Received: 30 March 2023 | Revised: 11 May 2023 | Accepted: 16 May 2023

DOI: 10.1002/hsr2.1307

ORIGINAL RESEARCH

Health Science Reports Open Access WILEY

Comparison of the short- and long-term prognosis of early-onset colorectal cancer compared with later-onset colorectal cancer: A systematic review and meta-analysis

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Funding information

National Natural Science Foundation of China, Grant/Award Number: 82104575; Clinical Research Project of Tongji Hospital Affiliated to Tongji University, Grant/Award Number: ITJ-ZD-2104

Abstract

Background and Aims: The annual incidence of early-onset colorectal cancer (EOCRC) is increasing at an alarming rate. The prognosis of EOCRC remains controversial, and whether the early onset is a risk factor for colorectal cancer remains unclear.

Methods: We searched four electronic bibliographic databases from database inception to April 25, 2022 for studies that included both early- and later-onset patients and performed a prognostic analysis. Random-effects models were used to summarize the prognostic information extracted by the investigators, including overall survival (OS), cancer-special survival (CSS), and disease-free survival (DFS). Network meta-analysis (NMA) was used to compare patients' long-term prognoses in different age subgroups.

Results: After 694 reports were screened, 13 studies were included in the final analysis, with a total of 448,781 CRC cases. In the meta-analysis of the 5-year OS, EOCRC had a better prognosis compared to LOCRC (hazard ratio [HR] 0.87, 95% confidence interval [CI], 0.74–0.99; relative risk [RR] 0.83, 95% CI, 0.78–0.89). No difference in prognosis was found between the two groups in terms of 5-year CSS (RR 0.99, 95% CI, 0.93–1.05), 5-year DFS (RR 0.90, 95% CI, 0.74–1.09), and short-term OS. In the NMA, patients aged <30 years had the worst outcome (surface under the cumulative ranking curve [SUCRA], 15.8%) in 5-year OS; consistent results were observed in the analysis of 5-year CSS (<30 years, SUCRA 4.5%), but the difference was not statistically significant.

Conclusion: Although patients with early-onset CRC had better OS than those with later-onset CRC, there was no difference in the CSS. Meanwhile, the trend for survival was worse in younger patients, especially in those ages 18–29 years. Thus, more attention should be paid to early diagnosis and treatment of EOCRC.

Taojun Jin and Xinxing Li contributed equally as the first authors to this study.Biao Gong and Zhiqian Hu contributed equally as corresponding authors to this study.

Systematic Review and Meta-Analysis Registration: The systematic review and Meta-analysis protocol was registered with PROSPERO (registration number CRD42022334697).

KEYWORDS

cancer-specific survival, colorectal cancer, early-onset, later-onset, meta-analysis, overall survival, prognosis, systematic review

1 | INTRODUCTION

Although the overall incidence of colorectal cancer (CRC) has declined globally,[1,2] the incidence of early-onset colorectal cancer (EOCRC) in patients aged <50 years is increasing at an alarming rate.[3,4] Based on a cohort study in 20 European countries, the incidence of CRC has increased in individuals aged 20–49 years. Notably, the fastest increase in incidence occurred in the youngest age group (aged 20–29 years), reaching an annual growth rate of 7.9%.[5] Researchers predict that within the next decade, 1 in 10 colon cancers and 1 in 4 rectal cancers will be diagnosed in adults under 50 years of age.[6] The Western dietary pattern, consumption of red and processed meat, smoking, overweight or obesity, CRC history in a first-degree relative, and alcohol consumption have been found to be significantly associated with the development of EOCRC.[7–10] these risk factors overlap with the identified risk factors for later-onset colorectal cancer (LOCRC).[11,12] Nearly one in five EOCRC patients carry pathogenic germline mutations (about half of them are mismatch repair gene mutations associated with Lynch syndrome), and about one in four patients report a family history of CRC in a first-degree relative,[13–15] but most remain disseminated. Compared with later-onset patients, patients with EOCRC had a higher proportion of progressive tumors at diagnosis, higher rates of poorly differentiated cancers, and a higher incidence of distal colon and rectal cancer, none of which could be explained by a single etiological factor, such as hereditary syndromes. Therefore, there is reason to believe that EOCRC is a unique subgroup of CRC.

The survival data for patients with EOCRC remain conflicting. Some studies have reported a poorer prognosis owing to the significantly higher proportion of progressive tumours in early-onset patients.[16,17] Although EOCRC has more metastatic regional lymph nodes, patients with early-onset EOCRC are more likely to receive systemic chemotherapy after surgical resection at each disease stage.[18] The higher incidence of microsatellite instability provides more opportunities for patients with EOCRC to receive immune checkpoint therapy. In recent years there has been a growing belief that there is no difference in prognosis between two cohorts based on retrospective cohort studies.[19–21] Whether EOCRC is a specific population requiring more attention remains unknown, and the guidelines have recommended no specific treatment options for this age group. Here, we performed a systematic review and meta-analysis of all available studies to compare CRC-related prognoses between early- and later-onset patients. Network meta-analysis (NMA) was used to compare the prognoses of patients in different age groups.

2 | METHODS AND MATERIALS

2.1 | Review registration and approach

The eligibility criteria, quality assessment, and protocol were registered with the International Prospective Register of Systematic Reviews (registration no. CRD42022334697).[22] This systematic review and meta-analysis followed the 2020 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[23] and Meta-analyses of Observational Studies in Epidemiology (MOOSE) reporting guidelines.[24]

2.2 | PICOS statement

The PICOS statement is as follows:

- P-patient, problem, population: EOCRC was defined as a diagnosis of CRC in patients younger than 50 years.
- I-intervention or exposure: Patient age at diagnosis was the primary exposure factor in this study.
- C-comparison, control, comparator: LOCRC was defined as the diagnosis of CRC in patients aged >50 years. We compared the prognosis between EOCRC and LOCRC groups using factors such as overall survival (OS), cancer special survival (CSS), and disease-free survival (DFS).
- O-outcomes: The outcomes were the hazard ratio (HR) and relative risk (RR) of OS, CSS, and DFS as prognostic risk factors.

2.3 | Search strategy

Two researchers (Taojun Jin and Xiaomao Yin) searched four electronic bibliographic databases (PubMed, Web of Science, Embase, and Cochrane Library) for articles published from the database inception to April 25, 2022. The articles were only published in English. We excluded nonhuman studies and irrelevant publication types in the article retrieval process. Search strategies

were based on the following keywords: colorectal, cancer, early onset, and prognosis, as listed in the Supporting Information: Methods. We also manually searched for relevant review articles, comments, and references of original articles.

2.4 | Eligibility criteria

The inclusion criteria were as follows: (1) EOCRC was defined in adult patients younger than 50 years of age; (2) both early-onset and later-onset cohorts were included; (3) the early onset cohort included more than 100 cases, with at least 1 year of follow-up; and (4) observational cohort studies and cross-sectional studies. Studies were excluded if: (1) only patients with early-stage cancer or progressive tumours were included; (2) follow-up information was unknown; (3) reuse of the same database; and (4) comments, abstracts, or reviews lacking complete data, as well as studies not published in English.

2.5 | Study selection and data extraction

After removing duplicates, each study was individually reviewed by two researchers (Taojun Jin and Xiaomao Yin), who first screened by title and abstract and second by full-text reading. The consensus was achieved through a joint discussion with a separate lead researcher (Xinxing Li) when the two researchers disagreed. For each included study, the data were extracted by two researchers using a standardized data form. We extracted the main variable factors from the studies, including the year of publication, country, tumor type, stage, participant age group, sample size, date resource, time of diagnosis, and outcomes in the individual groups. If conditions permit, we excluded data from the cohort of patients aged >80 years to reduce the effect of advanced age on outcomes. If the required data could not be retrieved from the text or Supporting Information, we systematically contacted the authors of the studies.

2.6 | Quality assessment

Two researchers (Taojun Jin and Xiaomao Yin) independently assessed the quality of the included studies and reached a consensus with a third researcher. Multiple tools were used to evaluate risk bias for cohort studies, including the Risk of Bias in Nonrandomized Studies of Exposures (ROBINS-E),[25,26] Newcastle-Ottawa Scale (NOS) checklist,[27] modified Critical Appraisal Skills Programme (CASP) checklist,[28] and Joanna Briggs Institute (JBI) Critical Appraisal checklist.[29] After comparing the efficacies of the three quality evaluation checklists, the optimal checklist was selected. The Agency for Healthcare Research and Quality (AHRQ) checklist[30] was used for the cross-sectional studies.

2.7 | Outcome measures

The primary outcomes analyzed were 5-year OS, CSS, and DFS, and the secondary outcomes included survival data for the other time cut-off values. We pooled similar prognostic data for the meta-analysis. OS included overall survival and all-cause survival; CSS included disease-specific survival and cancer-specific survival; and DFS included disease-free survival, progression-free survival, and recurrence-free survival. Patients were divided into early-onset and later-onset groups using an age cut-off of 50 years, and death or recurrence was extracted as an indicator of patient outcome. When the number of effects for each outcome was ≥3, the effect sizes were combined for meta-analysis.

2.8 | Statistical analysis

All analyses were performed using Stata version 17.0. HRs, RRs, and the corresponding 95% confidence intervals (CIs) were used to evaluate the outcomes. The RRs were not available directly from the researchers and needed to be converted from the survival or mortality rates of patients reported in the article. The pooled HRs and RRs were analyzed separately for the meta-analysis. The I^2 statistic was used to estimate heterogeneity, and pooled analyses were performed with a random effects meta-analysis model in the presence of high heterogeneity ($I^2 \geq 50\%$, $p_{heterogeneity} < 0.10$),[31,32] with fixed-effects models otherwise being utilized. Statistical significance was determined by a $p < 0.05$. Sources of heterogeneity were explored using subgroup and meta-regression methods.

Meta-regression was conducted to assess whether the geographic location, sample size, data source, tumor type, the advanced age of the patient, time span of patient enrollment, stage, and cohort type could affect the difference in prognosis between EOCRC and LOCRC patients. A sensitivity analysis was used to determine the reliability and quality of the results. When there were more than six independent studies, sensitivity analyses were performed by removing one study at a time from the meta-analysis and recalculating the pooled estimates. Egger's and Begg's tests were used to assess publication bias using funnel plots ($p < 0.05$).

In NMA, the outcomes included 5-year OS or CSS for the comparison between different age subgroups (≤30 years, ≤40 years, 41–50 years >50 years). The NMA was performed according to the PRISMA NMA guidelines.[33,34] The following steps were applied to the NMA.

Step 1: Network geometry was created to explore the comparative relationship between prognoses in different age subgroups.

Step 2: Consistency, whereby the direct comparison results are consistent with those estimated by indirect comparison.

Step 3: A network forest plot or interval plot was used to show the effect sizes for comparison between the age subgroups.

Step 4: Once differences in prognosis were assessed in the previous steps, the next step was to rank different age groups to

identify superiority by surface under the cumulative ranking curve (SUCRA).

Step 5: Network funnel plots were created to check for publication bias in the NMA.

3 | RESULTS

3.1 | Search and selection of studies

Figure 1 presents a flowchart of the literature search. A total of 1237 studies were obtained through electronic databases and manual searches up to April 25, 2022. After excluding duplicates and title or abstract screening, the full text was reviewed for 155 studies, and 21 studies were ultimately eligible for inclusion in the systematic review. Of the 21 studies, three were excluded because they did not provide the required prognostic data, five were excluded because they reused the same database (Supporting Information: Table S1), and 13 were finally included in the meta-analysis.

3.2 | Study characteristics

Twelve studies were cohort studies, and one was a cross-sectional study with 448,781 CRC cases (EOCRC, $n = 67,290$; LOCRC, $n = 381,491$).[16,20,35–45] Table 1 summarizes the basic information on these studies. Data for nine studies[16,20,36,37,39–42,45] were obtained from national/state databases or tumor registries ($n = 443,997$), and data for four[35,38,43,44] were obtained from tertiary care centers ($n = 4784$). The included studies were published from

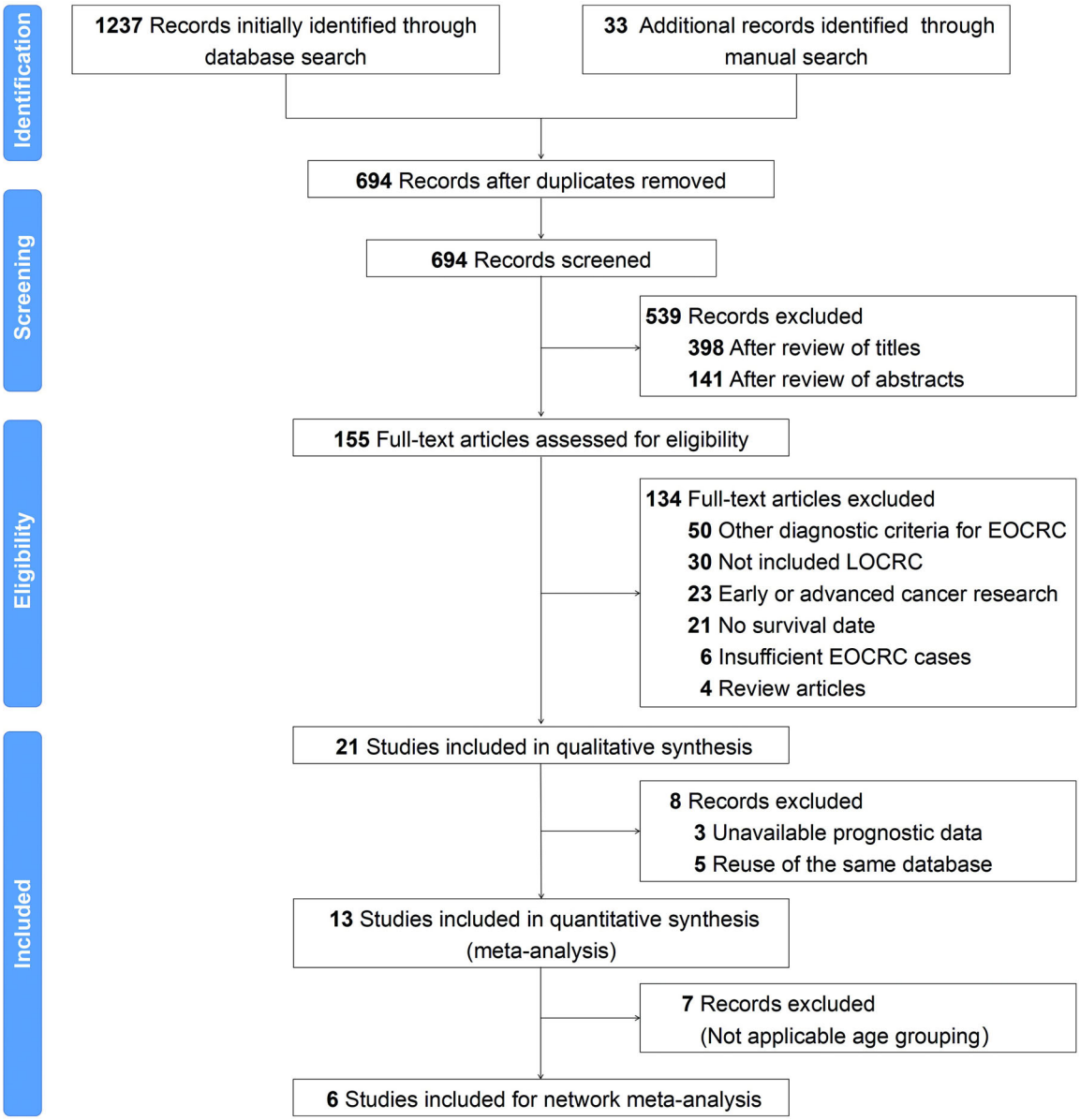

FIGURE 1 PRISMA flow diagram for data collection. EOCRC, early-onset colorectal cancer; LOCRC, later-onset colorectal cancer.

TABLE 1 Characteristics of the included studies.

References	Research type	Country	Tumor type	Stage	Age at diagnosis of EOCRC	N_{Total}	Data sources	Time of diagnosis	Outcomes
McClelland et al.[20]	Cohort study	The United States	CRC	I–IV	20–49 years	20–49 years: 35,084 50–79 years: 205,688	SEER database	2004–2015	OS, CSS
Takada et al.[35]	Cohort study	Japan	CRC	I–IV	<50 years	<50 years: 361 50–75 years: 3053[a]	Shizuoka Cancer Center	2007–2016	OS, CSS
Ibrahim et al.[36]	Cross-sectional study	Malaysia	CRC	I–IV	<50 years	<50 years: 893 ≥50 years: 5279	NCPR–CC database	2007–2017	OS
Saraste et al.[37]	Cohort study	Sweden	CRC	I–IV	<50 years	<50 years: 1675 50–74 years: 17,792[a]	SCRCR database	2010–2015	OS, DFS
Ghodssi et al.[38]	Cohort study	Iran	CRC	I–IV	16–50 years	16–50 years: 156 51–75 years: 240	Imam-Hossein Hospital	2008–2013	OS, CSS, DFS
Kelty et al.[39]	Cohort study	Australia	CRC	NR	18–49 years	18–49 years: 1069 50–69 years: 2151	The WA Cancer Registry The WA Death Registry	NR	OS, CSS
Laura, 2018[40]	Cohort study	Canada	CC	I–III	≤50 years	≤50 years: 448 >50 years: 6327	Ontario Cancer Registry	2002–2008	OS, CSS
Kolarich et al.[16]	Cohort study	The United States	RC	I–III	20–49 years	20–49 years: 9126 50–75 years: 33,980	National Cancer database	2004–2014	OS
Chou et al.[41]	Cohort study	China	CRC	NR	≤50 years	≤50 years: 10,086 51–80 years: 45,233[a]	Taiwan Cancer Registry database	1998–2005	OS, CSS
Boyce et al.[42]	Cohort study	Australia	CRC	NR	<50 years	<50 years: 2001 50–80 years: 23,493[a]	NSW Central Cancer Registry	2001–2008	OS, CSS
Yeo et al.[43]	Cohort study	Singapore	CRC	I–IV	≤50 years >50 years: 209	≤50 years: 330	Singapore General Hospital	2000–2005	CSS, DFS

(Continues)

TABLE 1 (Continued)

References	Research type	Country	Tumor type	Stage	Age at diagnosis of EOCRC	N_{Total}	Data sources	Time of diagnosis	Outcomes
Schellerer et al.[44]	Cohort study	Germany	CRC	I–III	≤50 years	≤50 years: 244 >50 years: 1718	University Hospital Erlangen	1996–2005	OS, CSS
Hubbard et al.[45]	Cohort study	Europe	CC	I–III	<50 years	<50 years: 5817 >50 years: 27,757	ACCENT database	1978–2003	OS, DFS, RFI

Abbreviations: ACCENT, Adjuvant Colon Cancer Endpoints; CSS, cancer special survival; DFS, disease free survival; EOCRC, early-onset colorectal cancer; NCPR-CC, National Cancer Patient Registry-Colorectal Cancer; NR, no report; NSW, New South Wales; OS, overall survival; RFI, recurrence free interval; SCRCR, Swedish colorectal cancer registry; SEER, Surveillance Epidemiology and End Results; WA, Western Australia.

[a]Advanced age patients were excluded.

2012 to 2022; two studies[40,45] only included colon cancer cases, and rectal cancer cases were only included in one study.[16] The study by McClelland et al.[20] included the largest number of cases (CRC, $n = 240,772$) with data from the SEER database and a time span of confirmed cases from 1973 to 2011. The age at early onset was defined as adult patients <50 years of age, with five studies[38,40,41,43,44] incorporating patients aged 50 years into the early onset cohort. For later-onset patients, different studies included different age groups (e.g., 50–69, 50–75, 50–79, ≥50 years). Considering that advanced age is a prognostic risk factor for CRC, we excluded patients of advanced age (i.e., >80 years) from three studies[35,37,41] when they could be excluded from LOCRC as a separate cohort in the prognosis analysis (Table 1).

In the risk bias assessment, the ROBINS-E checklist was more applicable for assessing the quality of the risk of bias in the studies included in this research (Supporting Information: Table S2). The age of patient onset was the only exposure factor in this study; thus, there was no difficulty in defining exposure factors, and exposure factors could not be terminated or adjusted (Supporting Information: Table S12). The ROBINS-E checklist was recommended for assessing confounding effects in studies, data completeness, and presentation of outcomes. The NOS checklist was less applicable to this study because the included articles were mainly derived from a database with complete follow-up. The exposure factor in this study was the age of the patient at onset, which facilitated the statistics (Supporting Information: Tables S3 and S4). The evaluation efficacy of the JBI Critical Appraisal checklist (Supporting Information: Tables S5 and S6) is comparable to the modified CASP checklist (Supporting Information: Tables S7 and S8), and the majority of studies are "low" risk of bias studies. The AHRQ checklist was used for this cross-sectional study (Supporting Information: Table S9). All results are described and tabulated.

The general characteristics of the included studies are summarized in Supporting Information: Table S10. Regarding the sex composition, the prevalence was higher in men in both age groups (EOCRC: $N_{male}/N_{female} = 1.16$; LOCRC: $N_{male}/N_{female} = 1.31$). The RR of the female prevalence was 1.09 (95% CI, 1.04–1.13) comparing early- and later-onset groups. Regarding the site of incidence, early-onset patients had a higher incidence of left hemicolectomy (RR 1.08; 95% CI, 1.02–1.14) and rectum (RR 1.18; 95% CI, 1.03–1.36) compared to later-onset patients; in terms of staging, early-onset was more common than later-onset in patients with III–IV at diagnosis (RR 1.21; 95% CI, 1.15–1.28). The incidence of mucinous adenocarcinoma was higher in early-onset patients (RR 1.43; 95% CI, 1.09–1.88).

3.3 | EOCRC patients had better overall survival

A total of 12 studies[16,20,35–40,44,45] for which data were available for 5-year OS were included in the meta-analysis. The HR for 5-year OS[35–39] compared the early-onset, and later-onset groups was 0.87 (95% CI, 0.74–0.99; $I^2 = 58.1\%$) (Table 2; Figure 2A) and the

TABLE 2 Summary of meta-analysis results.

	No of included studies	EOCRC		LOCRC		Model	HR/RR	(95% CI)	I^2, %	p Value
		Events	No of included patients	Events	No of included patients					
5 years OS	5	NA	3389	NA	21,168	Random effects	HR	0.85 (0.77, 0.92)	58.1	0.049
5 years OS	7	20,819	61,656	130,071	339,533	Random effects	RR	0.83 (0.78, 0.89)	94.7	<0.001
3 years OS	3	4604	18,268	22,761	75,159	Random effects	RR	0.81 (0.60, 1.08)	97.7	<0.001
1 years OS	3	1694	11,311	8776	47,624	Random effects	RR	0.99 (0.63, 1.54)	90.8	<0.001
5 years CSS	7	16,955	48,056	97,873	289,782	Random effects	RR	0.99 (0.93, 1.05)	87.3	<0.001
5 years DFS	4	2188	7217	12,826	40,653	Random effects	RR	0.90 (0.74, 1.09)	89.7	<0.001

Abbreviations: CI, confidence interval; CSS, cancer special survival; DFS, disease free survival; HR, hazard ratio; NA, not applicable; OS, overall survival; RR, relative risk.

meta-value[16,20,40–42,44,45] of the RR was 0.83 (95% CI, 0.78–0.89; I^2 = 94.7%) (Table 2; Figure 2B). The RR for 3-yearr OS[16,38,41] compared two groups was 0.81 (95% CI, 0.60–1.08; I^2 = 97.9%) (Table 2; Figure 2A) and the RR for 1-year OS[38,39,41] compare two groups was 0.99 (95% CI, 0.63–1.54; I^2 = 90.8%) (Table 2; Figure 2D); demonstrating no statistically significant difference.

3.4 | No difference in cancer-specific survival and disease-free survival

Seven studies[20,38,40–44] provided data for CSS, and the RR for 5-year CSS was 0.99 (95% CI, 0.93–1.05; I^2 = 87.3%), suggesting no statistical difference in cancer-specific prognosis (Table 2; Figure 2E). The pooled 5-year disease-free survival was 0.90 (95% CI, 0.74–1.09; I^2 = 89.7%), including four studies[37,38,43,45] (Table 2; Figure 2F).

3.5 | Meta-regression and subgroup analysis

We performed meta-regression and subgroup analysis for 5-year OS and 5-year CSS because of the high heterogeneity ($I^2 \geq 50\%$, $p_{heterogeneity} < 0.10$). Meta-regression analyses were conducted to further explore the impact of geographic location, sample size, patient data sources, tumor types, advanced-age patients (yes or no), the time span of patient enrollment, stage, and surgical cohort study (yes or no) on the heterogeneity of the main results (Table 3; Supporting Information: Table S11). We performed a subgroup analysis based on the meta-regression of the independent variables.

A meta-regression analysis of the 5-year OS indicated whether the study was a single surgical cohort account for heterogeneity (R^2 = 84.07%, p = 0.020) (Table 3). No factors for heterogeneity were found in the meta-regression analysis of the 5-year CSS ($p > 0.05$) (Supporting Information: Table S11). On the other hand, we performed subgroup analyses based on meta-regression of the variables. In the US population, early-onset patients have better 5-year OS (Americas, RR 0.78; 95% CI, 0.65–0.93) (Table 3), while studies in other regions suggested no difference between the two groups. In the subgroup analysis of 5-year CSS, early-onset patients had a better prognosis in the cohort with earlier disease stages (I–III, RR 0.85; 95% CI, 0.73–0.98) (Supporting Information: Table S11).

3.6 | Network meta-analysis

A total of six studies[16,20,40–43] with sample sizes ranging from 2426 to 240772 cases were included in the NMA. Studies were required to provide data for at least two age subgroups (≤30 years, ≤40 years, 41–50 years, and >50 years) to be included in the NMA. Five studies[16,20,40–42] were included in the NMA analysis of 5-year OS, and four studies[20,40,41,43] were included in the NMA analysis of 5-year CSS.

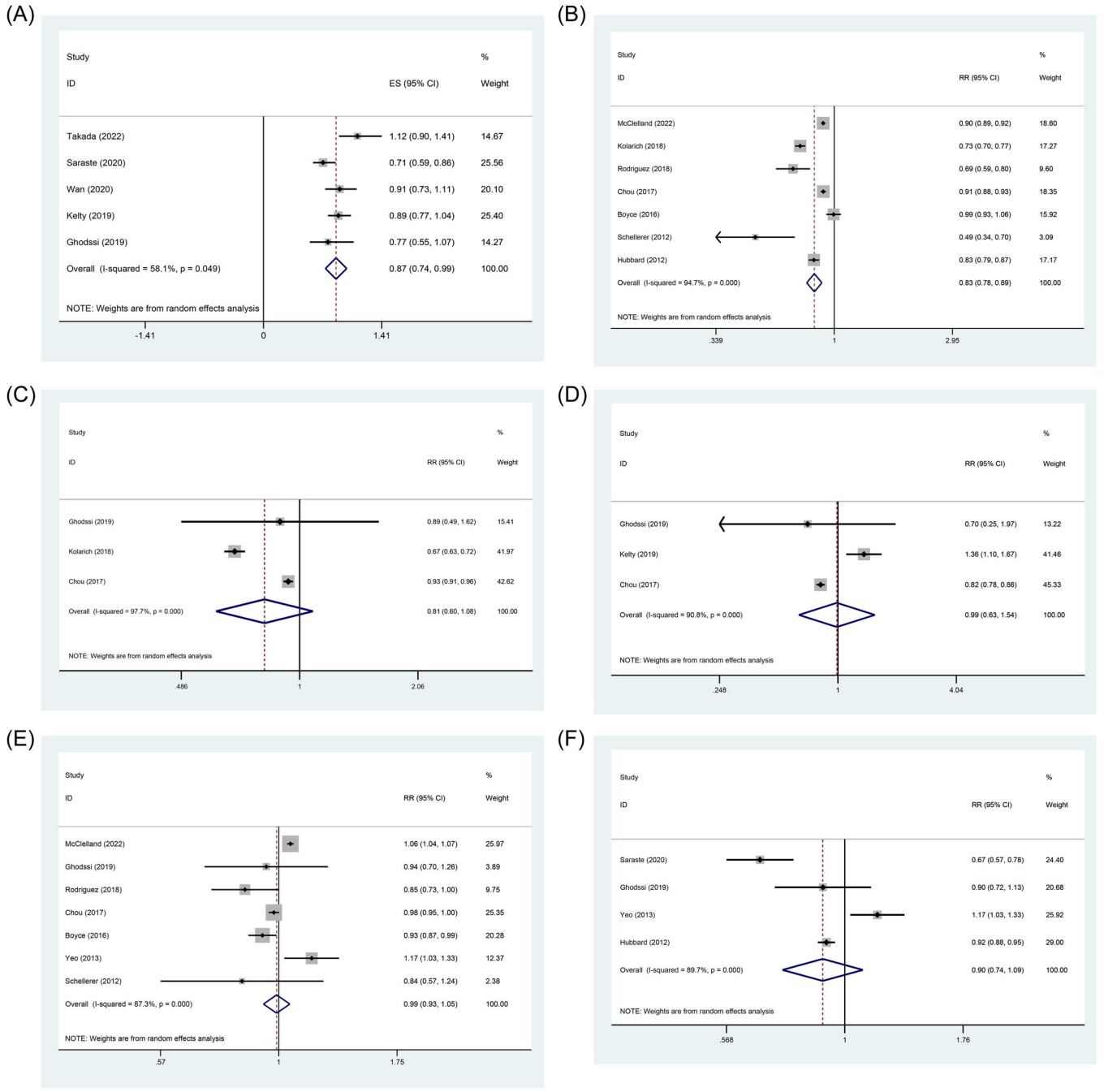

FIGURE 2 Forest plots for meta-analysis of prognosis between EOCRC and LOCRC. Random-effects meta-analysis of 5-year OS, pooled HRs (A); 5-year OS, pooled RRs (B); 3-year OS (C); 1-year OS (D); 5-year CSS (E); 5-year DFS (F). CSS, cancer-special survival; DFS, disease-free survival; EOCRC, early-onset colorectal cancer; HR, hazard ratio; LOCRC, later-onset colorectal cancer; OS, overall survival; RR, relative risk.

The network diagram presented a closed loop with four nodes, suggesting that patients of all ages could be compared in a mixed manner (Figure 3A,B). The node size indicates the number of studies included in the corresponding nodes. The consistency test suggests a direct agreement between the direct and circumstantial evidence (Supporting Information: Figure S1A,B). The following analysis can be performed: NMA forest plots and league tables compared prognoses and 95% CIs for each age group. Patients ≤40 years and 41–50 years had a better prognosis in the 5-year OS analysis than patients ≤30 years and >50 years (Supporting Information: Figures S2A and S3A). In the 5-year CSS analysis, there was no difference in prognosis between the age groups (Supporting Information: Figure S2B and S3B).

The SUCRA provides a more intuitive result, and SUCRA values close to 100% indicate a better prognosis. In the 5-year OS analysis, patients aged 41–50 years had the best overall survival (SUCRA, 87.2%), followed by patients ≤40 years (SUCRA, 78.2%), >50 years (SUCRA, 18.8%), and ≤30 years (SUCRA, 15.8%) (Figure 4A). In the analysis of 5-year CSS, the cancer-specific

TABLE 3 Meta-regression and subgroup analysis of 5-year overall survival.

Variable	No of included studies	Relative Risk (95% CI)	*p* Value	Adjusted R^2 (%)
Geographic location			0.776	−40.56
Americas	3	0.78 (0.65, 0.93)		
Asia and Oceania	2	0.94 (0.86, 1.03)		
Europe	2	0.66 (0.39, 1.10)		
Sample size of EOCR			0.055	51.77
≥500	5	0.87 (0.81, 0.93)		
<500	2	0.60 (0.43, 0.84)		
Patient data sources			0.068	42.28
Population-based	6	0.85 (0.79, 0.91)		
Hospital-based	1	0.49 (0.34, 0.70)		
Tumor types			0.385	29.58
CRC	4	0.91 (0.87, 0.96)		
RC	1	0.73 (0.70, 0.77)		
CC	2	0.77 (0.64, 0.92)		
Contain advanced age patients[a]			0.163	19.68
No	4	0.88 (0.81, 0.95)		
Yes	3	0.69 (0.55, 0.87)		
Time span of patient enrollment			0.811	−41.44
≥10 years	3	0.82 (0.72, 0.93)		
<10 years	4	0.82 (0.71, 0.94)		
Stage			0.576	−25.23
I–IV	1	0.90 (0.89, 0.92)		
I–III	4	0.73 (0.65, 0.82)		
NR	2	0.94 (0.86, 1.03)		
Single surgical cohort study			**0.020**[b]	**84.07**
No	4	0.90 (0.87, 0.94)		
Yes	3	0.68 (0.59, 0.79)		

Abbreviation: EOCR, early-onset colorectal cancer.

[a]Advanced age patients indicate those over the age of 80.

[b]Font bold indicates statistical significance ($p < 0.05$).

survival rate was higher in patients >50 years (SUCRA, 71.7%) than in other age groups, followed by patients aged 41–50 years (SUCRA, 67.1%), ≤40 years (SUCRA, 56.7%), and ≤30 years (SUCRA, 4.5%), which indicated that age is a protective factor for CSS (Figure 4B).

3.7 | Sensitivity analysis and publication bias

We undertook sensitivity analysis for results with >6 included studies and a large amount of heterogeneity ($I^2 \geq 50\%$, $P_{heterogeneity} < 0.10$). The patients' primary outcomes were stable (Supporting Information: Figure S4). Funnel plots were plotted for the main results (Figure 5A,B; Supporting Information: Figure S5A,B), AND NO evidence of publication bias was found using Egger's and Begg's tests (Figure 5C–F).

4 | DISCUSSION

This study is the first meta-analysis to use age at onset as a main prognostic comparison between EOCRC and LOCRC. The results of this systematic review and meta-analysis demonstrated that based on a large number of case reviews, the OS of EOCRC was better than

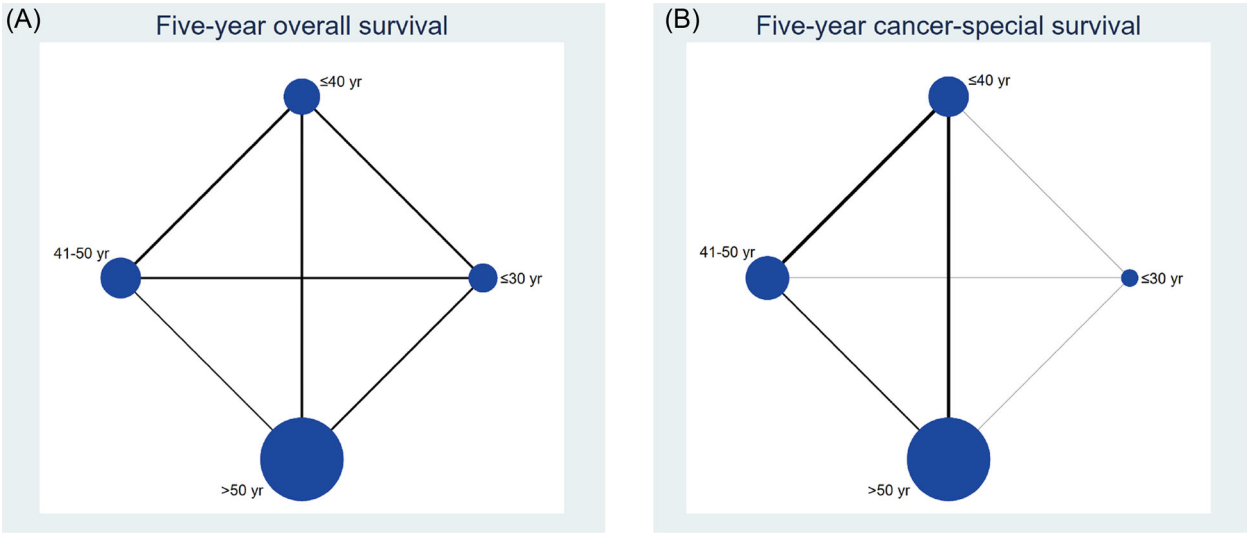

FIGURE 3 Network plot of colorectal cancer patients' 5-year overall survival (A) and 5-year cancer-special survival (B) in different age subgroups.

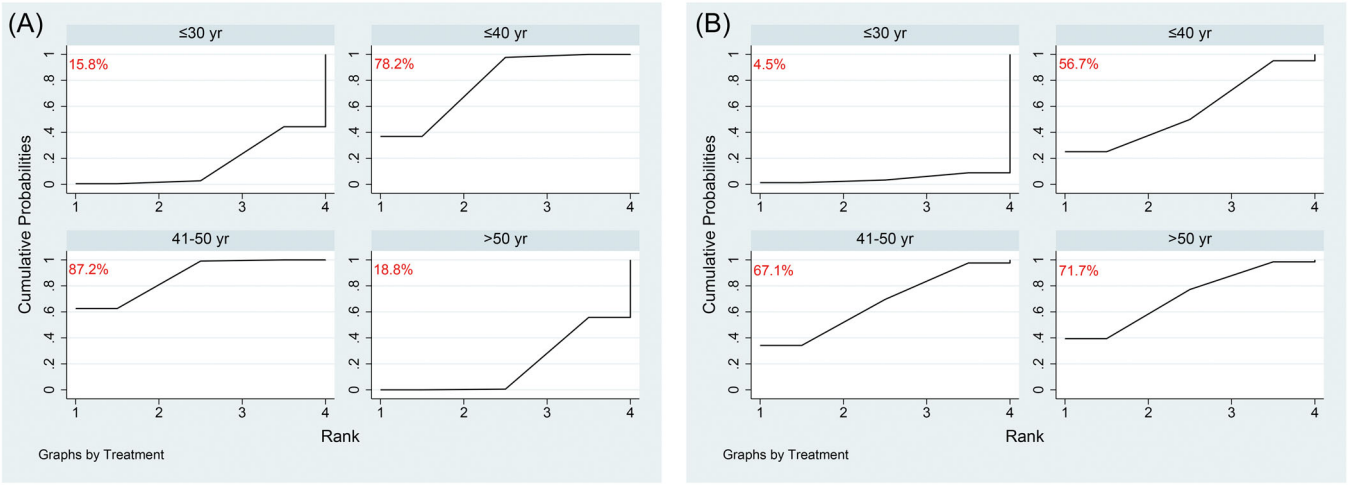

FIGURE 4 Cumulative ranking curve and SUCRA score of 5-year OS (A) and 5-year cancer special survival (B). SUCRA, surface under the cumulative ranking curve.

that of LOCRC, while there was no difference in distant CSS and DFS. No consensus guidelines regarding the treatment of EOCRC have been published. Because there is no difference in prognosis compared to LOCRC, some studies have concluded that EOCRC does not require aggressive treatment,[19] and this meta-analysis supports this conclusion.

A systematic review revealed that the prognostic associations of early-onset CRC are inconsistent. Several studies have shown poor survival outcomes due to a higher proportion of progressive tumours,[46,47] whereas others have reported a better prognosis than later-onset patients.[40,42,48] However, previous studies have certain limitations, such as inconsistent definitions of EOCRC or LOCRC,[49–51] studies only on patients with progressive tumours,[52,53] and insufficient study inclusion for prognostic analysis (fewer than 100 cases),[17,54] which do not allow for the exposure of actual prognostic differences between the two age groups. Our study found no differences in 5-year CSS, consistent with the results of several large-scale retrospective studies in recent years,[20,55] and similar results were obtained for metastatic CRC.[52] However, patients with LOCRC had a worse 5-year OS, associated with risk factors for death associated with increasing age, including ischaemic heart disease (coronary heart disease), stroke, chronic obstructive pulmonary disease, metabolic syndrome, and kidney disease.[56]

A wide range of scholars have noted the increasing incidence of EOCRC in the past decades.[3,5] Holowatyj et al.[57] published a call in Nature Reviews Cancer in 2021 for a global collaborative study on EOCRC at multiple levels of biology, genetics, and epidemiology to provide a basis for its prevention, detection, and treatment. Exposure elements known to be associated with the development of EOCRC are metabolic syndrome (abdominal obesity, hyperlipidaemia,

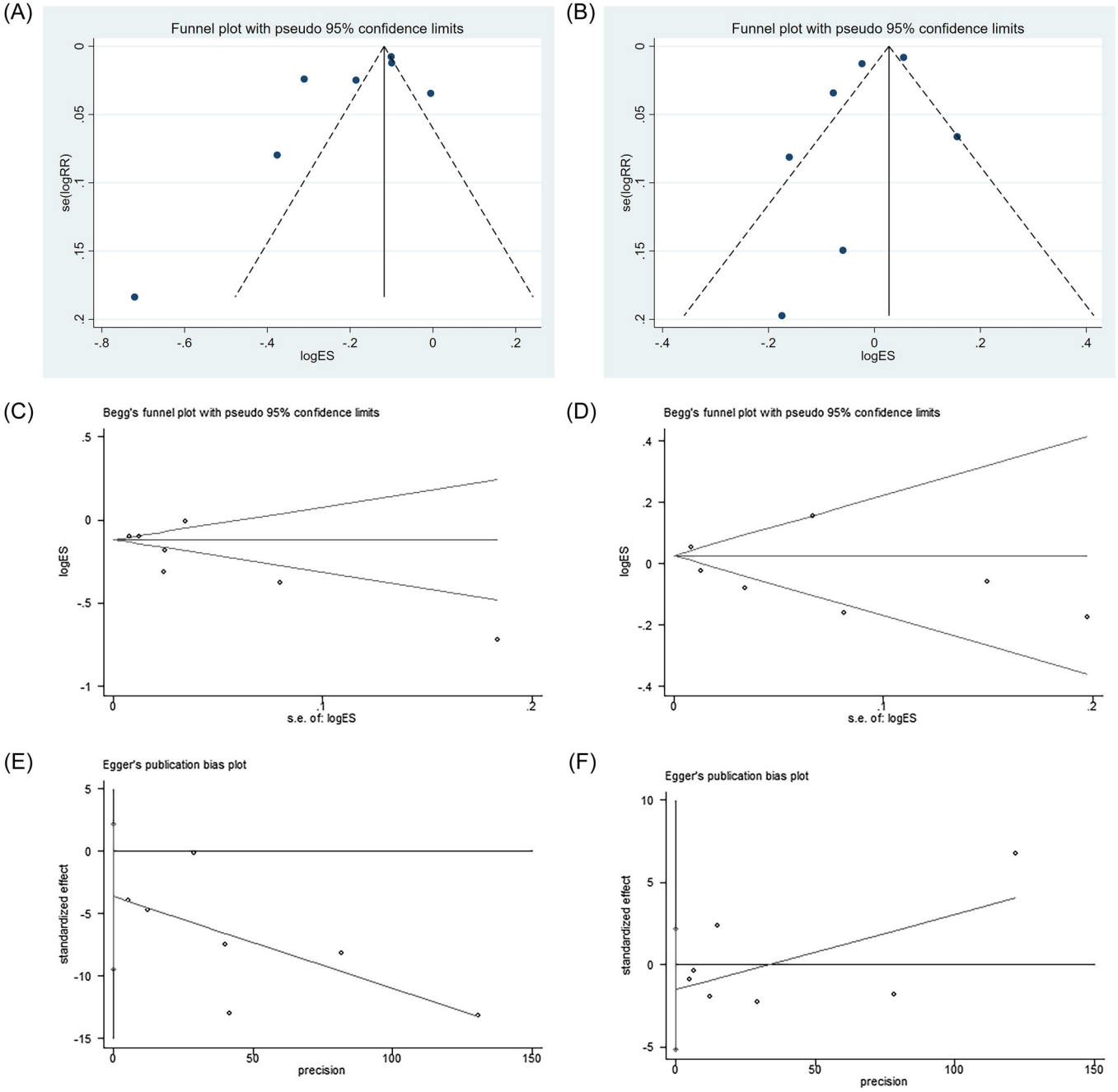

FIGURE 5 The funnel plot generated for the 5-year OS (A) and 5-year CSS (B) was visually symmetrical in appearance. Coupled with the Begg's and Egger's test, that suggests the absence of publication bias. Bgge regression test of 5-year OS, $p = 0.230$ (C); Bgge regression test of 5-year OS, $p = 1.000$ (D); Egger regression test of 5-year OS, $p = 0.171$ (E); Egger regression test of 5-year OS, $p = 0.340$ (F). CSS, cancer special survival; OS, overall survival.

elevated blood pressure, elevated triglycerides, and low HDL-C), diet (red and processed meat and dietary additives), antibiotics, alcohol consumption, family history, and gut microbiota,[7,58–61] most of which overlap with established risk factors for later-onset disease. Several large prospective cohort studies[62,63] are underway to examine early life exposure factors in patients with EOCRC to improve the risk stratification for EOCRC. Colonoscopy is the best visual screening modality for colorectal tumours. In 2018, the American Cancer Society (ACS) lowered the recommended age for CRC screening from 50 to 45 years based on modeling data,[64,65] suggesting that beginning screening at the age of 45 years was associated with a higher number of predicted life years gained and an improved balance between screening burden and benefit. Even so, those under 45 years of age, especially the youngest (20–29 years),[5] have the highest annual growth rate and will still miss the diagnosis. Nearly 86.4% of the EOCRC cases were symptomatic at diagnosis.[66] The lack of recognition and attention to symptoms and delayed consultations have increased the incidence of progressive

tumours.[6,67] Somatic markers of molecular characteristics found in EOCRC can provide information for screening and targeted therapeutic approaches.[68] Although there was no difference in tumor-specific survival in our study, previous studies have shown that EOCRC is a biologically and clinically distinct disease from LOCRC.[63,69] Based on next-generation genome sequencing, a high frequency of MSI-H and alterations in TP53 and CTNNB1 in EOCRC were more common in EOCRC.[59,70] A polygenic risk score based on 95 CRC-associated common genetic risk variants showed that the cumulative burden of genetic variants was more strongly associated with EOCRC.[71] Recently, a noninvasive diagnostic method was developed to achieve high EOCRC accuracy through liquid biopsy with a novel miRNA signature.[68]

The NMA suggested different prognoses according to age; the analysis of both 5-year OS and 5-year CSS suggested the worst prognosis among early onset patients aged <30 years, although the latter showed no statistical difference. Considering the difficulty of long-term follow-up of the 5-year CSS, including a larger sample in the future would provide more definitive results. In summary, there is reason to believe that patients <30 years is a noteworthy age group. More advanced studies are needed to provide a theoretical basis for individualized screening and treatment.

Our study has several limitations. The high heterogeneity in the results of the studies was because the included studies were mainly database-based with narrow confidence intervals for the data. Although the age at the inclusion of the later-onset patients was not uniform, we used meta-regression to demonstrate that excluding advanced-age patients did not affect the generation of results or heterogeneity. This study compared the prognostic differences between the overall EOCRC and LOCRC cohorts. It is difficult to avoid the heterogeneity of disease stages and treatment modalities among patients in the same cohort. In addition, the NMA showed refreshing results, but the number of included articles was low owing to the lack of studies that provided age subgroups and prognoses. High-quality prospective studies are still needed to examine the prognosis and survival of EOCRC.

In conclusion, this meta-analysis provides a comprehensive overview of CRC-related prognosis between early- and later-onset patients. EOCRC had a better 5-year OS than LOCRC, indicating a better long-term prognosis. However, there was no difference in prognosis between the two groups in terms of the 5-year CSS, 5-year DFS, and short-term OS. The increased incidence of EOCRC cannot be explained by genetic susceptibility solely. More intense treatment of EOCRC patients based on genetic mutations alone has been shown not to result in better clinical benefits. While substantial evidence supports the benefits of CRC screening in people over 45,[2] there is a lack of suitable screening strategies for patients under 45. Patients under 30 have the worst prognosis compared to other age groups, partly associated with the neglect of red flag symptoms and diagnosis delay.[68,72] In addition, it cannot be ruled out that this age group has unique molecular characteristics[57,70,71] that lead to poor prognosis. Attention to early symptoms and exploring exposure risk factors and biological markers will facilitate screening individuals with potential risks in young populations, which has more significant social benefits for the early diagnosis and treatment of patients.

AUTHOR CONTRIBUTIONS

Taojun Jin: Data curation; formal analysis; resources; software; supervision; writing—original draft. **Xinxing Li**: Investigation; methodology; resources; writing—original draft. **Jianmei Ji**: Formal analysis; software. **Jue Li**: Conceptualization; Methodology. **Xiaomao Yin**: Data curation; investigation. **Kai Xu**: Data curation; linvestigation. **Wenqiang Wang**: Data curation; investigation. **Wei Zhang**: Data curation; investigation. **Xiaowen Xu**: Funding acquisition; investigation. **Zhiqian Hu**: Conceptualization; funding acquisition; supervision; writing—review & editing. **Biao Gong**: Conceptualization; supervision; writing—review & editing.

ACKNOWLEDGMENTS

Professor Jue Li of Tongji University School of Medicine provided professional statistical consulting and guidance for this paper. Data collection, analysis, and interpretation of this work were funded by the Clinical Research Project of Tongji Hospital Affiliated to Tongji University, grant number: ITJ-ZD-2104. The publication of this research was funded by the National Natural Science Foundation of China, grant number: 82104575.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supporting Information. Further inquiries can be directed to the corresponding author.

TRANSPARENCY STATEMENT

The lead author Zhiqian Hu, Biao Gong affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394-424.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70(1):7-30.
3. Siegel RL, Torre LA, Soerjomataram I, et al. Global patterns and trends in colorectal cancer incidence in young adults. *Gut*. 2019;68(12):2179-2185.

4. Murphy CC, Singal AG, Baron JA, Sandler RS. Decrease in incidence of young-onset colorectal cancer before recent increase. *Gastroenterology*. 2018;155(6):1716-1719.
5. Vuik FE, Nieuwenburg SA, Bardou M, et al. Increasing incidence of colorectal cancer in young adults in Europe over the last 25 years. *Gut*. 2019;68(10):1820-1826.
6. Zaborowski AM, Abdile A, Adamina M, et al. Characteristics of early-onset vs late-onset colorectal cancer: a review. *Jama Surg*. 2021;156(9):865-874.
7. O'Sullivan DE, Sutherland RL, Town S, et al. Risk factors for early-onset colorectal cancer: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2022;20(6):1229-1240.
8. Li H, Boakye D, Chen X, et al. Associations of body mass index at different ages with early-onset colorectal cancer. *Gastroenterology*. 2022;162(4):1088-1097.
9. Gausman V, Dornblaser D, Anand S, et al. Risk factors associated with early-onset colorectal cancer. *Clin Gastroenterol Hepatol*. 2020;18(12):2752-2759.
10. Zheng X, Hur J, Nguyen LH, et al. Comprehensive assessment of diet quality and risk of precursors of early-onset colorectal cancer. *JNCI: J Natl Cancer Inst*. 2021;113(5):543-552.
11. Sharma R, Abbasi-Kangevari M, Abd-Rabu R, et al. Global, regional, and national burden of colorectal cancer and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Gastroenterol Hepatol*. 2022;7(7):627-647.
12. Schwingshackl L, Schwedhelm C, Hoffmann G, et al. Food groups and risk of colorectal cancer. *Int J Cancer*. 2018;142(9):1748-1758.
13. Stoffel EM, Koeppe E, Everett J, et al. Germline genetic features of young individuals with colorectal cancer. *Gastroenterology*. 2018;154(4):897-905.
14. Lieu CH, Golemis EA, Serebriiskii IG, et al. Comprehensive genomic landscapes in early and later onset colorectal cancer. *Clin Cancer Res*. 2019;25(19):5852-5858.
15. Pearlman R, Frankel WL, Swanson B, et al. Prevalence and spectrum of germline cancer susceptibility gene mutations among patients with early-onset colorectal cancer. *Jama Oncol*. 2017;3(4):464-471.
16. Kolarich A, George TJ, Hughes SJ, et al. Rectal cancer patients younger than 50 years lack a survival benefit from NCCN guideline-directed treatment for stage II and III disease. *Cancer*. 2018;124(17):3510-3519.
17. Zaborowski AM, Murphy B, Creavin B, et al. Clinicopathological features and oncological outcomes of patients with young-onset rectal cancer. *Br J Surg*. 2020;107(5):606-612.
18. Kneuertz PJ, Chang GJ, Hu CY, et al. Overtreatment of young adults with colon cancer more intense treatments with unmatched survival gains. *Jama Surg*. 2015;150(5):402-409.
19. Lipsyc-Sharf M, Zhang S, Ou FS, et al. Survival in young-onset metastatic colorectal cancer: findings from cancer and leukemia group B (Alliance)/SWOG 80405. *JNCI: J Natl Cancer Inst*. 2022;114(3):427-435.
20. McClelland PH, Liu T, Ozuner G. Early-onset colorectal cancer in patients under 50 years of age: demographics, disease characteristics, and survival. *Clin Colorectal Cancer*. 2022;21(2):e135-e144.
21. Cercek A, Chatila WK, Yaeger R, et al. A comprehensive comparison of early-onset and average-onset colorectal cancers. *JNCI: J Natl Cancer Inst*. 2021;113(12):1683-1692.
22. Xinxing LiTJ. Register name: Association between early onset and survival of colorectal cancer: a systematic review and meta-analysis. 2022. Accessed July 10, 2022. https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=334697
23. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *J Clin Epidemiol*. 2021;134:178-189.
24. Brooke BS, Schwartz TA, Pawlik TM. MOOSE reporting guidelines for meta-analyses of observational studies. *Jama Surg*. 2021;156(8):787-788.
25. Bero L, Chartres N, Diong J, et al. The risk of bias in observational studies of exposures (ROBINS-E) tool: concerns arising from application to observational studies of exposures. *Syst Rev*. 2018;7(1):242.
26. Morgan RL, Thayer KA, Santesso N, et al. A risk of bias instrument for non-randomized studies of exposures: a users' guide to its application in the context of GRADE. *Environ Int*. 2019;122:168-184.
27. Wells GSB, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Accessed June 25, 2022. https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
28. CASP. CASP Qualitative Checklist. Crit. Apprais. Ski. Program. 2018. Accessed June 25, 2022. https://www.casp-uk.net
29. J B I. Critical appraisal tools. Accessed June 25, 2022. https://www.joannabriggs.org/critical-appraisal-tools
30. Zeng X, Zhang Y, Kwong JSW, et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. *J Evid Based Med*. 2015;8(1):2-10.
31. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560. doi:10.1136/bmj.327.7414.557
32. Ahmed I, Sutton AJ, Riley RD. Assessment of publication bias, selection bias, and unavailable data in meta-analyses using individual participant data: a database survey. *BMJ*. 2012;344:d7762.
33. Shim S, Yoon BH, Shin IS, Bae JM. Network meta-analysis: application and practice using Stata. *Epidemiol Health*. 2017;39:e2017047.
34. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med*. 2015;162(11):777-784.
35. Takada K, Hotta K, Imai K, Ito S, Kishida Y, Ono H. Favorable survival after screening for young-onset colorectal cancer: benefits of screening in young adults. *Dis Colon Rectum*. 2022;65(8):996-1004.
36. Ibrahim NRW, Chan HK, Soelar SA, et al. Incidence, clinico-demographic profiles and survival rates of colorectal cancer in Northern Malaysia: comparing patients above and below 50 years of age. West Asia Organization for Cancer Prevention (WAOCP), APOCP's West Asia Chapter. (4). 2020.
37. Saraste D, Järås J, Martling A. Population-based analysis of outcomes with early-age colorectal cancer. *Br J Surg*. 2020;107(3):301-309.
38. Ghodssi-Ghassemabadi R, Hajizadeh E, Hajizadeh E, Kamian S, Mahmoudi M. Clinicopathological features and survival of colorectal cancer patients younger than 50 years: a retrospective comparative study. *J Egypt Natl Canc Inst*. 2019;31(1):6.
39. Kelty E, Ward SV, Cadby G, et al. Familial and non-familial risk factors associated with colorectal cancer survival in young and middle-aged patients. *Int J Colorectal Dis*. 2019;34(10):1673-1680.
40. Laura R, Kelly B, Safiya K, et al. Disease characteristics, clinical management, and outcomes of young patients with colon cancer: a population-based study. *Clin Colorectal Cancer*. 2018;17:e651-e661.
41. Chou CL, Tseng CJ, Shiue YL. The impact of young age on the prognosis for colorectal cancer: a population-based study in Taiwan. *Jpn J Clin Oncol*. 2017;47(11):1010-1018.
42. Boyce S, Nassar N, Lee CYY, Suen MK, Al Zahrani S, Gladman MA. Young-onset colorectal cancer in New South Wales: a population-based study. *Med J Aust*. 2016;205(10):465-470.
43. Yeo SA, Chew MH, Koh PK, Tang CL. Young colorectal carcinoma patients do not have a poorer prognosis: a comparative review of 2,426 cases. *Tech Coloproctol*. 2013;17(6):653-661.
44. Schellerer VS, Merkel S, Schumann SC, et al. Despite aggressive histopathology survival is not impaired in young patients with

colorectal cancer. *Int J Colorectal Dis*. 2012;27(1):71-79. doi:10.1007/s00384-011-1291-8
45. Hubbard J, Thomas DM, Yothers G, et al. Benefits and adverse events in younger versus older patients receiving adjuvant chemotherapy for colon cancer: findings from the adjuvant colon cancer endpoints data set. *J Clin Oncol*. 2012;30(19):2334-2339.
46. Lieu C, Renfro L, Gramont AD, et al. The impact of young age on survival in patients with metastatic colorectal cancer: analysis from the ARCAD Clinical Trials Program. 2014.
47. Kim TJ, Kim ER, Hong SN, Chang DK, Kim YH. Long-term outcome and prognostic factors of sporadic colorectal cancer in young patients. *Medicine*. 2016;95(19):e3641.
48. Mauri G, Sartore-Bianchi A, Russo A-G, Marsoni S, Bardelli A, Siena S. Early-onset colorectal cancer in young individuals. *Mol Oncol*. 2019;13(2):109-131. doi:10.1002/1878-0261.12417
49. Emile SH, Elfeki H, Shalaby M, Elbalka S, Metwally IH, Abdelkhalek M. Patients with early-onset rectal cancer aged 40 year or less have similar oncologic outcomes to older patients despite presenting in more advanced stage; a retrospective cohort study. *Int J Surg*. 2020;83:161-168.
50. Swartjes H, Brouwer NPM, de Nes LCF, et al. Incidence, treatment and relative survival of early-onset colorectal cancer in the Netherlands since 1989. *Eur J Cancer*. 2022;166:134-144.
51. Mckay A, Donaleshen J, Helewa RM, et al. Does young age influence the prognosis of colorectal cancer: a population-based analysis. *World J Surg Oncol*. 2014;12(1):370.
52. Goh SS, Loo EX, Lee DJ. Trends and clinical outcomes in young-onset colorectal cancer patients. *Ann Acad Med Singapore*. 2020;49(11):848-856.
53. Georgiou A, Khakoo S, Edwards P, et al. Outcomes of patients with early onset colorectal cancer treated in a UK specialist cancer center. *Cancers*. 2019;11(10):1558.
54. Wong S, Ling D, Yeow R, et al. Clinicopathological patterns and survival outcomes of colorectal cancer among young adults in Malaysia: an institutional cohort study. *Singapore Med J*. 2021;62(12):636-641.
55. Gao XH, Li J, Liu LJ, et al. Trends, clinicopathological features, surgical treatment patterns and prognoses of early-onset versus late-onset colorectal cancer: a retrospective cohort study on 34067 patients managed from 2000 to 2021 in a Chinese tertiary center. *Int J Sur*. 2022;104:106780.
56. WHO. World Health Statistics 2021. Accessed August 6, 2022. https://www.who.int/publications/i/item/9789240027053
57. Holowatyj AN, Perea J, Lieu CH. Gut instinct: a call to study the biology of early-onset colorectal cancer disparities. *Nat Rev Cancer*. 2021;21:339-340.
58. Jin EH, Han K, Lee DH, et al. Association between metabolic syndrome and the risk of colorectal cancer diagnosed before age 50 years according to tumor location. *Gastroenterology*. 2022;163(3):637-648.
59. Sinicrope FA. Increasing incidence of early-onset colorectal cancer. *N Eng J Med*. 2022;386(16):1547-1558. doi:10.1056/NEJMra2200869
60. Low EE, Demb J, Liu L, et al. Risk factors for early-onset colorectal cancer. *Gastroenterology*. 2020;159(2):492-501.
61. Zhang J, Haines C, Watson AJM, et al. Oral antibiotic use and risk of colorectal cancer in the United Kingdom, 1989-2012: a matched case-control study. *Gut*. 2019;68(11):1971-1978.
62. Gausman V, Liang P, O'Connell K, et al. Evaluation of early-life factors and early-onset colorectal cancer among men and women in the UK Biobank. *Gastroenterology*. 2022;162(3):981-983. doi:10.1053/j.gastro.2021.11.023
63. Akimoto N, Ugai T, Zhong R, et al. Rising incidence of early-onset colorectal cancer—a call to action. *Nat Rev Clin Oncol*. 2021;18(4):230-243.
64. Anderson JC, Samadder JN. To screen or not to screen adults 45–49 years of age: that is the question. *Am J Gastroenterol*. 2018;113(12):1750-1753.
65. Wolf AMD, Fontham ETH, Church TR, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. *CA Cancer J Clin*. 2018;68(4):250-281.
66. Dozois EJ, Boardman LA, Suwanthanma W, et al. Young-onset colorectal cancer in patients with no known genetic predisposition—can we increase early recognition and improve outcome? *Medicine*. 2008;87(5):259-263.
67. Connell LC, Mota JM, Braghiroli MI, Hoff PM. The rising incidence of younger patients with colorectal cancer: questions about screening, biology, and treatment. *Curr Treat Options Oncol*. 2017;18(4):23.
68. Burnett-Hartman AN, Lee JK, Demb J, Gupta S. An update on the epidemiology, molecular characterization, diagnosis, and screening strategies for early-onset colorectal cancer. *Gastroenterology*. 2021;160(4):1041-1049.
69. Stoffel EM, Murphy CC. Epidemiology and mechanisms of the increasing incidence of colon and rectal cancers in young adults. *Gastroenterology*. 2020;158(2):341-353.
70. Sinicrope FA. Lynch syndrome-associated colorectal cancer. *N Engl J Med*. 2018;379(8):764-773.
71. Archambault AN, Su YR, Jeon J, et al. Cumulative burden of colorectal cancer-associated genetic variants is more strongly associated with early-onset vs late-onset cancer. *Gastroenterology*. 2020;158(5):1274-1286.
72. Scott RB, Rangel LE, Osler TM, Hyman NH. Rectal cancer in patients under the age of 50 years: the delayed diagnosis. *Am J Surg*. 2016;211:1014-1018.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Jin T, Li X, Ji J, et al. Comparison of the short- and long-term prognosis of early-onset colorectal cancer compared with later-onset colorectal cancer: a systematic review and meta-analysis. *Health Sci Rep*. 2023;6:e1307. doi:10.1002/hsr2.1307