Comparative analysis of sporadic, IBD-associated, early-onset and late-onset colorectal cancer: a systematic review and meta-analysis

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Abstract

Background: Colorectal cancer (CRC) remains a multifaceted disease with variations in aetiology, clinical presentation and prognostic factors.

Objectives: This study explores the features and outcomes of sporadic (S-CRC), inflammatory bowel disease-associated CRC (IBD-CRC), early-onset CRC (EO-CRC) and late-onset CRC (LO-CRC).

Design: This is a systematic review and meta-analysis performed following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Statement, comparing S-CRC versus IBD-CRC and EO-CRC versus LO-CRC.

Data sources and methods: The literature search was conducted on PubMed and Embase databases. The primary endpoint was the overall 5-year survival rate of CRC. Secondary aims included the features of CRC at diagnosis.

Results: Fifty studies and 6,148,851 patients with CRC were included in the analysis. Comparing S-CRC and IBD-CRC, the overall survival was higher in S-CRC (61.88 (range 41.3–78.7) vs 55.54 (51.9–80.9) months). IBD-CRC showed a minor mean age of diagnosis (63.5 (45–78) vs 69.1 ((40–78) years), a minor risk of stage IV (odd ratio (OR) 1.091; 95%CI 1.031–1.155, $p = 0.003$, I^2 60.24%), higher risk of mucinous tumour (OR 3.150 95%CI 2.797–3.548, $p < 0.001$, I^2 96.56%), emergency diagnosis (OR 1.598, 95%CI 1.509–1.693, $p < 0.001$, I^2 77.40%), and synchronous neoplasia (OR 1.942 95%CI 1.705–2.211, $p < 0.001$, I^2 0.00%). Comparing EO-CRC and LO-CRC, OS was longer in EO-CRC (79.42 (54–96) vs 77.58 (32–92) months). EO-CRC had a higher risk of being diagnosed at stage IV (OR 1.471, 95%CI 1.456–1.486, $p < 0.001$, I^2 97.12%), and of having mucinous tumours (OR 1.0142, 95%CI 1.015–1.070, $p = 0.002$, I^2 60.48%) versus LO-CRC. Comparing IBD-CRC, EO-CRC and LO-CRC, IBD-CRC had the shortest OS (61.88 months), the highest rate of mucinous cancer (13%) and emergency diagnosis (24%), whereas metastatic disease at diagnosis was more common in EO-CRC (22.6%).

Conclusion: IBD-CRC was associated with a younger mean age at diagnosis, higher risk of mucinous cancers, emergency presentation, and synchronous neoplasia compared to S-CRC. EO-CRC had a higher risk of being diagnosed at stage IV and of mucinous tumours versus LO-CRC. IBD-CRC seemed to have an overall shorter survival rate and a higher prevalence of mucinous cancers, suggesting different pathways of progression and more aggressive features.

Trial registration: Prospero Registration ID1021182.

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Plain language summary

Comparative analysis between sporadic vs inflammatory bowel disease-associated and early-onset vs late-onset colorectal cancer

Colorectal cancer (CRC) remains a multifaceted disease with variations in etiology, clinical presentation, and prognostic factors. This study explores the characteristics of sporadic CRC (S-CRC), inflammatory bowel disease-associated CRC (IBD-CRC), early-onset CRC (EO-CRC), and late-onset CRC (LO-CRC). The review was conducted through a systematic review and meta-analysis comparing sporadic CRC with IBD-CRC and EO-CRC with LO-CRC. The literature search was conducted using PubMed and Embase databases. The primary endpoint was 5-year overall survival rate for CRC. Upon completion of the review, 50 studies and 6,148,851 CRC patients were included in the analysis. When comparing S-CRC and IBD-CRC, overall survival was higher in S-CRC, with IBD-CRC showing a lower mean age at diagnosis (63.5 [45-78] vs 69.1 [40-78] years), a lower risk of stage IV, higher risk of mucinous tumor, emergency diagnosis, and synchronous neoplasia. When comparing EO-CRC and LO-CRC, overall survival was higher in EO-CRC, although it had a higher risk of being diagnosed at stage IV and of presenting mucinous tumors compared to LO-CRC. When comparing IBD-CRC, EO-CRC, and LO-CRC, the first presented the shortest OS (61.88 months), the highest rates of mucinous cancer (13%) and emergency diagnosis (24%), while metastatic disease at diagnosis was more frequent in EO-CRC (22.6%). In conclusion, different analyzed groups of CRC presented differential features, suggesting different pathways of progression, as well as more aggressive features, particularly in IBD.

Keywords: colorectal cancer, Crohn's disease, early onset colorectal cancer, inflammatory bowel disease, ulcerative colitis

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Introduction

Colorectal cancer (CRC) is among the leading causes of cancer-related mortality worldwide.[1] Despite significant advancements in early detection and treatment, CRC remains a multifaceted disease with variations in aetiology, clinical presentation, and prognostic factors.[2] This diversity is particularly evident among its subtypes, each characterised by unique features and behaviours. For instance, inflammatory bowel disease-associated CRC (IBD-CRC) differs significantly from sporadic CRC (S-CRC),[3] as well as early-onset CRC (EO-CRC) presents distinct characteristics compared to late-onset CRC (LO-CRC).[4]

S-CRC represents the majority of CRC cases showing no predisposing conditions in the affected subjects.[5] Its pathogenesis is primarily driven by genetic and epigenetic changes contributing to the adenoma-carcinoma sequence. Key molecular alterations include APC, KRAS and TP53 gene mutations. Moreover, lifestyle factors such as diet, obesity and smoking also contribute to its development.[6,7] On the contrary, IBD-CRC is believed to arise in the setting of chronic inflammation primarily due to long-standing IBD, which contributes to the development of a carcinogenic microenvironment. Unlike the adenoma-carcinoma sequence seen in S-CRC, IBD-CRC often follows an inflammation-dysplasia-carcinoma pathway. Key molecular alterations in this setting also include early TP53 mutations and a higher prevalence of CpG island methylator phenotype alterations.[8,9] The latter alterations may also contribute to differences in histological features compared to S-CRC. According to available literature, IBD-CRC more frequently shows mucinous and signet-ring cell subtypes, which may contribute to its more aggressive behaviour and poorer prognosis compared to S-CRC.[10]

Historically, CRC has been considered a disease affecting individuals of later ages. However, over the past decades, there has been a notable increase in the incidence of CRC among patients younger than 50, particularly in Western regions.[11] The mechanisms of cancer onset and progression in this subset of CRC (EO-CRC) are yet to be elucidated. While hereditary syndromes partially contribute to its pathogenesis, they account for only a small proportion of EO-CRC. As for IBD-CRC, EO-CRC is often associated with more aggressive histological subtypes, including mucinous and signet-ring cell carcinoma.[12,13] Most of the studies also show a wide variety of differences between both age-of-onset CRCs.[14,15]

Despite these differences, survival outcomes between EO-CRC and LO-CRC remain debated. Some studies suggest that younger patients may have longer survival due to greater physiological resilience and increased likelihood of receiving aggressive treatment.[16–18]

While numerous studies have investigated the characteristics of S-CRC versus IBD-CRC and EO-CRC versus LO-CRC, no comprehensive meta-analysis has systematically and comprehensively synthesized these findings. A detailed comparison is necessary to clarify discrepancies in survival outcomes, histopathological differences and tumour features across these CRC subtypes, which could eventually impact the current screening programmes.

The current study explores the multiple facets of EO-CRC, LO-CRC and IBD-CRC, aiming to provide a refined characterization of subtypes that could aid in optimising tailored strategies for prevention, early detection and management.

Methods

The current systematic review and meta-analysis were performed following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement.[19]

Search strategy and data sources

The literature search was conducted on PubMed and the Embase database. Two screeners independently performed the literature screening (G.F. and O.N.). Data were extracted independently from included studies by the reviewers; any discrepancy between the two reviewers would be resolved by a third reviewer. This meta-analysis was prospectively registered (PROSPERO ID 1021182). The detailed search strategy is shown in Supplemental Table 1.

Inclusion and exclusion criteria

Only studies that included patients with CRC and compared sporadic versus IBD-associated cancers or EO-CRC versus LO-CRC were included in the analysis. Studies with non-extractable data, with no full-text available, written in languages other than English, and with a number of patients included lower than 1000 were excluded. In case of more than one study conducted at the same centre, only the most recent one was included.

Study aims and endpoint measures

The primary aim of the study was to assess the survival in each group of CRC, using as endpoint the 5-year overall survival (OS).

Secondary endpoints included the mean age of cancer diagnosis, tumour location, presence of metastatic disease at the diagnosis, histological features, synchronous cancer/s and emergency diagnosis.

Direct comparisons were made between S-CRC versus IBD-CRC, and EO-CRC versus LO-CRC using a meta-analytic approach. Features of IBD-CRC, EO-CRC and LO-CRC were also compared.

Statistical analysis

All collected data regarding the endpoints were reported in an Excel table showing the number of patients involved in the studies and the extracted data associated with the endpoints. A meta-analysis was realized using MedCalc® (MedCalc Software Ltd, Acacialaan, Ostend, Belgium) statistical software. The meta-analysis was performed according to the Cochrane Collaboration the Quality of Reporting of Meta-analyses (QUORUM) guidelines.[20] The estimated effect measures are reported as odds ratios (OR) with 95% confidence intervals (CI). The ratio represented the probability of occurrence of an adverse event in the group of patients and the point estimate of OR was considered statistically

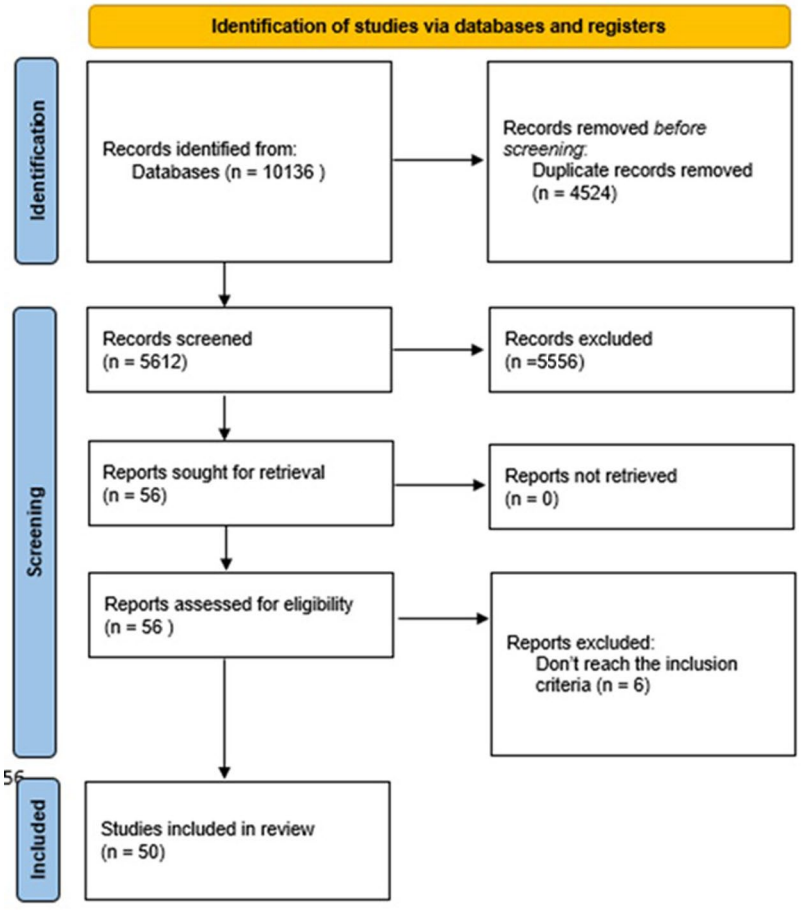

Figure 1. Flow chart of study selection according to PRISMA statement.
PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analysis.

significant if the 95% CI did not include the value '1'. The meta-analysis regarding differences in colon versus rectal localization was expressed in relative risk (RR) with 95% CI.

Risk of bias assessment and quality of the studies

The Joanna Briggs Institute's (JBI) critical appraisal checklist for studies reporting prevalence data was utilized to evaluate the quality of the studies.[21] This tool assessed studies according to 10 questions. If the answer was yes, the question was assigned a score of 1. If the answer was no, unclear, or not applicable, it was assigned a score of 0.

Results

The search yielded 10,136 studies and 4524 duplicates were excluded. After removing abstracts, reviews, meta-analyses, and case reports, the titles of 5612 articles were screened; all their full-text articles were assessed for eligibility. The flowchart for study inclusion is reported in Figure 1. There was 100% agreement among reviewers in the extraction of data.

In total, 50 studies,[12,22–70] including 6,148,851 patients with CRC, were included in the analysis. The characteristics of the included studies are summarized in Table 1.

S-CRC versus IBD-CRC

Seventeen studies provided data on the comparison between S-CRC and IBD-CRC. 3,748,665 patients with CRC were included, of whom 25,149 had IBD (0.55%, 95%CI 0.543–0.558, I^2 99.91%).

Out of them, 61.23% (95%CI 60.589–61.860, I^2 98.77%) of patients with IBD-CRC had

Table 1. Characteristics of included studies.

First author	Year	Country	Study design	Comparison	*N* PTS	*N* PTS EO-CRC	*N* PTS IBD-CRC	Mean age (years)
Aguiar Junior et al.	2020	Brazil	Retrospective	EO-CRC (<49 yo) vs LO-CRC	2279	449	–	–
Gausman et al.	2019	USA	Retrospective	EO-CRC (<49 yo) vs LO-CRC	3071	269	34	68.5
Fairley et al.	2006	USA	Retrospective	EO-CRC (<49 yo) vs LO-CRC	542,149	42,017	–	–
Okamoto et al.	2023	Japan	Retrospective	EO-CRC (<50 yo) vs LO-CRC	4758	771	–	58.7
Martinez-Perez et al.	2023	Spain	Retrospective	EO-CRC (<50 yo) vs LO-CRC	1475	80	–	71.5
Badesha et al.	2023	Canada	Retrospective	EO-CRC (<50 yo) vs LO-CRC	6232	532	–	–
Park et al.	2022	Korea	Retrospective	EO-CRC (<50 yo) vs LO-CRC	1126	111	–	–
Okamoto et al.	2024	Japan	Retrospective	EO-CRC (<50 yo) vs LO-CRC	2764	491	0	58.6
Ruiz-Grajales et al.	2024	Colombia	Retrospective	EO-CRC (<50 yo) vs LO-CRC	1022	138	10	66
Song et al.	2024	China	Retrospective	EO-CRC (<50 yo) vs LO-CRC	7709	1,675	–	–
Gao et al.	2022	China	Retrospective	EO-CRC (<50 yo) vs LO-CRC	16,941	3,254	–	60.5
Liu et al.	2024	China	Retrospective	EO-CRC (<50 yo) vs LO-CRC	4572	991	–	59.4
Tae Son et al.	2023	Korea	Retrospective	EO-CRC (<45 yo) vs LO-CRC	1992	93	–	66.3
Wang et al.	2022	China	Retrospective	EO-CRC (<45 yo) vs LO-CRC	5457	253	0	62.5
Kim et al.	2016	Korea	Retrospective	EO-CRC (<45 yo) vs LO-CRC	2516	693	–	53.9
Liming Wang et al.	2020	Japan	Retrospective	EO-CRC (<45 yo) vs LO-CRC	3095	139	–	59.1
XY Liu et al.	2022	China	Retrospective	EO-CRC (<45 yo) vs LO-CRC	4599	403	–	62.8
Liao et al.	2024	Taiwan	Retrospective	EO-CRC (<50 yo) vs LO-CRC	5704	1,240	–	56.5
Brim et al.	2025	USA	Retrospective	EO-CRC (<45 yo) vs LO-CRC	2210	176	12	63.8
Chen et al.	2022	China	Retrospective	EO-CRC (<50 yo) vs LO-CRC	4468	947	–	59.6
Gefen et al.	2023	Usa	Retrospective	EO-CRC (<50 yo) vs LO-CRC	662,102	61,539	–	–
R Chen et al.	2025	Singapore	Retrospective	EO-CRC (<49 yo) vs LO-CRC	53,044	6,183	–	–
O' Sullivan et al.	2022	Canada	Retrospective	EO-CRC (<50 yo) vs LO-CRC	8748	1,269	–	–
Hutajuli et al.	2024	Indonesia	Retrospective	EO-CRC (<50 yo) vs LO-CRC	1276	149	–	–
Murata et al.	2016	Japan	Retrospective	EO-CRC (<40 yo) vs LO-CRC	2338	81	–	63
McKlay et al.	2014	Canada	Retrospective	EO-CRC (<45 yo) vs LO-CRC	2086	70	–	70.1
Foppa et al.	2022	Italy	Retrospective	EO-CRC (<50 yo) vs LO-CRC	2073	423	0	63.4
Cheng et al.	2021	USA	Retrospective	EO-CRC (<50 yo) vs LO-CRC	753,506	102,168	–	–
McClelland et al.	2022	USA	Retrospective	EO-CRC (<50 yo) vs LO-CRC	240,772	35,084	–	–

(Continued)

Table 1. (Continued)

First author	Year	Country	Study design	Comparison	*N* PTS	*N* PTS EO-CRC	*N* PTS IBD-CRC	Mean age (years)
You et al.	2011	USA	Retrospective	EO-CRC (<50 yo) vs LO-CRC	1008	333	0	68.7
Saraste et al.	2020	Sweden	Retrospective	EO-CRC (<50 yo) vs LO-CRC	34,434	1,675	–	73
Burnett-Hartmenn et al.	2019	USA	Retrospective	EO-CRC (<50 yo) vs LO-CRC	12,234	1,424	–	–
Yeo et al.	2013	Singapore	Retrospective	EO-CRC (<50 yo) vs LO-CRC	2426	330	0	65
Uchino et al.	2024	Japan	Retrospective	IBD-CRC vs S-CRC	138,301	–	1374	64.3
Birch et al.	2022	UK	Retrospective	IBD-CRC vs S-CRC	390,614	–	5141	71.9
Samadder et al.	2017	USA	Retrospective	IBD-CRC vs S-CRC	12,578	–	101	66.9
Peyrin-Biroulet et al.	2012	France	Retrospective	IBD-CRC vs S-CRC	19,451	–	38	–
Ording et al.	2013	USA	Retrospective	IBD-CRC vs S-CRC	107,024	–	891	–
Watanabe et al.	2011	Japan	Retrospective	UC-CRC vs S-CRC	108,536	–	169	62.5
Katayama et al.	2024	USA	Retrospective	IBD-CRC vs S-CRC	93,325	–	2010	75
Stjargrim et al.	2019	Sweden	Retrospective	IBD-CRC vs S-CRC	14,090	–	492	–
Bogach et al.	2019	Canada	Retrospective	IBD-CRC vs S-CRC	849,354	–	783	–
Adams et al.	2013	USA	Retrospective	IBD-CRC vs S-CRC	7202	1,829	250	–
Raja Ali et al.	2011	Ireland	Retrospective	IBD-CRC vs S-CRC	22,325	–	170	69
Vitali et al.	2022	Germany	Retrospective	IBD-CRC vs S-CRC	3773	–	63	65.6
Flores et al.	2021	USA	Retrospective	IBD-CRC vs S-CRC	1,190,759	121,487	10,997	67.7
Gearhart et al.	2012	USA	Retrospective	IBD-CRC vs S-CRC	109,064	–	1201	77
Ohman et al.	1982	Sweden	Retrospective	UC-CRC vs S-CRC	1061	–	29	63.3
Shaukat et al.	2011	USA	Retrospective	UC-CRC vs S-CRC	47,543	–	155	74
Kuryba et al.	2022	UK	Retrospective	IBD-CRC vs S-CRC	633,665	–	1285	–

EO-CRC, early-onset colorectal cancer; IBD-CRC, inflammatory bowel disease-associated colorectal cancer; LO-CRC, late-onset colorectal cancer; UC-CRC, ulcerative colitis-associated colorectal cancer; yo, year old.

ulcerative colitis (UC) while 36.07% (95%CI 35.451–36.703, I^2 98.89%) had Crohn's disease (CD).

The OS of patients with S-CRC was longer than that of patients with IBD-CRC (61.88 (range 41.3–78.7) vs 55.54 (51.9–80.9) months). The mean age at diagnosis of S-CRC patients was 69.1 (40–78) years, while that of IBD-CRC patients was 63.5 (45–78) years. In both S-CRC and IBD-CRC, colon cancer was more frequent than rectal cancer, RR 2.144 (95%CI 2.39–2.150, $p < 0.001$, I^2 99.99%) for S-CRC and RR 1.897 (95%CI 1.855–1.940, $p < 0.0001$, I^2 99.54%) in IBD-CRC (Figure 2). The risk of metastatic disease at diagnosis was higher in patients with S-CRC, OR 1.091 (95%CI 1.031–1.155, $p = 0.003$, I^2 60.24%; Figure 3).

Mucinous tumours were more frequent in IBD-CRC versus S-CRC, OR 3.150 (95%CI 2.797–3.548, $p < 0.001$, I^2 96.56%; Supplemental Figure 1), as was the emergency diagnosis, OR 1.598 (95%CI 1.509–1.693, $p < 0.001$, I^2 77.40%; Supplemental Figure 2). The risk of synchronous lesions was found to be higher in

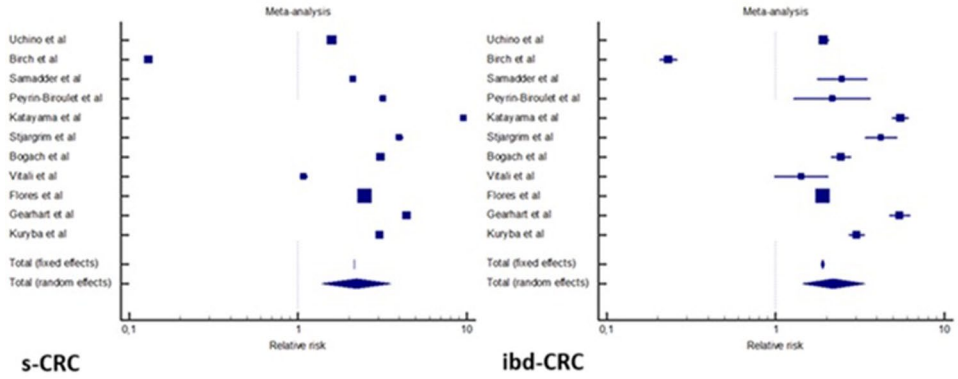

Figure 2. Meta-analysis on colon versus rectum localization in S-CRC and IBD-CRC. Forest plots comparing colic and rectal localization of CRC in patients with sporadic (left) and colitis-associated (right). The effect size is expressed as relative risk.
CRC, colorectal cancer; IBD-CRC, inflammatory bowel disease-associated colorectal cancer; S-CRC, sporadic colorectal cancer.

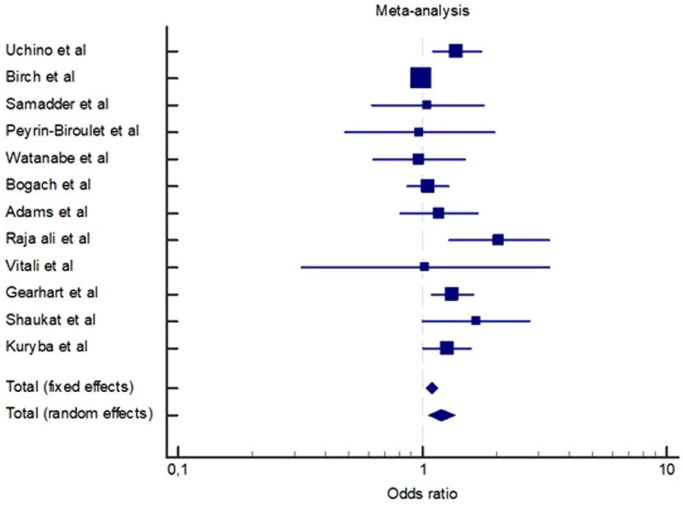

Figure 3. Meta-analysis on risk of stage IV in S-CRC versus IBD-CRC. A forest plot comparing sporadic CRC versus colitis-associated CRC on risk of diagnosis with stage IV. The effect size is expressed as odds ratio.
CRC, colorectal cancer; IBD-CRC, inflammatory bowel disease-associated colorectal cancer; S-CRC, sporadic colorectal cancer.

IBD-CRC versus S-CRC, OR 1.942 (95%CI 1.705–2.211, $p < 0.001$, I^2 0.00%; Supplemental Figure 3).

EO-CRC versus LO-CRC

Thirty-three studies provided data comparing EO-CRC and LO-CRC, with 2,400,186 patients included in the analysis; of them, 265,450 (10.87%, 95%CI 10.831–10.910, I^2 99.86%) had EO-CRC.

The mean age of the EO-CRC patients was 41.6 (36–44.9) years versus 64.5 (60–73) years in LO-CRC.

OS was longer in EO-CRC than in LO-CRC (79.42 (54–96) vs 77.58 (32–92) months).

In both EO-CRC and LO-CRC patients, the colon was the most common site compared to the rectum: in EO-CRC, the RR was 2.112 (95%CI 2.097–2.127, $p < 0.001$, I^2 99.38%), in LO-CRC,

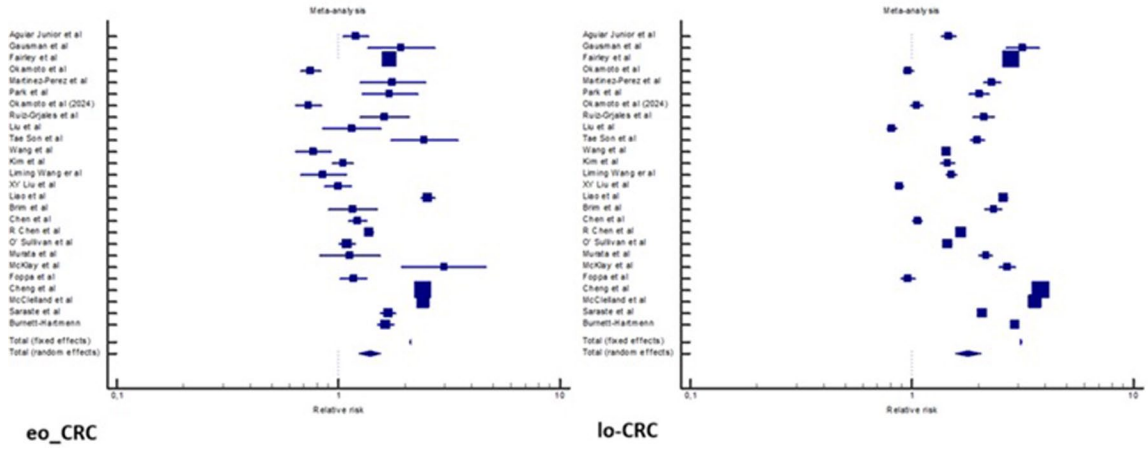

Figure 4. Meta-analysis on colon versus rectum localization in EO-CRC and LO-CRC. Forest plots comparing colic and rectal localization of CRC in patients with early onset (left) and late onset (right). The effect size is expressed as a relative risk.
CRC, colorectal cancer; EO-CRC, early-onset colorectal cancer; IBD-CRC, inflammatory bowel disease-associated colorectal cancer; LO-CRC, late-onset colorectal cancer.

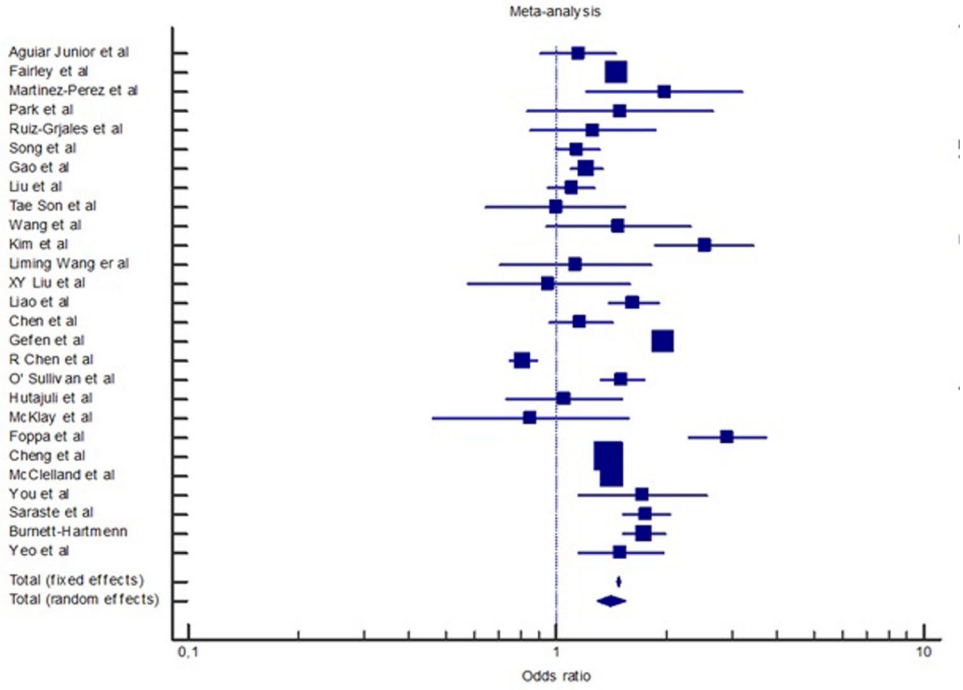

Figure 5. Meta-analysis on risk of stage IV in EO-CRC versus LO-CRC. A forest plot comparing early-onset CRC versus late-onset CRC on risk of diagnosis with stage IV. The effect size is expressed as odds ratio.
CRC, colorectal cancer; EO-CRC, early-onset colorectal cancer; LO-CRC, late-onset colorectal cancer.

the RR was 3.115 (95%CI 3.106–3.124, $p < 0.001$, I^2 99.94%) (Figure 4). EO-CRC had a higher risk of being diagnosed at stage IV compared to LO-CRC, OR 1.471 (95%CI 1.456–1.486, $p < 0.001$, I^2 97.12%; Figure 5).

The risk of mucinous cancer was higher in EO-CRC than in LO-CRC, OR 1.0142 (95%CI 1.015–1.070, $p = 0.002$, I^2 60.48%; Supplemental Figure 5). Emergency diagnosis did not differ between EO-CRC and LO-CRC (OR 1.441,

Table 2. Features of EO-CRC, LO-CRC and IBD-CRC among the included studies.

Feature	IBD-CRC	EO-CRC	LO-CRC
Overall survival, months	61.88 (41.3–78.7)	79.42 (54–96)	77.58 (32–92)
Mean age of onset, years	63.5 (45–78)	41.6 (36–44.9)	64.5 (60–73)
Mucinous cancers	13%[a]	9.7%	9.5%
Stage IV	13%	22.6%[b]	15.54
Synchronous tumours	1.3%	1.4%	2.6%
Emergency diagnosis	24%[c]	7%	9.9%

Worse features are in red; intermediate in yellow; best in green.
[a]IBD-CRC versus S-CRC, OR 3.150 (95%CI 2.797–3.548, $p < 0.001$, I^2 96.56%).
[b]EO-CRC versus LO-CRC, OR 1.471 (95%CI 1.456–1.486, $p < 0.001$, I^2 97.12%).
[c]IBD-CRC versus S-CRC, OR 1.598 (95%CI 1.509–1.693, $p < 0.001$, I^2 77.40%).
EO-CRC, early-onset colorectal cancer; IBD-CRC, inflammatory bowel disease-associated colorectal cancer; LO-CRC, late-onset colorectal cancer; OR, odds ratio; S-CRC, sporadic colorectal cancer.

95%CI 0.983–2.111, $p = 0.061$, I^2 88.47%; Supplemental Figure 6).

Overall comparisons: IBD-CRC versus EO-CRC versus LO-CRC

Table 2 shows the main findings, comparing the features of IBD-CRC, EO-CRC and LO-CRC. IBD-CRC had the shortest OS (61.88 months), the highest rate of mucinous cancer (13%), and the highest rate of emergency diagnosis (24%). EO-CRC was associated with the highest risk of metastatic disease at diagnosis (22.6%).

Quality of studies

The overall strength of evidence is summarized in Supplemental Table 2. Low risk of bias was found for 90% of the studies (risk scores 8–10). Five studies had a medium risk with scores between 5 and 7.

Discussion

This systematic review and meta-analysis aimed to provide a comprehensive comparison of clinical, histopathological, and prognostic factors between S-CRC and IBD-CRC, as well as between EO-CRC and LO-CRC. The findings underscore the heterogeneity among these CRC subtypes, with practical implications. Regarding differences between S-CRC and IBD-CRC, the meta-analysis found that IBD-CRC is diagnosed at a younger mean age than S-CRC (63.5 years vs 69.1 years). This observation may be explained by two factors: first, the chronic inflammatory process in colitis may accelerate carcinogenesis; second, patients with long-standing colitis undergo regular surveillance, enabling earlier CRC detection. Notably, metastatic disease at diagnosis was more prevalent in the S-CRC group than in the IBD-CRC group (OR 1.091, 95%CI 1.031–1.155, $p = 0.003$), probably for the same reasons related to increased endoscopic surveillance.

Despite this, OS was lower in IBD-CRC than in S-CRC, EO-CRC and LO-CRC which may be attributed, among other causes, to a more aggressive histopathological phenotype. IBD-CRC was more frequently associated with mucinous histology and had a higher prevalence of synchronous lesions, previously reported in 1.1%–8.1% of cases.[71] Additionally, IBD-CRC was more commonly located in the right colon, which could be explained by both specific epigenetic modifications,[72,73] and sustained inflammation in the right colon, more commonly affected together with the terminal ileum in CD.

Emergency diagnoses were found to be higher in the IBD group (OR 1.598, $p < 0.001$) than in the sporadic group. However, this information should be interpreted with caution, as the included studies do not provide a clear definition of emergency diagnosis.

The current study also seems to support the hypothesis that EO-CRC is a distinct entity from LO-CRC.[15,74] According to the meta-analysis, EO-CRC was associated with a higher risk of

mucinous cancers and a higher likelihood of metastatic disease at diagnosis, emphasizing the need for improved screening strategies in younger populations, as the majority of cases are currently uncovered by these screening programmes.[75]

Of note, EO-CRC showed better OS than LO-CRC. This finding could be attributed to a better frailty profile of EO-CRC patients, who can undergo more extensive surgery and chemotherapy.[76] Colonic location was more frequent than rectal location in both EO-CRC and LO-CRC, with an RR of 2.112 and 3.115, respectively, suggesting that flexible sigmoidoscopy is not an appropriate screening tool in young patients.

The current study highlights the need to at least consider to lower the screening age in European countries, as has already been implemented in the United States.[77] A "one-size-fits-all" approach may not be an optimal strategy for CRC screening; this applies not only to patients with IBD but also to individuals with risk factors for EO-CRC, such as obesity, red meat consumption, Caucasian ethnicity, smoking habits and, mainly, family history of CRC.[78,79] As for IBD-CRC prevention, EO-CRC deserves a tailored approach for appropriate prevention and early intervention.

Regarding the histopathological findings, both IBD-CRC and EO-CRC had a high prevalence of mucinous cancers, associated with a more aggressive pattern. Mucinous tumours are less responsive to standard chemotherapy, particularly 5-fluorouracil-based regimens, but seem to benefit from targeted therapy or immunotherapy, especially in cases with microsatellite instability or high CpG island methylator phenotype.[80] This is important when considering the ideal multimodal treatment in IBD-CRC and EO-CRC and warrants further investigation in the coming years.

However, the current study could not provide a meta-analysis comparing EO-CRC in IBD-related versus non-IBD-related CRC, as no studies were identified that provided data for this analysis. A recent study by Arif et al., which compared sporadic, hereditary, and IBD-related EO-CRC, showed that patients with IBD have a lower age of onset ($p < 0.0001$), are more frequently male (68.2% vs 50.4%, p 0.005), higher risk of metastatic disease at diagnosis (39.8% vs 30.3%, $p < 0.0001$) and of mucinous tumours (17.6% vs 5%, $p < 0.0001$).[81]

Although EO-CRC shows a heterogeneous molecular basis, it is important to note that some of them show alterations related to chronic inflammation processes, suggesting a potential common pathway with IBD-CRC.[82,83]

Study limitations and strengths

The findings of the present meta-analysis should be interpreted with due consideration to the substantial heterogeneity observed in most comparisons, largely attributable to the retrospective design of the included studies and to variations in patient populations and data reporting. An additional limitation is that the available data did not allow distinct analyses for CD versus UC. Given their distinct inflammatory patterns and potentially different carcinogenic pathways, this inability to stratify by disease type may have impacted the results.

Nevertheless, this study has several strengths. It included a large sample of over 6 million CRC patients, which extensively represents the global population and analyses the features of different CRC subtypes using a meta-analytical approach where feasible, highlighting differences in presenting features, outcomes and tumour biology. Finally, it ensures direct clinical implications which can be translated into practice.

Conclusion

CRC remains a significant clinical challenge worldwide, despite notable advances in diagnosis and management. This comparative analysis of S-CRC, IBD-CRC, EO-CRC and LO-CRC provides a comprehensive overview of the current state of knowledge in the field. Key differences in age and stage at diagnosis, tumour location and histological features highlight the need for tailored screening strategies and targeted prevention programmes. Enhancing early detection efforts could facilitate timely diagnosis and optimise treatment

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

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Supplemental material

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