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Meta-Analysis

Influence of diabetes mellitus on inflammatory bowel disease course and treatment outcomes. A systematic review with meta-analysis

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ABSTRACT

Background: Diabetes Mellitus (DM) may occur in IBD and influence the disease progression.
Aim: To compare disease course and treatment outcomes in IBD patients with and without DM.
Methods: This is a systematic review with meta-analysis comparing patients with IBD plus DM with patients with IBD only. Primary endpoints: need for surgery, IBD-related complications, hospitalizations, sepsis, mortality. Quality of life and costs were assessed.
Results: Five studies with 71,216 patients (49.1% with DM) were included. Risk for IBD-related complications (OR=1.12, I^2 98% $p = 0.77$), mortality (OR=1.52, I^2 98% $p = 0.37$) and IBD-related surgery (OR=1.20, I^2 81% $p = 0.26$) did not differ. Risk of IBD-related hospitalizations (OR=2.52, I^2 0% $p < 0.00001$) and sepsis (OR=1.56, I^2 88% $p = 0.0003$) was higher in the IBD+DM group. Risk of pneumonia and urinary tract infections was higher in the IBD+DM group (OR=1.72 and OR=1.93), while risk of *C. Difficile* infection did not differ (OR=1.22 I^2 88% $p = 0.37$). Mean Short Inflammatory Bowel Disease Questionnaire score was lower in the IBD+DM group (38.9 vs. 47, $p = 0.03$). Mean health care costs per year were $10,598.2 vs $3747.3 ($p < 0.001$).
Conclusion: DM might negatively affect the course of IBD by increasing the risk of hospitalization and infections, but not IBD-related complications and mortality.

1. Introduction

The etiopathogenesis of Inflammatory Bowel Disease (IBD) is not fully understood, but it is generally agreed that genetic, environmental, and host-related factors contribute to the development of intestinal inflammation and fibrosis [1]. Recent evidence shows that patients with IBD are at high risk of developing other autoimmune diseases, including psoriasis, and multiple sclerosis [2,3]. The incidence of Diabetes Mellitus (DM) has increased dramatically worldwide due to increasing obesity, decreasing physical activity, and increasing age. According to some estimates, the prevalence will rapidly increase from 2.8% in 2000 to 4.4%–7.7% in 2030 and up to 9.9% of the total population in 2045 [4,5]. In addition, both genetic factors, including variants in the HLA, INS, PTPN2, and IFIH1 genes, and environmental factors, including diet, gut microbiota, and infections, play important roles in the development of DM [6,7].

It has been suggested that IBD and type 1 DM share a similar immune-mediated pathogenesis, suggesting a possible epidemiological link [8,9]. A recent meta-analysis suggests no association between IBD and type 1 DM. However, a subgroup analysis suggests that patients with CD or UC from certain regions have a

Abbreviations: IBD, Inflammatory Bowel Disease; DM, Diabetes Mellitus; SIBDQ, Short Inflammatory Bowel Disease Questionnaire; CD, Crohn's Disease; UC, Ulcerative Colitis; QoL, Quality of Life; OR, Odds Ratio; HR, Hazard Ratio; UTI, Urinary tract infection.

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higher risk of developing type 1 DM than patients without IBD [10].

However, the impact of coexisting DM, both type 1 and type 2, on the course of IBD has received little attention, although it could influence the choice of therapy and associated outcomes [11]. Some recent studies have shown that DM is associated with increased disease severity [12], but more importantly, DM appears to increase the risk of infection and all-cause mortality [13].

The aim of this systematic review is to compare patients with IBD and DM with patients with IBD without DM in order to understand whether DM can alter the natural history of the disease and affect the outcome of treatment.

2. Materials and methods

The systematic review with meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Statement [14] and the checklist of Meta-Analyses of Observational Studies in Epidemiology (MOOSE) [15], and was recorded on PROSPERO (ID CRD42022315509)

2.1. Search strategy and data sources

A literature search of MEDLINE (PubMed) and Embase libraries was performed combining the following terms: "inflammatory bowel disease" OR "Crohn's disease" OR "ulcerative colitis" AND "diabetes". A cross-reference search was performed. The detailed search strategy is shown in Supplementary Table 1. The following data were independently extracted from the included studies by the reviewers: first author, journal, year of publication, study type, number of patients (IBD and IBD+DM), type of IBD, and DM included. The last search date was January 22, 2022. Data on corticosteroid, biological, and immunosuppression therapy were also extracted.

2.2. Inclusion and exclusion criteria

Studies comparing patients with IBD and DM (IBD+DM group) with patients with IBD alone were included, without publication restrictions. We considered type I and II of diabetes, without age restrictions. Only studies that included data on at least one primary outcome were included. Reviews, case reports, meta-analyses, noncomparative studies, and studies without calculable endpoints, were not included.

2.3. Endpoints and outcome measures

The primary endpoints included the need for surgical intervention, i.e. bowel resection, surgical exploration, and treatment of perianal disease; mortality, i.e. death from any cause; sepsis, defined as an excessive inflammatory response to generalized infection; IBD-related hospitalizations; IBD-related complications, defined as active fistulizing disease, intra-abdominal abscess, stricturing disease, bowel obstruction, perianal abscess, bowel perforation, toxic colitis, and toxic megacolon.

Secondary endpoints included risk of pneumonia, urinary tract infection (UTI) and C. Difficile infection, Quality of life (QoL) and healthcare costs associated with treatment.

2.4. Statistical analysis

The meta-analysis was conducted in accordance with the MOOSE guidelines [15]. The estimated effect measures are reported as odds ratios (OR) with 95% confidence intervals (95%CI). The ratio represented the probability of occurrence of an event in the group of patients with IBD compared with the group of patients with IBD and DM. An OR>1 indicated worse outcomes for the IBD+DM group, and the point estimate of OR was considered statistically significant if the 95%CI did not contain a value of "1″. OR were combined with the *"Mantel-Haenszel chi-squared method"* by using the *"random effect"* technique [16]. When possible, patients were stratified into CD and UC.

Data were analysed using RevMan 5.4. The relative extent of observed heterogeneity was quantified using the I^2 statistic, ranging from 0%–100% [17]. Statistical sensitivity analysis for patients' medical therapy was carried out using the Chi-Square Test.

2.5. Assessment of the strength of evidence and risk of bias

The overall quality and strength of evidence were assessed using the GRADE approach [18]. Each study was assessed using the Newcastle Ottawa Scale (NOS) [19], and the risk of bias in selected studies was assessed using the ROBINS-I tool for non-RCT studies [20].

3. Results

A search of the literature yielded 8954 records. After the exclusion of 1284 duplicates and 4 records removed from publication, titles and abstracts were screened to select 6 articles. The latter were found by full text analysis. Five reports were eligible for our meta-analysis [12,13,21–23]. The selection process is shown in Fig. 1. Of the selected studies, 71,216 patients with a diagnosis of IBD were included in the analysis: 36,248 patients (50.9%) without vs. 34,968 patients (49.1%) with DM. The studies were published between 2012 and 2021; each study included patients with UC and CD, except for the study by Harper et al. [23], which included patients with CD only. Data from the included studies are summarized in Table 1.

Three studies defined the number of CD vs UC patients [12,13,22]. Three studies [12,13,22] provided data on biologics, immunomodulators, systemic steroids, or 5-aminosalicylic acid therapy.

3.1. Treatment of IBD

Analysis of IBD therapy in the included patients is summarized in Table 2. Patients with DM used less biologics (30% vs 21% $p < 0.00001$) and immunomodulators (35% vs 30.1% $p = 0.006$), while they were treated to a greater extent with 5-aminosalicylic acid (58.6% vs 63.2% $p = 0.01$). There was no significant difference between the two groups regarding systemic steroid therapy ($p = 0.51$).

3.2. Primary outcomes

Regarding IBD-related complications, two studies provided data suitable for meta-analysis [13,21]. They showed no difference in risk between the two groups (OR=1.12, 95%CI 0.52–2.45 (Fig. 2a) $p = 0.77$), but heterogeneity was very high (I^2 98%). The risk of IBD-related hospitalization was reported in two studies [12,13], and it was higher in IBD+DM patients (OR=2.52, 95%CI 2.17–2.98, I^2 0% (Fig. 2b) $p < 0.00001$). Mortality was assessed in two studies [13,21], and the need for IBD-related surgery in four studies [12,13,21,22], with no differences between the two groups, (OR=1.52, 95%CI 0.61–3.81, I^2 98% [Fig. 2c] $p = 0.37$ and OR=1.20, 95%CI 0.88–1.63, I^2 81% [Fig. 2e] $p = 0.26$, respectively). The risk of sepsis was higher in the IBD+DM group (OR=1.56, 95%CI 1.06–2.29, I^2 88% [Fig. 2d] $p = 0.0003$).

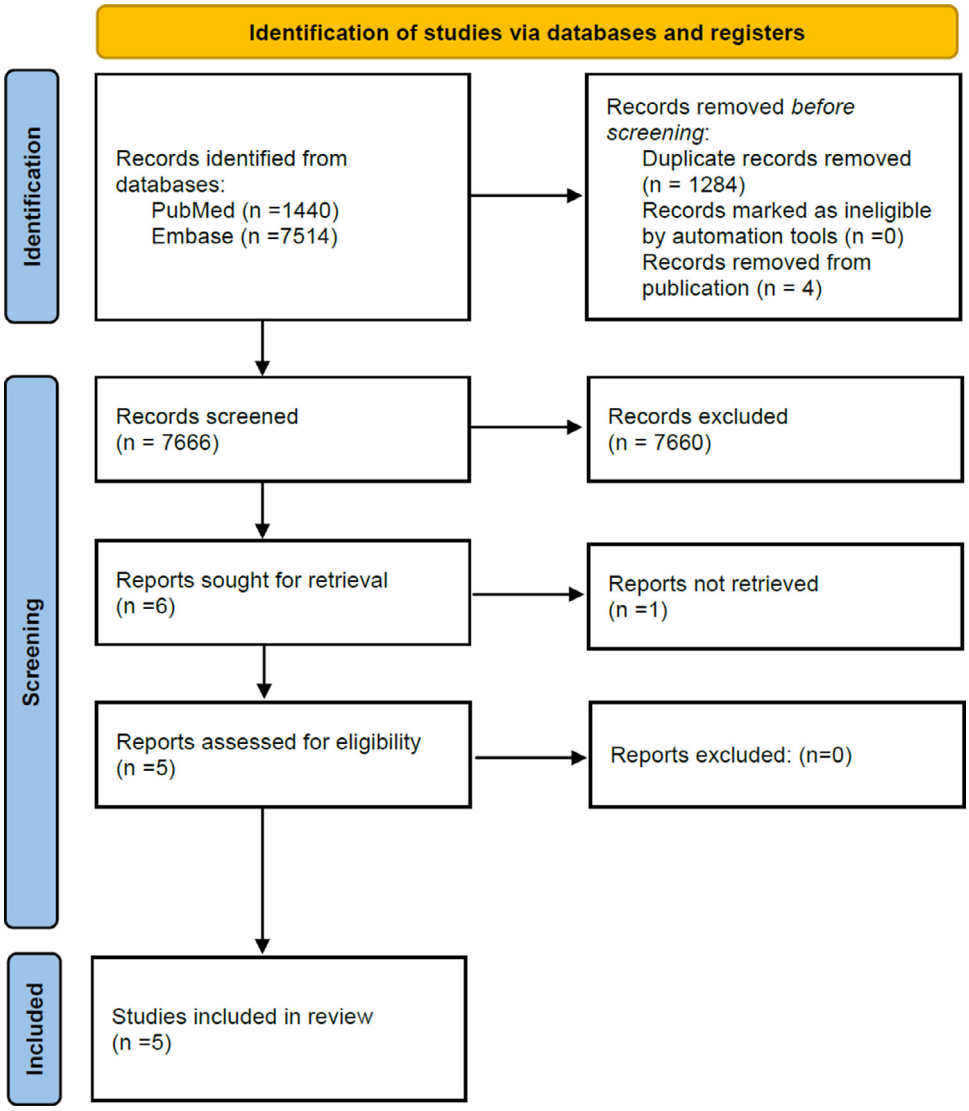

Fig. 1. PRISMA flowchart. Flow chart of study selection for the current meta-analysis according to PRISMA Statement.

Table 1
Characteristics of included studies.

Author	Year	Study type	Journal	N° Patients		Type of IBD	Type of DM	NOS
				IBD (CD)	IBD + DM (CD+DM)			
Uwagbale et al. [21]	2021	retrospective	Cureus	33,870 (nd)	33,870 (nd)	UC+CD	DM1+DM2	5
Harper et al. [22]	2012	retrospective	Alimentary Pharmacolology & Therapeutics	224 (224)	16 (16)	CD	DM1+DM2	4
Kumar et al. [13]	2020	retrospective	Digestive Disease and Science	1584 (657)	901 (402)	UC+CD	DM2	5
Din et al. [12]	2020	retrospective	Inflammatory bowel Disease	400 (234)	141 (79)	UC+CD	DM1+DM2	6
Ananthakrishnan et al. [23]	2016	retrospective	Alimentary Pharmacolology & Therapeutics	170 (na)	40 (na)	UC+CD	DM1+DM2	5

IBD (Inflammatory Bowel Disease), DM (Diabetes Mellitus), CD (Crohn Disease), NOS (Newcastle-Ottawa Scale).

Table 2
Medications for IBD of included patients.

Medications	IBD (%)	IBD+DM (%)	*p* Value (significant at $p < 0.05$)
Biologics use	663/2208 (30%)	221/1058 (21%)	<0.00001
Immunomodulators use	773/2208 (35%)	319/1058 (30,1%)	0.006
Systemic Steroids use	716/2208 (32,4%)	331/1058 (31,3%)	0.51
5-aminoslicylic acids use	1163/1984 (58,6%)	659/1042 (63,2%)	0.01

IBD (Inflammatory Bowel Disease), DM (Diabetes Mellitus).

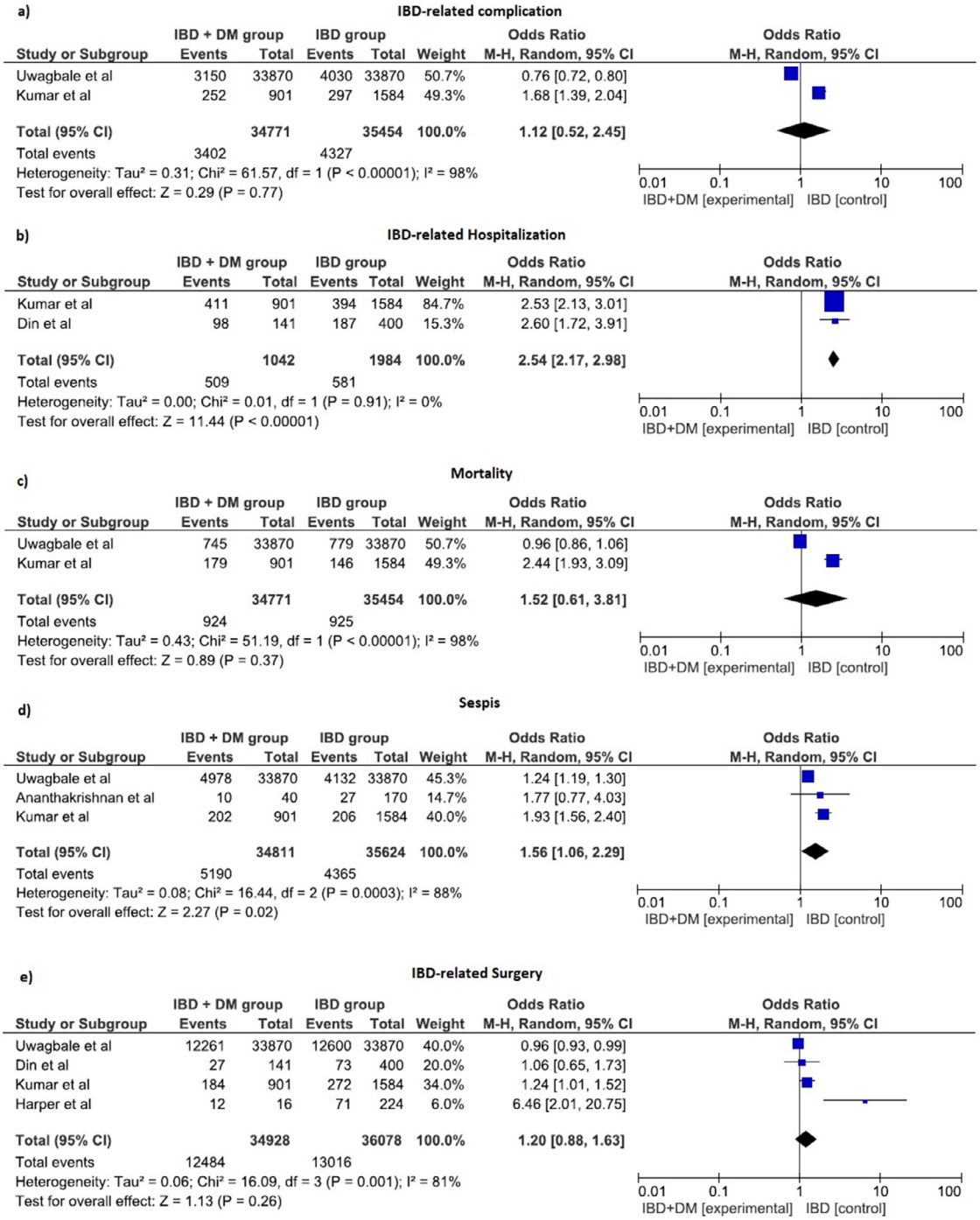

Fig. 2. Risk of IBD-related complication, IBD-related hospitalization, mortality, sepsis and IBD-related surgery. Forest plot with odds ratio of single studies reporting data on IBD-related complication, IBD-related hospitalization, mortality, sepsis and IBD-related surgery and overall odds ratio.
IBD (Inflammatory Bowel Disease), DM (Diabetes Mellitus).

3.3. Secondary outcomes

Ananthakrishnan et al. [23] provided data on different types of infections. Pneumonia and UTIs were extracted as these were also reported by Kumar et al. [13]. In addition, the latter study provided data on *C. Difficile* infections, which were compared with data collected by Uwagbale et al. [21]. The results of the analysis are shown in Fig. 3.

DM increased the risk of pneumonia (OR=1.72 95%CI 1.38–2.14, I^2 0% (Fig. 3a) $p < 0.00001$) and UTIs (OR=1.93 95%CI 1.51–2.47 I^2 8% (Fig. 3b) $p < 0.00001$), with no statistical difference for *C. difficile* infection (OR=1.22 95%CI 0.78–1.90 I^2 88% (Fig. 3c) $p = 0.37$).

One of the five included studies [22] provided mean Short Inflammatory Bowel Disease Questionnaire (SIBDQ) scores [24]. The mean SIBDQ score was lower in the IBD+DM group than in the IBD group (38.9 and 47.0, respectively, $p = 0.03$).

Median annual health care costs were reported by Uwagbale et al. [21] to be $9216 (median IQR 5578–16,199) for IBD+DM vs $9147 (median IQR 5471–16,272) for IBD group (OR 1.00 (95%CI 0.99–1.01) $p = 0.8839$). Din et al. [12] instead report median health

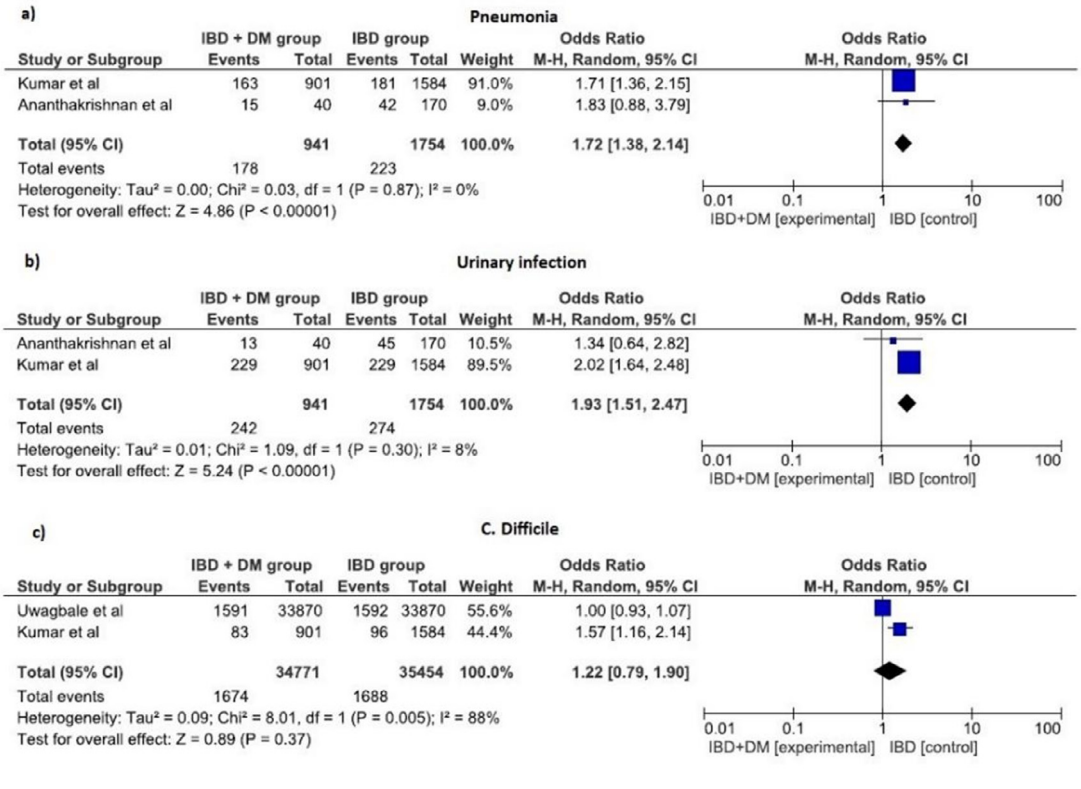

Fig. 3. Risk of pneumonia, urinary infection, C.Difficile infection. Forest plot with odds ratio of single studies reporting data on pneumonia, urinary infection, C.Difficile infection and overall odds ratio.
IBD (Inflammatory Bowel Disease), DM (Diabetes Mellitus).

care costs per year of $10,598.2 [IQR 37,808.4] versus $3747.3 [IQR 20,182.9] ($p < 0.001$).

3.4. CD and UC analysis

The only study that included data on CD and UC was that of Kumar et al. [13]. Therefore, we compared the data from the latter paper with the data from Harper et al. [22], which included only CD patients. Therefore, it was only possible to perform the meta-analysis on the outcome of CD-related surgery. The analysis showed a OR of 3.03, 95%CI 0.92-9.99, I^2 76% (Supplementary Figure 1) $p = 0.07$).

3.5. Sensitivity analysis

Due to the large heterogeneity observed in the analysis of some data, the studies responsible for the heterogeneity were removed, where possible. Specifically, forest plots in which it was possible to eliminate studies were only those that included more than 2 studies, so those concerning sepsis and those concerning the need for surgery. The resulting analysis is shown in Supplementary Figure 2. As for surgical interventions related to IBD, after excluding the studies by Uwagbale et al. [21] and by Harper et al. [22], a OR of 1.21 was found (95%CI 1.00–1.46, I^2 0% $p = 0.05$, Supplementary Figure 2a).

As for sepsis, after excluding the study by Uwagbale et al. [21], the OR was 1.92 (95%CI 1.56–2.37, I^2 0% $p < 0.00001$ Supplementary Figure 2b).

3.6. Level of evidence and risk of bias

The overall strength of evidence is summarized Table 3. The quality of the studies was low due to their retrospective nature. The certainty of the evidence found was low or very low for almost all outcomes, except for IBD-related hospitalizations, which had a moderate level of evidence. Table 1 and Supplemental Table 2 show the NOS score of each study.

4. Discussion

The present study showed that DM does not appear to worsen the course of IBD in terms of complications, need for surgery and mortality; on the other hand, patients with DM report a lower quality of life with an increased risk of developing pneumonia, UTI, sepsis, and an increased risk of hospitalization.

In detail our systematic review found that DM is a risk factor for complications in IBD. Kumar et al. [13] reported a rate of IBD-related complications in diabetic patients of 28% versus 18% in patients without DM. In contrast, the data from our meta-analysis show no significant difference between the two groups, but these data are affected by a large heterogeneity and the risk of bias was high.

The number of surgical procedures in both CD and UC has decreased over the past 3 decades [25], likely as a result of more effective medical therapy. Recent population-based cohorts reported surgical intervention rates of 10–14% at 1 year and 18 −35% at 5 years follow-up [25].

Uwagbale et al. [21] reported a surgical rate in patients with IBD and DM of 26% versus 28.9% of patients with IBD alone (OR 0.90 95%CI 0.85 - 0.95) while Kumar et al. [13] reported a Hazard Ratio (HR) of 1.20 (95%CI 0.98–1.47). The latter paper also reported a separate analysis for patients with CD and UC. The risk of IBD-related surgery was higher in patients with CD (HR 1.66 95%CI 1.30–2.13) than in patients with UC (HR 0.96 95%CI 0.75–1.31). Unfortunately, with the available data from the included studies, it

Table 3
GRADE score. A consensus on rating quality of evidence and strength of recommendations.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with IBD+DM	Risk difference with IBD
IBD-related complications	70,225 (2 observational studies)	⊕◯◯◯ Very low	**OR 1.12** (0.52 to 2.45)	10 per 100	**1 more per 100** (4 fewer to 11 more)
IBD-related hospitalization	3026 (2 observational studies)	⊕⊕⊕◯ Moderate	**OR 2.54** (2.17 to 2.98)	49 per 100	**22 more per 100** (19 more to 25 more)
Mortality	70,225 (2 observational studies)	⊕◯◯◯ Very low	**OR 1.52** (0.61 to 3.81)	3 per 100	**1 more per 100** (1 fewer to 7 more)
Sepsis	70,435 (3 observational studies)	⊕⊕◯◯ Low	**OR 1.56** (1.06 to 2.29)	15 per 100	**7 more per 100** (1 more to 14 more)
IBD-related surgery	71,006 (4 observational studies)	⊕◯◯◯ Very low	**OR 1.20** (0.88 to 1.63)	36 per 100	**4 more per 100** (3 fewer to 12 more)
Pneumonia	2695 (2 observational studies)	⊕⊕◯◯ Low	**OR 1.71** (1.38 to 2.14)	19 per 100	**10 more per 100** (5 more to 14 more)
Urinary infection	2695 (2 observational studies)	⊕⊕◯◯ Low	**OR 1.93** (1.51 to 2.47)	257 per 1.000	**143 more per 1.000** (86 more to 204 more)
C.Difficile infection	70,225 (2 observational studies)	⊕◯◯◯ Very low	**OR 1.22** (0.79 to 1.90)	48 per 1.000	**10 more per 1.000** (10 fewer to 40 more)

IBD (Inflammatory Bowel Disease), DM (Diabetes Mellitus), CI (confidence interval), OR (odds ratio).
*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio.
GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

was not possible to compare the influence of DM in CD and UC separately. Harper et al. [22], who studied patients with CD and DM, also suggested that patients with DM had a higher risk of requiring surgery for CD than patients without DM (adjusted OR of 5.40 (95% CI 1.65–17.64) over a 5-year period).

The current meta-analysis indicated that DM was unlikely to increase the need for surgery related to inflammatory disease.

Forest plots generated in our study showed no difference for all-causes mortality. Uwagbale et al. [21] reported a rate of all-cause mortality of 2.2% in IBD+DM patients versus 2.3% in patients without DM (OR 0.96 95%CI 0.87–1.07). Kumar et al. [13] showed a HR of 1.67 (IBD–DM vs IBD 95%CI 1.34–2.08), in the subanalysis, the HR revealed for CD was similar to that found for UC (1.44 (1.12–1.86) for CD vs 1.39 (0.98–1.97) for UC) DM is a known risk factor in colorectal surgery, leading to increased risk of anastomotic leaks, infectious and non-infectious complications [26]. In the current meta-analysis, infections were more likely to be observed in patients with IBD and DM. Specifically, we found that the association of IBD and DM was related to an increased risk of pneumonia, UTIs, and sepsis.

Ananthakrishnan et al. [23] pointed out that DM was an independent risk factor for infections in IBD patients receiving immunomodulatory therapy, particularly in relation to pneumonia, UTIs, and sepsis, which is consistent with our results. The findings of Kumar et al. [13] showed that concomitant Type 2 DM carried an additional risk of sepsis, pneumonia, UTI, and skin and soft tissue infections as compared to IBD alone.

A study by Choi et al. reported DM as a covariate associated with an increased risk of CD-related hospitalizations [27]. Similarly, our study showed an increased risk of hospitalizations in patients with DM and IBD, with DM appearing to increase this risk 2.5-fold. Kumar et al. [13] showed an incidence rate of IBD-related hospitalizations of 79.6 versus 36.6 per 1000 patient-years of follow-up in the IBD–DM versus IBD cohorts. Type 2 DM was an independent predictor of IBD-related hospitalizations, with an adjusted HR of 1.97 (95% CI 1.71–2.28) for IBD–DM versus IBD. Consistent with our meta-analysis, Din et al. [12] also reported higher healthcare utilisation in patients with DM and IBD than in patients with IBD alone. They report hospitalisations at 69.5% and 46.8% and access to emergency department at 66% and 53% in the group IBD+DM and IBD, respectively.

Regarding IBD therapy, patients with DM seemed to use fewer biologics and immunomodulators. In contrast, we found increased use of 5-ASA compounds, which are usually used in patients with milder disease. This may be due to clinicians' fear of infection in diabetic patients. However, it cannot be ruled out that patients with DM may have less severe IBD and therefore reduced need for advanced therapies. A recent study [28] has shown that patients with IBD and type 2 DM have lower risk of adverse clinical events when treated with GLP-1-based therapies compared with treatment with other antidiabetic agents. These results suggest that treatment with GLP-1-based therapies may improve the disease course of IBD. Unfortunately, in the studies selected for this meta-analysis, data on patients' antidiabetic therapy and its impact on the course of IBD were not available. Therefore, it is important to further investigate the role of DM and associated treatment on IBD.

A meta-analysis published in 2017 [29] concluded that no treatment strategy carries a greater risk of severe infection than another, although wide confidence intervals suggested that a clinically significant difference cannot be ruled out.

We found no significant differences between the two groups with respect to systemic steroid therapy. Unfortunately, it was not clear from the data of the included studies whether DM influenced the decision for one treatment or the other.

It is known that corticosteroids such as prednisone and methylprednisolone are used to treat IBD in the acute phase. However, more than 50% of patients do not respond to therapy (steroid resistance) or relapse after treatment discontinuation (steroid dependence), and about half of them have side effects of varying severity [30]. Hyperglycaemia and corticosteroid-induced DM are the most common systemic manifestations in IBD on steroid treatment and are a real problem in the management of IBD patients with DM mellitus when relapses of bowel disease occur [31].

The present study has several limitations. Firstly, we could not perform a subset analysis for CD and UC, as the only study that performed a similar analysis was that of Kumar et al. [13], who found a higher HR for UC patients in terms of IBD flares, IBD-related complications, sepsis, C. difficile infection, and pneumonia. In addition, it was impossible to conduct a sub-analysis by type of diabetes, as no included study provided data on this issue. Data on health-related quality of life and costs should be read with caution, as only limited information could be retrieved. Future studies should consider filling this knowledge gap.

Secondly, due to the retrospective nature of the included studies, the quality of the evidence and the strength of the resulting recommendations are low.

Further studies on this topic are needed to better understand whether DM, the type of DM, and therapy for DM could somehow alter the course of inflammatory bowel disease, and its medical and surgical treatment.

Conflicts of interest and source of funding

None declared.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2022.08.017.

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