

Evaluating the role of capsule endoscopy for non-responsive, refractory and complicated celiac disease: a systematic review and meta-analysis

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Abstract

Background Small-bowel capsule endoscopy (CE) is used in selected adults with nonresponsive, refractory, or complicated celiac disease (CD), but its diagnostic yield (DY), clinical impact, and safety remain uncertain.

Methods We searched Medline, EMBASE, CENTRAL, and PubMed from January 2000 to November 30, 2025, for studies of CE in adults with established CD and persistent symptoms, suspected refractory disease, or suspected complications. Two reviewers independently selected studies, extracted data, and assessed risk of bias using ROBINS-E; certainty was assessed using GRADE. Random-effects meta-analyses using generalized linear mixed models estimated pooled DY and secondary outcomes. Meta-regression and subgroup analyses were considered exploratory.

Results Seventeen studies, including 994 adults, were eligible. The pooled DY of CE in complex CD was 82% (95% confidence interval [CI] 67-91%), with substantial heterogeneity ($I^2=82.5\%$). DY was highest in refractory CD cohorts. Pooled DY was 3% for ulcerative jejunitis and 3% for small-bowel malignancy. Capsule retention was uncommon. CE findings were associated with management changes in several studies; however, this outcome was reported in only 9 studies, and definitions varied. Egger's test and trim-and-fill analysis suggested possible small-study effects, reducing the adjusted DY estimate to 79%. The pooled conversion to device-assisted enteroscopy was estimated at 18% (95%CI 9-30%).

Conclusions CE may be a valuable second-line, noninvasive triage tool in selected high-risk patients with complex CD, particularly refractory CD. However, the available evidence remains of very low certainty and should be interpreted cautiously, given the substantial methodological and clinical heterogeneity across studies.

Keywords Capsule endoscopy, small bowel, diagnostic yield, refractory celiac disease, complicated celiac disease

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Introduction

Celiac disease (CD) is a chronic, immune-mediated enteropathy triggered by gluten exposure in genetically susceptible individuals [1,2]. Although adherence to a strict gluten-free diet (GFD) remains the cornerstone of treatment, up to 30% of adults continue to experience ongoing symptoms despite reported adherence [3,4]. These cases may represent non-responsive CD (NRCD) or refractory CD (RCD), which are associated with nutritional deficiencies, impaired quality of life, and an elevated risk of lymphoproliferative malignancy [5-7].

NRCD is characterized by persistent symptoms, abnormal serology or ongoing mucosal abnormalities after 6–12 months of a strict GFD. In most cases, NRCD reflects inadvertent gluten exposure or alternative gastrointestinal (GI) pathology (e.g., irritable bowel syndrome), rather than true treatment failure [3,4]. In contrast, RCD is defined by persistent or recurrent malabsorptive symptoms with ongoing villous atrophy, despite strict GFD for ≥ 12 months, after exclusion of alternative causes of enteropathy [8,9]. RCD is further subdivided into type I, characterized by a normal intraepithelial lymphocyte phenotype, and type II, defined by an aberrant clonal intraepithelial lymphocyte population, which carries a substantially poorer prognosis [8,9]. Complicated CD (CCD) encompasses structural and malignant sequelae, including ulcerative jejunitis, strictures and enteropathy-associated T-cell lymphoma (EATL); these typically arise in longstanding NRCD or RCD and carry high morbidity and mortality [8,9]. Early recognition and precise differentiation of these disease states is critical for guiding appropriate further management.

For clinicians managing patients who have persistent symptoms despite confirmed dietary adherence, determining the optimal diagnostic pathway remains challenging. Traditional evaluation relies on repeated esophagogastroduodenoscopy with duodenal biopsies; however, this is invasive, prone to sampling error, and limited to the proximal small bowel (SB) [10]. SB capsule endoscopy (CE) provides a minimally invasive assessment of the entire SB, and is more sensitive than conventional endoscopy for detecting villous atrophy and complications in established CD [10,11]. According to the European Society of Gastrointestinal Endoscopy (ESGE) guidelines, CE is recommended in suspected NRCD or RCD as a second-line test, after serology, biopsies and dietary review, to assess villous atrophy and identify complications [12]. Cross-sectional imaging and device-assisted enteroscopy (DAE) are generally used for the targeted characterization or biopsy of lesions identified on CE [10,11,13].

Despite these recommendations, the evidence supporting CE in NRCD or CCD remains fragmented and of low

certainty. Existing meta-analyses have primarily examined CE at initial diagnosis, rather than its diagnostic yield (DY) in high-risk NRCD, RCD or CCD cohorts [14,15]. Evidence regarding the clinical impact of CE, specifically how findings influence subsequent investigations or management, remains limited [10]. We therefore conducted a systematic review and meta-analysis to evaluate the DY of CE in NRCD, RCD and CCD, identify factors associated with diagnostic performance, and assess procedure-related complications.

Materials and methods

This study protocol was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines (see supplemental table 1) [16]. The protocol was registered with the PROSPERO International Register of Systematic Reviews (Registration ID: CRD420251243243). No amendments were made to the protocol following registration. This study aimed to systematically evaluate the DY, clinical impact and safety of CE in adult patients with NRCD, RCD, or CCD.

Eligibility criteria

We included full-text observational studies (retrospective or prospective) that evaluated the use of CE in adults with established CD presenting with NRCD, RCD or CCD. All types of CE were included, and all referral indications were considered, including symptomatic patients, asymptomatic patients undergoing evaluation, positive serology or previously confirmed RCD. Conference abstracts were excluded because of insufficient methodological detail and/or limited extractable data. Review articles, systematic reviews, editorials, study protocols, case reports and studies with < 10 participants were excluded.

Information sources

We conducted a comprehensive literature search across the following electronic databases: Medline (Ovid), EMBASE (Ovid), Cochrane Central Register of Controlled Trials (CENTRAL), and PubMed. The search strategy incorporated controlled vocabulary terms (e.g., MeSH terms) and free-text keywords relevant to CD and CE. The complete search strategy for each database is available in Supplementary Table 2, in accordance with the PRISMA-S (PRISMA-Search) guidelines. The search was limited to studies published between 1 January 2000 and 30 November 2025, and only English language publications were included. To ensure comprehensiveness, we also conducted a manual review of reference lists of full-text articles and relevant systematic reviews.

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Study selection

All records were imported into Rayyan (Rayyan Systems Inc.), a web-based platform designed for systematic review screening. Duplicate entries were identified and removed. Title and abstract screening, followed by full-text eligibility assessment, were independently performed by 2 reviewers (IIL and RN). Disagreements were resolved through discussion and consensus.

Inclusion criteria

- Participants had a confirmed diagnosis of CD established by serology and/or duodenal histology
- The study included adults with established CD undergoing CE for any clinical indication
- The sample size was ≥ 10 participants
- Any CE system was permitted, including gastric, SB, colon, or panenteric capsules, irrespective of manufacturer
- The study did not need CD as a primary or secondary endpoint, provided that relevant CE outcomes were extractable

Exclusion criteria

- Pediatric studies (<18 years of age) or non-human studies
- Studies with suspected but unconfirmed CD
- Studies focusing exclusively on obscure GI bleeding or non-CD indications
- Studies using CE primarily for the initial diagnosis of CD, rather than for evaluation, surveillance or assessment of complications

Data compilation

The final set of studies was reviewed, and data extraction was independently performed by IL and RN. Extracted variables included patient demographics, disease duration and indications for CE. Clinical data included the number of patients with NRCD, RCD or CCD, subsequent DAE, elevated biomarkers, and symptomatic presentations. NRCD refers to persistent symptoms, abnormal serology or mucosal abnormalities, despite 6–12 months of a GFD [3,4]. RCD was defined by ongoing malabsorptive symptoms and villous atrophy, despite ≥ 12 months of GFD, and both Type 1 and 2 were included [8,9]. CCD encompassed structural or malignant complications arising from longstanding NRCD or RCD, including ulcerative jejunitis, strictures and EATL. For the purposes of this meta-analysis, complex CD (CxCD) was used as an operational umbrella term encompassing NRCD, RCD, and CCD; however, these entities are clinically distinct and should not be considered equivalent in terms of disease severity, risk profile or DY. Villous atrophy on CE was identified by macroscopic surrogate markers, including

scalloping of mucosal folds, mosaic pattern, fissuring, nodularity, and absence of villi. DY was defined as the proportion of CE examinations identifying 1 or more clinically significant small-bowel abnormalities in patients with CxCD. The histological reference standard varied across studies, and the Marsh–Oberhuber classification based on duodenal biopsies was most commonly used, while flow cytometry for aberrant intraepithelial lymphocytes was used to subtype RCD in 3 studies [17–19]. Technical details included CE system type, completion rate, bowel preparation quality, use of patency capsule and adverse events. Diagnostic outcomes included overall and lesion-specific DY (ulcers, ulcerative jejunitis, Crohn's disease, malignancy), and whether CE changed diagnosis or altered patient management.

Risk of bias

The risk of bias (RoB) for all non-randomized studies was evaluated using the ROBINS-E tool for non-randomized studies of exposures. We acknowledge that QUADAS-2 is the standard tool for diagnostic accuracy studies; however, given that our review focused on DY and downstream clinical impact, rather than sensitivity and specificity, and included observational studies without a uniform reference standard, we selected ROBINS-E as a more appropriate framework to assess bias relevant to an exposure–outcome paradigm. ROBINS-E assesses potential bias arising from confounding, participant selection, exposure classification, deviations from intended exposure, missing data, outcome measurement and selective reporting [20]. Two reviewers independently assessed each domain and assigned ratings of low, moderate, serious or critical risk, with disagreements resolved by consensus or third-reviewer adjudication; overall study ratings reflected the highest-risk domain. The certainty of evidence for each outcome was assessed using the GRADE framework, considering RoB, inconsistency, indirectness, imprecision and publication bias [21].

Statistical analysis

We performed random-effects meta-analyses using a generalized linear mixed model to estimate pooled DYs for active RCD, as well as secondary outcomes, including ulcerative jejunitis, impact on management, conversion to DAE, lymphoma, and non-lymphomatous small-bowel tumors. Heterogeneity was assessed using the I^2 statistic and the Cochran's Q test. To explore potential sources of heterogeneity, we performed univariate meta-regression using the “rma” function in the “metafor” package [22]. Effect sizes were calculated as logit-transformed proportions using the “escalc” function. Prespecified moderators included mean age, ulcer and tumor DY, CE completion rate, proportion with positive celiac serology (tTG), proportion with established RCD, and symptom burden. Subgroup and sensitivity analyses were performed based on study-level characteristics and RoB.

All analyses were conducted using R (version 4.3.2) [23] with the “meta” [24], “metafor” and “dplyr” [25] packages.

Results

Literature search and study selection

A systematic search conducted on 30 November 2025 identified 574 records across 4 databases. Following duplicate removal and title/abstract screening, 27 articles underwent full-text review, from which 17 studies met the inclusion criteria for the systematic review and meta-analysis. The reasons for the exclusion of the remaining 11 studies are detailed in Fig. 1, with the most common being inclusion of suspected rather than confirmed CD, and conference-only abstracts. One additional study focusing on chronic diarrhea in patients with established CD was identified through reference checking. Of the included studies, 6 were retrospective and the remainder

prospective, contributing a total of 994 patients to the meta-analysis (Supplementary Table 3). The mean age across cohorts ranged from 45.9–55.8 years (Table 1).

Across the 17 included studies, a wide variety of positive findings encompassed: (i) macroscopic markers of villous atrophy, including scalloping of mucosal folds, mosaic pattern, fissuring, nodularity, and flattening or absence of villi; (ii) mucosal inflammation, including erosions, erythema and edema; (iii) ulcerative lesions, including aphthous ulcers and ulcerative jejunitis or jejunoileitis; (iv) stricturing disease; and (v) suspected small-bowel malignancy, including mass lesions and circumferential thickening. These features are consistent with the established CE criteria for CD described in the ESGE CE guidelines [26] and the European Society for the Study of Celiac Disease’s 2025 updated diagnostic guidelines [12]. In addition, the definitions and granularity of “management change” varied considerably across studies, ranging from broad categories to specific therapeutic interventions (Supplementary Table 4).

The RoB assessment was performed using the ROBINS-E tool, summarized in Supplementary Table 5. The majority of

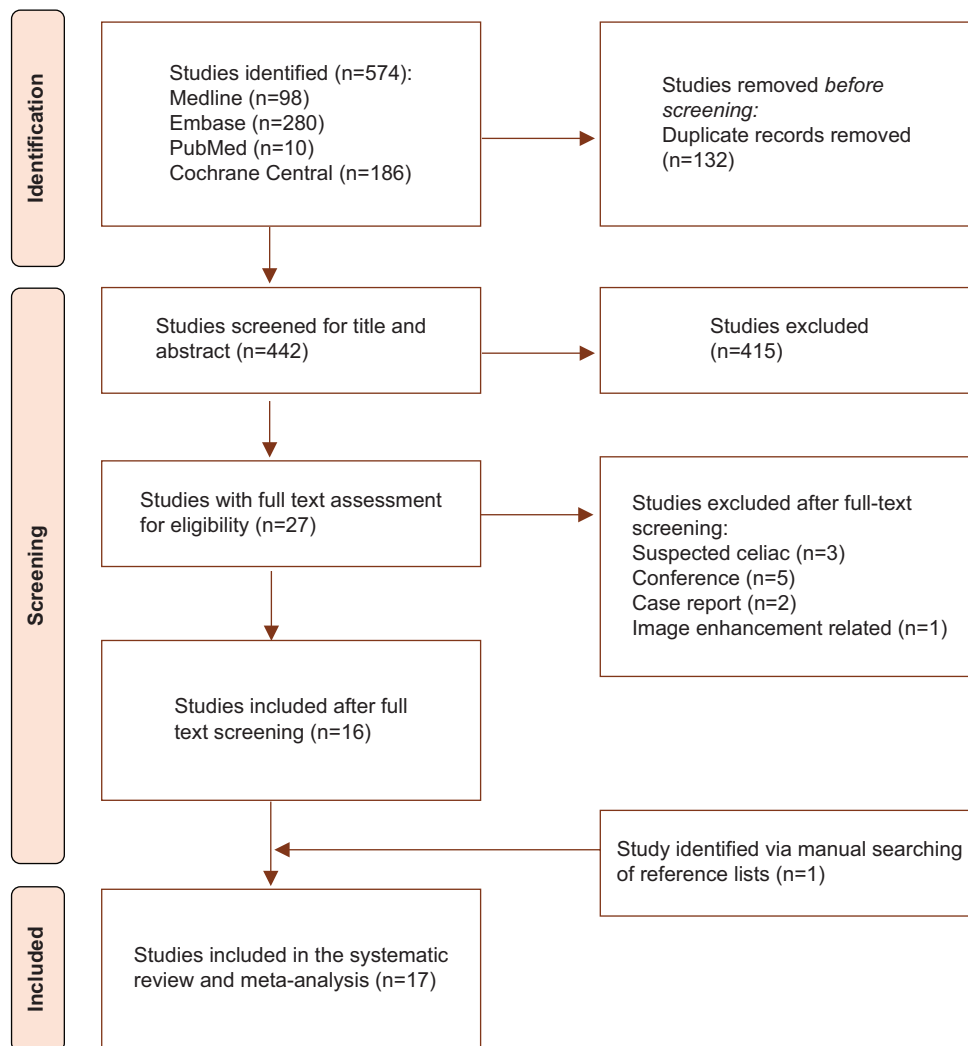


Figure 1 PRISMA flowchart

Table 1 Characteristics of included studies

Author and Location [ref.]	Year	Study type	Mean/ median Age	Age range or SD	Bowel cleansing adequacy	CE completion rate	Male sex, proportion	Sample size included/enrolled (pediatric/adult)	CE type (manufacturer, model)
Daum <i>et al</i> (Germany) [33]	2007	Single-center, retrospective	51.0	(28-85)	0.86	0.64	0.5	14	M2A capsule
Maiden <i>et al</i> (United Kingdom) [34]	2009	Single-center, prospective	57.0	(18-82)	-	0.84	0.26	19	M2A capsule
Barret <i>et al</i> (France) [35]	2012	Single-center, retrospective	47.0	-	0.53	0.62	0.32	38	M2A capsule
Tomba <i>et al</i> (Italy) [36]	2014	Single-center, prospective	49.0	4.6	1	0.96	0.19	52	PillCam SB2
Perez <i>et al</i> (Spain) [37]	2018	Multi-center, retrospective	46.6	16.6	1	0.95	0.30	189	PillCam SB3/Mirocam
Chetcuti Zammit <i>et al</i> (United Kingdom) [38]	2019	Single-center, prospective	52.5	15.5	-	0.96	0.28	23	PillCam SB3
Branchi <i>et al</i> (Italy) [11]	2020	Single-center, prospective	51.2	16.6	0.88	1	0.08	13	PillCam SB3
Branchi <i>et al</i> (Italy) [11]	2020	Single-center, prospective	51.2	16.6	1	0.85	0.08	16	Capsocam
Chetcuti Zammit <i>et al</i> (United Kingdom) [4]	2020	Single-center, prospective	54.3	15.7	-	0.93	0.3	100	PillCam SB3
Ferretti <i>et al</i> (Italy) [30]	2022	Single-center, prospective	49.0	16	0.96	0.96	0.34	151	PillCam SB3
Katsinelos <i>et al</i> (Greece) [39]	2011	Multi-center, prospective	45.9	16.7	-	-	0.49	10	Not specified
Kurien <i>et al</i> (United Kingdom) [40]	2013	Single-center, prospective	56.0	(22-83)	-	-	0.30	69	PillCam SB or PillCam SB2
Shiha <i>et al</i> (United Kingdom) [17]	2025	Multi-center, retrospective	53.0	35-65	-	0.91	0.36	146	PillCam SB3
Elli <i>et al</i> (Italy) [18]	2023	Multi-center, retrospective	52.5	(50-62)	-	-	0.30	66	M2A, M2A Plus, PillCam SB2, PillCam SB3, and PillCam Crohn's capsule.
Chetcuti Zammit <i>et al</i> (United Kingdom) [19]	2020	Single-center, prospective	49.7	16.9	-	0.97	0.40	35	PillCam SB2/3
Atlas <i>et al</i> (USA) [41]	2011	Single-center, prospective	55.8	13	-	0.76	0.24	42	M2A capsule
Foerster <i>et al</i> (Germany) [42]	2021	Single-center, retrospective	48.0	-	0.91	1	0.36	11	PillCam Crohn's capsule

CE, capsule endoscopy; SD, standard deviation

studies were observational and predominantly single center, with small sample sizes and substantial heterogeneity in study design, patient selection and outcome definitions. RoB was rated as serious in 5 studies, particularly for selection bias, unclear indications, and non-consecutive or highly preselected cohorts. Reader blinding was inconsistently applied, and reference standards varied substantially across studies, with many lacking systematic histological confirmations or relying only on biopsies of high-risk lesions.

As summarized in Supplementary Table 6, the certainty of the evidence, as assessed using GRADE, across the included studies was predominantly very low. This was driven by small observational designs, indirectness and substantial imprecision. Only 2 studies achieved a low-certainty rating, with secondary outcomes similarly limited by inconsistent reference standards, unblinded outcome assessment, and sparse reporting of clinical impact or adverse events.

Overall results

The pooled DY of CE in CxCD was 82% (95%CI 67-91%), with substantial heterogeneity ($I^2=82.5\%$). This estimate should be interpreted in the context of heterogeneous definitions of positive CE findings across studies. Subgroup analysis identified disease phenotype as the primary determinant of yield, with the highest DY observed in RCD (99%, 95%CI 82-100%; $I^2=0$) (Fig. 2). The pooled DY for CCD further highlighted this pattern, with a markedly higher yield in the RCD subgroup (18%, 95%CI 4-56%; $I^2=86.3\%$) compared with NRCD (4%, 95%CI 2-10%; $I^2=0\%$), indicating that complications are concentrated in RCD populations (Fig. 3). Accordingly, pooled estimates should not be interpreted uniformly across disease phenotypes. CE findings were associated with changes in clinical management in a substantial proportion of patients (Supplementary Fig. 1), although this outcome was highly heterogeneous and is presented descriptively. The pooled conversion rate to DAE was 18% (95%CI 9-30%; $I^2=88.8\%$), supporting a role for CE as a triage investigation, with only a minority requiring further invasive assessment. For specific findings, the pooled DY was 9% (95%CI 5-16%; $I^2=70.2\%$) for ulcers, 3% (95%CI 1-7%; $I^2=64.3\%$) for confirmed ulcerative jejunitis, and 3% (95%CI 1-6%) for malignancy (Supplementary Fig. 2,3). Capsule retention was uncommon (0.05%, 95%CI 0.02-0.14%). Completion rates ranged from 62-100%, and bowel preparation adequacy from 53-100%. PillCam (Medtronic, USA) was the most frequently used system (8 studies), followed by M2A (Given Imaging, Israel) (5 studies), panenteric PillCam Crohn's capsule (2 studies), and MiroCam (IntroMedic, South Korea) (1 study).

Publication bias was evaluated using funnel plot inspection, Egger's regression test, and the trim-and-fill method. The funnel plot visualization suggested mild asymmetry, which was confirmed statistically by Egger's regression test ($t=2.19$, $df=15$, $P=0.0446$), suggesting potential small-study effects or publication bias. Application of the trim-and-fill method

imputed 4 potentially missing studies on the left side of the funnel plot, shifting the pooled estimate downward to 79% (standard error 34%; $P=0.0186$) (Supplementary Fig. 4). Although the adjusted effect remained statistically significant, the attenuation suggests that the observed DY may be modestly inflated in the published literature.

Meta-regression

Meta-regression analyses were undertaken to explore covariates that might influence the DY of CE in CxCD. The exploratory univariate model was examined, with the results summarized in Supplementary Table 7. Two factors demonstrated significant associations with higher DY for positive CE findings: the proportion of patients with known RCD and the proportion of patients whose clinical management was altered following CE. Studies enrolling a greater proportion of patients with established RCD consistently reported higher DYs.

A dedicated meta-regression evaluating the DY of malignancy was also performed. Known RCD again emerged as a significant predictor of higher malignancy detection ($P=0.006$), as shown in the bubble plot (Supplementary Fig. 5). Similarly, a higher reported impact of CE on clinical decision-making was strongly associated with more malignant DY ($P=0.004$). Sensitivity analyses using leave-one-out procedures showed stable effect estimates across all studies. No individual study exerted disproportionate influence on the pooled results (Supplementary Fig. 6).

Subgroup analysis

A subgroup analysis was undertaken using covariates identified as significant in the meta-regression. The relationship between DY and the impact of CE on subsequent management was first examined. Studies were stratified by the proportion of patients whose management changed following CE (high >55%, moderate 30-55%, low <30%). Only 9 eligible studies reported this outcome. The high-impact group demonstrated a nearly maximal pooled DY of 99% (95%CI 20-100%; $I^2=0\%$), with progressively lower yields in the moderate- and low-impact groups; the between-group difference was significant ($P<0.001$) (Fig. 4). This gradient suggests a direct association between DY and downstream changes in management.

A further subgroup analysis assessed whether the proportion of patients with known RCD influenced tumor-specific DY. Studies without established RCD reported a pooled malignant DY of 2% (95%CI 1-4%; $I^2=0\%$), whereas studies including patients with known RCD showed a higher yield of 4% (95%CI 2-10%; $I^2=69.5\%$) (Supplementary Fig. 3). This pattern reflects the recognized increased risk of EATL and ulcerative jejunoileitis in established RCD, particularly type 2. Subgroup analyses by age, disease duration, study design and CE type revealed no significant differences between strata.

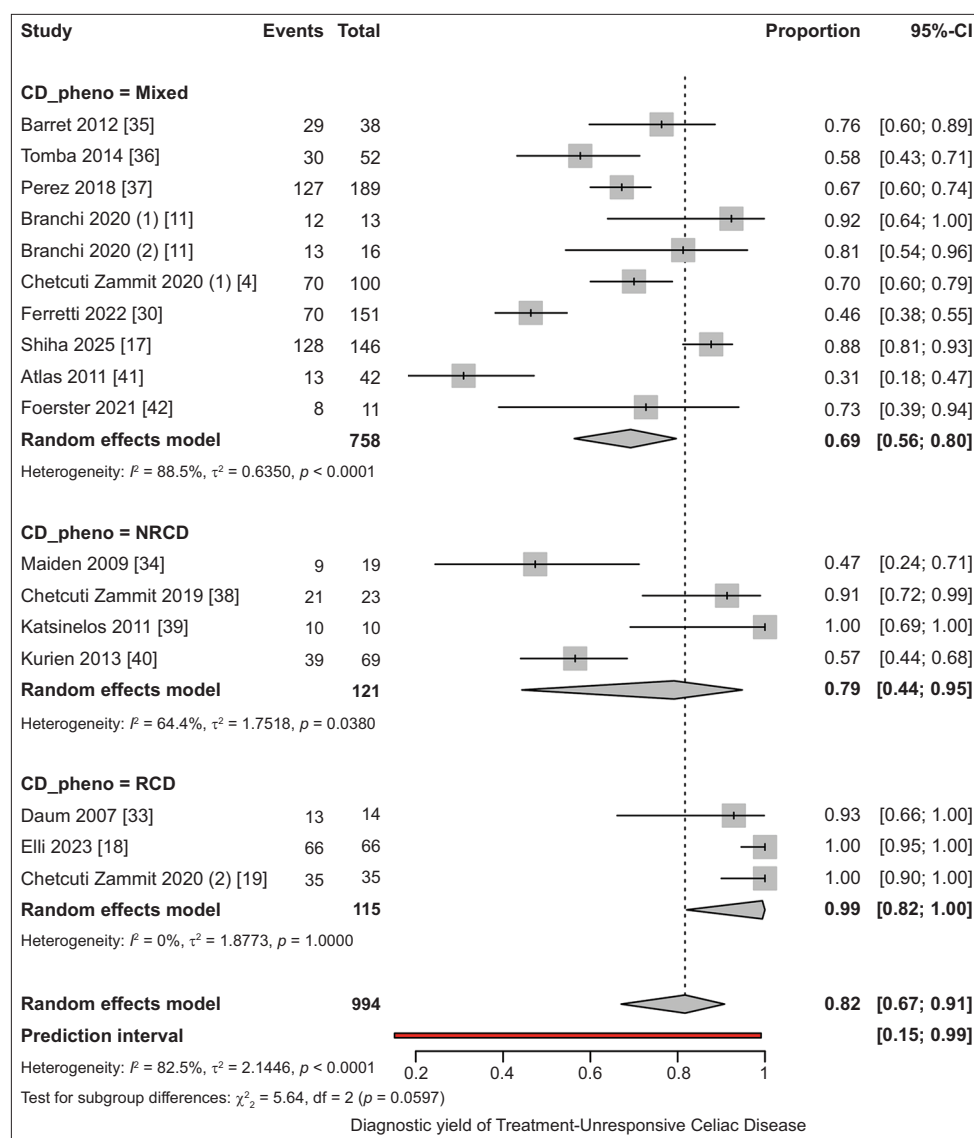


Figure 2 Pooled diagnostic yield of capsule endoscopy in CxCD, stratified by disease phenotype. Forest plot demonstrating the overall pooled diagnostic yield of 82% (95%CI 67-91%) with substantial heterogeneity ($I^2=82.5\%$). Subgroup analysis shows marked variation by phenotype, with the highest yield observed in RCD (99%, 95%CI 82-100%) compared with NRCD (79%, 95%CI 44-95%) and mixed (69%, 95%CI 56-80%) cohorts. The prediction interval (15-99%) highlights considerable between-study variability, indicating that diagnostic yield should be interpreted in the context of the underlying disease phenotype

CxCD, complex celiac disease; NRCD, non-responsive celiac disease; RCD, refractory celiac disease; CI, confidence interval; I^2 , Higgins heterogeneity statistic; τ^2 , between-study variance; df , degrees of freedom; χ^2 , chi-squared statistic

Discussion

CD, particularly when associated with persistent villous atrophy, carries an increased risk of complications and mortality. Current ESGE guidelines emphasize clinical review, serology, and repeat duodenal biopsies for surveillance, reserving CE and DAE for the uncommon scenario of suspected NRCD or RCD. These targeted modalities are therefore used selectively in a high-risk subgroup. However, no previous systematic review and meta-analysis has specifically evaluated the DY of CE in this context, its influence on subsequent management, or

the covariates that may affect DY. Furthermore, the certainty of evidence supporting the use of CE in patients with persistent symptoms despite strict dietary adherence, seronegative CD, or suspected RCD or CCD remains limited [12].

This work presents the first systematic review and meta-analysis to characterize the DY of CE in NRCD, RCD and CCD. Across studies, the pooled DY was 82% (95%CI 67-91%), a figure comparable to the DY of 80% (95%CI 74-87%) reported for CE within 48 h of overt GI bleeding [27], and broadly consistent with the DY range of 55-68% described in Crohn's disease [28,29]. These findings demonstrate that CE has a high DY for detecting clinically important abnormalities in

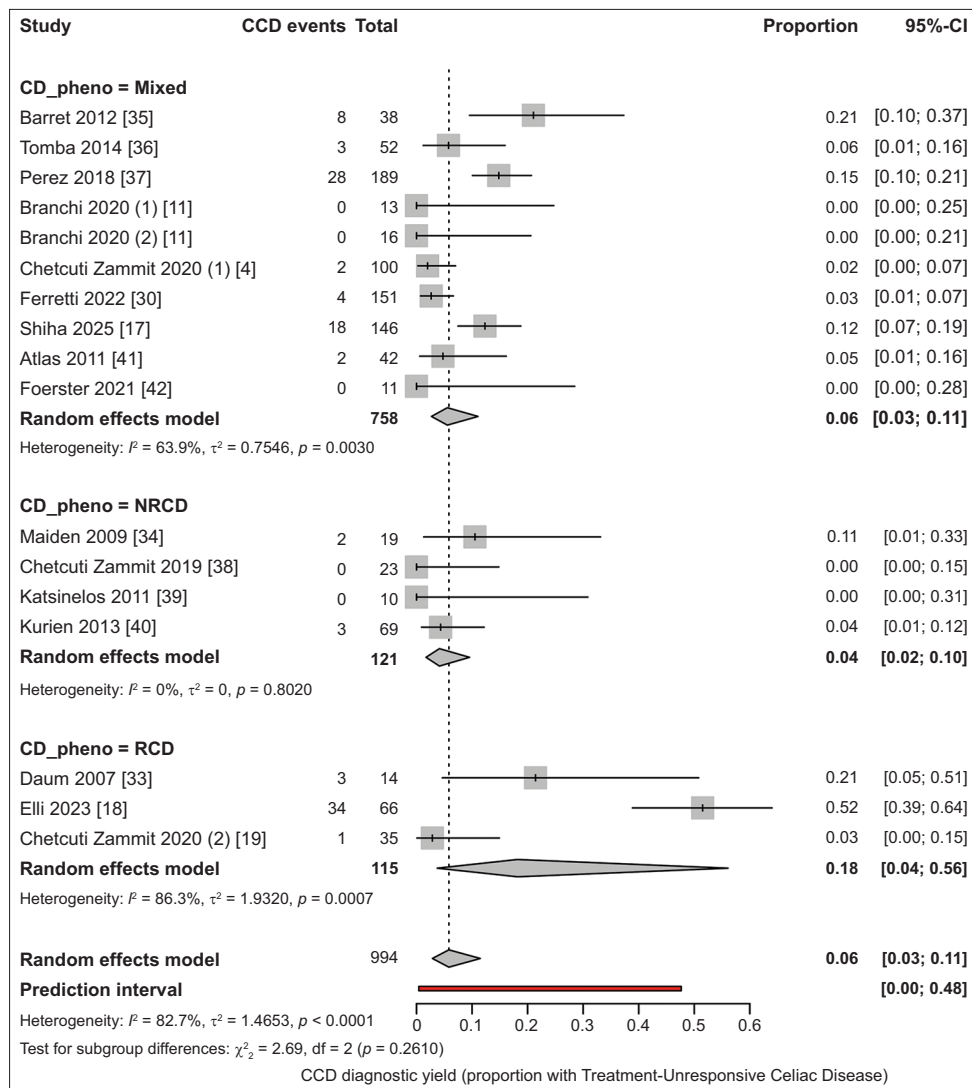


Figure 3 Pooled diagnostic yield of CCD, stratified by disease phenotype within the CxCD cohort. Forest plot showing an overall pooled CCD diagnostic yield of 6% (95%CI 3-11%) with substantial heterogeneity ($I^2=82.7\%$). Subgroup analysis demonstrates higher yield in RCD (18%, 95%CI 4-56%) compared with NRCD (4%, 95%CI 2-10%) and mixed (6%, 95%CI 3-11%) cohorts, highlighting the concentration of complications in RCD populations. The wide prediction interval (0-48%) reflects considerable between-study variability
 CCD, complicated celiac disease; CxCD, complex celiac disease; NRCD, non-responsive celiac disease; RCD, refractory celiac disease; CI, confidence interval; I^2 , Higgins heterogeneity statistic; τ^2 , between-study variance; df , degrees of freedom; χ^2 , chi-squared statistic

this population, including villous atrophy, erosions, ulcerative jejunoileitis and EATL. Diagnostic performance in this cohort mirrored that of DAE, which achieved an 83% yield (19/23 cases) in the sole published series [30]. The RCD subgroup exhibited a DY of 99% ($I^2=0$). In contrast, the NRCD subgroup had the lowest CCD DY, at 4% (95%CI 2-10%; $I^2=0\%$), compared with 18% in the RCD group. These findings demonstrate the critical role of CE in the high-risk RCD cohort. Despite a high DY of 82% with CE, DAE was performed in only 18% of cases (95%CI 9-30%). These findings are consistent with a role for CE as a noninvasive triage investigation before DAE in patients with suspected CCD, although prospective comparative studies are required to define this sequential approach. CE may therefore be considered a first-line, noninvasive investigation in high-

risk patients, with DAE reserved for targeted biopsy, evaluation of ulcerative jejunoileitis, or assessment of stricturing disease, in line with ESGE guidance [26].

Given the high DY, a central question is whether CE meaningfully influences clinical management in this population. In our study, CE findings were associated with changes in clinical management in a substantial proportion of patients across studies; however, this outcome was highly heterogeneous and should be interpreted descriptively rather than as a precise pooled estimate (Supplementary Fig. 1). The proportion of patients experiencing a management change was lower than that reported for CE in suspected general small-bowel disease, in which management changes occur in approximately 70% of patients [31]. An exploratory subgroup analysis suggested

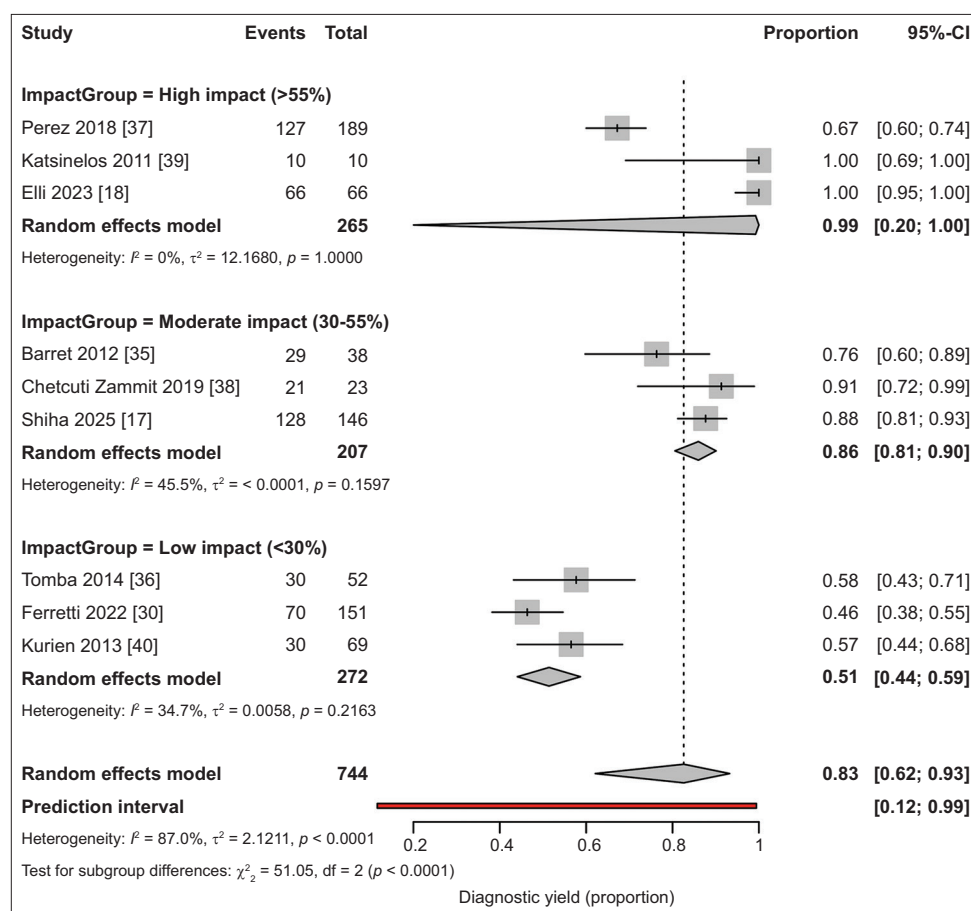


Figure 4 Subgroup analysis of diagnostic yield stratified by reported impact of capsule endoscopy on clinical management. Studies were grouped by the proportion of patients experiencing a change in management following capsule endoscopy (high >55%, moderate 30-55%, low <30%). Diagnostic yield increased across groups, with the highest yield observed in studies reporting high clinical impact (99%, 95%CI 20-100%), compared with moderate (86%, 95%CI 81-90%) and low (51%, 95%CI 44-59%) impact groups. A statistically significant between-group difference was observed ($P < 0.001$). However, only 9 studies reported management change and definitions varied across studies; therefore, these findings should be considered exploratory
CI, confidence interval; I^2 , Higgins heterogeneity statistic; τ^2 , between-study variance; df , degrees of freedom; χ^2 , chi-squared statistic

higher DY in studies reporting greater management change. However, only 9 studies contributed data, while outcome definitions were heterogeneous, limiting the robustness of this observation. Within the subset of patients with confirmed RCD only, studies showed higher malignant DYs (6%; 95%CI 1-37%; $I^2=0$) compared with studies without RCD (2%; 95%CI 0-6%; $I^2=0$) (Supplementary Fig. 3). These findings reinforce the use of CE as a surveillance tool in this high-risk cohort [12]. However, few studies distinguished between RCD type 1 and type 2, precluding subtype-specific analyses. Although the need for surveillance in RCD is clear, the optimal interval and duration remain uncertain and represent important areas for future research. Importantly, these findings should be interpreted in the context of disease phenotype. The DY and clinical impact of CE were highest in patients with established RCD, whereas evidence supporting its use in NRCD alone remains more limited and of lower certainty.

Across a limited number of studies, patients with negative CE findings did not subsequently develop new CD-related

complications during follow-up, suggesting a high negative predictive value for clinically significant small-bowel pathology. In a large multicenter European cohort, no patient with a negative examination was later found to have EATL, ulcerative jejunoileitis, or other major complications, with alternative non-celiac diagnoses identified in a substantial proportion. Therefore, a negative small-bowel CE appears clinically reassuring, with available evidence suggesting a low risk of missed celiac-related complications and frequent identification of alternative diagnoses. It may therefore support a strategy of conservative management and avoidance of further invasive investigation, although this inference is based on limited and heterogeneous data. Assessment of publication bias suggested the presence of small-study effects. Funnel plot asymmetry, supported by Egger's regression test, and subsequent trim-and-fill analysis indicated that the pooled DY may be modestly overestimated, with adjustment reducing the estimate from 82% to 79%. These findings are consistent with the recognized tendency for single-arm diagnostic studies with lower yields to

be under-reported, although the limited number of included studies constrains the reliability of formal bias assessment.

Limitations of this study include the predominance of retrospective studies, which resulted in a substantial proportion being rated as having a serious RoB, and contributed to an overall very low certainty of evidence. Missing data were frequent, with many studies omitting both negative CE examinations and information on how findings influenced subsequent management. Rare outcomes, such as malignancy, further contributed to imprecision, because multicenter studies varied in their definitions of GFD adherence and indications for CE, thereby exacerbating the already substantial heterogeneity. A potential overestimation of CCD DY cannot be excluded, as some studies lacked clarity on whether structural and malignant findings, such as strictures and malignancy, were reported as distinct entities, introducing a risk of double-counting individual patients. These methodological constraints reduce confidence in the pooled estimates and underscore the need for larger, prospective, standardized studies to better define the DY and clinical impact of CE in NRCD and RCD. Advances in artificial intelligence (AI), particularly in lesion characterization, may eventually enable the prediction of the RCD subtype directly from CE imaging, without the need for DAE and biopsy [32]. A notable methodological limitation across the included studies is the absence of a uniformly applied, validated scoring system for CE in CD, and the variation in histological reference standards. The threshold defining a “positive” examination differed substantially between study cohorts (Supplementary Table 8). This substantial heterogeneity in the definition of a positive CE examination and clinical impact constitutes a key study-level limitation, undermining direct cross-study comparability and limiting the interpretation of pooled DY estimates. Consequently, the pooled estimates should be regarded as summary measures across heterogeneous definitions of clinically significant findings, rather than precise estimates applicable to a single standardized diagnostic threshold. A further limitation is the absence of a uniformly applied reference standard across studies, with CE findings not consistently validated against histology or DAE in all participants. This limits the ability to interpret DY in relation to underlying disease status, and may have contributed to heterogeneity in reported yields. In addition, most studies were conducted in tertiary referral settings, and included highly selected populations enriched for refractory disease, raising the possibility of spectrum bias and overestimation of DY. Standardization of CE reporting criteria and reporting outcome in CD remains a priority for future prospective studies.

In conclusion, this study adds to the growing evidence on the DY of CE across NRCD, RCD and CCD cohorts, and suggests that it can meaningfully inform subsequent clinical management. Its noninvasive nature and low conversion to subsequent DAE suggest it may have a role as a second-line investigation and triage tool in patients with CxCD. However, these findings should be interpreted cautiously, given the substantial heterogeneity and predominantly very-low-certainty evidence. Future studies should evaluate the role of AI

in image interpretation, although robust prospective evidence is needed before AI-assisted approaches can be integrated into routine diagnostic pathways for NRCD, RCD and CCD.

Summary Box

What is already known:

- Capsule endoscopy (CE) is recommended as a second-line investigation in suspected refractory or complicated celiac disease (CD), but no prior systematic review has evaluated its diagnostic yield specifically in this population
- Up to 30% of adults with CD have persistent symptoms, despite a gluten-free diet, and these cases carry an elevated risk of complications including ulcerative jejunitis and lymphoma

What the new findings are:

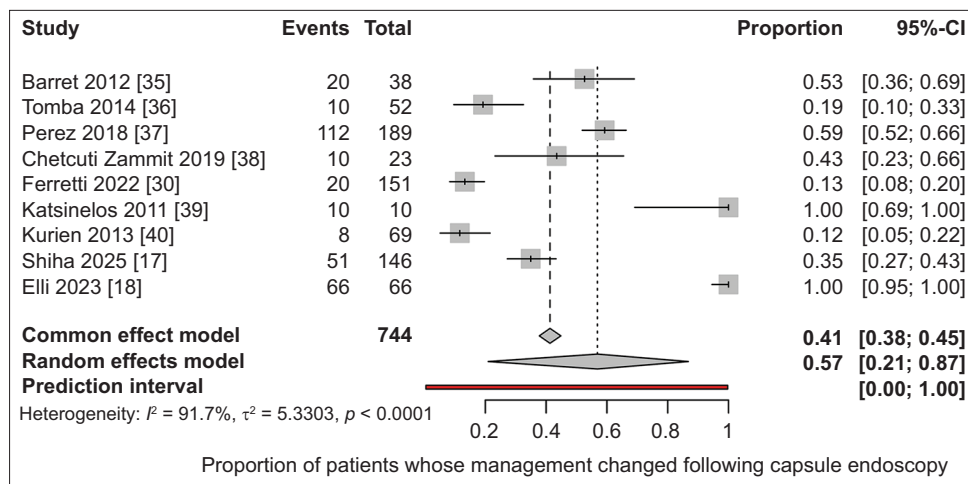
- The pooled diagnostic yield of CE in complex CD was 82% (95% confidence interval 67-91%), rising to 99% in refractory CD, with low pooled rates of ulcerative jejunitis (3%) and small-bowel malignancy (3%)
- The proportion of patients with known refractory CD and the proportion experiencing management change were significantly associated with a higher diagnostic yield, and only 18% required conversion to device-assisted enteroscopy

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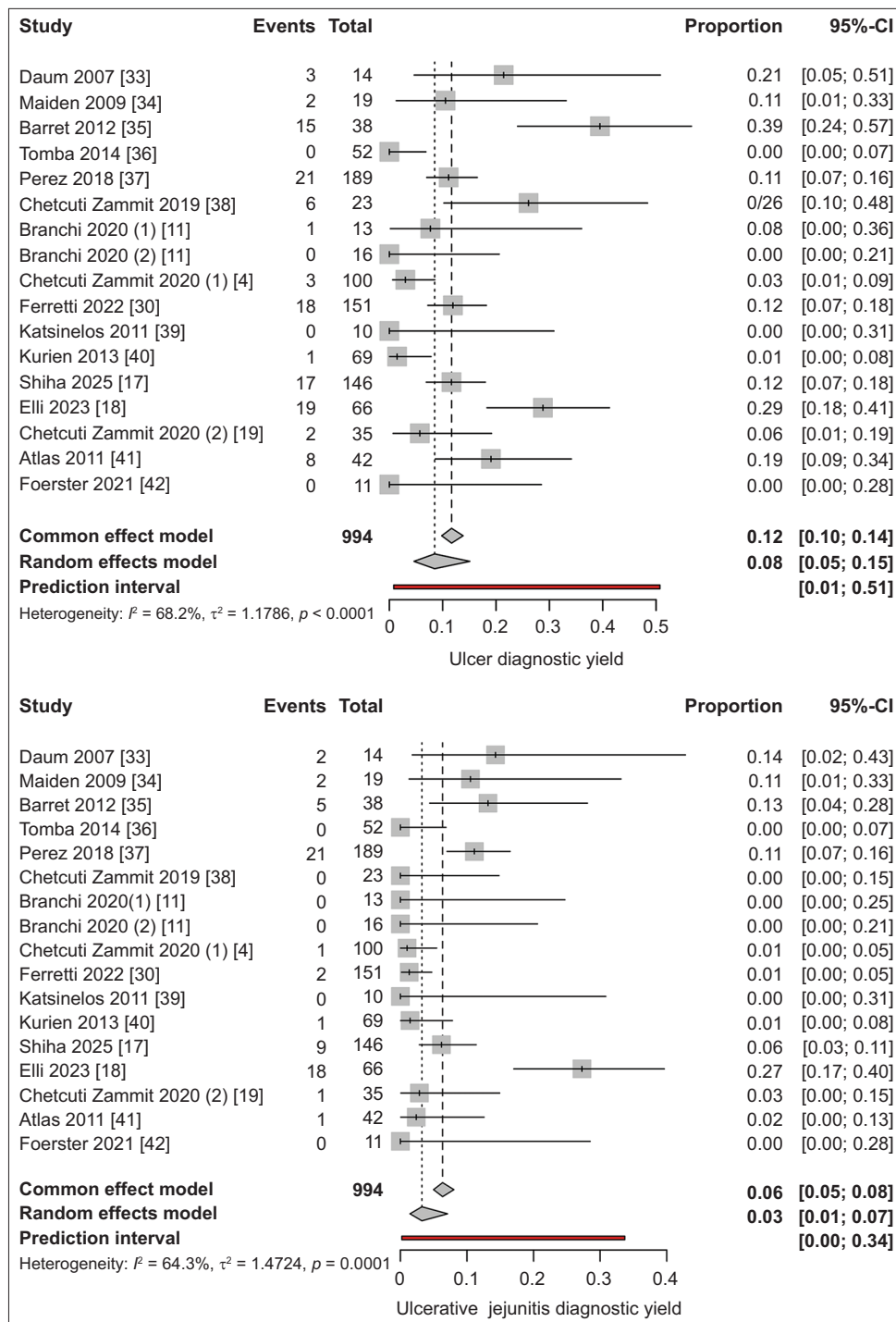
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Supplementary material

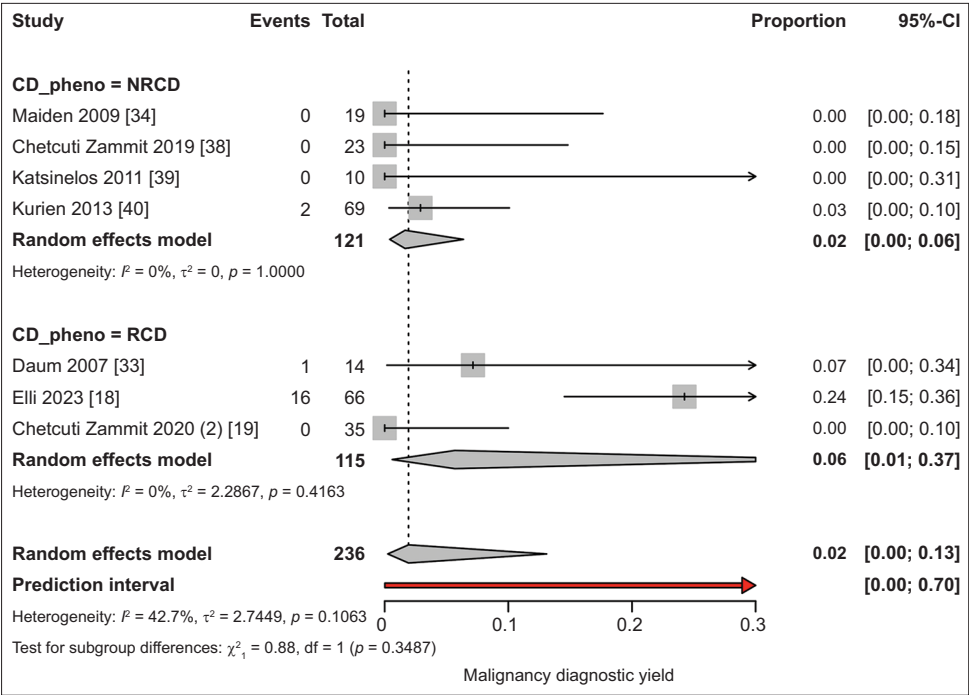


Supplementary Figure 1 Pooled proportion of patients whose management changed following capsule endoscopy in non-responsive or refractory celiac disease

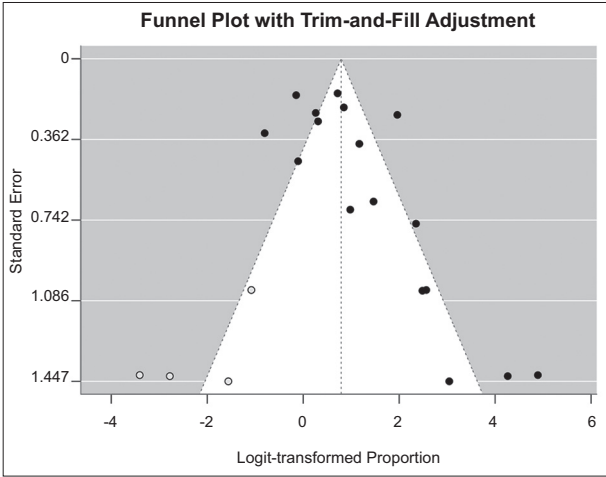
CI, confidence interval; I^2 , Higgins heterogeneity statistic



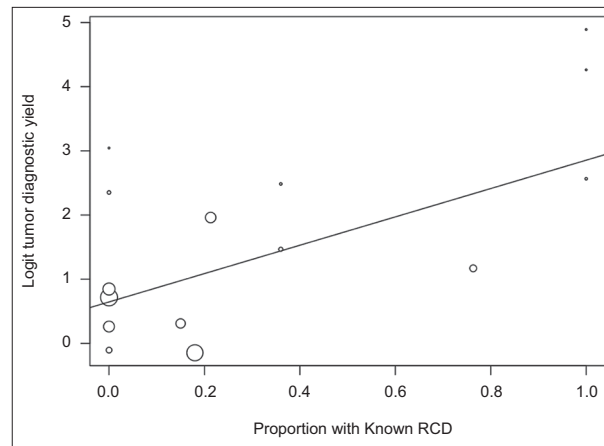
Supplementary Figure 2 Forest plot of (A) ulcers diagnostic yield (left) and (B) ulcerative jejunitis (right)
 CI, confidence interval; I^2 , Higgins heterogeneity statistic



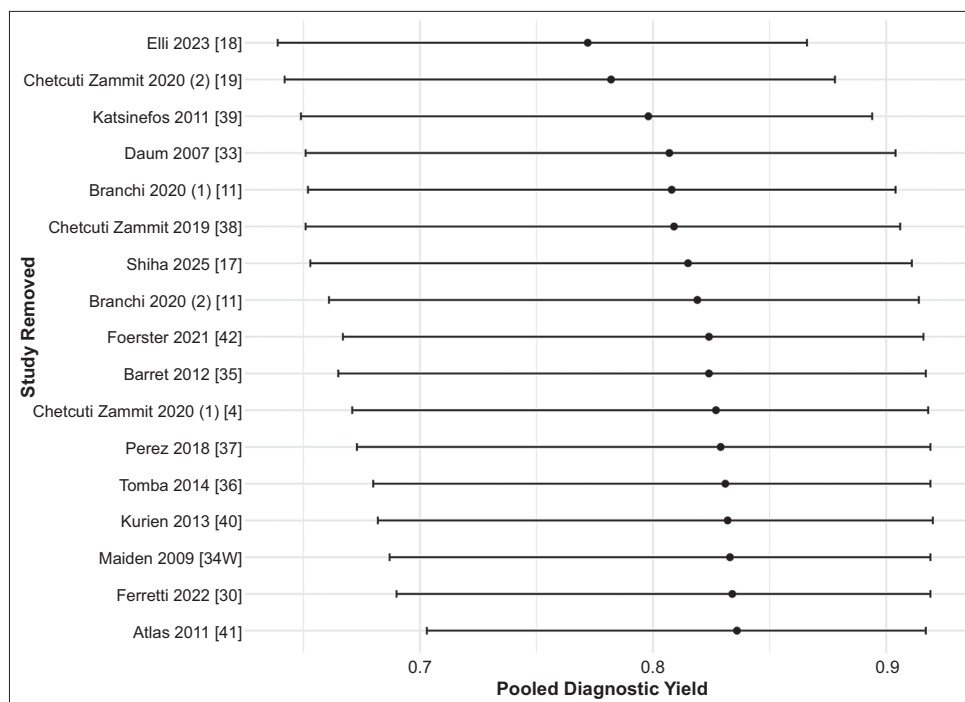
Supplementary Figure 3 Forest plot of malignancy diagnostic yield in studies reporting RCD vs. no RCD patients
RCD, refractory celiac disease; CI, confidence interval; I^2 , Higgins heterogeneity statistic



Supplementary Figure 4 The funnel plot of the selected studies reveals asymmetry. Application of the trim-and-fill method imputed 4 potentially missing studies on the left side of the funnel plot. This was generated using the “metafor” R package



Supplementary Figure 5 Bubble plot illustrating the upward trend in tumor diagnostic yield as the proportion of participants with established refractory celiac disease (RCD) increases across studies



Supplementary Figure 6 Leave-one-out sensitivity analysis. The graph shows the effect of excluding each study on the overall pooled effect size. Black dots represent the pooled estimates after removing 1 study, with black lines indicating the 95% confidence intervals. The gray line marks the overall pooled diagnostic yield. The minimal deviation and overlapping confidence intervals suggest that no single study significantly influenced the results

Supplementary Table 1 PRISMA 2020 checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	P. 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	P. 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	P. 4
Objectives	4	Provide an explicit statement of the objective (s) or question (s) the review addresses.	P. 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	P. 5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	P. 5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	P. 5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	P. 5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	P. 6, Appendix
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	P. 5-6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool (s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	P. 6 and Appendix
Effect measures	12	Specify for each outcome the effect measure (s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.	P. 6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	P. 5-6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	P. 6
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	P. 6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice (s). If meta-analysis was performed, describe the model (s), method (s) to identify the presence and extent of statistical heterogeneity, and software package (s) used.	P. 6
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).	P. 6
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	P. 6, Appendix
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	P. 12, Appendix
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	P. 6, Appendix

(Contd...)

Supplementary Table 1 (*Continued*)

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	P. 6-7, Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	P. 6-7, Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Table 1, Appendix
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Appendix
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.	Figure 2 and 4, Appendix
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	P. 7-9, Appendix
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	P. 10-12, Figures 2-3
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	P. 13-14, Appendix
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	P. 13, Appendix
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	P. 12, Appendix
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	P. 7, Appendix
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	P. 14-15
	23b	Discuss any limitations of the evidence included in the review.	P. 15
	23c	Discuss any limitations of the review processes used.	P. 15
	23d	Discuss implications of the results for practice, policy, and future research.	P. 15
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	P. 4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	P. 4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	P. 16
Competing interests	26	Declare any competing interests of review authors.	P. 16
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	P. 16

Supplementary Table 2 The PECO framework

Domain	Search Terms
Population	Adult patients (age >18) with coeliac/ceeliac disease, including refractory and complicated forms. General coeliac/ceeliac disease: "celiac disease", "coeliac disease", "celiac sprue", "coeliac sprue", "gluten-sensitive enteropathy", "gluten sensitive enteropathy", "gluten enteropathy" Refractory/persistent disease: "refractory celiac disease", "refractory coeliac disease", "RCD", "RCD1", "RCD2", "type I/II refractory celiac/coeliac" "nonresponsive celiac/coeliac disease", "unresponsive celiac/coeliac disease", "persistent villous atrophy", "ongoing villous atrophy", "persistent enteropathy" Complicated celiac disease: "complicated celiac/coeliac disease" Specific complications: "ulcerative jejunitis", "ulcerative jejunoileitis", "small bowel strictures", "small intestinal strictures" Malignant transformation (celiac-associated): "enteropathy-associated T-cell lymphoma", "EATL", "small bowel lymphoma"
Exposure	Capsule endoscopy (CE) used for diagnosis or monitoring of celiac disease: Small bowel capsule endoscopy (SBCE), Colon capsule endoscopy (CCE), Panenteric capsule endoscopy (PCE), Gastric capsule endoscopy Commercial systems: PillCam, OMOM, MiroCam, EndoCapsule, NaviCam, CapsoCam
Comparison	Conventional diagnostic modalities used in celiac disease or its complications: Upper GI endoscopy (OGD/EGD) with duodenal biopsies, Ileocolonoscopy/colonoscopy, Push enteroscopy, balloon-assisted or device-assisted enteroscopy, CT, CT enterography, CT enteroclysis, MR enterography (MRE)/MRI, Small bowel follow-through/barium studies, Abdominal or small bowel ultrasound, Other radiological or cross-sectional imaging investigating refractory or complicated celiac disease
Outcome	Outcomes describing the diagnostic yield and clinical impact of CE in celiac disease, particularly refractory or complicated cases Diagnostic outcomes: Diagnostic yield for lesions (ulcerative jejunitis, strictures, atrophy, neoplasia including EATL/adenocarcinoma), Diagnostic accuracy (sensitivity, specificity, predictive values) Clinical impact: Management change (immunosuppression, chemotherapy, surgery, nutritional interventions), Risk stratification for complications (lymphoma, stricturing disease, ulcerative jejunitis), Symptom improvement, mucosal healing, survival, quality of life

PECO, Population, exposure, comparison, outcome; EATL, enteropathy-associated T-cell lymphoma; GI, gastrointestinal; OGD, esophagogastroduodenoscopy; EGD, esophagogastroduodenoscopy; CT, computed tomography; MRE, magnetic resonance enterography

Supplementary Table 3 Additional information for all studies

Author [ref.]	Positive findings diagnostic yield (%)	Ulcerative jejunitis DY (%)	Malignancy DY (%)	Ulcers DY (%)	Adverse event (%)	Proportion of patients with known RCD (%)	Management change following CE (%)	Enteroscopy conversion (n)
Daum (2007) [33]	92.9	14.3	7.1	21.4	–	100	–	2
Maiden (2009) [34]	47.4	10.5	0	10.5	–	0	–	–
Barret (2012) [35]	76.3	13.2	7.9	40	–	76.3	52.6	26
Tomba (2014) [36]	58	0	5.7	0	1.9	15	18.9	9
Perez (2018) [37]	67.2	11.1	3.7	11.1	0.5	0	59.3	25
Chetcuti Zammit (2019) [38]	91.3	–	0	26.1	–	0	42.4	–
Branchi (2020) [11]	52	–	0	4	0	36	–	–
Branchi (2020) [11]	65	–	0	0	0	36	–	–
Chetcuti Zammit (2020) [4]	70	1	1	3.3	1	0	–	–
Ferretti (2022) [30]	46	1.3	1.3	11.9	0.7	18	13.4	21
Katsinelos 2011 [39]	100	–	0	0	0.8	0	100	–
Kurien (2013) [39]	56.5	1.4	2.9	1.4	–	0	11.6	8
Shiha (2025) [17]	87.6	6.2	6.1	11.6	0.1	21.3	34.8	20
Elli (2023) [18]	100	27	24.3	29	–	100	100	25
Chetcuti Zammit (2020) [19]	51.4	2.9	0	5.7	0	0	–	–
Atlas (2011) [41]	31	2.4	2.4	19	0	–	–	1
Foerster (2021) [42]	72.7	0	0	0	0	–	–	–

DY, diagnostic yield; CE, capsule endoscopy; RCD, refractory celiac disease

Supplementary Table 4 Clinical impact of capsule endoscopy on management in celiac disease: study-level attribution

Domain	Specific findings/interventions	Studies reporting this
Pharmacological escalation	Initiation or escalation of corticosteroids (budesonide/prednisolone) following CE findings of persistent villous atrophy or inflammation Use of immunosuppressive therapy (e.g., azathioprine) guided by CE findings and disease severity	(Shiha <i>et al</i> 2025) [17]
	Subtype-directed therapy: corticosteroids for RCD1; immunosuppressants (azathioprine, cyclosporine, cladribine) for RCD2; chemotherapy for EATL	Ferretti <i>et al</i> (2022) [30]
Referral for device-assisted enteroscopy (DAE)	CE-triggered referral for tissue acquisition, confirmation of suspected lesions, or therapeutic intervention CE-guided DBE confirming complications (ulceration, strictures, malignancy) and enabling therapy (e.g., dilation, capsule retrieval)	(Shiha <i>et al</i> 2025) [17]
	CE-directed enteroscopy in suspected complicated CD	Ferretti <i>et al</i> (2022) [30]; Barrett <i>et al</i> (2012) [35]
Dietary and nutritional interventions	Reinforcement of GFD adherence following persistent villous atrophy or ongoing symptoms Nutritional optimization, including supplementation and support in patients with severe disease	(Shiha <i>et al</i> 2025) [17]
	Requirement for advanced nutritional support (e.g., parenteral nutrition in severe RCD)	Elli <i>et al</i> (2023) [18]
Surgical referral	Referral for surgery in patients with strictures or suspected malignancy not amenable to endoscopic therapy	(Shiha <i>et al</i> 2025) [17]; Ferretti <i>et al</i> (2022) [30]
De-escalation/triage	Avoidance of further invasive investigations in patients with negative or low-risk CE findings	Perez-Cuadrado-Robles <i>et al</i> (2018) [37]
	CE-based reclassification of disease severity leading to avoidance of unnecessary enteroscopy	Ferretti <i>et al</i> (2022) [30]

CE, capsule endoscopy; RCD, refractory celiac disease; RCD1, refractory celiac disease type 1; RCD2, refractory celiac disease type 2; EATL, enteropathy-associated T-cell lymphoma; DAE, device-assisted enteroscopy; DBE, double-balloon enteroscopy; CD, celiac disease; GFD, gluten-free diet

Supplementary Table 5 The risk of bias assessment using the ROBINS-E tool

Study [ref.]	Type of included studies	Bias due to confounding	Bias in participant selection	Bias in classification of exposure	Bias in deviations from exposure	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported result	Overall RoB	Justification
Daum (2007) [33]	Retrospective single-center	Low	Moderate	Low	Low	Low	Low	Moderate	Low	Only 64% of examinations complete, so only 9 patients completely analyzed in the end (<10)
Maiden (2009) [34]	Prospective single-center	Low	Serious	Moderate	Low	Moderate	Moderate	Moderate	Serious	Single observer only. Single tertiary clinic, small sample, only those who agreed to VCE, unclear whether recruitment was consecutive, or how many eligible patients were missed
Barret (2012) [35]	Retrospective single-center	Low	Serious	Low	Low	Low	Moderate	Low	Serious	Selection of a non-consecutive subset of RCD patients (only 29/63) who had both CE+endoscopy within a year, these are likely more severe/complex disease
Tomba (2014) [36]	Prospective single-center	Low	Serious	Low	Low	Low	Low	Moderate	Serious	10/19 patients had non-compliance with GFD+only over 50 so more likely for complications. Includes pts with ALARM Sx too (not just CD Sx) so more likely to have malignancy
Perez (2018) [37]	Retrospective multicenter	Low	Moderate	Low	Low	Low	Moderate	Moderate	Moderate	Only included CE patients who had 1 year follow up. Multicenter-definition of GFD adherence based on center-specific guideline. Doesn't explicitly say CE readers were blinded to patient details
Chetcuti Zammit (2019) [38]	Prospective single-center	Moderate	Moderate	Low	Low/moderate	Moderate	Low	Moderate	Moderate	More about role of a second look SBCE in patients with RCD who were eligible for our study
Branchi (2020) [11]	Prospective single-center	Low	Moderate	Low	Low	Moderate	Low	Low	Moderate	Prospective, randomized, each patient receives both capsule types. Clear definitions and blinded expert reading. However selected, small, single-center cohort. 5 patients had missing data/incomplete examination
Chetcuti Zammit (2020) [4]	Prospective single-center	Moderate	Moderate	Low	Low	Moderate	Low	Moderate	Moderate	Tertiary-center, highly selected symptomatic/RCD cohort with incomplete capsules, however robust blinded SBCE readings

(Contd...)

Supplementary Table 5 (Continued)

Study [ref.]	Type of included studies	Bias due to confounding	Bias in participant selection	Bias in classification of exposure	Bias in deviations from exposure	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported result	Overall RoB	Justification
Ferretti (2022) [30]	Prospective single-center	Moderate	Moderate	Low	Low	Low/moderate	Low	Moderate	Moderate	Risk factors e.g., anemia associated with positive findings, but no adjustment done. Highly selected tertiary cohort and mixture of indications including non GFD adherence
Kurien (2013) [39]	Prospective single-center	Moderate	Moderate	Low	Low	Low/moderate	Moderate	Moderate	Moderate	Tertiary single-center, videos read by 3 experienced readers, aware of clinical symptoms but blinded to serology and histology. No systematic reference standard given for findings. Completion/retention rates not reported
Shiha (2025) [17]	Retrospective multicenter	Low	Moderate	Low	Low	Low	Low	Moderate	Moderate	Retrospective; tertiary center, several expert capsule readers with pre-defined definitions
Elli (2023) [18]	Retrospective multicenter	Moderate	Moderate	Low	Low	Moderate	Moderate	Serious	Serious	Includes all RCD patients attending center, however capsule endoscopy was not performed in 6/37 patients; in five of these, CE was contraindicated owing to intestinal stenosis on cross-sectional imaging (CT, MR or small-bowel ultrasound) or a positive patency test. Capsule data merged with DBE, cannot extract capsule data alone. Not recorded negative CE exams, completeness rates
Chetcuti Zammit (2020) [19]	Prospective single-center	Moderate	Low	Low	Low	Moderate	Low	Moderate	Low	Not all eligible patients during the period had SBCE; expert readers not blinded
Atlas (2011) [41]	Prospective single-center	Low	Moderate	Low	Low	Moderate	Moderate	Moderate	Moderate	Consecutive tertiary-center NRCD patients, single, unvalidated capsule reader, 24% incomplete small-bowel visualization
Foerster (2021) [42]	Retrospective single-center	Low	Serious	Low	Low	Moderate	Moderate	Moderate	Serious	Single-center retrospective, established CD but no mention if had CE because RCD/NRCD etc., no indication given. Small sample. Single blinded interpreter. Complete bowel examined in only 36%

The assessments are categorized as: low, moderate, serious and critical risk of bias. No information should be stated if there are insufficient data.

ROBINS-E, Risk Of Bias In Non-randomized Studies of Exposures; RoB, risk of bias; CE, capsule endoscopy; Sx, Symptoms; SBCE, small-bowel capsule endoscopy; VCE, video capsule endoscopy; GFD, gluten-free diet; RCD, refractory celiac disease; NRCD, non-responsive celiac disease

Supplementary Table 6 GRADE Assessment

Study [ref.]	Primary outcome	GRADE certainty	Justification	Secondary outcome	GRADE certainty	Justification	Overall rating
Daum (2007) [33]	DY of CE for ulcerative jejunitis/intestinal T-cell lymphoma in RCD	Very Low	Observational case series; single center; small sample size; and rare adverse events	Clinical impact, safety, feasibility, procedural success	Very low	Observational and small number; imprecision	Very low
Maiden (2009) [34]	DY of CE for small bowel pathology in NRCD	Very low	Observational; small sample; imprecision	Diagnostic accuracy; clinical impact; safety and technical outcomes	Very low	Same limitations; indirectness; imprecision with rare events	Very low
Barret (2012) [35]	DY of CE for complications of NRCD/RCD	Very low	Observational retrospective; limited population; non-consecutive; imprecision	Diagnostic accuracy/concordance with histology, clinical impact, safety	Very low	Same limitations; rare events	Very low
Tomba (2014) [36]	DY of CE detecting small-bowel malignancy in 'at risk' CD	Very low	Observational; not blinded; indirectness with population; rare events so imprecision	Clinical impact, safety, feasibility	Very Low	Observational; no comparator; imprecision with rare events of adverse effects	Very low
Perez (2018) [37]	DY of CE for small-bowel pathology/complications in NRCD or alarm features	Low	Observational multicenter; population aligns	Clinical impact, safety, feasibility	Low	Observational; limited indirectness and imprecision, moderate risk of bias	Low
Chetcuti Zammit (2019) [38]	DY of SBCE in established CD	Very low	Observational; small sample; indirectness	Lesion/complication characterization and extent of small-bowel involvement	Very low	Observational; rare events; same risk of bias	Very low
Branchi (2020) [11]	DY of SBCE in suspected/known complicated/NRCD	Very low	Randomized controlled; single center, only subset of 25/508 CD patients evaluated. Mixed indications, includes non-compliant pts	Diagnostic accuracy of capsule endoscopy vs. duodenal histology for small-bowel atrophy	Very low	Observational; selection issues; readers aware of capsule type; indirectness and imprecision	Very low
Chetcuti Zammit (2020) [4]	DY in NRCD/RCD/complicated CD	Very low	Observational; bias with pt selection, indirectness and imprecision, rare neoplastic events	Diagnostic accuracy (sensitivity/specificity vs duodenal histology); completion rate; retention/adverse events	Low	Observational with rare events, so imprecision; risk of bias with selected cohort.	Very low
Ferretti (2022) [30]	DY in NRCD/RCD/complicated CD	Low	Observational; mixed indications, highly selective tertiary population; no comparator; modest sample size	Diagnostic accuracy, other secondary outcomes e.g. lesion/complication characterization, clinical impact, completion, retention/adverse events	Very low	Same risk of bias; rare adverse events so imprecision and indirectness.	Very low

(Contd...)

Supplementary Table 6 (Continued)

Study [ref.]	Primary outcome	GRADE certainty	Justification	Secondary outcome	GRADE certainty	Justification	Overall rating
Kurien (2013) [39]	DY of CE for significant small-bowel pathology in non-responsive CD	Very low	Observational with rare adverse events in a single center so imprecision.	Characterization of CD-related complications. Clinical impact/change in management	Very low	Same risk of bias, rare events so imprecision. Sparse and mostly descriptive data on management change. No comparator, no data on completion	Very low
Shiha (2025) [17]	DY for small bowel complications in NRCD/RCD/complicated CD	Very low	Observational, retrospective single-center; rare events; imprecision with small number events; mixed CD population including seronegative CD/RCD/NRCD	Completion rate, bowel prep, adverse events	Very low	Risk of bias, indirectness and imprecision	Very low
Elli (2023) [18]	DY for small bowel lesions/complications in RCD	Very low	Retrospective; some pts not examined; no specific stats for capsule; indirectness, imprecision	Lesion/complication characterization	Very low	Same issues; does not separate capsule from DBE	Very low
Chetcuti Zammit (2020) [19]	DY in equivocal/seronegative CD	Very low	Observational; unblinded outcome assessment; indirectness with population	Diagnostic accuracy; clinical impact; completion rate; complications	Very low	Rare events; no comparator	Very low
Atlas (2011) [41]	DY in NRCD	Very low	Observational; risk of bias; imprecision	Specific complications found	Very low	Same limitations, rare events so imprecision	Very low
Foerster (2021) [42]	DY of capsule in CD	Very low	Observational, risk of bias, serious imprecision, indirectness with population selection	Completion rate, capsule retention, adverse events, clinical impact	Very low	Same limitations, rare events with complications and clinical impact	Very low

The assessments are categorized as: very low, low, moderate, high. No information should be stated if there is insufficient data

GRADE, Grading of Recommendations, Assessment, Development and Evaluations; DBE, Double-balloon Enteroscopy; DY, diagnostic yield; CE, capsule endoscopy; RCD, refractory celiac disease; NRCD, non-responsive celiac disease; CD, celiac disease

Supplementary Table 7 Meta-regression results

Covariates	Regression	Beta	R ² [†]	SE	P-value
Mean age	Univariate	−0.0880	0.000	0.089	0.320
Male sex (%)	Univariate	3.169	0.000	3.079	0.303
Median duration of disease	Univariate	−0.2293	0.000	0.318	0.471
Ulcers DY	Univariate	1.840	0.000	2.698	0.495
Ulcerative jejunitis DY	Univariate	6.661	0.017	4.763	0.162
Tumor DY	Univariate	11.322	0.134	6.417	0.078
Completion rate	Univariate	0.749	0.092	2.632	0.776
Bowel adequacy	Univariate	−1.5702	0.639	1.781	0.378
Impacting subsequent management	Univariate	3.462	0.523	1.195	0.004*
Patients with persistent elevated tTG	Univariate	−0.7953	0.000	1.411	0.573
Patients with Known RCD	Univariate	2.210	0.436	0.799	0.006*
Patients with persistent symptoms	Univariate	−0.9688	0.087	0.973	0.320

Covariates	Regression	Estimate	SE	Z-Value	P-value
Mean age	Multivariate	0.372	0.274	1.3573	0.1747
Ulcers DY	Multivariate	6.6115	4.851	1.3629	0.1729
Ulcerative jejunitis DY	Multivariate	−37.2288	42.947	−0.8669	0.386
Tumor DY	Multivariate	−0.3513	21.8788	−0.0161	0.9872
Male sex	Multivariate	−3.2957	4.306	−0.7654	0.444
Capsule M2A capsule	Multivariate	2.1192	3.8318	0.5531	0.5802
Capsule mixed capsules	Multivariate	7.3895	5.5212	1.3384	0.1808
Capsule not specified	Multivariate	7.0843	4.0238	1.7606	0.0783
Capsule Pillcam SB	Multivariate	1.0183	1.4871	0.6847	0.4935
Known RCD	Multivariate	6.2476	2.508	2.491	0.0127*
Symptoms	Multivariate	0.0904	2.5987	0.0348	0.9722

[†]R² denotes the proportion of between-study variance (τ^2) explained by the covariate relative to the intercept-only model; negative values were truncated to 0
 DY, diagnostic yield (proportion of patients with the finding)

Intercept not shown. *P<0.05

DY, diagnostic yield; SE, standard error; RCD, refractory celiac disease; tTG, tissue transglutaminase antibody

Supplementary Table 8 Heterogeneity in the operationalization of a positive capsule endoscopy examination across included studies

Study [ref.]	Definition of a positive capsule endoscopy examination
Chetcuti Zammit <i>et al</i> [38]	Presence and extent of macroscopic features (e.g., villous atrophy, scalloping, fissuring, mosaic pattern), with emphasis on quantifying the proportion of affected small bowel mucosa
Ferretti <i>et al</i> [30]	Findings categorized into celiac disease-related abnormalities and complications (including ulceration and mass lesions), with recognition of non-specific findings
Perez-Cuadrado-Robles <i>et al</i> [37]	Findings interpreted in relation to clinical context and disease severity
Branchi <i>et al</i> [11]	Image interpretation performed using predefined criteria and/or expert consensus among readers

Search strings used in each database:

Embase Classic + Embase

Search Strategy:

1. exp Capsule Endoscopy/OR capsule endoscop* OR video capsule endoscop* OR video capsule colonoscop* OR wireless capsule endoscop* OR wireless capsule colonoscop* OR capsule colonoscop* OR pillcam*
2. exp Colonoscopy/OR colonoscop* OR exp Sigmoidoscopy/OR sigmoidoscop* OR endoscop* OR exp Endoscopy/OR exp Endoscopy, Gastrointestinal/OR Colonography, Computed Tomographic/OR colonograph* OR exp Tomography, X-Ray Computed/OR (CT scan OR CT colonoscopy* OR computer tomography colonoscop* OR computed tomography colonoscop* OR computed tomography scan) OR virtual colonoscop* OR reinvestigat* OR conver* OR (subsequent AND (investigation* OR endoscopy* OR colonoscop*))
3. 1 AND 2
4. Limit to publication years 2000–2025
5. Limit to publication type "Article"
6. Diagnostic accuracy OR clinical article OR clinical trial OR comparative study

Final Records: 2,125

Ovid MEDLINE(R) ALL

Search Strategy:

1. exp Capsule Endoscopy/OR capsule endoscop* OR video capsule endoscop* OR video capsule colonoscop* OR wireless capsule endoscop* OR wireless capsule colonoscop* OR capsule colonoscop* OR pillcam*
2. exp Colonoscopy/OR colonoscop* OR exp Sigmoidoscopy/OR sigmoidoscop* OR endoscop* OR exp Endoscopy/OR exp Endoscopy, Gastrointestinal/OR Colonography, Computed Tomographic/OR colonograph* OR exp Tomography, X-Ray Computed/OR (CT scan OR CT colonoscopy* OR computer tomography colonoscop* OR computed tomography colonoscop* OR computed tomography scan) OR virtual colonoscop* OR reinvestigat* OR conver* OR (subsequent AND (investigation* OR endoscopy* OR colonoscop*))
3. 1 AND 2
4. Limit to publication years 2000–2025
5. Limit to publication type "Clinical Trial", "Observational Study", "Comparative Study", "Evaluation Study", "Meta-Analysis", "Validation Study", "Controlled Clinical Trial", "Randomized Controlled Trial"

Final Records: 950

PubMed (Search Strategy example):

(Celiac Disease[MeSH Terms] OR Sprue, Celiac[MeSH Terms] OR Enteropathy, Gluten-Sensitive[MeSH Terms] OR celiac[tiab] OR coeliac[tiab] OR ((celiac[tiab] OR coeliac[tiab]) AND sprue[tiab]) OR (gluten[tiab] AND enteropathy[tiab]) OR "refractory celiac disease"[tiab] OR "refractory coeliac disease"[tiab] OR (refractory[tiab] AND (celiac[tiab] OR coeliac[tiab])) OR "nonresponsive celiac

disease"[tiab] OR "non-responsive celiac disease"[tiab] OR "nonresponsive coeliac disease"[tiab] OR "non-responsive coeliac disease"[tiab] OR "unresponsive celiac disease"[tiab] OR "unresponsive coeliac disease"[tiab] OR "persistent enteropathy"[tiab] OR (villous[tiab] AND atrophy[tiab] AND (persistent[tiab] OR ongoing[tiab])) OR "complicated celiac disease"[tiab] OR "complicated coeliac disease"[tiab] OR "ulcerative jejunitis"[tiab] OR "ulcerative jejunoileitis"[tiab] OR ((small bowel[tiab] OR "small intestine"[tiab] OR "small intestinal"[tiab]) AND (stricture[tiab] OR strictures[tiab])) OR "enteropathy-associated T-cell lymphoma"[tiab] OR "enteropathy associated T cell lymphoma"[tiab] OR EATL[tiab] OR ("small bowel lymphoma"[tiab] AND (celiac[tiab] OR coeliac[tiab] OR enteropathy[tiab]))

AND

("Adult"[MeSH Terms] OR adult[tiab] OR adults[tiab])

AND

("Capsule Endoscopy"[MeSH] OR "capsule endoscopy"[tiab] OR "wireless capsule endoscopy"[tiab] OR SBCE[tiab] OR CCE[tiab] OR PCE[tiab] OR "small bowel capsule"[tiab] OR "colon capsule"[tiab] OR "panenteric capsule"[tiab] OR "gastric capsule"[tiab] OR "capsule imaging"[tiab] OR "capsule colonoscopy"[tiab] OR PillCam[tiab] OR OMOM[tiab] OR MiroCam[tiab] OR EndoCapsule[tiab] OR NaviCam[tiab] OR CapsoCam[tiab])

AND

("Colonoscopy"[MeSH] OR "Endoscopy, Gastrointestinal"[MeSH] OR "Magnetic Resonance Imaging"[MeSH] OR "Tomography, X-Ray Computed"[MeSH] OR "Ultrasonography"[MeSH] OR "Radiology"[MeSH] OR "Fluoroscopy"[MeSH] OR colonoscopy[tiab] OR ileocolonoscopy[tiab] OR gastroscopy[tiab] OR EGD[tiab] OR OGD[tiab] OR "upper endoscopy"[tiab] OR endoscopy[tiab] OR enteroscopy[tiab] OR "push enteroscopy"[tiab] OR "balloon-assisted enteroscopy"[tiab] OR "device-assisted enteroscopy"[tiab] OR "double-balloon enteroscopy"[tiab] OR "single-balloon enteroscopy"[tiab] OR MRI[tiab] OR "magnetic resonance imaging"[tiab] OR "MR enterography"[tiab] OR CT[tiab] OR "computed tomography"[tiab] OR "CT enterography"[tiab] OR "CT colonography"[tiab] OR "CT colonoscopy"[tiab] OR ultrasound[tiab] OR US[tiab] OR "abdominal imaging"[tiab] OR "radiologic imaging"[tiab] OR "radiological imaging"[tiab] OR fluoroscopy[tiab] OR "small bowel follow-through"[tiab] OR enteroclysis[tiab] OR "barium study"[tiab] OR "contrast imaging"[tiab])

AND

("Sensitivity and Specificity"[MeSH] OR "Treatment Outcome"[MeSH] OR "Clinical Decision-Making"[MeSH] OR "diagnostic yield"[tiab] OR "diagnostic accuracy"[tiab] OR sensitivity[tiab] OR specificity[tiab] OR "predictive value"[tiab] OR "diagnostic performance"[tiab] OR "change in management"[tiab] OR "treatment decision"[tiab] OR "clinical outcome"[tiab] OR "symptom resolution"[tiab] OR "therapeutic impact"[tiab] OR "clinical utility"[tiab] OR "quality of life"[tiab])