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Risk factors for recurrence in stage I colorectal cancer after curative resection: a systematic review and meta-analysis

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Purpose: Patients with stage I colorectal cancer (CRC) rarely experience recurrence after curative resection. Therefore, the risk factors for stage I CRC recurrence are yet to be established. We aimed to identify risk factors for stage I CRC recurrence.
Methods: MEDLINE, Embase, and Cochrane Library were searched for articles published between 1990 and 2022. The pooled proportions and hazard ratios (HRs) were calculated. Fixed- or random-effect models were considered based on heterogeneity, using Cochran's Q-statistic and the I^2-test.
Results: Nine studies involving 19,440 patients were included. Nine analyzed risk factors were identified. T2 stage (pooled HR, 2.070; 95% confidence interval [CI], 1.758–2.438; $P < 0.001$; I^2=0.0%), lymphovascular invasion (HR, 1.685; 95% CI, 1.420–1.999; $P < 0.001$; $I^2 = 0.0\%$), venous invasion (HR, 1.794; 95% CI, 1.515–2.125; $P < 0.001$; $I^2 = 0.0\%$), CEA level (HR, 1.472; 95% CI, 1.093–1.983; $P = 0.011$; $I^2 = 1.8\%$) and rectal cancer (HR, 2.981; 95% CI, 2.378–3.735; $P < 0.001$; $I^2 = 0.0\%$) were risk factors for the recurrence. However, the risk of recurrence in right-sided colon cancer was lower than in left-sided colon cancer. (HR, 0.712; 95% CI, 0.537–0.944; $P = 0.018$; $I^2 = 0.0\%$). No statistically significant differences were observed in the number of harvested lymph nodes, age, and sex.
Conclusion: T2 stage, lymphovascular invasion, venous invasion, CEA level, rectal cancer, and left-sided colon cancer were risk factors for recurrence in stage I CRC. Intensive monitoring and surveillance are warranted for patients with high-risk features of recurrence.
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Key Words: Colorectal neoplasms, Recurrence, Risk factors, Systematic review

INTRODUCTION

The global burden of colorectal cancer (CRC) remains significant and is expected to increase, necessitating effective strategies for its management [1,2]. Regular screening effectively reduces CRC-related deaths [3]. Consequently, the proportion of patients with stage I CRC has also increased due to the introduction of regular screening [4,5]. Although stage I CRC has a good prognosis, a subset of patients experience recurrence. The recurrence rate for patients with stage I CRC who have risk

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factors for recurrence is as high as for patients with stage II–III CRC [6]. The recurrence-free survival rate for patients with high-risk stage I CRC was less than 80%. In addition, the prognosis of patients with stage I CRC who experience recurrence has been as poor as that of patients with advanced disease [7]. Therefore, a study on the risk factors for recurrence in stage I CRC is necessary for tailored treatment and improved outcomes in these patients.

Due to the low recurrence rate, there have been few studies that have evaluated the risk factors for recurrence in stage I CRC. The reported recurrence rate ranges from 2.9% to 10% [8-12]. Uncertainty persists regarding the risk factors for the recurrence shared with stage II–III CRC. In addition, most studies on this topic have been retrospective, presenting methodological heterogeneity. Therefore, risk factors for recurrence in stage I CRC are not well established. This systematic review and meta-analysis aims to identify the risk factors for recurrence in stage I CRC after curative resection.

METHODS

Eligibility criteria

Studies, with original data, on the risk factors for the recurrence of stage I CRC and univariate Cox regression analysis for recurrence-free survival in stage I CRC were included. Studies published before 1990, case reports, reviews, and those in languages other than English were excluded from the initial screening. The following studies were excluded: (1) studies involving patients who underwent preoperative chemoradiotherapy, (2) those involving patients who underwent adjuvant chemotherapy, (3) those involving patients without data on univariate hazard ratios (HR) for stage I CRC recurrence, and (4) those involving patients treated with local or trans-anal excision.

Information sources and search strategy

This review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) guidelines [13]. MEDLINE, Embase, and the Cochrane Library were searched for articles published from 1990 to 31 August 2022 on stage I CRC recurrence. A systematic search was conducted using Medical Subject Headings terms and specific search strategies (Supplementary Material 1). The study protocol was published in the PROSPERO (International Prospective Register of Systematic Reviews; CRD42022349258).

Selection process and publication bias

Two authors independently screened the abstracts and conducted full-text reviews. Disagreements were resolved through discussion. The Newcastle-Ottawa quality assessment scale was used, and studies scoring 6 or higher were included [14]. The visual funnel plot was used to assess the possibility of publication bias.

Data collection process and data items

Two authors independently extracted data. The extracted data included authors, publication year, country, single/multicenter study, study design, number of patients, follow-up period, and univariate HR analysis data for stage I CRC recurrence. All the recurrence risk factors covered in each study were included. Depending on the study, lymphovascular invasion was grouped as lymphovascular or lymphatic invasion. In addition, factors defined only as venous invasion were investigated separately.

Effect measures and synthesis methods

The meta-analysis was conducted using STATA software ver. 17.0. (Stata Corp). The primary outcomes were relevant risk factors for the recurrence of stage I CRC. Risk factors addressed in 3 or more studies were analyzed. Pooled proportions and HR were calculated using the inverse variance method. Cochran's Q-statistic and I^2-tests were used to evaluate the heterogeneity of the included studies [15]. The fixed- and random-effects models were used depending on the heterogeneity of the included studies. A P-value of Q-test >0.10 or I^2 <50% indicated a lack of heterogeneity between studies, and a fixed-effects model was used to calculate the pooled HR. Otherwise, a random-effects model was applied, followed by a sensitivity analysis to identify highly sensitive literature [16]. The sensitivity analysis was performed using the leave-one-out method, examining the results of K meta-analyses where K studies were available for analysis. The final meta-analysis was then conducted after excluding the highly sensitive literature. A P-value of <0.05 was considered statistically significant.

RESULTS

Ethics statements

Approval from the Institutional Review Board was not required because this study was a meta-analysis of published studies, and informed consent was waived due to its retrospective nature.

Study selection

The search retrieved 3,340 articles, 1,704 from PubMed, 1,554 from Embase, 10 from Cochrane Library, and 72 from manual searching. After the initial screening, 210 records underwent full-text review, with 9 studies meeting the eligibility criteria (Fig. 1).

Study characteristics and risk of bias in studies

Nine studies involving 19,440 patients were included in this systematic review. All the included studies were retrospective

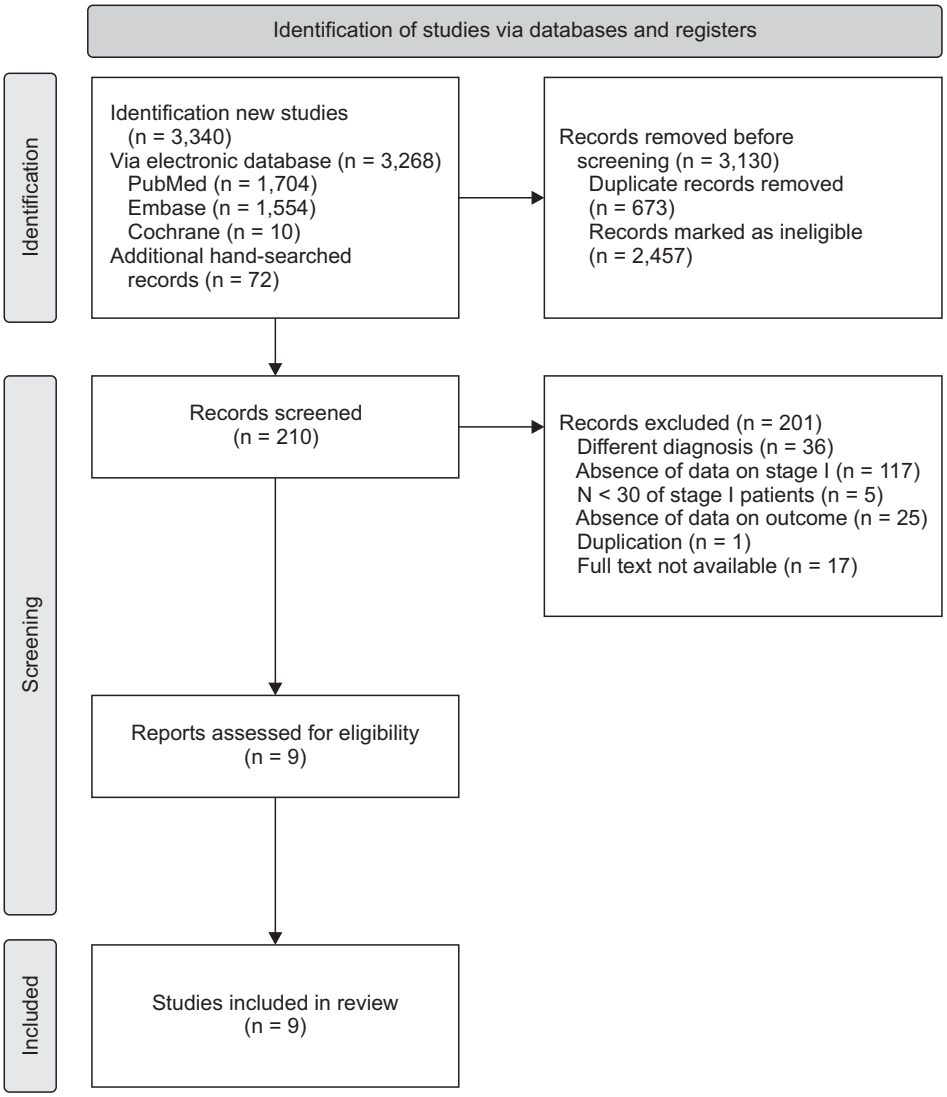

Fig. 1. A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of the literature search.

observational studies. The Newcastle-Ottawa scale scores for all included studies ranged from 6 to 9. The characteristics and quality assessments of the included studies are presented in Tables 1 and 2 [6,11,17-23].

Quantitative meta-analysis

In the investigation of factors influencing the recurrence of stage I CRC, 15 relevant risk factors were identified. These factors include the T-stage, lymphovascular invasion, venous invasion, rectal cancer, sidedness, CEA level, differentiation, tumor size, number of harvested lymph nodes, age, sex, perineural invasion, tumor budding, laparoscopic surgery, and body mass index. A meta-analysis was conducted on the factors assessed in at least 3 studies. A quantitative meta-analysis was conducted on 12 factors available for comprehensive examination: T-stage, lymphovascular invasion, venous invasion, rectal cancer, sidedness, CEA level, differentiation, tumor size, number of harvested lymph nodes, age, and sex. Tumor size was excluded from the analysis because each study applied a different cut-off value. Differentiation could not be analyzed because of statistical asymmetry. Ultimately, the meta-analysis was carried out on 9 risk factors.

Results of synthesis

T-stage

The relationship between T-stage and the recurrence risk of stage I CRC was reported in 6 studies. The results showed that T2 stage had a higher risk of recurrence than T1 stage (HR, 2.070; 95% confidence interval (CI) = 1.758–2.438; $P < 0.001$). There was no heterogeneity among the 6 included studies ($I^2 = 0.0\%$; $P = 0.487$), and a fixed-effects model was applied (Fig. 2A, 3A).

Lymphovascular invasion

The impact of lymphovascular invasion on the recurrence of stage I CRC was discussed in 5 studies. Due to substantial

Table 1. Characteristics of studies and 9 meta-analyzed factors in each study

Study	Year	Country	Design	No. of patients	Follow-up (mo)	T-stage	LVI	VI	CEA	Location	Sideness	Harvested LN	Age	Sex
Teloken et al. [11]	2016	Australia	RO	1,193	38.4	●				●				
Liu et al. [19]	2017	China	RO	870	28.3						●			
Lee et al. [17]	2017	Korea	RO	860	59.8	●	●		●	●	●	●	●	●
Kouyama et al. [20]	2018	Japan	RO	632	57.5		●	●		●			●	●
Lee et al. [18]	2018	Australia	RO	1,104	N/A						●			
Leijssen et al. [21]	2019	United States	RO	519	51.4	●	●	●		●		●	●	●
Fujii et al. [22]	2020	Japan	RO	844	N/A	●		●		●				●
Ozawa et al. [23]	2021	Japan	RO	5,879	70.8	●	●	●		●		●	●	●
Fukui et al. [6]	2022	Japan	RO	7,539	71	●	●	●	●		●		●	●

RO, retrospective observational; LVI, lymphovascular invasion; VI, venous invasion; LN, lymph node.

Table 2. Summary of the results of Newcastle-Ottawa scale quality assessment

Study	Year	Selection				Comparability	Outcome			Total
		Representativeness	Selection of unexposed cohort	Exposure detection	Outcome not present initially		Assessment	Follow-up adequacy	Follow-up length	
Teloken et al. [11]	2016	★	★	★	★	★★	★	☆	☆	7
Liu et al. [19]	2017	★	★	★	★	★☆	★	☆	☆	6
Lee et al. [17]	2017	★	★	★	★	★★	★	★	★	9
Kouyama et al. [20]	2018	☆	★	★	★	★★	★	☆	★	7
Lee et al. [18]	2018	★	★	★	★	★☆	★	☆	☆	6
Leijssen et al. [21]	2019	★	★	★	★	★★	★	☆	☆	7
Fujii et al. [22]	2020	★	★	★	★	★★	★	☆	☆	7
Ozawa et al. [23]	2021	★	★	★	★	★★	★	★	★	9
Fukui et al. [6]	2022	★	★	★	★	★★	★	★	★	9

★ denotes 1 point, and ☆ denotes 0 points. The maximum score is 9. Scores below 6 are considered low quality, scores between 6 and 7 indicate intermediate quality, and scores of 8–9 represent high quality.

heterogeneity, a random-effects model was applied. A subsequent sensitivity analysis revealed that removing a study by Leijssen et al. [21] reduced the I^2 to 0.00% (P = 0.669). Excluding each of the remaining 4 studies resulted in I^2-values ranging from 58.03 to 84.88. Among these relatively homogeneous studies, lymphovascular invasion was identified as a risk factor for recurrence (HR, 1.685; 95% CI,1.420–1.999; P < 0.001) (Fig. 2B, 3B).

Venous invasion

The effect of venous invasion on the recurrence of stage I CRC was described in 5 studies. Venous invasion was associated with the recurrence of stage I CRC (HR, 1.794; 95% CI, 1.515–2.125; P < 0.001). Taking heterogeneity into consideration, a fixed-effects model was used for the analysis (I^2 = 0.0%; P = 0.788) (Fig. 2C, 3C).

CEA

The impact of CEA level on the recurrence of stage I CRC was discussed in 3 studies. CEA level was associated with the recurrence of stage I CRC (HR, 1.472; 95% CI, 1.093–1.983; P = 0.011). As no distinct heterogeneity was found, a fixed-effects model was used for analysis (I^2 = 1.8%; P = 0.166) (Fig. 2D, 3D).

Rectal cancer

Six studies reported differences between colon and rectal cancers. Patients with stage I rectal cancer had a higher risk of recurrence than those with stage I colon cancer (HR, 2.981; 95% CI, 2.378–3.735; P < 0.001). No heterogeneity was seen among the 6 studies included (I^2 = 0.0%; P = 0.442). A fixed-effects model was therefore used for analysis (Fig. 2E, 3E).

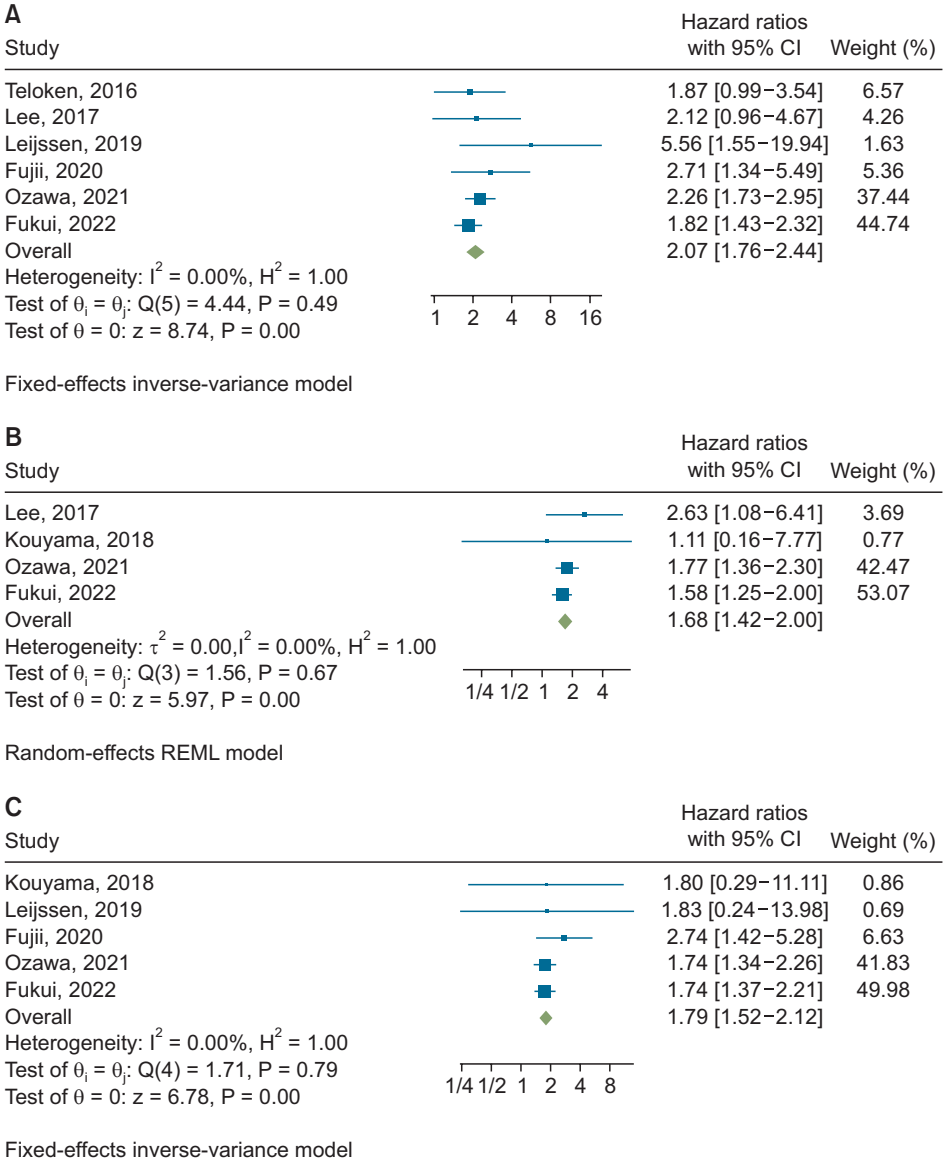

Fig. 2. Forest plots depicting (A) T-stage, (B) lymphovascular invasion, (C) venous invasion, (D) carcinoembryonic antigen, (E) rectal cancer, and (F) right-sided colon cancer. CI, confidence interval.

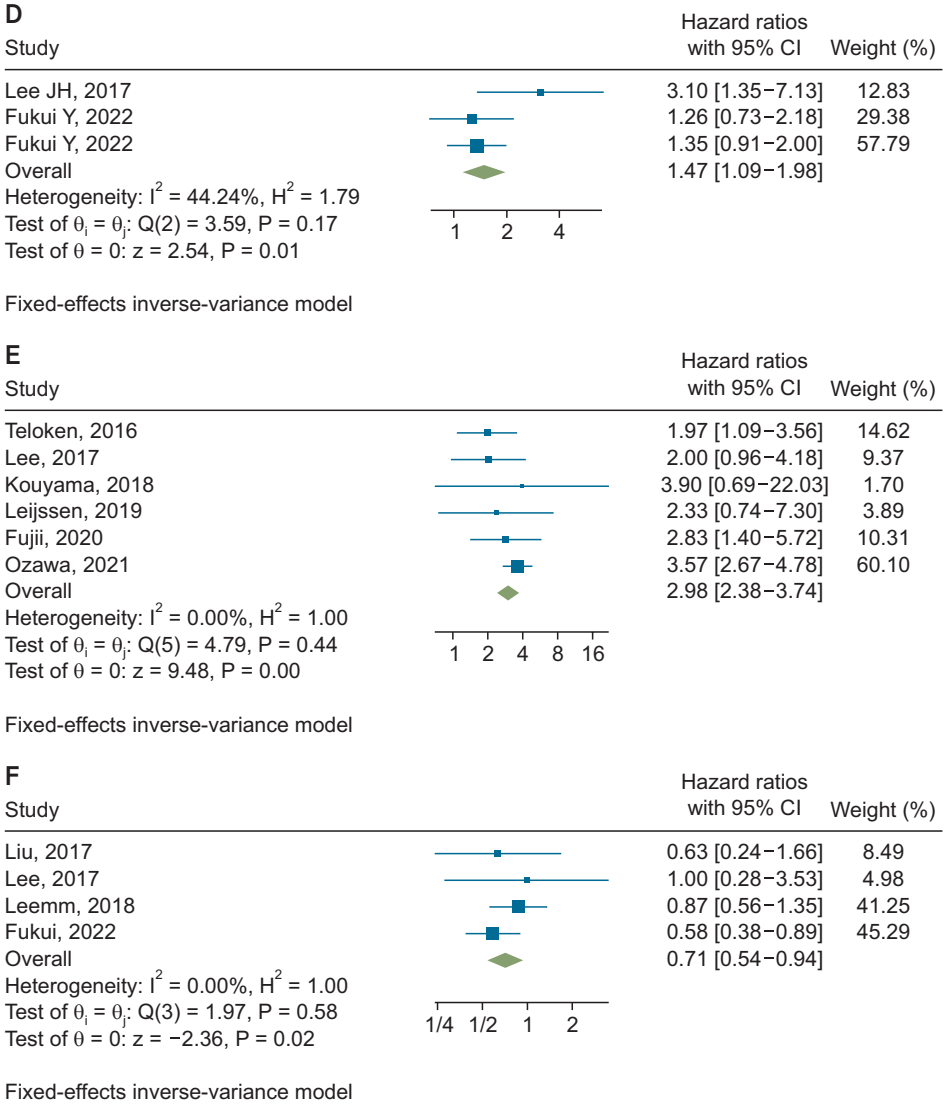

Fig. 2. Continued.

Sidedness

The difference in recurrence between right- and left-sided colon cancers was investigated in 4 studies. Patients with right-sided stage I colon cancer had a lower risk of recurrence than those with left-sided stage I colon cancer (HR, 0.712; 95% CI, 0.537–0.944; P = 0.018). There was no heterogeneity among the 4 included studies (I^2 = 0.0%; P = 0.578), and a fixed-effects model was applied (Fig. 2F, 3F).

Number of harvested lymph nodes/age/sex

No statistically significant differences were observed in the number of harvested lymph nodes (HR, 0.863; 95% CI, 0.678–1.099; P = 0.234), age (HR, 1.028; 95% CI, 0.861–1.228; P = 0.758) and sex (HR, 1.181; 95% CI, 0.982–1.421; P = 0.077).

DISCUSSION

The risk factors for recurrence in stage I CRC after curative resection have not been well established because of its favorable prognosis compared with advanced CRC. However, with the increasing number of patients with stage I CRC, it has become necessary to predict the possibility of recurrence and identify the recurrence risk factors of stage I CRC. The reported risk factors for stage I CRC recurrence vary among the studies. The risk factors that have been widely studied include T2 stage, lymphatic and venous invasion, rectal cancer, elevated serum CEA level, and perineural invasion [17,24,25]. In the current study, T2 stage, lymphatic invasion, venous invasion, CEA level, rectal cancer, and left-sided colon cancer were risk factors for the recurrence of stage I CRC. The results of the current study indicated that the risk factors demonstrated a similar pattern to those observed in the advanced stages of CRC. Among the well-known risk factors for CRC recurrence, differentiation and perineural invasion were not analyzed in the current meta-analysis.

The prognostic value of lymphovascular invasion and venous

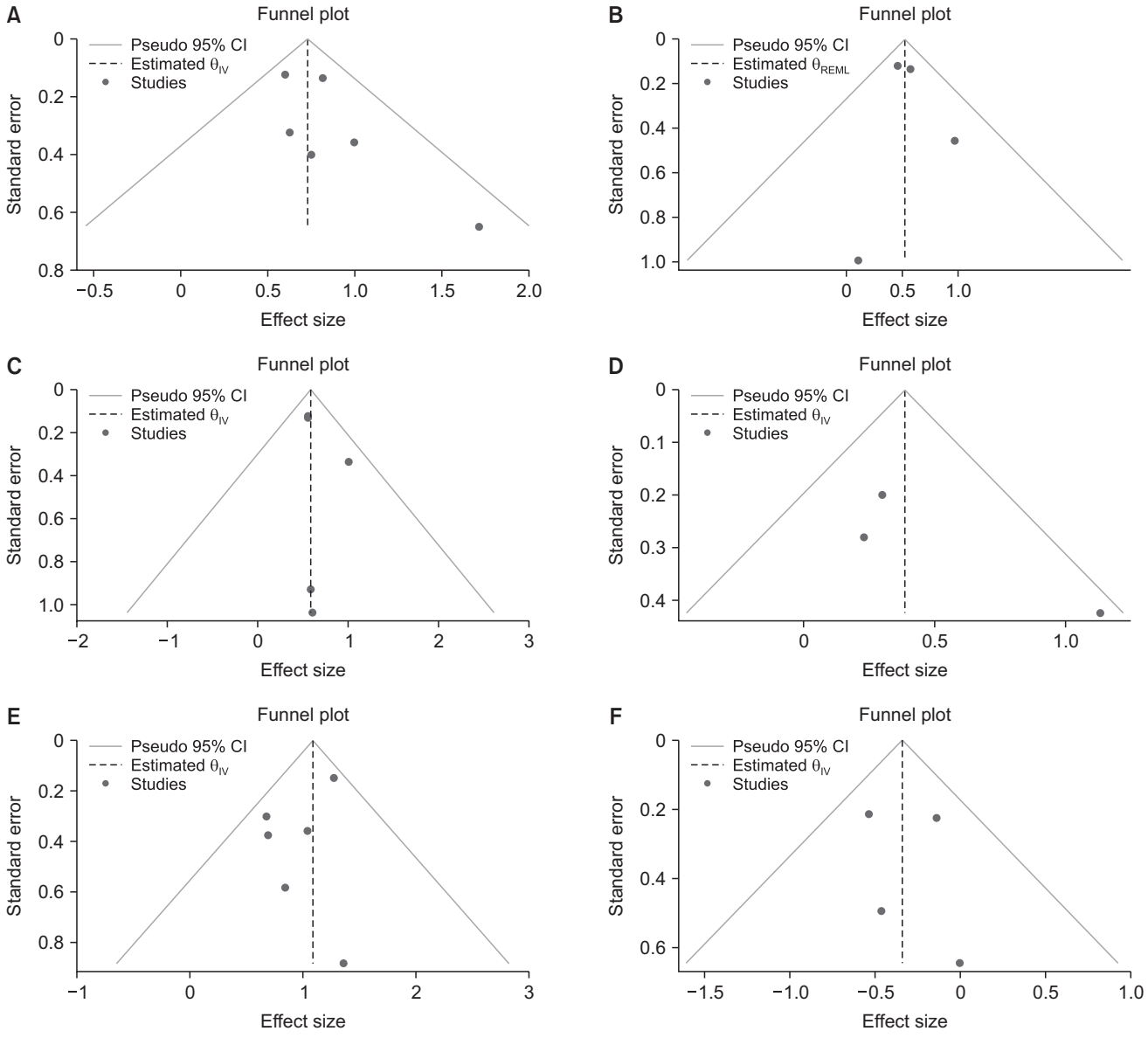

Fig. 3. Funnel plots depicting (A) T-stage, (B) lymphovascular invasion, (C) venous invasion, (D) CEA, (E) rectal cancer, and (F) right-sided colon cancer. CI, confidence interval.

invasion in patients with stage I CRC has not yet been fully established. In the current meta-analysis, lymphovascular invasion and venous invasion were risk factors for stage I CRC recurrence. Lymphovascular invasion and venous invasion are histopathological findings that are considered to be an early step in the systemic dissemination of cancer cells, and they are associated with a poor prognosis in CRC [26-28]. In the recurrence pattern of stage I CRC, local recurrence is rare, and systemic recurrence is the main recurrence pattern [11]. Therefore, lymphovascular invasion and venous invasion are believed to be a significant risk factor for recurrence.

Tumor location is a factor that has a significant influence on CRC recurrence. Rectal cancer has a higher risk of recurrence than colon cancer [29,30]. Consistent with previous studies, the risk of recurrence of stage I rectal cancer was higher than that of stage I colon cancer. The prognosis of rectal cancer is poor due to surgical difficulties caused by anatomical factors such as a narrow pelvis and a complex lymphatic drainage pattern [31]. Moreover, this also appears to apply to stage I CRC. In the current meta-analysis, right-sided stage I colon cancer demonstrated a lower risk of recurrence than left-sided stage I colon cancer. Generally, right-sided colon cancers have a worse prognosis than left-sided colon cancers [18,32]. However, patients with right-sided colon cancer are significantly older and have poorly differentiated and locally advanced tumors [19,33,34]. For this reason, the prognoses of right-sided and left-sided colon cancers were difficult to compare directly. However, the 5-year recurrence-free survival rate of right-sided

colon cancer was significantly higher than that of left-sided colon cancer in a propensity-matched study [35]. In addition, right-sided colon cancer represents a significantly low tumor recurrence rate in early-stage colon cancer [36]. Consistent with previous studies, left-sided colon cancer was a risk factor for stage I CRC recurrence in the current study. Right-sided colon cancer and left-sided colon cancer are considered distinct cancers, and their different characteristics are thought to be attributable to variances in embryologic origin, fecal exposure, and detection time of tumor [37]. Further research is needed to evaluate the differences in sidedness by using clinicopathological and genetic factors in stage I colon cancer.

Perineural invasion is an independent risk factor for CRC recurrence [38,39]. However, only 2 studies have investigated perineural invasion as a risk factor for stage I CRC recurrence. Therefore, we could not perform a meta-analysis of perineural invasion. The rate of positive perineural invasion increases with the CRC stage; however, the positive perineural invasion rate in stage I CRC is very low [40,41]. For this reason, research on perineural invasion in stage I CRC is lacking, and a large-scale study of perineural invasion as a risk factor for stage I CRC recurrence is warranted.

Differentiation is an established risk factor for CRC recurrence [20,42]. However, Differentiation could not be analyzed because of asymmetry. In a meta-analysis, the observed measure of the treatment effect was assumed to follow a normal distribution [43,44]. The original metric for the treatment effect in this study was the HR, and thus it was transformed into the log metric for normalization [45,46]. In the same context, the CI of the log HR should be symmetric. However, variables such as differentiation showed asymmetry beyond the most lenient tolerance to determine CI asymmetry. Consequently, the analysis failed to yield valid results. The number of individual studies and the level of diversity in the studies may have contributed to this failure.

Patients with stage I CRC rarely experience recurrence after radical surgery. Colonoscopy performed 1 year after curative surgery is recommended for these patients according to the National Comprehensive Cancer Network guidelines [47]. However, the intensiveness of surveillance in stage I CRC is similar to that of stage II–III patients in the Japanese Society for Cancer of the Colon and Rectum guidelines [48]. The purpose of surveillance is for the early detection of local recurrence or distant metastasis and treatment of recurrent disease. For high-risk stage I CRC patients, more intensive surveillance is warranted to effectively manage and mitigate the risk of recurrence. In this context, emerging evidence suggests that circulating tumor DNA (ctDNA) analysis could be a valuable tool in monitoring high-risk patients [49,50]. Studies have shown that ctDNA can detect minimal residual disease and predict recurrence with high sensitivity and specificity. Incorporating ctDNA analysis into postoperative surveillance protocols could enhance the early detection of recurrence and facilitate timely interventions, potentially improving survival outcomes for high-risk stage I CRC patients.

The current study has several limitations. First, the number of studies included was relatively small. Additionally, all the included studies were retrospective in nature. Therefore, there is a possibility of publication bias, and different definitions were applied in each study. Next, perineural invasion and differentiation which were the previously known risk factors for CRC recurrence were excluded from the analysis for various reasons. Additionally, patterns of recurrence could not be analyzed due to the lack of reported results in the included studies. Therefore, further high-quality research is necessary to address these limitations and validate our findings. Based on these results, customized surveillance and treatment strategies for patients with these risk factors are suggested.

In conclusion, the T2 stage, lymphovascular invasion, venous invasion, CEA level, rectal cancer, and left-sided colon cancer are risk factors for the recurrence of stage I CRC. Intensive monitoring and surveillance are warranted for patients with high-risk features of recurrence.

SUPPLEMENTARY MATERIALS

Supplementary Material 1 can be found via https://doi.org/10.4174/astr.2025.108.1.39.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Author Contribution

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Formal Analysis: SHS, YJK
Writing – Original Draft: SHH, JHL
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