937	0.873-1.005	0.070
Weight-based dosing (yes vs no)	2.201	0.884-5.480	0.090
Albumin (<3.5 g/dL vs ≥3.5 g/dL)	3.110	0.930-11.13	0.065
Disease duration (per 1 y)	1.121	1.040-1.209	0.003
Prior anti-TNF failure (yes vs no)	1.118	0.405-3.085	0.829

CI, confidence interval; TNF, tumour necrosis factor.

Our findings build upon an evolving and conflicting body of evidence on the potential negative impact of obesity in patients with IBD, in particular its impact on treatment response to biologics.[18-20] While obesity has been consistently shown to negatively impact treatment response to anti-TNF agents in rheumatic diseases, this evidence has been inconsistent in patients with IBD. In a meta-analysis of 16 studies with 3130 patients with IBD, we observed that obesity does not significantly influence treatment response to anti-TNF agents (odds of failing therapy, 1.20; 95% CI, 0.88-1.64).[21] However, there is considerable heterogeneity with differences in study design, obesity exposure categories, clinical outcomes and variable adjustment for key confounding variables. Moreover, most of these studies have been conducted in patients with Crohn's disease. It is possible that in patients with Crohn's disease, local mesenteric creeping fat may play a more vital role in pathogenesis than systemic obesity.[22,23] In contrast, there has been limited assessment of the impact of obesity on response to biologic agents in patients with UC. In a study of 24 patients with UC treated with infliximab, Harper and colleagues observed a 30% increase in risk of UC flare per unit increase in BMI, adjusting for prior surgery, steroid use, extra-intestinal manifestations, age and disease duration. However, due to the small sample size, this multivariate model was likely overfitted.[14] Subgroup analysis of ULTRA-2 trial of adalimumab in UC observed a nonsignificant 1.5-fold higher risk of failing to achieve clinical remission in patients weighing ≥70 kg vs <70 kg.[24]

Obesity is recognised as a perpetual state of chronic low-grade inflammation, through systemic and paracrine increase in levels of cytokines, chemokines and adipokines, and is also associated with dysbiosis.[4,22,23] Obesity increases leptin secretion from adipocytes and resistin secretion from macrophages and leukocytes that increase levels of pro-inflammatory cytokines such as TNF, interleukin-1 and -6. Besides its direct impact on inflammation, obesity can also modify pharmacokinetics of biologic agents. Population pharmacokinetic studies of all approved biologic agents in IBD have identified high body weight as a risk factor associated with increased clearance of drug, resulting in shorter half-life and lower serum trough drug concentrations.[9-11] This effect might be related to rapid proteolysis and to a "TNF-sink" phenomenon with higher inflammatory burden due to adipose tissue in patients with obesity. This may explain why patients with obesity treated even with weight-based regimens such as infliximab, had inferior response to therapy.

Our study is one of the largest studies evaluating the impact of BMI on treatment response to biologics in patients with UC, with systematic data collection and evaluation of patient-important outcomes. By limiting analyses to new users of biologics followed at our centre and by adjusting for key confounders, we were able to overcome potential limitations of a tertiary referral centre retrospective cohort study. However, our study has some limitations which merit attention. First, our data on association between BMI and biologic trough concentrations needs to be interpreted with caution, since routine biologic trough concentration assessments were not performed, and drug clearance estimates were not performed. Trough concentrations in our cohort were measured selectively and variably, in patients losing response to biologic therapy and do not accurately represent the association between BMI and biologic trough concentrations. Hence, we were only able to hypothesise why obesity may negatively impact treatment response based on systemic drug exposure. We also did not routinely measure thiopurine metabolite levels. Secondly, findings on subgroup analysis should be interpreted with caution. Within strata of weight-based and fixed-dose therapies, though the summary estimates for all outcomes except endoscopic remission were very similar, overall results were sometimes borderline insignificant. These are likely a reflection of smaller sample size in subgroup analyses. Thirdly, we were unable to evaluate the impact of obesity on achieving clinical remission or response based on validated disease activity indices in this retrospective study. Instead we relied on pragmmatic clinically relevant outcomes including surgery, hospitalisation or need for treatment modification, which may be subject to provider preferences. The secondary outcomes including IBD-related surgery and/or hospitalisation as well as achieving endoscopic remission, however, are more robust with limited risk of bias. All endoscopies at our centre are performed by providers with clinical and research focus on IBD, which decreases risk of misinterpretation. Fourth, we were not able to study whether the association between BMI and response to biologics varied between anti-TNF agents and vedolizumab, due to a small number of patients on vedolizumab, most of whom had prior anti-TNF exposure. Finally, there is potential risk of considerable weight changes in patients with severe disease starting biologics, either weight loss due to severe disease activity or weight gain due to corticosteroid-dependent disease.[25]

Our findings have important clinical implications. In clinical practice, physicians may consider aggressive treatment and close proactive monitoring in patients with high BMI treated with biologic agents. Some potential changes include empirically using higher doses of anti-TNF therapy in overweight and obese patients, frequent therapeutic drug monitoring and/or use of combination therapy with immunomodulators to increase drug concentration and decrease risk of immunogenicity. Clinical trials should consider obesity as a potential effect modifier, and perform and report appropriate analyses. Finally, high BMI may offer a potential therapeutic intervention by directly targeting the obesity itself for treatment with a multi-disciplinary approach in IBD patients. Small RCTs and

cohort studies in patients with psoriasis, psoriatic arthritis and rheumatoid arthritis have suggested a beneficial effect of intentional weight loss on treatment response to anti-TNF agents.[22-24,26-28]

In conclusion, in a cohort of biologic-treated patients with UC, we observed that high BMI is independently associated with increased risk of treatment failure, including IBD-related surgery or hospitalisation, and may be a lower risk of achieving endoscopic remission. These effects were seen in patients treated with weight-based dosing regimens as well as fixed-dose agents. Prospective cohort studies and post-hoc analyses of RCTs with individual participant level data are warranted to confirm this association. If this effect is consistent, interventional studies targeting obesity should be explored for difficult-to-treat obese patients with UC.

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AUTHORSHIP

Guarantor of the article: Dr. Siddharth Singh had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Author contributions: SK, AZ, WJS, SS, study concept and design; SK, SS, acquisition of data; SK, NHN, JP, SS, analysis and interpretation of data; SK, SS, drafting of the manuscript; NHN, JP, PSD, BSB, NVC, EE, ELG, AZ, WJS, critical revision of the manuscript for important intellectual content; SK, NHN, JP, PSD, BSB, NVC, EE, ELG, AZ, WJS, SS, approval of the final manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information will be found online in the supporting information tab for this article.

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