Tumor-stroma ratio as a clinical prognostic factor in colorectal carcinoma: A meta-analysis of 7,934 patients

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Abstract. The tumor-stroma ratio (TSR) has been regarded as an important factor associated with tumor metastasis, based on the 'seed and soil' theory, which may have guiding significance for the selection of chemotherapy regimens. Therefore, a high TSR may be a new risk factor for tumor recurrence in patients with stage II colorectal cancer (CRC). The present study aimed to evaluate the prognostic value of TSR in CRC, especially for the computer-calculated TSR. A comprehensive literature retrieval was performed using the PubMed, Web of Science, Embase and Cochrane Library databases to identify relevant studies published up to December 13, 2023. Pooled hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated to estimate the prognostic value of the TSR in CRC. A total of 21 studies published between 2007 and 2023 were included in the present meta-analysis. The combined analysis demonstrated that a high TSR was significantly associated with worse overall survival (OS; HR=1.84; 95% CI, 1.44-2.34; P<0.001), disease-free survival (DFS; HR=1.85; 95% CI, 1.27-2.68; P<0.001), cancer-specific survival (CSS; H=1.97; 95% CI, 1.46-2.65; P<0.001) and recurrence free survival (RFS; HR=1.55; 95% CI, 1.25-1.92; P<0.001) in patients with CRC. Moreover, an elevated computer-calculated TSR was also associated with poor OS (HR=1.89; 95% CI, 1.48-2.40; P<0.001) and DFS (HR=1.85; 95% CI, 1.27-2.68; P<0.001). However, a high TSR was not associated with poor OS in patients with stage I CRC (HR=1.01; 95% CI, 0.48-2.14; P=0.97). In conclusion, the results of the present meta-analysis indicate that a high TSR is associated with poor OS, DFS, CSS and RFS in patients with CRC, especially for those with stage II-III. In addition, TSR calculated by computer using whole-slide images may also be an effective prognostic marker for OS and DFS in patients with CRC.

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Introduction

Globally, colorectal carcinoma (CRC) is the third most common type of cancer and also the third highest cause of tumor-associated mortalities, representing a serious health hazard to the population (1). It is estimated that CRC incidence and mortality will increase globally by 2035, which may be related to risk factors including cigarette smoking, physical inactivity, red meat consumption and obesity (2). Although surgical resection is still the most effective treatment for patients diagnosed with CRC, chemotherapy serves an important postoperative role (3). Currently, oxaliplatin-based adjuvant chemotherapy is recommended for stage III and high-risk stage II patients with CRC who are undergoing radical resection, which can markedly prolong overall survival (OS) (4). Currently, T stage 4, poor histological differentiation, vascular infiltration, perineural invasion, preoperative intestinal obstruction, tumor perforation, incisal positive, insufficient distance for cut edge and examining <12 lymph nodes are considered to be high-risk factors for tumor recurrence; however, a high tumor-stroma ratio (TSR) is not (5). The TSR has been regarded as an essential factor associated with for tumor metastasis based on the theory of 'seed (carcinoma cell) and soil (tumor stroma)' (6). Research suggests that during cancer progression, normal stromal compartments transform due to increased cancer-associated fibroblasts, which were generated from normal fibroblasts and epithelial cells in response to platelet-derived growth factor, fibroblast growth factor and transforming growth factor-β. Crosstalk between signaling molecules contributes to the production of a number of cytokines and growth factors, creating an environment conducive to tumor growth and invasion (7,8). Therefore, the TSR may be an improved prognostic predictor for CRC, which can guide the selection of the chemotherapy regimen.

Several studies have suggested a potential prognostic role of the TSR in CRC; however, controversy remains regarding its use (9,10). Although a meta-analysis focusing on the prognostic value of the TSR in patients with CRC was previously performed, it had a small sample size (11). Furthermore, the application of visual assessment ('eyeballing'), systematic point counting and tissue section [whole-slide images (WSI)]

scanning has improved the accuracy of TSR calculations (12). Therefore, computer-aided quantification of tumor-stroma is more credible than manual estimation. However, there is no meta-analysis on the prognostic value of computer-aided quantification of tumor-stroma in CRC, to the best of our knowledge. Therefore, the current study aimed to perform a meta-analysis of all eligible published studies to evaluate the prognostic value of the TSR in CRC, especially for the TSR calculated by computer.

Materials and methods

The present meta-analysis is registered with PROSPERO (www.crd.york.ac.uk/prospero; registration no. CRD42022364340).

Search strategy. The meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (13). A comprehensive search strategy was developed to screen eligible peer-reviewed articles, associated with several specific key words: 'Colorectal cancer', 'tumor stromal ratio' and 'prognosis'. Furthermore, the free text associated with the key words was retrieved from the PubMed MeSH-database, which was used to form search strings with key words (colorectal neoplasms, colorectal tumors, colorectal cancer, colorectal OR carcinomas, tumor stroma, stroma score, tumour-stroma ratio, carcinoma-stromal ratio, tumor-stroma proportion, tumour stroma percentage, proportion of tumour cells, stromal part of adenocarcinomas and high amount of stroma) to allow for a thorough search of the databases [Web of Science (https://www.webofscience.com), PubMed (https://pubmed.ncbi.nlm.nih.gov), Cochrane (https://www.cochranelibrary.com) and Embase (https://www.embase.com)] for all relevant studies. The last search was updated on December 13, 2023. Research lists of articles passing the initial screening process were also used as auxiliary sources to improve the search strategy. The reference lists of the collected studies were manually searched to further increase the robustness of the search results.

Study selection. All relevant articles were screened by two independent authors (AS and PCY) according to the included criteria after blind screening of titles and abstracts. All studies that met the inclusion criteria were included. If a disagreement occurred, a third co-author (JYX) was consulted to carefully scrutinize the papers and decide whether a study was to be included in the final research selection.

Inclusion criteria. The inclusion criteria were as follows: i) Patients diagnosed with CRC who underwent radical resection; ii) assessment of the association of the TSR and survival data; iii) evaluation of survival-associated outcomes, such as OS and disease-free survival (DFS); and iv) studies published in English.

Exclusion criteria. The exclusion criteria were as follows: i) Non-research references, such as case reports, letters or systematic reviews; ii) studies with duplicate data; iii) key information extraction was not available; and iv) research using non-human models.

Data extraction. The data extracted from the tables and figures of the selected articles were tabulated in Microsoft Excel 16.18 software (Microsoft Corporation). In the present meta-analysis, the extracted data elements were as follows: First author/s, publishing year, study design, sample size, cohort characteristics of the study (such as age and sex), tumor position, estimated method of determining the TSR, treatment, histopathological stage, cut-off value, follow-up time and hazard ratio (HR) estimates with 95% confidence interval (CI) for OS, DFS, relapse-free survival (RFS) and disease-specific survival (DSS).

Quality assessment. Quality assessment of the final selection articles was performed using the Newcastle-Ottawa Scale (NOS) by two independent authors (GH and LPL). The NOS contains three parts: Selection (0-4 points); comparability (0-2 points); and outcome assessment (0-3 points). A study was considered to be high-quality if the scores were >6.

Statistical analysis. Stata software version 15.1 for Mac (StataCorp LP) was used to perform the present meta-analysis to generate forest plots by evaluating the HRs and associated 95% CIs of OS, DFS, DSS and RFS from the included articles directly or estimated using the methods by Parmar *et al* (14). To assess the results of meta-analysis it is important to determine the effect size and its impact (15). Therefore, Cochran's Q-test and Higgins' I^2 statistic were used to evaluate the heterogeneity of the pooled results. Significant heterogeneity was considered if $P<0.1$ for the Q-test or $I^2>50\%$ (16). According to the recommendations provided by the Cochrane Handbook for Systematic Reviews of Interventions (https://training.cochrane.org/handbook), the choice between a fixed-effects and a random-effects meta-analysis should never be made on the basis of a statistical test for heterogeneity. Therefore, a random-effects model was adopted in the present meta-analysis regardless of the I^2 values found.

To assess the potential source of heterogeneity among studies, subgroup analysis and meta-regression were applied utilizing variables such as ethnicity, cancer position, carcinoma stage, treatment, TSR calculation method and regression analysis type.

Sensitivity analysis was performed to evaluate the credibility of outcomes in the present meta-analysis. To assess the publication bias of selection literature, visual inspection of the Begg's funnel plot and Egger's test were performed, and $P<0.05$ was considered to indicate statistical significance.

Results

Search results and study characteristics. A total of 4,708 articles were identified from the database searches, with 3,811 studies obtained after removing duplicate records. Subsequently, a further 3,716 studies were eliminated by reviewing the titles and abstract according to the PICOS principle (Population, Intervention, Comparison, Outcomes and Study framework; https://training.cochrane.org/handbook). A total of 74 studies were then excluded after the articles were read [non-research references (n=29); research with duplicate data (n=37); key information extraction unavailable (n=5); and non-human research (n=3)]. Finally, a total of 21 studies

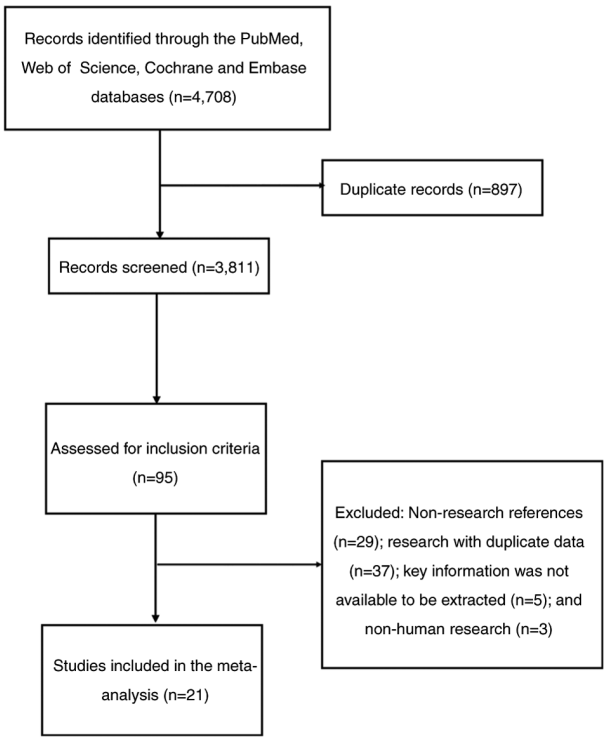

Figure 1. Flow diagram of the study selection process.

published between August 13, 2007 and January 15, 2023 were included in the present meta-analysis (9,10,12,17-34). Notably, the study by Zhao *et al* (33) contained two independent sub-datasets, which were considered two independent studies in the present article. Therefore, there were 22 studies included in the present meta-analysis (Fig. 1). Characteristics of the 22 eligible studies are summarized in Table I. Among the 22 included articles, there was a total of 7,934 patients, with the number of patients in individual studies ranging from 88 to 1,212. A total of nine studies were performed in the Netherlands, seven in China, two in the United Kingdom, and one in Germany, Turkey and Egypt, respectively. Moreover, eight studies included patients with colon carcinoma, 12 studies with patients with CRC and one study with patients with rectal cancer. The prognostic value of the TSR was assessed in the eligible studies: 16 studies evaluated the association between the TSR and OS; eight studies assessed the association of the TSR and DFS; three studies evaluated the association between the TSR and cancer-specific survival (CSS); and four studies assessed the prognostic impact of the TSR on RFS. The cut-off values ranged from 40.0-65.5%. A total of 19 studies were retrospective and two were prospective trials. The NOS scores of all studies ranged from 6-9 (Table I), which indicates that they are of a high quality (NOS scores ≥6).

Prognostic impact of the TSR on OS in patients with CRC. A total of 16 studies provided data from 6,134 patients for the OS analysis (9,10,17,19,20,22-25,28-34). A random-effects model was performed with a significant heterogeneity detected in these data (I^2=77.5%; P<0.001; Table II). It was demonstrated that an elevated TSR predicted a decreased OS with a combined HR of 1.84 (95% CI, 1.44-2.34; P<0.001; Fig. 2A). Subgroup analysis by ethnicity indicated that the TSR was a negative predictor of overall survival both in Asian (HR=2.17; 95% CI, 1.44-3.28; P<0.001) and Caucasian populations (HR=1.58; 95% CI, 1.20-2.10; P=0.001). When the TSR estimation method was considered, both computer-aided calculations (HR=1.88; 95% CI, 1.48-2.40; P<0.001) and artificial estimations (HR=1.82; 95% CI, 1.34-2.48; P<0.001) of the TSR were negative prognostic factors. When performing subgroup analyses stratified by analysis method (multivariate analysis), an increased TSR was revealed to be a negative predictor for OS (HR=1.81; 95% CI, 1.41-2.32; P<0.001). However, there was no statistical significance for the univariate analysis (HR=1.80; 95% CI, 0.65-4.99; P=0.26). Considering different cancer types, the TSR was a negative prognostic marker for colon cancer (HR=1.75; 95% CI, 1.36-1.26; P<0.001) and CRC (HR=1.90; 95% CI, 1.27-2.83; P=0.002). Furthermore, an increased TSR predicted a worse outcome both in patients undergoing surgery only (HR=2.21; 95% CI, 1.24-3.96; P=0.008) and surgery + chemotherapy (HR=1.56; 95% CI, 1.33-1.83; P<0.001). However, although an elevated TSR had a negative prognostic value for patients with stage II-III CRC (HR=1.60; 95% CI, 1.33-1.93; P<0.001), this was not demonstrated for those with stage I (H=1.01; 95% CI, 0.48-2.14; P=0.97).

Prognostic role of the TSR for DFS in CRC. A total of nine studies provided data from 3,962 patients for the DFS analysis (10,12,20,21,24,25,28,29,34). The combined data demonstrated that an increased TSR was associated with worse DFS for patients with CRC (HR=1.83; 95% CI, 1.50-2.22; P<0.001; Fig. 2B). Moreover, heterogeneity existed among the studies (I^2=51.2%; P=0.037). A high TSR was associated with poor DFS irrespective of ethnicity (HR=1.73; 95% CI, 1.08-2.78; P=0.022 vs. HR=1.85, 95% CI, 1.47-2.32; P<0.001), analysis method (HR=3.20, 95% CI, 1.57-6.53; P=0.001 vs. HR=1.64, 95% CI, 1.43-1.87; P<0.001) and cancer type (HR=2.22, 95% CI, 1.42-3.48; P<0.001 vs. HR=1.56, 95% CI, 1.32-183; P<0.001 vs. HR=2.05, 95% CI, 1.11-3.78; P=0.022). Moreover, a high TSR also predicted poor DFS in patients receiving postoperative adjuvant chemotherapy (HR=1.64; 95% CI, 1.44-1.88; P<0.001) and in patients with stage II and III CRC (HR=1.64; 95% CI, 1.42-1.90; P<0.001). Notably, an increased TSR calculated by computer was also associated with worse DFS in patients with CRC (HR=1.85; 95% CI, 1.27-2.68; P<0.001) (Table II).

Prognostic role of TSR for CSS and RFS in patients with CRC. A total of three studies reported the association of CSS and the TSR, with 820 patients included (12,22,27). The combined data indicated that an elevated TSR was associated with worse CSS in patients with CRC (HR=2.00; 95% CI, 1.38-2.89; P<0.001; Fig. 2C). No significant heterogeneity was detected (I^2=33.3%; P=0.22). Moreover, the data from 651 patients extracted from four studies were used to perform the meta-analysis focusing on the prognostic role of the TSR for RFS in patients with CRC (17,18,26,31). A random-effects model was adopted, although no significant heterogeneity among the studies was detected (I^2=15.3%; P=0.315; Table II). Pooled HR from the eligible studies was demonstrated to be 1.57 (95% CI, 1.22-2.02; P<0.001), indicating that a high TSR predicted a poor RFS (Fig. 2D). Subgroup analysis was performed based on ethnicity and cancer type, which revealed that a high TSR

Table I. Major features of the studies included in the present meta-analysis.

First author/s, year	Country	Study design	Sample size	Histology	Sex, % male	TSR estimate method	Treatment	Stage	Cut-off value, %	Follow up, months	Survival analysis	NOS score	(Refs.)
Dang *et al*, 2020	Netherlands	Retrospective	223	CRC	56.1	Artificial	Surgery	I	50	43 (18-84)[c]	OS	9	(9)
Zhao *et al*, 2021	China	Retrospective	179	CRC	60.9	Computer	Surgery + adjuvant chemotherapy	II	50	59[d]	OS/DFS	8	(10)
Geessink *et al*, 2019	Netherlands	Retrospective	129	RC	67	Computer	Surgery + adjuvant chemotherapy + radiotherapy	I-III	65.47	67.2 (27.6-99.6)[a]	CSS/DFS	9	(12)
Aboelnasr *et al*, 2023	Egypt	Retrospective	103	CRC	30.9	Artificial	NA	I-IV	50	NA	OS/RFS	8	(17)
Fan *et al*, 2022	China	Retrospective	207	CRC	60.9	Artificial	Surgery + adjuvant chemotherapy	II	50	NA	RFS	7	(18)
Fu *et al*, 2020	China	Retrospective	353	CRC	42	Artificial	Surgery	I-III	50	24 (16-37)[c]	OS	7	(19)
Huijbers *et al*, 2013	Netherlands	Perspective	710	CC	50	Artificial	Surgery + adjuvant chemotherapy	II-III	50	55.4 (0-84.9)[a]	OS/DFS	9	(20)
Huijbers *et al*, 2018	Netherlands	Retrospective	965	CRC	56.8	Artificial	Surgery + adjuvant chemotherapy	II-III	50	NA	DFS	8	(21)
Hynes *et al*, 2017	United. Kingdom	Retrospective	445	CC	53.3	Artificial	Surgery + adjuvant chemotherapy	II-III	50	66 (1.2-120)[a]	OS/CSS	9	(22)
Li *et al*, 2021	China	Retrospective	996	CRC	58	Artificial	NA	I-IV	50	NA	OS	8	(23)
Li *et al*, 2023	China	Retrospective	198	CC	52.5	Computer	Surgery + adjuvant chemotherapy	III	50	NA	OS/DFS	7	(24)
Mesker *et al*, 2007	Netherlands	Retrospective	122	CC	59	Artificial	Surgery	I-III	50	148[d]	OS/DFS	7	(25)
Miller *et al*, 2021	Germany	Retrospective	253	CC	57	Computer	Surgery + adjuvant chemotherapy	II-IV	40	43.2[d]	RFS	9	(26)

Table I. Continued.

First author/s, year	Country	Study design	Sample size	Histology	Sex, % male	TSR estimate method	Treatment	Stage	Cut-off value, %	Follow up, months	Survival analysis	NOS score	(Refs.)
Park *et al*, 2016	United. Kingdom	Retrospective	246	CRC	52	Artificial	Surgery + adjuvant chemotherapy	I-III	50	150 (87-206)[a]	CSS	9	(27)
Sandberg *et al*, 2019	Netherlands	Retrospective	201	CRC	50.7	Artificial	Surgery + adjuvant chemotherapy	I-IV	50	68 (0-229)[a]	OS/DFS	9	(28)
Smit *et al*, 2021	Netherlands	Retrospective	246	CC	54	Artificial	Surgery + adjuvant chemotherapy	II-III	50	47 (4-158)[a]	OS/DFS	9	(29)
Vogelaar *et al*, 2016	Netherlands	Retrospective	97	CC	NA	Artificial	Surgery + adjuvant chemotherapy	I-III	NA	78 (0-144)[a]	OS	8	(30)
Zengin 2019	Turkey	Retrospective	88	CC	60	Artificial	Surgery	I	50.4	84 (10-205)[a]	OS/RFS	8	(31)
Zhang *et al*, 2021	China	Retrospective	147	CRC	61	Artificial	Surgery + adjuvant chemotherapy	I-IV	50	48 (1-91)[a]	OS	6	(32)
Zhao *et al*, 2020	China	Retrospective	499	CRC	60.3	Computer	Surgery	I-IV	48.80	89 (79-96)[b]	OS	9	(33)
	China	Retrospective	315	CRC	59.7	Computer	Surgery	I-IV	48.80	51 (50-53)[b]	OS	9	
Zunder *et al*, 2018	Netherlands	Perspective	1212	CRC	55.5	Artificial	Surgery + adjuvant chemotherapy	II-III	50	NA	OS/DFS	9	(34)

[a]Median (range); [b]median (95% CI); [c]median (interquartile range); [d]median. CRC, colorectal cancer; NA, not available; NOS, Newcastle-Ottawa Scale; OS, overall survival; DFS, disease-free survival; CSS, cancer-specific survival; RFS, recurrence free survival; TSR, tumor-stroma ratio.

Table II. Subgroup analysis of pooled hazard ratios and 95% confidence intervals for the association between the tumor-stroma ratio and overall survival, disease-free survival, cancer-specific survival and recurrence free survival in patients with colorectal cancer.

A, OS

Variable	Studies, n	Patients, n	Effects model	HR (95% CI)	P-value	Heterogeneity I^2, %	Heterogeneity P-value	(Refs.)
Total OS	17	6,134	Random	1.84 (1.44-2.34)	<0.001	77.5	<0.001	(9,10,17,19,20,22-25,28-34)
Ethnicity								
Asian	9	2,878	Random	2.17 (1.44-3.28)	<0.001	83.1	<0.001	(10,17,19,23,24,31-33)
Caucasian	8	3,256	Random	1.58 (1.20-2.10)	0.001	67.7	0.003	(9,20,22,25,28-30,34)
TSR estimation method								
Computer-aided	4	1,191	Random	1.88 (1.48-2.40)	<0.001	0.0	0.770	(10,24,33)
Artificial estimation	13	4,943	Random	1.82 (1.34-2.48)	<0.001	82.6	<0.001	(9,17,19,20,22,23,25,28-32,34)
Analysis method								
Univariate	3	4,67	Random	1.80 (0.65-4.99)	0.260	75.4	0.007	(24,25,32)
Multivariate	14	5,667	Random	1.81 (1.41-2.32)	<0.001	78.0	<0.001	(9,10,17,19,20,22,23,28-31,33,34)
Treatment								
Surgery + chemotherapy	9	3,435	Random	1.56 (1.33-1.83)	<0.001	0.0	0.792	(10,20,22,24,28-30,32,34)
Surgery only	6	1,600	Random	2.21 (1.24-3.96)	0.008	91.6	<0.001	(9,19,25,31,33)
Cancer type								
Colon	7	1,906	Random	1.75 (1.36-1.26)	<0.001	54.0	0.043	(20,22,24,25,29-31)
Colorectal	10	4,228	Random	1.90 (1.27-2.83)	0.002	84.4	<0.001	(9,10,17,19,23,28,32-34)
Stage								
I	2	311	Random	1.01 (0.48-2.14)	0.970	82.4	0.017	(9,31)
II-III	6	2,990	Random	1.60 (1.33-1.93)	<0.001	0.0	0.830	(10,20,22,24,29,34)
Other	9	2,833	Random	2.37 (1.54-3.64)	<0.001	84.0	<0.001	(17,19,23,25,28,30,32,33)

B, DFS

Variable	Studies, n	Patients, n	Effects model	HR (95% CI)	P-value	Heterogeneity I^2, %	Heterogeneity P-value	(Refs.)
Total DFS	9	3,962	Random	1.83 (1.50-2.22)	<0.001	51.2	0.037	(10,12,20,21,24,25,28,29,34)
Ethnicity								
Asian	2	377	Random	1.73 (1.08-2.78)	0.022	0.0	0.779	(10,24)
Caucasian	7	3,585	Random	1.85 (1.47-2.32)	<0.001	63.2	0.012	(12,20,21,25,28,29,34)

Table II. Continued.

B, DFS

Variable	Studies, n	Patients, n	Effects model	HR (95% CI)	P-value	Heterogeneity I^2, %	Heterogeneity P-value	(Refs.)
TSR estimation method								
Computer-aided	3	506	Random	1.85 (1.27-2.68)	0.001	0.0	0.879	(10,12,24)
Artificial estimation	6	3,456	Random	1.84 (1.43-2.36)	<0.001	68.9	0.007	(20,21,25,28,29,34)
Analysis method								
Univariate	2	320	Random	3.20 (1.576.53)	0.001	50.5	0.155	(24,25)
Multivariate	7	3,642	Random	1.64 (1.43-1.87)	<0.001	0.0	0.933	(10,12,20,21,28,29,34)
Treatment								
Surgery + chemotherapy	8	3,840	Random	1.64 (1.44-1.88)	<0.001	0.0	0.961	(10,12,20,21,24,28,29,34)
Surgery only	1	122	-	4.18 (2.63-6.65)	<0.001	-	-	(25)
Cancer type								
Colon	4	1,276	Random	2.22 (1.42-3.48)	<0.001	72.0	0.013	(20,24,25,29)
Colorectal	4	2,557	Random	1.56 (1.32-183)	<0.001	0.0	0.986	(10,21,28,34)
Rectal	1	129	-	2.05 (1.11-3.78)	0.022	-	-	(12)
Stage								
II-III	6	3,510	Random	1.64 (1.42-1.90)	<0.001	0.0	0.934	(10,20,21,24,29,34)
Other	3	452	Random	2.34 (1.23-4.48)	0.010	82.1	0.004	(12,25,28)

C, CSS

Variable	Studies, n	Patients, n	Effects model	HR (95% CI)	P-value	Heterogeneity I^2, %	Heterogeneity P-value	(Refs.)
Total CSS	3	820	Random	2.00 (1.38-2.89)	<0.001	33.3	0.220	(12,22,27)

Table II. Continued.

D, RFS

Variable	Studies, n	Patients, n	Effects model	HR (95% CI)	P-value	Heterogeneity		(Refs.)
						I^2, %	P-value	
Total RFS	4	651	Random	1.57 (1.22-2.02)	<0.001	15.3	0.315	(17,18,26,31)
Ethnicity								
Asian	3	398	Random	1.70 (1.16-2.48)	<0.001	39.7	0.190	(17,18,31)
Caucasian	1	253	-	1.38 (0.81-2.34)	0.232	-	-	(26)
Cancer type								
Colon	2	341	Random	1.47 (1.16-1.87)	0.001	0.0	0.783	(26,31)
Colorectal	2	310	Random	2.14 (0.92-4.97)	0.077	61.8	0.106	(17,18)

CI, confidence interval; HR, hazard ratio; OS, overall survival; DFS, disease-free survival; CSS, cancer-specific survival; RFS, recurrence-free survival; TSR, tumor-stroma ratio.

was associated with worse RFS for Asian patients (HR=1.59, 95% CI, 1.26-2.01 P<0.001) or patients with colon cancer (HR=1.47, 95% CI, 1.16-1.87 P=0.001) (Table II).

Meta-regression analysis. The results of the meta-regression analysis demonstrated that publication year (P=0.29), follow-up time (P=0.58), analysis method (P=0.63), treatment (P=0.72), cancer type (P=0.87), tumor stage (P=0.17) and ethnicity (P=0.29) did not contribute to the source of heterogeneity (Table SI).

Sensitivity analysis. To assess the reliability of the pooled HR of OS, DFS, CSS and RFS, a sensitivity analysis was performed (Fig. 3). There was no significant change in overall HR when each eligible study from the present meta-analysis was removed sequentially. Thus, the reliability of the results of the present study was confirmed.

Publication bias. Begg's funnel and Egger's test were performed to detect potential publication bias, with no significant bias demonstrated in studies on the TSR with respect to OS (Begg's P=0.266; Egger's P=0.310; Fig. 4A and B), DFS (Begg's P=0.076; Egger's P=0.328; Fig. 4C and D), CSS (Begg's P=1.000; Egger's P=0.574; Fig. 4E and F) or RFS (Begg's P=0.308; Egger's P=0.368; Fig. 4G and H).

Association between the TSR and clinicopathological features. Only 7/21 studies evaluated the relationship between the TSR and clinicopathological features (Table III) (9,17-19,21,23,34). A high TSR was reported to be markedly associated with increased T stage in the studies by Fu *et al* (19) and Huijbers *et al* (21). Furthermore, these two studies reported that patients with CRC with a high TSR had a higher probability of lymphatic metastasis than those with a low TSR (19,21); however, in the study by Aboelnasr *et al* (17), the conclusion was reversed. Unfortunately, it was not possible to generate a pooled odds ratios (OR) value through meta-analysis for these results as they were produced using the χ^2 test.

Discussion

To the best of our knowledge, the present research is the first meta-analysis to assess the prognostic value of the TSR on OS, DFS, CSS and RFS in CRC. As a novel prognostic marker, the TSR can be calculated directly according to a systematic evaluation process using pathological sections by pathologists (35). Furthermore, with the progression of convolutional neural networks (CNNs), the image analysis field has been revolutionized. CNNs have been used to classify medical images and detect TSR in histopathological images (36). Fully automated TSR assessments have also been applied on WSIs generated through scanning the selected hematoxylin and eosin-stained tissue sections using digital Whole Slide Scanning software (33). Therefore, the prognostic value of the tumor-stroma percentage calculated using CNNs in CRC was more objective.

The present meta-analysis collected data from 21 studies with 7,934 patients to assess the prognostic role of the TSR in CRC. Significant prognostic efficacy in different subgroups suggested that the TSR was a robust prognostic marker for

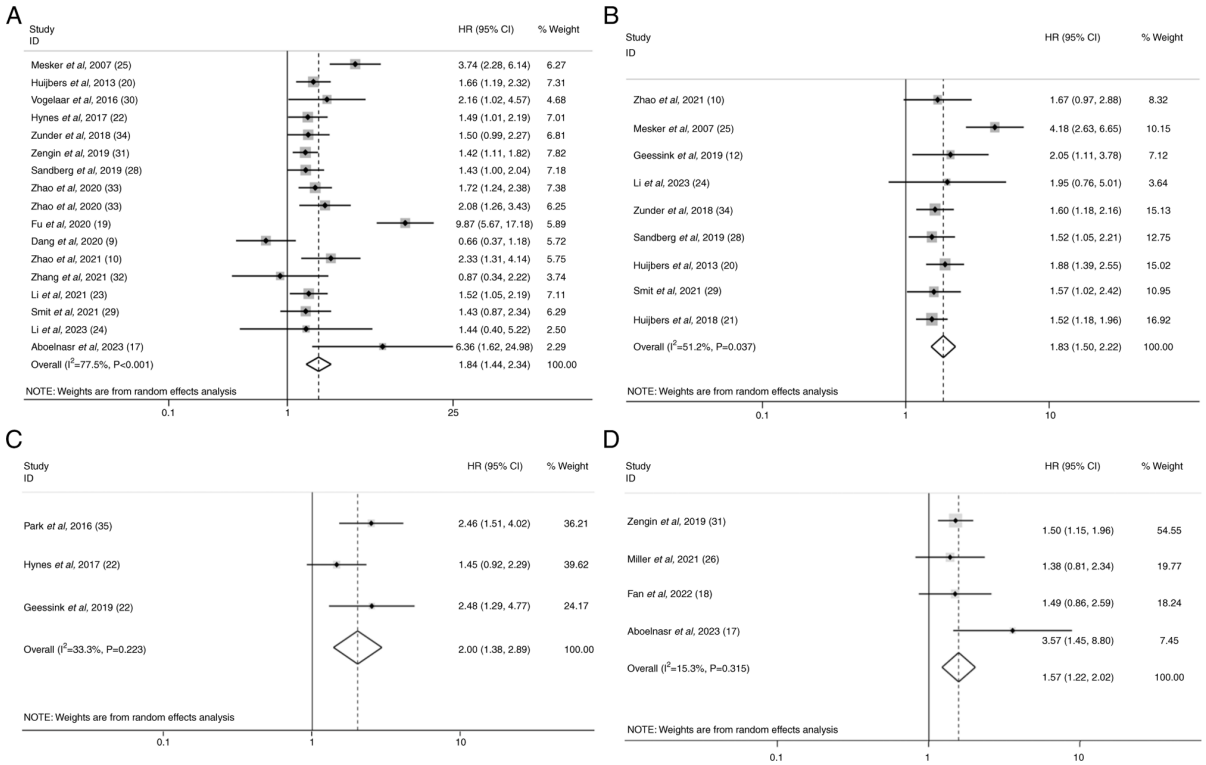

Figure 2. Forest plots of the relationship between the tumor-stroma ratio and survival in patients with colorectal carcinoma. (A) Overall survival. (B) Disease-free survival. (C) Cancer-specific survival. (D) Recurrence free survival. CI, confidence interval; HR, hazard ratio.

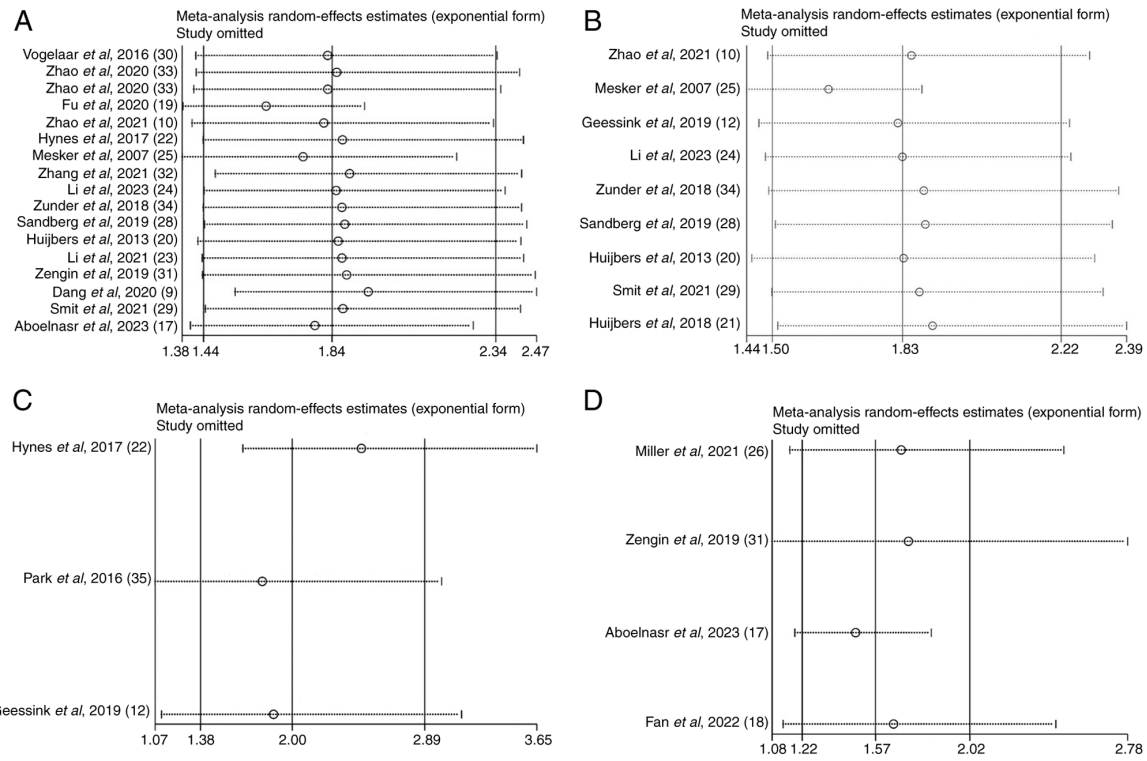

Figure 3. Sensitivity analysis of the effect of the tumor-stroma ratio on survival in patients with colorectal cancer. (A) Overall survival. (B) Disease-free survival. (C) Cancer-specific survival. (D) Recurrence-free survival.

long-term survival outcomes, including OS, DFS, CSS and RFS. Furthermore, computer-calculated TSR using WSIs was also an effective prognostic marker for OS and DFS. However, although an elevated TSR was associated with a negative prognosis in patients with stage II-III CRC (HR=1.60; 95% CI, 1.33-1.93; P<0.001), it was not associated with a negative

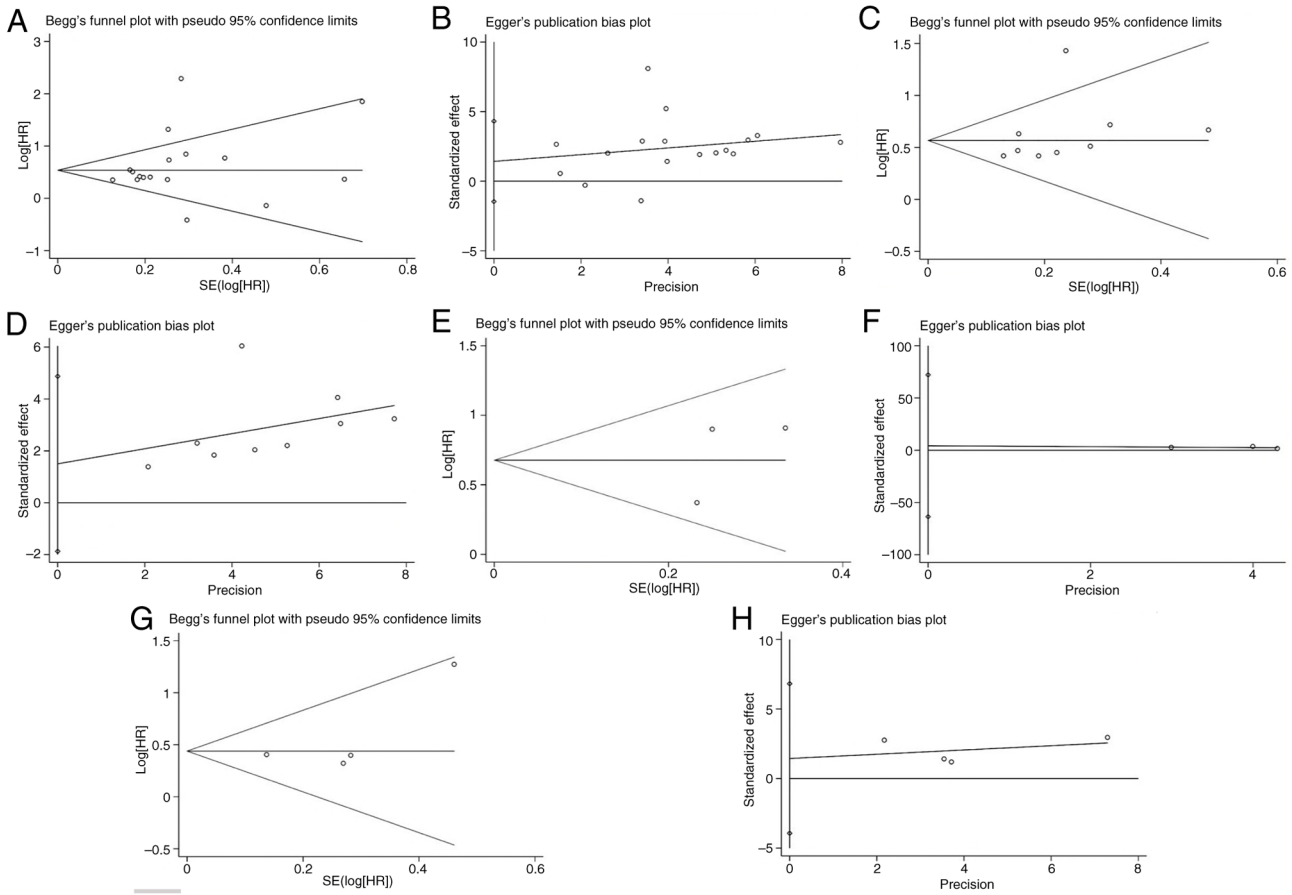

Figure 4. Publication bias tested by Begg's and Egger's tests. (A) Begg's test (P=0.266) and (B) Egger's test (P=0.310) for overall survival. (C) Begg's test (P=0.076) and (D) Egger's test (P=0.328) for disease-free survival. (E) Begg's test (P=1.000) and (F) Egger's test (P=0.574) for cancer-specific survival. (G) Begg's test (P=0.308) and (H) Egger's test (P=0.368) for recurrence-free survival. SE, standard error; HR, hazard ratio.

prognosis in those with stage I CRC (HR=1.01; 95% CI, 0.48-2.14; P=0.97).

The tumor microenvironment has attracted attention in the field of carcinoma immunology. Neoplastic cells are not only found in the tumor itself, but also in the surrounding stroma, including immune cells, signaling molecules, the extracellular matrix (ECM) and fibroblasts (37). Several inflammatory cells and mediators have been reported to have complex interactions with tumor cells (38). Stromal cells drive tumor progression and invasion through modulation of the ECM, secretion of soluble factors and stimulation of cell migration (39). Stromal cells, considered a scaffold for tumor cells, provide survival signals such as C-X-C motif chemokine ligand 12 and insulin growth factor, and lay down extracellular elements including glycoprotein, integrins, collagen and proteoglycans (7). ECM deposition increases tumor-stromal density and tension, which may generate a protective environment for cancer cells, preventing the efficacy of anticancer agents such as biologics and chemotherapy (7,39) Furthermore, several studies evaluating the association between tumor-stroma percentage and clinicopathological features in CRC have been published over previous years, which have reported that a high TSR predicts worse pathological outcomes, such as tumor budding, vessel invasion, lymphatic invasion and microsatellite instability (18,20,23). Therefore, a high tumor-stromal percentage may predict a poor survival outcome. In addition, the process of assessing the TSR is inexpensive, easily performed and reproducible (35), rendering the TSR a promising marker to predict the survival outcome of CRC in clinical practice.

Several studies has reported the relationship between the TSR and clinicopathological features previously (9,17-19,21,23,34). Unfortunately, the OR for the association between a high TSR and tumor invasion, lymphatic metastasis and poor differentiation were not available among the studies. Therefore, a meta-analysis on the association between the TSR and tumor classification or stage classification could not be performed. Moreover, among the included studies, there were none that reported the relationship between the TSR and genetic mutations. Therefore, it is necessary perform further research exploring the association between the TSR and tissue classification, stage classification, treatment selection or genetic mutations.

The prognostic role of the TSR in solid tumors has been reported in several meta-analyses in: i) A meta-analysis of nine studies focusing on the clinical significance of the TSR in head and neck cancers indicates that a high TSR is associated with worse DFS or CSS in patients with head and neck cancers (40); ii) a meta-analysis of 12 studies assessing the prognostic value of the TSR in women with breast cancer reports that a high TSR predicts poor survival in women with breast cancer (41); iii) a meta-analysis of data from 2,031 patients with non-small cell lung cancer indicates that stroma richness may be a predictor of poor survival in patients with

Table III. Associations between clinicopathological characteristics of colorectal cancer and the tumor-stroma ratio.

		Tumor differentiation				T stage			N stage			TNM stage			
First author/s, year	TSR	Well	Moderate	Poor	P-value	T1/T2	T3/T4	P-value	N_0	N_+	P-value	I/II	III/IV	P-value	(Refs.)
Aboelnasr *et al*, 2023	High	NA	NA	NA	NA	19	48	0.187	44	23	0.001	NA	NA	NA	(17)
	Low	NA	NA	NA		6	30		12	24		NA	NA		
Fan *et al*, 2022	High	17	69	28	0.221	NA	NA	NA	NA	NA	NA	NA	NA	NA	(18)
	Low	13	47	33		NA	NA		NA	NA		NA	NA		
Fu *et al*, 2020	High	9	104	20	0.138	21	112	0.017	36	97	<0.001	NA	NA	NA	(19)
	Low	32	155	33		60	160		169	51		NA	NA		
Huijbers *et al*, 2018	High	NA	NA	NA	NA	4	311	0.001	118	205	0.001	118	205	0.870	(21)
	Low	NA	NA	NA		54	564		238	404		238	404		
Li *et al*, 2021	High	37	320[a]		0.122	64	293	0.326	202	155	0.035	202	155	0.024	(23)
	Low	48	591[a]			131	508		405	234		408	231		
Smit *et al*, 2021	High	NA	NA	NA	NA	54	55	0.566	54	55	0.566	54	55	0.298	(29)
	Low	NA	NA	NA		17	120		76	60		77	60		
Zunder *et al*, 2018	High	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	61	278	0.540	(34)
	Low	NA	NA	NA		NA	NA		NA	NA		136	688		

[a]Moderate and poor differentiation. TSR, tumor-stroma ratio; NA, not available; T, tumor; N, node; M, metastasis.

lung squamous cell carcinoma, but a predictor of improved survival in patients with lung adenocarcinoma (42); and iv) a meta-analysis of the prognostic value of the TSR in rectal cancer, with data from 5,408 patients, demonstrated that a high TSR is notably associated with worse survival outcomes (43).

The present meta-analysis evaluated the prognostic value of the TSR in CRC; however, necessary subgroup analysis was not performed; and a meta-analysis of 13 studies focusing on the impact of the TSR on the prognosis of CRC indicated that a high TSR was associated with worse DFS or OS in patients with CRC (44). Although subgroup analysis was performed for tumor stage in the meta-analysis, it was not performed for the TSR estimation method, analysis method, ethnicity or cancer type. Furthermore, the prognostic value of the TSR for CSS and RFS was not available in the meta-analysis by Gao *et al* (44), therefore, the conclusions are incomplete. The present meta-analysis demonstrated the prognostic efficacy of the TSR for OS, DFS, RFS and CSS in CRC, which is in-line with previous findings with other cancer types. In addition, the present study also revealed that the TSR calculated by computer using WSIs was also an effective prognostic marker for OS and DFS. Furthermore, the present meta-analysis demonstrated that an elevated TSR holds a negative prognostic value for patients with stage II-III CRC, but not for those with stage I CRC. Lastly, the references included in the present meta-analysis was quite abundant, including 22 studies with 7,934 patients.

Based on the results of the present meta-analysis and other published studies, the TSR may assist in the determination of cancer prognosis and help develop treatment regimens for patients with CRC. For example, patients with CRC with a high TSR may benefit more from postoperative chemotherapy of bevacizumab-capecitabine + oxaliplatin (XELOX) than XELOX alone. However, administering postoperative chemotherapy of bevacizumab-XELOX may lead to a worse OS in patients with CRC with a low TSR (34). Moreover, although patients with CRC with a high TSR may benefit from bevacizumab-dependent adjuvant chemotherapy, whether the patient benefits from other chemotherapy regimens is still unclear (45). Furthermore, although the present meta-analysis demonstrated that an increased TSR predicted a worse outcome both in patients undergoing surgery alone and surgery + chemotherapy, whether patients with CRC with a high TSR benefit from chemotherapy was still unclear. Additionally, a meta-analysis focusing on the association between the TSR and treatment selection could be not performed due to a lack of adequate data. Therefore, further investigations focusing on the treatment of patients with CRC with a high TSR are needed to explore more efficient postoperative chemotherapy regimens.

Although the present research is the first meta-analysis to assess the prognostic value of the TSR on OS, DFS, CSS and RFS in CRC, to the best of our knowledge, there are also several limitations. First, most of the eligible studies adopted a retrospective design, which led to heterogeneity among studies as the selection criteria could not be strictly controlled. Second, several HRs were extracted from univariate analyses performed without consideration of confounding factors, which may have caused an overestimation of effect sizes. Third, the definition of the TSR cut-off values in the selected studies was inconsistent, which could cause bias in the results.

In conclusion, the findings of the present meta-analysis indicated that a higher TSR was associated with poor OS, DFS, CSS and RFS in patients with CRC, especially for those with stages II-IIIs. In addition, a TSR calculated by computer using WSIs was also an effective prognostic marker for OS and DFS in patients with CRC. Therefore, the TSR may serve an important role in developing treatment regimens for CRC; however, further prospective studies are needed to validate the results of the present study due to its limitations.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

AS, PCY, LPL, GH and JYX collected and extracted the data and performed the quality assessment. AS, PCY, LPL and GH analyzed the data. AS and JYX conceived and designed the present study and wrote the paper. All authors read and approved the final manuscript. AS and JYX confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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