Composite outcomes in observational studies of ulcerative colitis: A systematic review and meta-analysis

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Abstract

Background: Ulcerative colitis (UC) has been the focus of numerous observational studies over the years and a common strategy employed in their design is the use of composite and aggregate outcomes.

Objective: This systematic review and meta-analysis aims to identify composite and aggregate outcomes of observational studies in UC and to evaluate how the number and type of variables included and the length of follow-up affect the frequency of patients that achieve these outcomes.

Methods: A systematic literature search was carried out using MEDLINE [via PubMed], Scopus, and Web of Science online databases. Observational studies that included UC patients and reported composite or aggregate outcomes were identified. A set of variables considered to be representative of progressive or disabling UC was defined, the proportion of patients attaining the outcomes was determined and a random-effects meta-analysis was performed by dividing the identified studies into subgroups according to different criteria of interest.

Results: A total of 10,264 records were identified in the systematic search, of which 33 were retained for qualitative analysis and 20 were included in the meta-analysis. The mean frequency for composite outcomes was 0.363 [95% confidence interval (CI) 0.323-0.403]. The frequency of composite outcome for the subgroup of studies that included the variable “Biologics” was significantly higher than for those in which this variable was not reported [0.410; 95% CI 0.364-0.457 versus 0.298; 95% CI 0.232-0.364; \( p = 0.006 \)]. Composite outcomes were also more frequent as the follow-up duration increased.

Conclusion: The frequency of composite outcomes in observational studies of UC is dependent on the specific identity of the variables being reported. Moreover, longer...
INTRODUCTION

Ulcerative colitis is a chronic inflammatory disease restricted to the colon, with onset usually occurring in early adulthood and a high chance of relapse episodes during the lifetime of the patient. Along with Crohn’s Disease (CD), it constitutes the main component of Inflammatory Bowel Disease (IBD). Treatment targets for UC have become more diversified in recent years, incorporating objective measures of inflammation such as endoscopic procedures, histology and biomarkers.

Given the considerable costs and complex logistics associated with Randomized Clinical Trials (RCTs), observational studies have become a valuable source of information in the development of novel therapeutical approaches for chronic diseases. However, because they are not subjected to the strict methodological regulations that govern RCTs, observational studies present a remarkable heterogeneity in terms of their basic design, number of patients enrolled, duration of the monitoring and number and type of endpoint variables being reported. In particular, the inconsistency on the reported outcomes between individual studies and the potential for reporting biases has led to calls for the development of core outcome sets (COS).

Outcomes are particularly appropriate to maximize statistical power and therefore compensate for a potentially small patient population in a given study. We focused specifically in estimating the frequency of patients achieving composite and aggregate outcomes and in determining if and how this value was affected by the number and type of variables included in the study, as well as by its total duration.

MATERIALS AND METHODS

Search strategy

This study was conducted following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Guidelines and the Cochrane Collaboration Guidelines for reporting meta-analyses. Literature search was performed from inception to 14 July 2020 using three electronic databases: MEDLINE (via PubMed, https://pubmed.ncbi.nlm.nih.gov), Scopus (https://www.elsevier.com/solutions/scopus) and Web of Science (http://www.isiwebofknowledge). The words or medical subject heading terms used were: “((‘aggressive disease’) OR (‘disabling disease’) OR (‘disabling outcome’) OR (‘disabling outcomes’) OR (‘composite outcome’) OR (‘composite outcomes’) OR (‘composite event’) OR (‘composite events’) OR (‘composite endpoint’) OR (‘composite endpoints’) OR (‘composite’) OR (composit)) OR.

The frequency of composite outcomes in observational studies of UC is dependent on the specific identity of the variables being reported and on the follow-up duration. Reporting of the variable “Biologics” significantly increased the frequency of composite outcomes. These findings may be useful for the design of future observational studies of UC.
Eligibility criteria

Studies enrolling both adults and children previously diagnosed with UC using clinical, endoscopic, and/or pathological features were considered eligible for inclusion in this systematic review. The inclusion criteria were: [i] cohort, case-control, and cross-sectional studies with UC patients; [ii] studies evaluating composite or aggregate outcomes; and [iii] outcomes representing UC progression. There were no publication year restrictions but only articles written in English were included. The exclusion criteria were: [i] randomized controlled trials and post-hoc analysis, systematic reviews and meta-analysis, review articles, descriptive and diagnostic studies, animal and in vitro studies, study protocols, guidelines, editorials, and only abstracts available; [ii] studies selecting patients with diseases other than UC; studies evaluating only CD patients [iii] studies that did not define a composite or aggregate outcome of interest; [iv] studies reporting an improvement outcome; [v] studies that did not differentiate between UC and CD patients.

Study selection and data collection process

Two reviewers (CA and MS) independently screened the titles and abstracts according to the eligibility criteria and if a particular study failed to meet these criteria, it was excluded. In the second phase, the full text of all the remaining potentially relevant studies was analyzed, and the eligibility criteria were used again to discard non-relevant studies. Disagreement was resolved via consensus between the two reviewers. The following information was collected from the selected studies: authors’ names; publication year; country of origin; study design; observation period; number of patients (discriminated between UC and CD, if applicable); UC extent; subgroups (if applicable); outcome name, definition and reported variables (among the ones chosen for analysis). The number of patients achieving the defined outcome and its corresponding proportion was calculated if not explicitly stated. The proportion of patients achieving each variable of the composite outcome was not assessed. The observation period refers to the mean or median time of follow-up or the time of...
### TABLE 1  Characteristics of the studies included in the systematic review

| Study | Country | Study design | Observation period | Number of patients (N) | Disease extension | Subgroups | Outcome (C/A) | Outcome definition | Variables | No of patients with outcome/N % |
|-------|---------|--------------|--------------------|------------------------|-------------------|-----------|--------------|---------------------|-----------|-------------------------------|
| Acosta et al., 2016 | Spain | Unicentric prospective cohort | 12 months | 187 | E1: 28.8% | NA | Clinical relapse (A) | Rectal bleeding and any of the need for any remission induction treatment; any treatment escalation; and the need for hospitalization or colectomy | Hospitalization, Surgery, Steroids, Immunosuppressors, Biologics, Clinical assessment, Therapy modification | 49/187 26% |
| Ahmad et al., 2019 | USA | Unicentric retrospective cohort | 30 days | 268 | CSE, GPPs | GPPs | Disease course (C) | IBD-related hospitalization, surgery, or emergency department visit | Hospitalization, Surgery, Steroids, Immunosuppressors, Biologics | 19/114 17% |
| Ananthakrishnan et al. 2017 | USA | Multicentric prospective cohort | 365 ± 45 days | 871, adults | E1: CT, MT | E1: 5%, 10% | Combination therapy (anti-TNF and immunomodulator) | Monotherapy (anti-TNF) | New IBD-related surgery, hospitalizations, penetrating complications (new abscess or fistula), need for corticosteroids or new biologic | Hospitalization, Surgery, Steroids, Immunosuppressors, Biologics | 51/114 45% |
| Ardizzone et al., 2011 | Italy | Unicentric prospective cohort | 8 (1-59) months | 157 | Proctosigmoiditis: 15.3% | NA | Aggressive clinical course (C) | Hospitalizations and/or immunosuppressive treatment (IV cyclosporin A and/or oral azathioprine/mercaptopurine) and/or colectomy (proctocolectomy and ileal pouch-anal anastomosis) | Hospitalization, Surgery, Immunosuppressors | 74/157 47% |
| Basci et al., 2019 | UK | Unicentric prospective cohort | IBD1: 5.6 (3.6–7.1) years | 118, adults | E1: IBD1, IBD2 | IBD1 | Aggressive disease (C) | Treatment escalation with immunomodulators, biological therapies or surgery | Surgery, Immunosuppressors, Biologics | 27/52 52% |
| Bitton et al., 2001 | USA and Canada | Multicentric prospective cohort | 12 months (or until relapse) | 74 | Proctitis: 7% | Proctosigmoiditis: 36% | Clinical relapse (A) | Worsening of bowel function and rectal bleeding with endoscopic relapses > 1 | Clinical assessment, Endoscopic assessment | 27/74 36% |
| Study                  | Country      | Study design              | Observation period | Number of patients (N) | Disease extension | Outcome (C/A) | Outcome definition                                                                 | Variables | No of patients with outcome/N % |
|-----------------------|--------------|---------------------------|--------------------|------------------------|-------------------|---------------|-------------------------------------------------------------------------------------|-----------|-------------------------------|
| Buda et al., 2014     | Italy        | Unicentric prospective cohort | 12 months          | 19                     | NA                | NA            | Relapse (A)                                                                 | CAI ≥ 3 and abnormal mucosa at endoscopy     | 7/19            | 37%                           |
| Carvalho et al., 2015 | Portugal     | Unicentric retrospective cohort | 12 months          | 138                    | E1: 46.4%         | NA            | Clinical relapse (C)                                                                                            | Intensification or modification of medication (steroids, immunosuppressors, biologics and others not specified), UC-related hospitalization or surgery | 28/138   | 20%                           |
| Christensen et al., 2017 | USA         | Unicentric retrospective case-control | 22 (14–34) months$^b$ | 310                    | E1$: 11.0%        | Histologic normalization | Clinical relapse (C)                                                                 | SCAI > 2, subscore > 1 for stool frequency or rectal bleeding, or medication escalation for symptoms, hospitalization for UC relapse, or colectomy for refractory UC | 77/310   | 25%                           |
| Cushing et al., 2020  | USA          | Unicentric prospective cohort | 2 years            | 83                     | Pancolitis: 55%    | NA            | Clinical relapse (C)                                                                                            | Change in UC therapy (i.e., dose escalation, class change, and/or need for systemic corticosteroids), UC-related hospitalization, or UC-related surgery | 26/83    | 31%                           |
| Fabian et al., 2019   | Czech republic | Unicentric retrospective cohort | 12 months (minimum) | 41                     | NA                | NA            | Complicated disease course (C)                                                                 | Acute severe colitis (PUCAI > 65), necessity of colectomy or infliximab initiation | 13/41    | 32%                           |
| Frieti et al., 2017   | Italy        | Unicentric prospective cohort | 36 months          | 52                     | Pancolitis: 23.1%  | NA            | Clinical relapse (C)                                                                                            | Need of steroids, immunomodulators, and/or biological drugs | NA                  | NA                            |
| Fries et al., 2017    | Italy        | Multicentric retrospective cohort | 3 years            | 1091                   | E$: Elderly (>65), adults (40–64), young (<40) | NA            | Clinical relapse (C)                                                                                            | Need for more intensive medical therapy or surgery | 411/1091 | 38%                           |
| Study                  | Country            | Study design               | Observation period | Number of patients (N) | Disease extension | Subgroups | Outcome (C/A)                        | Outcome definition                                                                 | Variables*                                                                 | No of patients with outcome/N |
|-----------------------|--------------------|----------------------------|--------------------|------------------------|-------------------|-----------|-------------------------------------|----------------------------------------------------------------------------------|--------------------------------------------------------------------------------|-------------------------------|
| Fuentes et al., 2017  | The Netherlands    | Unicentric prospective cohort | 35 (21.5–37) months* | 12                     | E1*: 13%, 11%, 12% | E2*: 56%, 60%, 52% | E3*: 31%, 29%, 36% | Clinical relapse (C)                        | SCFAI ≥5 and/or need for rescue therapy                                             | Therapy modification            |                                |
| Gubatan et al., 2017  | USA                | Unicentric prospective cohort | 12 months          | 70                     | Left-sided colitis: 38.6% | NA        | Clinical relapse (C)                        | SCFAI ≥2, medication intensification (increase in dose of current regimen, addition of another medication, or change in class of medication due to symptom relapse), or UC-related hospitalization | Hospitalization | 20/70                          | 29%                           |
| Höie et al., 2007     | Several European countries | Multicentric prospective cohort | 10 years           | 771                    | NA                | NA        | Relapse (C)                                    | Dose increase of ongoing medical treatment or introduction of new medication, or surgery | Surgery                          | NA                            | NA                            |
| Jairath et al., 2019  | Canada             | Multicentric prospective cohort | DC: 32 weeks       | 4314 adults            | E1*: IBD1, IBD2 | E1*: 11%                        | Depression                         | Aggressive disease (C)                                    | Surgery or hospitalization                                                | Hospitalization                | NA                            | NA                            |
| Kochar et al., 2018   | USA                | Multicentric prospective cohort | 24 ± 10 months#    | 4314 adults            | CD: 2798       | E1*: 11%                        | Depression                         | Aggressive disease (C)                                    | Surgery or hospitalization                                                | Hospitalization                | NA                            | NA                            |
| Kurnool et al., 2018* | USA                | Unicentric retrospective cohort | 2 years#           | 160                    | Pancolitis: 61% | NA        | Treatment failure (C)                       | IBD-related surgery, hospitalization, or treatment modification (including index biologic dose escalation, drug discontinuation, or addition/continuation of corticosteroids ≥3 months after starting index biologic therapy) | Hospitalization                | NA                            | NA                            |
| Lee et al., 2011      | UK                 | Unicentric prospective cohort | IBD1: 575 (435–685) days$ | 67                     | E1*: IBD1, IBD2 | IBD1               | Disease course (C)                       | Treatment escalation with immunomodulators, biologics or surgery              | Surgery                          | 16/32                          | 50%                           |
| Study               | Country          | Study design                  | Observation period | Number of patients (N) | Disease extension | Subgroups | Outcome (C/A) | Outcome definition                                                                 | Variables | No of patients with outcome/N | %e |
|---------------------|------------------|-------------------------------|--------------------|------------------------|------------------|-----------|---------------|-------------------------------------------------------------------------------------|-----------|-----------------------------|----|
| Lobatón et al., 2017 | Belgium and Spain | Multicentric prospective cohort | 12 months          | 96                     | E1: 15%          | NA        | Clinical relapse (C)  | Clinical Mayo partial score ≥3 and/or need of introducing steroids or any other treatment escalation | Steroids | 22/96                       | 23% |
| Lund et al., 2011   | USA              | Multicentric retrospective cohort | NA                 | 610                    | NA               | NA        | Flare (C)      | Oral steroids or infliximab (de novo prescription), or oral/rectal 5-ASA, or need for colectomy | Surgery   | NA                          | NA |
| Magro et al., 2018  | Portugal         | Multicentric retrospective cohort | 12 (7-19) years  | 1481                   | E1: DC, VC       | NA        | Progressive disease (C) | One or more of the following events: Fibrovascular bridges, stenosis, pseudopolyps, lead pipe or shortening or hastral markings, colectomy, 2 or more hospitalizations, 2 or more corticosteroid course requirements/year, corticosteroid dependency or refractoriness, need to switch the immunosuppressive drug (AZA or MTX) or the anti-TNF drug (IFX or ADA) or add immunosuppressive drugs to anti-TNF treated patients. | Hospitalization, Steroids, Biologics | 445/1210 | 37% |
| Meyer et al., 2019  | France           | Multicentric equivalence cohort | RP: 423 (189-757) days  | 3112                   | NA               | CT-P13    | Effectiveness (C) | Death, UC-related surgery (colectomy and/or rectal resection and intestinal stoma), all-cause hospitalization (except childbirth) or reimbursement of another anti-TNF (adalimumab/golimumab) or vedolizumab | Hospitalization, Surgery, Biologics | 1453/3112 | 47% |
| Nguyen et al., 2020 | USA              | Unicentric retrospective cohort | 24 (14.8-34.7) months | 160                    | NA               | NA        | Treatment failure (C) | IBD-related surgery, hospitalization, or treatment modification (including index biologic dose escalation, drug discontinuation, or addition/continuation of corticosteroids ≥3 months after starting index biologic therapy) | Hospitalization, Surgery, Biologics | 110/160 | 69% |
| Niewiadomski et al., 2015 | Australia   | Multicentric retrospective and prospective cohort | 18 (12-82) months  | 252                    | Proctitis: 32%  | NA        | Disabling UC (C)  | More than two courses of steroids, further hospitalization after diagnosis, ongoing active disease, intestinal resection | Hospitalization, Surgery, Steroids | 24/96 | 25% |
| Study          | Country               | Study design                | Observation period | Number of patients (N) | Disease extension | Subgroups                  | Outcome (C/A)                                                                 | Outcome definition                                                                 | Variables                                                                 | No of patients with outcome/N | %   |
|---------------|-----------------------|-----------------------------|--------------------|------------------------|-------------------|-----------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|-------------------------------|------|
| Ozaki et al., 2018 | Japan                | Unicentric retrospective cohort | 608.6 days         | 194                    | Proctitis: 19.1% | NA                          | Clinical relapse (C)           | Partial Mayo Score ≥ 3 or modification of induction treatment [dose escalation, addition of steroids, tacrolimus, topical formulations or biologics] | Surgery, Immunosuppressors, Biologics, Clinical assessment, Therapy modification | 671/94                        | 35%  |
| Pereira et al., 2020 | Portugal and Belgium | Multicentric retrospective cohort | 17 (11–25) years | 931                    | Proctitis: 21.4% | Discovery cohort            | Complicated disease (C)       | Need hospitalization, corticosteroid or corticosteroid resistant or no responder to immunosuppressors or need biologics or colectomy | Hospitalization, Surgery, Steroids, Biologics                                         | NA                            | NA   |
| Riley et al., 1991 | UK                   | Unicentric prospective cohort | 12 months          | 82                     | Proctitis: 23%  | NA                          | Relapse (A)                    | Symptomatic deterioration with hemorrhagic in endoscopy                      | Clinical assessment, Endoscopic assessment                                         | 27/82                         | 33%  |
| Stallmach et al., 2014 | Germany              | Multicentric retrospective cohort | 60 months         | 262                    | Proctitis: 16.4% | NA                          | Progressive disease (C)       | Need for immunosuppressive therapy, thiopurines or methotrexate or anti-TNF-α antibodies or cyclosporine A or tacrolimus | Immunosuppressors, Biologics                                                 | 104/262                      | 40%  |
| Thomsen et al., 2020 | Denmark              | Multicentric retrospective cohort | Thiopurines and allopurinol: 83 person-years | 10,367, adults          | Thio | NA                          | Clinical relapse (C)           | Need for anti-TNFα treatment or IBD-related hospitalization, IBD-related major surgery or death | Hospitalization, Surgery, Biologics                                             | 1960/4883                     | 40%  |
| Ungaro et al., 2019 | USA                  | Multicentric retrospective cohort | 155 to 287 days   | 3589                   | NA              | NA                          | Adverse clinical events (C)   | New corticosteroid use or UC-related hospitalization or surgery               | Hospitalization, Surgery, Steroids                                             | NA                            | NA   |
occurrence of the outcome, when available. The variables considered were selected as the most clinically relevant parameters in IBD assessment and approach, but did not necessarily include all the aspects referred to in the reported outcomes.

Endpoints under analysis

A composite outcome was defined as an outcome composed by two or more variables and to achieve the outcome the patient needed to present at least one variable. An aggregate outcome was defined as the simultaneous presence of all the parameters considered. The outcomes represented disease progression and included the following variables: hospitalization, surgery, steroids, immunosuppressors, biologics, clinical assessment, endoscopic assessment and therapy modification. Hospitalization was defined as one or more inpatient stays for any UC-related cause. Surgery was defined as at least one surgery for any UC-related cause. Steroids was defined as reported de novo use, dose increase, change, dependency or refractoriness to corticosteroids. Immunosuppressors was defined as reported de novo use, switch, dose increase or unspecified immunosuppressive therapy. Biologics was defined as reported as de novo use, switch, dose increase or treatment frequency increase of any therapeutic agent targeting tumor necrosis factor-α or other pro-inflammatory mediators. Clinical Assessment was defined as reported UC clinical symptoms or manifestations, extra intestinal manifestations, imagiological disease activity evaluation or UC clinical scores modification towards worsening disease. Endoscopic Assessment was defined as reported endoscopic scores or any other endoscopic evaluation. Therapy modification was defined as medication adjustments for UC-related symptoms or increase in UC activity when the drug was not identified.

Quality assessment

The methodological quality was assessed by using the validated Critical Appraisal Skills Programme checklist, which systematically assesses the validity, results, and relevance for each study included in the analysis. Each item of the checklist was evaluated using a color scheme: [i] green if the study met all the parameters included in each item; [ii] yellow if the study met the parameters partially or if it did not have enough information; [iii] red if the study did not meet the parameters included in each item.

Statistical analysis

The main data analyzed in this meta-analysis were the proportions of patients achieving a composite outcome. The proportion of patients achieving the outcome was calculated and compared according to the predefined variables reported in the study. The following comparisons between subgroups were performed:
frequency of composite outcome according to [i] total number of variables; [ii] presence of each predefined variable; [iii] presence of a combination of two different predefined variables; [iv] total length of study follow-up; [v] number of patients included in the studies. In addition, the entire population of outcomes was divided in subgroups reporting a specific predefined “core” variable, and differences within these subgroups according to the presence or absence of the remaining predefined variables were statistically tested. Comparisons were not performed when the subgroups defined by the presence or absence of the considered variable were composed by only one or two outcomes.

To perform the meta-analysis, the “metaprop” function from the “meta” package of the R statistical programming language was used and the “PRAW” summary measure was employed for the pooling of studies. A random-effects model was adopted taking into consideration the differences observed across studies.

Cochran’s Q test and the $I^2$ statistic were used to assess statistical heterogeneity.\textsuperscript{10} In addition, Egger’s test was used to detect potential publication bias.\textsuperscript{11} A sensitivity analysis was performed to assess the influence of any individual study on the overall results. A Venn diagram and Upset plot were generated using the “UpsetR” and “nVennR” packages included within the R software, to graphically illustrate the distribution of the predefined variables among the individual studies included in the meta-analysis.

All analyses and charts were executed using R software version 4.1.0 and a $p$-value lower than 0.05 was considered statistically significant.

**RESULTS**

**Literature search and study selection**

The selection strategy followed is summarized in Figure 1. The electronic database search yielded 10,250 records (1885 in PubMed, 4323 in Scopus, and 4042 in Web of Science); the manual search identified 14 additional studies. Following the removal of duplicates ($n = 4444$), 5820 records remained, of which 5582 were excluded on the screening phase. The remaining 238 records were evaluated for eligibility. Following full-text assessment, 205 articles were excluded, and the remaining 33 articles were selected for the qualitative analysis. Twenty of those 33 were included in the meta-analysis (Figure 1).

**Quality assessment**

The results of the methodological quality assessment are summarized in Supplementary Table 1. All the selected studies clearly stated the issue being evaluated, but nearly all of them exhibited some problem related to the recruitment of the patient cohorts. In addition, some of the studies failed to take confounding factors into consideration and adapt their design and/or analysis accordingly.\textsuperscript{12–17} The follow-up was considered complete enough and of suitable duration in most of the cases, and the results were deemed to be believable in general.
Characteristics of included studies

Study characteristics are summarized in Table 1. Of all the articles selected for this systematic review, 26 included only UC patients,\textsuperscript{12, 14, 16–40} while the remaining seven\textsuperscript{13, 15, 17, 41–44} also included CD patients. Both the number of patients and the observation period of individual studies showed wide variations, ranging from twelve\textsuperscript{38} to 10,367 patients\textsuperscript{44} and from 30 days\textsuperscript{13} to a median of 17 years,\textsuperscript{33} respectively. One of the selected articles\textsuperscript{13} included two cohorts of patients with the outcomes discriminated by cohort. In this case, each cohort was considered as an independent outcome for the purposes of the analysis. Twenty-nine composite outcomes were registered from a total of 28 studies,\textsuperscript{12–15, 17–23, 27–30, 32–44} and five aggregate outcomes from five studies.\textsuperscript{16, 24–26, 31} The outcomes where heterogeneous in terms of the reporting of pre-defined variables considered here: the variable Hospitalization was reported in 17 outcomes,\textsuperscript{13, 15, 17, 18, 20, 22, 23, 26, 30, 32, 33, 35, 36, 39, 41, 44} Surgery in 22 outcomes,\textsuperscript{13–15, 17, 20–23, 26–30, 32, 33, 35, 36, 39, 41–44} Steroids in 15 outcomes,\textsuperscript{13, 15, 19, 20, 22, 23, 26–28, 30–32, 33, 35, 40, 41} Immunosuppressors in 11 outcomes,\textsuperscript{13, 19, 20, 22, 26, 29, 34–36, 42, 43} Biologics in 18 outcomes,\textsuperscript{13, 14–19, 23, 26–28, 30–33, 35, 41–44} Clinical Assessment in 14 outcomes,\textsuperscript{12, 14–16, 18, 19, 24–26, 31–38, 41} Endoscopic Assessment in 6 outcomes\textsuperscript{11, 15, 23, 35, 39, 40} and Therapy Modification in 12 outcomes.\textsuperscript{18, 19, 22, 23, 26, 27, 29, 30, 35, 38–40} (Supplementary Figure 1). The total

(b)

| Outcome | Proportion | 95%-CI | Weight |
|---------|------------|--------|--------|
| G = 2   |            |        |        |
| Stallmach et al, 2014 | 0.397 | [0.337; 0.459] | 5.4% |
| Fries et al, 2017  | 0.377 | [0.348; 0.406] | 5.9% |
| Fuentes et al, 2017 | 0.500 | [0.211; 0.789] | 1.5% |
| Yamamoto et al, 2018 | 0.280 | [0.213; 0.356] | 5.2% |
| Ahmad et al, 2019-01 | 0.167 | [0.103; 0.248] | 5.2% |
| Random effects model | 0.322 | [0.000; 0.412] | 23.2% |

Heterogeneity: $P = 90\%$, $\tau^2 = 0.0082$, $\chi^2 = 38.24$ ($p<0.001$)

| Outcome | Proportion | 95%-CI | Weight |
|---------|------------|--------|--------|
| G = 3   |            |        |        |
| Arvizzone et al, 2011 | 0.471 | [0.391; 0.552] | 5.0% |
| Lee et al, 2011   | 0.500 | [0.319; 0.681] | 2.8% |
| Lobaton et al, 2017 | 0.229 | [0.150; 0.326] | 4.8% |
| Gubatan et al, 2017 | 0.286 | [0.184; 0.406] | 4.3% |
| Ahmad et al, 2019-02 | 0.447 | [0.354; 0.543] | 4.6% |
| Biasci et al, 2019 | 0.519 | [0.376; 0.660] | 3.6% |
| Fabian et al, 2019 | 0.317 | [0.181; 0.481] | 3.4% |
| Meyer et al, 2019 | 0.467 | [0.349; 0.485] | 6.0% |
| Thomsen et al, 2020 | 0.000 | [0.388; 0.415] | 6.1% |
| Random effects model | 0.404 | [0.357; 0.451] | 40.6% |

Heterogeneity: $P = 88\%$, $\tau^2 = 0.0031$, $\chi^2 = 67.03$ ($p<0.001$)

| Outcome | Proportion | 95%-CI | Weight |
|---------|------------|--------|--------|
| G = 4   |            |        |        |
| Niewiadomski et al, 2015 | 0.250 | [0.167; 0.349] | 4.7% |
| Christensen et al, 2017 | 0.248 | [0.201; 0.300] | 5.6% |
| Random effects model | 0.249 | [0.000; 1.000] | 10.4% |

Heterogeneity: $P = 0\%$, $\tau^2 = 0$, $\chi^2 = 0$ ($p = 0.97$)

| Outcome | Proportion | 95%-CI | Weight |
|---------|------------|--------|--------|
| G = 5   |            |        |        |
| Ozaki et al, 2018 | 0.345 | [0.279; 0.417] | 5.2% |
| Nguyen et al, 2020 | 0.688 | [0.610; 0.758] | 5.1% |
| Random effects model | 0.316 | [0.181; 0.581] | 10.3% |

Heterogeneity: $P = 98\%$, $\tau^2 = 0.0573$, $\chi^2 = 46.67$ ($p = 0.001$)

| Outcome | Proportion | 95%-CI | Weight |
|---------|------------|--------|--------|
| G = 6   |            |        |        |
| Carvalho et al, 2015 | 0.203 | [0.139; 0.280] | 5.1% |
| Magro et al, 2018  | 0.368 | [0.341; 0.396] | 5.9% |
| Cushing et al, 2020 | 0.313 | [0.216; 0.424] | 4.4% |
| Random effects model | 0.297 | [0.184; 0.409] | 15.6% |

Heterogeneity: $P = 90\%$, $\tau^2 = 0.0087$, $\chi^2 = 20.28$ ($p < 0.001$)

Test for subgroup differences: $\chi^2 = 24.77$, $df = 4$ ($p<0.001$)

FIGURE 2 (Continued)
number of predefined variables that were reported ranged from 2 in 11 different outcomes\(^2\)\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)\(^6\)\(^7\)\(^8\)\(^9\)\(^10\)\(^11\)\(^12\)\(^13\)\(^14\)\(^15\) to seven in a single outcome\(^2\)\(^2\) (Supplementary Figure 2).

**Composite and aggregate outcomes**

Twenty one composite outcomes\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)\(^6\)\(^7\)\(^8\)\(^9\)\(^10\)\(^11\)\(^12\)\(^13\)\(^14\)\(^15\)\(^16\)\(^17\)\(^18\)\(^19\)\(^20\)\(^21\)\(^22\)\(^23\)\(^24\)\(^25\)\(^26\)\(^27\)\(^28\)\(^29\)\(^30\)\(^31\)\(^32\)\(^33\)\(^34\)\(^35\)\(^36\)\(^37\)\(^38\)\(^39\)\(^40\)\(^41\)\(^42\)\(^43\)\(^44\)\(^45\)\(^46\)\(^47\)\(^48\)\(^49\)\(^50\)\(^51\)\(^52\)\(^53\)\(^54\)\(^55\)\(^56\)\(^57\)\(^58\)\(^59\)\(^60\)\(^61\)\(^62\)\(^63\)\(^64\)\(^65\)\(^66\)\(^67\)\(^68\)\(^69\)\(^70\)\(^71\)\(^72\)\(^73\)\(^74\)\(^75\)\(^76\)\(^77\)\(^78\)\(^79\)\(^80\)\(^81\)\(^82\)\(^83\)\(^84\)\(^85\)\(^86\)\(^87\)\(^88\)\(^89\)\(^90\)\(^91\)\(^92\)\(^93\)\(^94\)\(^95\)\(^96\)\(^97\)\(^98\)\(^99\)\(^100\)\(^101\)\(^102\) were included in the meta-analysis. The mean frequency for composite outcomes was 0.363 [95% confidence interval (CI) 0.323-0.403] (Figure 2a).

The funnel plot and sensitivity analysis are depicted in Supplementary Figures 3 and 4. The results of Egger's test on the frequency of composite outcomes were not significant (\(p = 0.166\)), indicating that the dataset was unbiased. This can also be visually appreciated by the symmetry of the corresponding funnel plot in which the standard error was plotted against the outcome frequency. No outliers were detected on the results of the sensitivity analysis, with the mean being unaffected by the sequential exclusion of each individual outcome (Supplementary Figure 4).

**Subgroup analysis**

Significant differences between subgroups were observed when the frequency of composite outcomes was discriminated according to the total number of predefined variables reported (Figure 2b). However, a post-hoc test was performed and although it presented only a statistically significant result, overall, it failed to show any significant trend (Supplementary Table 2).

The presence of specific variables in the study outcome had a significant effect on the frequency of composite outcomes. The frequency corresponding to the subgroup of studies that included the variable “Biologics” was significantly higher than for those in which this variable was not reported (0.410; 95% CI 0.364-0.457 vs. 0.298; 95% CI 0.232-0.364; \(p = 0.006\); Figure 3a). On the other hand, the studies that included the variable “Clinical Assessment” exhibited a significantly lower frequency of composite outcomes compared to the subgroup where this variable was not present (0.279; 95% CI 0.244-0.314 vs. 0.402; 95% CI 0.357-0.448; \(p < 0.001\); Figure 3b). No significant differences between subgroups were identified when the remaining predefined variables were considered (Supplementary Figure 5).

**FIGURE 3** Frequency of composite outcomes according to the presence of individual predefined variables reported in the study.

(a) Subgroups determined by the presence or absence of the variable “Biologics”, \(n = 21\). (b) Subgroups determined by the presence or absence of the variable “Clinical Assessment,” \(n = 21\).
A further statistical analysis was performed in which the studies were assigned to subgroups based on the reporting of specific variable pairs. The presence of the pair “Biologics” and “Surgery” in the outcome definition was associated with higher frequencies of composite outcome comparing with the outcomes where this variable was not present. The complete set of statistical comparisons using paired variables and their corresponding statistical significance are summarized in Table 2.

To further characterize the impact that the reporting of individual variables has on the frequency of composite outcomes, we tested the effect that this reporting had within subgroups defined by the presence of a specific “core” variable. In the groups defined by the presence of the core variables “Hospitalization,” “Surgery” and “Steroids,” the reporting of the variable “Biologics” significantly increased the frequency of composite outcomes (Table 3).

When the individual studies were divided into subgroups according to the length of their respective follow-up periods, the frequency of composite outcomes for those in which it was a year long or longer was significantly higher than for those that lasted less than a year (0.398; 95% CI 0.343-0.454 vs. 0.272; 95% CI 0.000-0.359; p = 0.020; Figure 4a). Moreover, the six studies with a follow-up period equal or longer than two years exhibited a significantly higher frequency of composite outcomes compared to the rest (0.464; 95% CI 0.379-0.549 vs. 0.311; 95% CI 0.234-0.387; p = 0.008, Figure 4b).

Considering the number of patients included in the studies, we found that studies with more than 50 patients compared to the ones that include 50 or less patients had a significantly higher frequency of composite outcome achievement (0.416; 95% CI 0.372-0.461 vs. 0.295; 95% CI 0.237-0.353; p = 0.001), respectively (Supplementary Figure 6).

**DISCUSSION**

Assessment of disease progression in UC patients is particularly challenging because considering clinical symptoms in isolation could result in either underestimation or overestimation of actual disease activity. For this reason, symptom-based scoring assessments have gradually been losing ground to what are considered as more objective measures of inflammation, namely endoscopic and histological evaluation, and the use of biomarkers. In the present

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**Figure 3** (Continued)
systematic review and meta-analysis we attempted to assess the prevalence of composite and aggregate outcomes that combine these different methods of quantifying disease progression, focusing specifically on observational studies reported in the literature.

As perhaps it is to be expected from a dataset composed of observational studies conducted worldwide in the course of a decade, there was a marked heterogeneity between the studies in terms of number of patients enrolled, total duration of the study and variables included in the outcome. Interestingly, the mean frequency of composite outcomes was unaffected by the total number of variables included in the outcome. Because this result seems counterintuitive, it is possible that the relatively small number of studies that reported four or more variables was simply not enough to show a clear statistical trend, and this may become evident as future or ongoing observational studies are incorporated into the available literature.

However, it was clear from the analysis of the present dataset that the reporting of the variable "Biologics" significantly increased the frequency of composite outcomes. This was evident on the overall analysis of the entire dataset, on the analysis by paired variables in combination with the variable "Surgery," and on three out of seven subgroups defined by the presence of a "core" variable. It should be noticed that this increase in the frequency of composite outcomes was not observed with the inclusion of the other predefined variables considered, indicating that merely reporting additional variables regardless of their specific identity does not necessarily increase the chances of observing a composite outcome.

### Table 2

| First variable | Second variable | No of outcomes | Frequency of composite outcome in subgroup | Significance |
|----------------|-----------------|----------------|------------------------------------------|--------------|
| Hospitalization | Surgery        | 10             | 0.359 [0.300; 0.419] 0.362 [0.317; 0.407] | p = 0.940   |
| Steroids       |                 | 5              | 0.365 [0.000; 0.511] 0.361 [0.319; 0.403] | p = 0.960   |
| Immunosuppressors |              | 4              | 0.339 [0.000; 0.437] 0.369 [0.323; 0.415] | p = 0.590   |
| Biologics      |                 | 6              | 0.409 [0.345; 0.473] 0.341 [0.291; 0.391] | p = 0.100   |
| Clinical assessment |            | 3              | 0.254 [0.215; 0.293] 0.380 [0.339; 0.421] | p < 0.001   |
| Endoscopic assessment |        | 1              | 0.368 [0.341; 0.395] 0.363 [0.319; 0.407] | p = 0.850   |
| Therapy modification |          | 5              | 0.348 [0.000; 1.000] 0.367 [0.330; 0.404] | p = 0.840   |
| Surgery        | Steroids       | 5              | 0.365 [0.000; 0.511] 0.361 [0.319; 0.403] | p = 0.960   |
| Immunosuppressors |              | 6              | 0.383 [0.296; 0.469] 0.356 [0.308; 0.405] | p = 0.600   |
| Biologics      |                 | 9              | 0.416 [0.360; 0.473] 0.323 [0.270; 0.376] | p = 0.020   |
| Clinical assessment |            | 3              | 0.254 [0.000; 0.295] 0.378 [0.337; 0.419] | p < 0.001   |
| Endoscopic assessment |        | 1              | 0.368 [0.341; 0.395] 0.363 [0.319; 0.407] | p = 0.850   |
| Therapy modification |          | 5              | 0.365 [0.000; 0.502] 0.362 [0.322; 0.402] | p = 0.960   |
| Steroids       | Immunosuppressors | 5            | 0.334 [0.263; 0.405] 0.373 [0.325; 0.421] | p = 0.380   |
| Biologics      |                 | 6              | 0.394 [0.000; 0.509] 0.349 [0.304; 0.394] | p = 0.480   |
| Clinical assessment |            | 3              | 0.279 [0.000; 1.000] 0.378 [0.335; 0.420] | p = 0.020   |
| Endoscopic assessment |        | 1              | 0.368 [0.341; 0.395] 0.363 [0.319; 0.407] | p = 0.850   |
| Therapy modification |          | 5              | 0.356 [0.000; 1.000] 0.364 [0.324; 0.403] | p = 0.940   |
| Immunosuppressors | Biologics     | 8              | 0.371 [0.314; 0.428] 0.356 [0.303; 0.410] | p = 0.710   |
| Clinical assessment |            | 1              | 0.345 [0.278; 0.412] 0.364 [0.322; 0.405] | p = 0.640   |
| Endoscopic assessment |        | 1              | 0.368 [0.341; 0.395] 0.363 [0.319; 0.407] | p = 0.850   |
| Therapy modification |          | 3              | 0.286 [0.000; 1.000] 0.376 [0.334; 0.418] | p = 0.090   |
| Biologics      | Clinical assessment | 2            | 0.340 [0.280; 0.401] 0.366 [0.323; 0.408] | p = 0.500   |
| Endoscopic assessment |        | 1              | 0.368 [0.341; 0.395] 0.363 [0.319; 0.407] | p = 0.850   |
| Therapy modification |          | 4              | 0.388 [0.000; 1.000] 0.356 [0.317; 0.395] | p = 0.780   |
| Clinical assessment | Endoscopic assessment | 1    | 0.280 [0.212; 0.349] 0.367 [0.327; 0.408] | p = 0.030   |
| Therapy modification |          | 5              | 0.282 [0.228; 0.343] 0.382 [0.339; 0.425] | p = 0.009   |

*: statistically significant from the mean of the subgroup that does not include both variables, p < 0.05.
**TABLE 3** Subgroup analysis. The entire population of outcomes was divided in subgroups reporting a specific predefined Core Variable, and differences within these subgroups according to the presence or absence of the remaining predefined variables were statistically tested and each square represents the test’s result.

| Core Variable | Secondary Variable | Hosp | Sur | Ster | Immuno | Bio | CA | EA | TM |
|---------------|--------------------|------|-----|------|--------|-----|----|----|----|
| Hosp (11)     |                    |      |     |      |        |     |    |    |    |
| Sur (14)      |                    | p=0.300 | p=0.890 | p=0.790 | p=0.040 | p<0.001 | p=0.890 |        |
| Ster (8)      |                    | p=0.790 | p=0.790 |      | p=0.730 | p=0.020 | p=0.130 | p>0.990 |
| Immuno (9)    |                    | p=0.170 | p=0.880 | p=0.010 |        |        |        | p=0.009 |
| Bio (12)      |                    |      |      |      |        | p=0.970 | p=0.510 | p=0.590 | p=0.030 | p=0.780 |
| CA (8)        |                    | p=0.190 | p=0.230 | p=0.820 |        |        |        |        | p=0.790 |
| EA (2)        |                    |      |      |      |        |        |        |        |        |        |
| TM (9)        |                    |      |      |      |        |        |        |        |        | p=0.900 | p=0.440 | p=0.750 | p=0.250 | p=0.470 | p=0.240 |

The frequency of composite outcomes increases in the subgroup reporting the secondary variable.

The frequency of composite outcomes decreases in the subgroup reporting the secondary variable.

No significant differences were observed between the groups.

The statistical test could not be performed for that particular combination or the subgroups defined by the presence or absence of the considered variable were composed by only one or two outcomes.

The *p* values corresponding to each statistical test appear within the corresponding square.

Abbreviations: (n), number of outcomes in the subgroup reporting the Core Variable; Bio, Biologics; CA, Clinical Assessment; EA, Endoscopic Assessment; Hosp, Hospitalization; Immuno, Immunosuppressors; Ster, Steroids; Sur, Surgery; TM, Therapy Modification.

"Biologics" encompasses several different therapeutic agents targeting pro-inflammatory mediators. Unlike immunosuppressors, which have been assigned to a different category in the present analysis, these compounds do not suppress the entire immune system but employ a more selective mechanism of action. Biological therapy has been incorporated relatively recently as a tool for the management of UC (the first therapeutic agent to be developed, Infliximab, only received approval by the FDA in 2005). This fact may explain why the variable is linked to higher frequencies of composite outcomes in the present study, as it is less likely to have been selected as the sole outcome in detriment of other ways of assessing disease progression with a longer tradition in the field.

Our data also highlight how the frequency of composite outcomes is directly dependent on the total duration of the follow-up period in observational studies of UC, with the mean frequency being higher for follow-up periods longer than a year and even higher for those studies that lasted two years or longer. This result is intuitive but it needs to be underlined, as the monitoring of event-free survival should be an important criterion in therapy evaluation and recording the
frequency of composite outcomes during an extended follow-up period would therefore be a suitable method to do this.

The present report represents the first systematic review and meta-analysis of outcomes in observational studies of UC, and it complements a previous report by other authors focused on UC outcomes but restricted to RCTs. In agreement with the results presented here, that study identified remarkable heterogeneity in the reporting of outcomes, which further emphasizes the current need to reach a consensus on core outcomes for UC. In fact, as described previously, the development of an IBD-specific COS involves four steps: (i) a systematic literature review to identify outcomes previously used in IBD RCTs; (ii) qualitative interviews conducted with patients, clinicians, researchers and other stakeholders to recognize another important outcomes; (iii) an international two-round Delphi survey (to prioritize outcomes for inclusion); (iv) a consensus meeting to accredit and disseminate the findings.

A particular strength of our study is that by focusing on observational studies we were able to include long-term studies (as long as 19 years of continuous monitoring), which is not possible in the case of RCTs, and thus report on the effect that multi-year monitoring has on the frequency of composite outcomes. This is particularly relevant considering the chronic nature of the disease.

Among the limitations of our study is the relatively small number of studies that were included in the analysis. This was a direct consequence of the lack of observational studies of UC available in the literature in which the outcome is properly and unambiguously reported, but the reduced statistical power may have obscured some trends that would perhaps become evident otherwise. We did not assess the reliability of the outcome variables considered, and patient-reported outcome measures were not included because they have yet to be properly validated.

In summary, the present meta-analysis illustrates the heterogeneity that is prevalent for the reporting of clinical outcomes in observational studies of UC. Furthermore, it identifies a specific variable whose inclusion impacts the frequency of composite outcomes in these studies, and provides evidence that the follow-up period is critical to maximize this frequency. Our results suggest that by monitoring treatment with the therapeutic agents included under the general category “Biologics” in addition to a standard clinical assessment, by extending the follow-up period to two years or above and by including more than 50 patients in each study, future observational studies can effectively increase the frequency of patients achieving composite outcomes in the results. Considered together with information already provided by other systematic

![FIGURE 4](image_url)
reviews in the area, these conclusions have relevance for the development of effective methods to optimize outcome reporting in the UC field.

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CONFLICT OF INTERESTS

Fernando Magro received a fee for presenting from: AbbVie, Ferring, Falk, Hospira, PharmaKern, MSD, Schering, Laboratórios Vitoria, Vifor Pharma, OM Pharma. Axel Dignass reports fees for participation in clinical trials, review activities, such as data monitoring boards, statistical analysis, end point committees from Falk, Abbvie, Janssen, Gilead, Pfizer; consultancy fees from Abbvie, MSD, Ferring, Roche/Genentech, Takeda, Vifor, Pharmacosmos, Boehringer-Ingelheim, Falk, Janssen, Pfizer, Sandoz/Hexal, BMS/Celgene, Tillotts, Galapagos, Amgen and Fresenius Kabi; payment from lectures including service on speakers bureaus from Falk Foundation, Ferring, MSD, Abbvie, Vifor, Janssen, Pfizer, Tillotts, Takeda, Gilead/Galapagos; payment for manuscript preparation from Falk Foundation, Thieme, Takeda and UniMed Verlag. Silvio 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, Alphawassermer, Genentech, Grunenthal, Pfizer, Astra Zeneca, Novo Nordisk, Cosmo Pharmaceuticals, Vifor and Johnson & Johnson, Nikkiso Europe GMBH, Theravance. Laurent Peyrin-Biroulet has served as a speaker, consultant, and advisory board member for 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, Samsung Bioepis, Theravance.

AUTHOR CONTRIBUTIONS

Fernando Magro contributed to the study conception and design, drafting of the manuscript, data collection, data interpretation and provided an intellectual contribution. Catarina Alves, Mafalda Santiago, and Maria Manuela Estevinho contributed to the drafting of the manuscript, data collection, data interpretation and analysis. All other authors contributed to data collection and critically revised the manuscript. All authors approved the final version of the manuscript and the authorship list and take responsibility for the accuracy and integrity of any part of the work. Writing assistance was provided by

| Outcome      | Proportion | 95%-Cl       | Weight |
|--------------|------------|--------------|--------|
| One_Year_FU  | 0.471      | [0.391; 0.552] | 5.5%   |
| Ardizzione et al., 2011 | 0.500 | [0.319; 0.681] | 3.7%  |
| Lee et al., 2011 | 0.250 | [0.167; 0.349] | 5.4%  |
| Niewiadomski et al., 2015 | 0.203 | [0.139; 0.280] | 5.7%  |
| Carvalho et al., 2015 | 0.246 | [0.160; 0.315] | 7.0%  |
| Christensen et al., 2017 | 0.229 | [0.150; 0.326] | 5.4%  |
| Lobatón et al., 2017 | 0.286 | [0.184; 0.406] | 5.0%  |
| Guaban et al., 2017 | 0.345 | [0.276; 0.417] | 5.7%  |
| Ozaki et al., 2018 | 0.280 | [0.213; 0.356] | 5.7%  |
| Yamamoto et al., 2018 | 0.201 | [0.130; 0.268] | 5.7%  |
| Ahmad et al., 2019-01 | 0.167 | [0.103; 0.248] | 5.7%  |
| Fabian et al., 2019 | 0.317 | [0.281; 0.451] | 4.3%  |
| Meyer et al., 2019 | 0.467 | [0.449; 0.485] | 6.3%  |
| Cushing et al., 2020 | 0.313 | [0.216; 0.424] | 5.1%  |
| Randen effects model | 0.311 | [0.234; 0.387] | 69.5% |

Heterogeneity: $I^2 = 0.0176, \chi^2 = 225.99 (p<0.001)$

| Outcome      | Proportion | 95%-Cl       | Weight |
|--------------|------------|--------------|--------|
| One_Year_FU  | 0.397      | [0.337; 0.459] | 5.8%   |
| Stallmach et al., 2014 | 0.377 | [0.348; 0.406] | 6.2%  |
| Fries et al., 2017 | 0.500 | [0.211; 0.789] | 2.2%  |
| Fuentes et al., 2017 | 0.368 | [0.341; 0.396] | 6.2%  |
| Magro et al., 2018 | 0.519 | [0.376; 0.660] | 4.4%  |
| Bisci et al., 2019 | 0.688 | [0.610; 0.758] | 5.6%  |
| Nguyen et al., 2020 | 0.464 | [0.307; 0.549] | 30.5% |

Heterogeneity: $I^2 = 0.0110, \chi^2 = 298.88 (p<0.001)$

Randen effects model

Heterogeneity: $I^2 = 0.0110, \chi^2 = 298.88 (p<0.001)$

Test for subgroup differences: $\chi^2 = 6.93, df = 1 (p = 0.008)$

F I G U R E  4  (Continued)
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**DATA AVAILABILITY STATEMENT**

The data that supports the findings of this study are available in the supplementary material of this article (also in the main text document).

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