


Concurrent Comparison of the Prognostic Values of Tumor Budding, Tumor Stroma Ratio, Tumor Infiltrating Pattern and Lymphocyte-to-Monocyte Ratio in Colorectal Cancer Patients

Technology in Cancer Research & Treatment
 Volume 20: 1-11
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 DOI: 10.1177/15330338211045826
journals.sagepub.com/home/tct


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Abstract

Objectives: Tumor budding (TB), tumor stroma ratio (TSR), tumor infiltrating pattern (TIP), and preoperative lymphocyte-to-monocyte ratio (LMR) were previously reported to be useful prognostic factors in colorectal cancer (CRC); however, the correlation among these markers and their individual prognostic potency have not been extensively studied. **Methods:** A cohort of 147 stage I-IV CRC patients was obtained retrospectively, and the patients were divided into subgroups based on low or high TB/TSR/LMR, TIPa (expansile + intermediate) and TIPb (infiltrative) values. The differences in relapse-free survival (RFS) and overall survival (OS) intervals among these subgroups were determined by Kaplan–Meier analysis followed by log-rank tests. The Cox proportional hazard model was applied for the univariate and multivariate analysis of RFS and OS rates. **Results:** TB, TIP, and LMR, but not TSR, are useful markers for predicting patient survival. Patients with a poor histological grade and large tumor diameter were more likely to present with high TB, TIPb, and low LMR values; in addition, those with advanced T, N, and TNM stages and elevated preoperative CA199 levels had high TB and TIPb levels. TB, TIP, and LMR were significant prognostic factors for the RFS (TB: HR [hazard ratio] = 2.28, 95% CI = 1.30-4.00, $P < .01$; TIP: HR = 2.60, 95% CI = 1.46-4.60, $P < .01$; LMR: HR = 0.79, 95% CI = 0.65-0.96, $P = .02$) and OS (TB: HR = 2.43, 95% CI = 1.32-4.48, $P < .01$; TIP: HR = 2.49, 95% CI = 1.34-4.63, $P < .01$; LMR: HR = 0.79, 95% CI = 0.64-0.98, $P = .03$) intervals. In addition, TB and LMR were independent prognostic factors for the RFS interval (TB: HR = 1.80, 95% CI = 1.01-3.19, $P = .05$; LMR: HR = 0.80, 95% CI = 0.67-0.96, $P = .01$), but only LMR was an independent factor for OS rates (HR = 0.80, 95% CI = 0.65-0.98, $P = .03$). **Conclusion:** Although TB, TIP, and LMR are useful prognostic markers for CRC, the LMR is likely to be the only independent prognostic factor for both RFS and OS outcomes in practice.

Keywords

colorectal cancer, tumor budding, tumor stroma ratio, tumor infiltrating pattern, lymphocyte-to-monocyte ratio

Introduction

Colorectal cancer (CRC) is still a deadly disease in many countries, including China,^{1,2} and there is a decreasing trend in the age of patients who die from CRC.³ To date, the majority of metastatic cases of CRC, except for a small cluster featuring high microsatellite instability (MSI) that respond well to immunotherapy,⁴ are poorly controlled and patients have poor survival rates. The search for biomarkers that guide not only patient selection for certain therapeutic regimens but can also be used for prognostic prediction is increasingly important.

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Previously, a group of biomarkers collected from hematoxylin and eosin (HE) staining slides, including tumor budding (TB), tumor stroma ratio (TSR, also referred to as tumor stroma proportion), and tumor infiltrating pattern (TIP, also referred to as tumor growth pattern), were reported to be useful prognostic indicators in many malignant diseases, including gastric cancer,⁵⁻⁷ breast cancer,^{8,9} lung cancer,¹⁰ and CRC.¹¹⁻¹⁴ TB is defined as “a single tumor cell or a cell cluster consisting of 4 tumor cells or less”¹⁵ and has been reported to be closely correlated with disease recurrence and poor patient prognosis in CRC.^{12,16-18} In addition, TSR has also been found to be a predictor of local tumor growth and invasion,^{13,19} and TIP has been found to be associated with disease recurrence in CRC.^{14,20} It is notable that TB, TSR, and TIP are morphological parameters that were collected from HE slides. It is plausible that these parameters are innately connected, and that their individual prognostic potency is not identical; however, few related studies have been conducted.

It is well recognized that systematic inflammatory markers, including the neutrophil-to-lymphocyte ratio (NLR) and lymphocyte-to-monocyte ratio (LMR), are simple and reliable prognostic indicators in many malignant diseases, such as head and neck cancer,²¹ gastric cancer,²² pancreatic cancer,²³ breast cancer,²⁴ and CRC.²⁵⁻²⁸ In particular, the LMR has been proven to be superior for predicting prognosis than other markers, including the NLR, in CRC.²⁹ Notably, several studies have suggested that TB, TSR, and TIP are associated with cancer-related inflammation;³⁰ nonetheless, the underlying correlations among TB, TSR, TIP, and LMR have never been reported.

In this study, we aimed to explore the correlation among these markers and determine their individual prognostic potency in CRC.

Methods

Patient Enrollments

From January 2011 to October 2016, patients who underwent colectomy either laparotomy or laparoscopic surgery were enrolled at the Hainan Hospital of Chinese PLA General Hospital. Patients who met the following criteria were included: 1. age \geq 18 years old; 2. no neoadjuvant therapies; and 3. radical excision of the primary tumor. The exclusion criteria were as follows: 1. age $<$ 18 years old; 2. complications requiring glucocorticoids or other immunosuppressors; 3. any neoadjuvant therapies; 4. absence of laboratory tests within a week before surgery or key information loss in postoperative pathological reports; 5. multiple or recurrent malignancies, *in situ* lesions; and 6. lost to follow-up or follow-up period was less than 36 m. Clinicopathological parameters were collected as previously described.³¹ The study was approved by the ethics committee of the Hainan Hospital of the PLA General Hospital (approved ID: 301HLFYLS15), and written informed consent was obtained from the patients or his/her authorized relatives.

Determination of TB, TSR, and TIP and Definition of Subgroups

Surgical tissue samples were immediately processed by standard pathological procedures in the Department of Pathology as previously described,³² and 5- μ m HE-stained sections were analyzed by conventional microscopy (DM3000, Leica). In brief, the slides were first observed under a 20 \times objective lens to determine the most invasive front (areas with mucinosity, necrosis or breakage were excluded). TB was defined as “an isolated

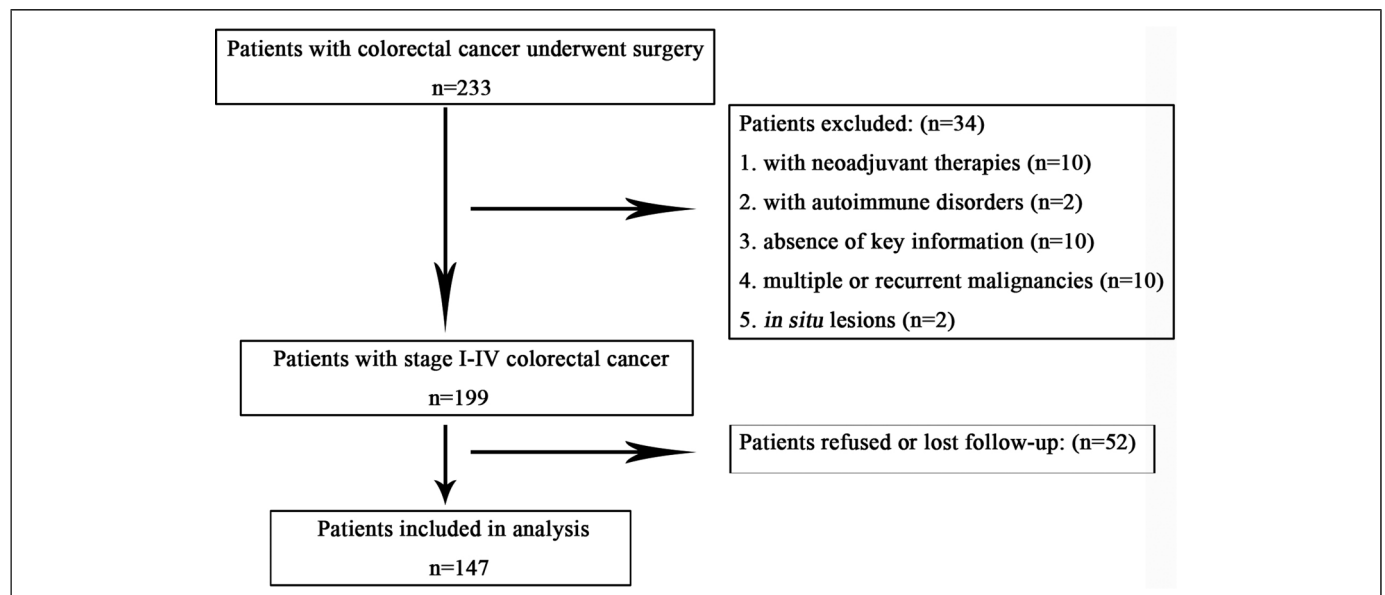


Figure 1. Flow diagram of the study.

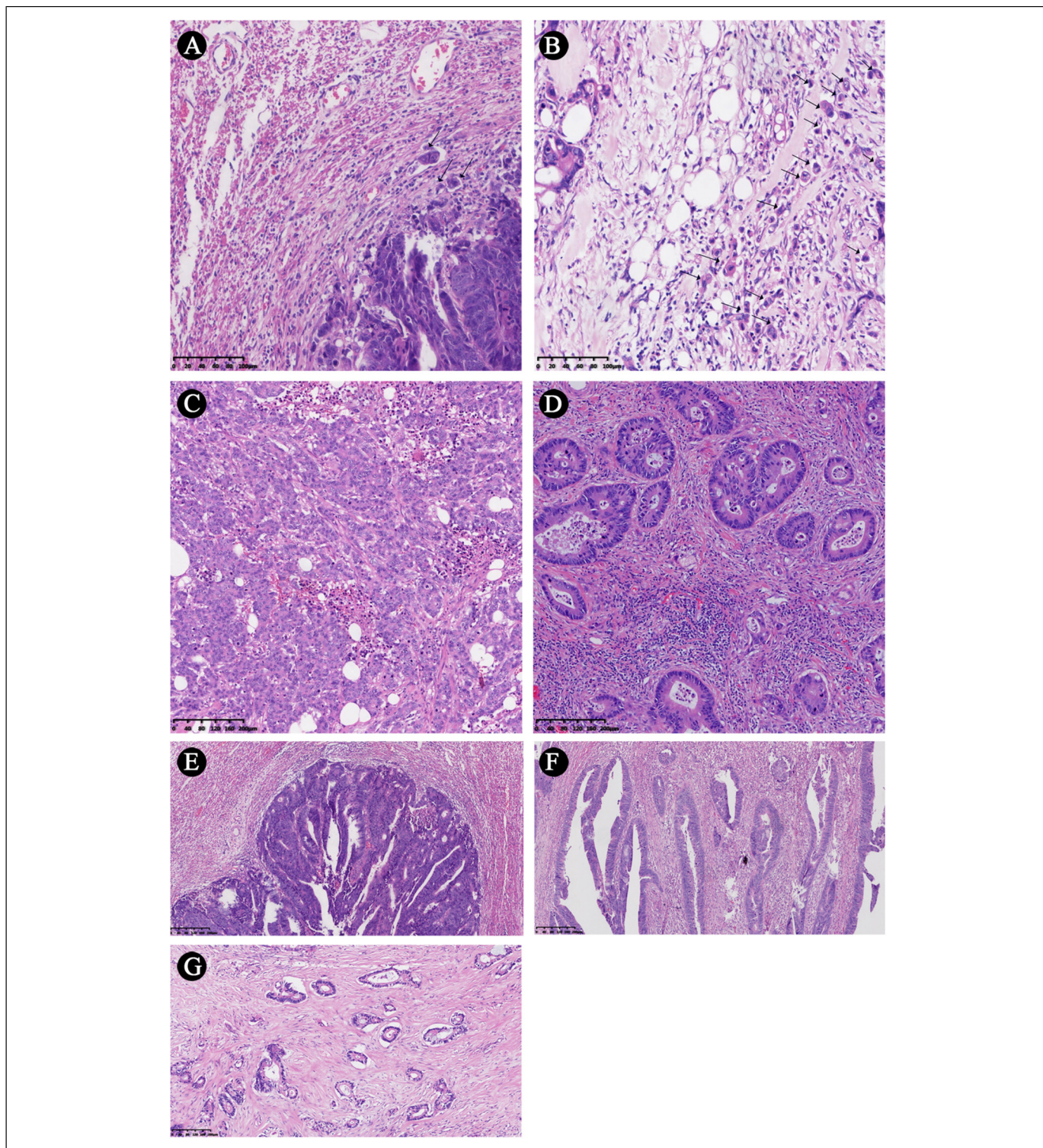


Figure 2. H&E staining to evaluate TB, TSR, TIP: (A) low TB; (B) high TB (black arrows indicate typical buddings); (C) low TSR; (D) high TSR; (A-D with magnification $\times 200$); (E) TIP expansile growth pattern; (F) TIP intermediate growth pattern; (G) TIP infiltrating growth pattern (E-G with magnification $\times 100$).

Abbreviations: TB, tumor budding; TSR, tumor stroma ratio; TIP, tumor infiltrating pattern.

cancer cell or a cluster composed of fewer than 5 cancer cells³³ and was determined according to the recommendations for reporting TB in CRC in the ITBCC 2016.¹⁵ At least 10 individual

fields were identified as the “hotspot,” and the final results were divided into low (<5 buds and 5-9 buds) and high (≥ 10 buds) subgroups as previously reported.³⁴ For TSR, after selecting

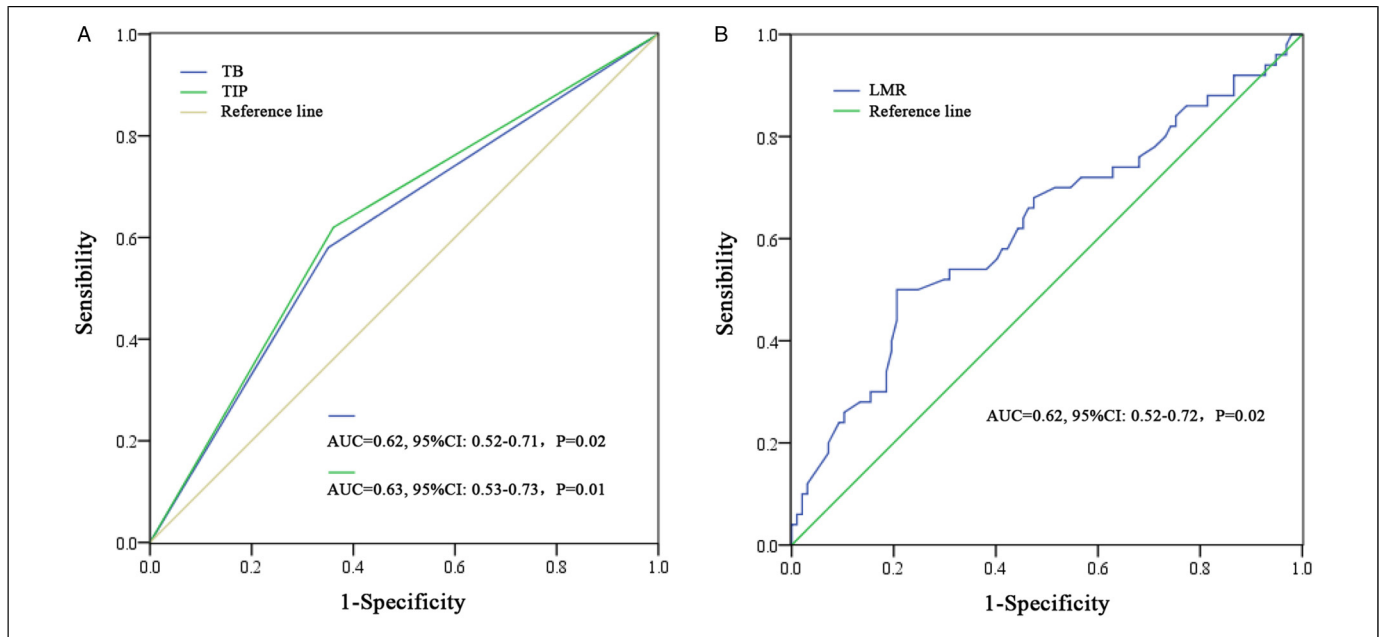


Figure 3. Receiver operating characteristic curve analysis of TB, TIP (A) and LMR (B) in patients. Abbreviations: TB, tumor budding; TIP, tumor infiltrating pattern; LMR, lymphocyte-to-monocyte ratio.

target areas in the same manner as for TB, areas were chosen where both tumor (present at all borders of the image field) and stromal tissue were visible under a $10\times$ objective and patients were classified into TSR low ($\leq 50\%$) or high ($>50\%$) subgroups.^{19,35} For TIP, the definitions of expansile (the invasive margin was pushing or well circumscribed), intermediate (large-to medium-sized glands presented and the border was not clear) and infiltrative (cancer cells invaded in a diffuse pattern with extensive penetration of normal tissue, often with no legible margin) were determined in selected target areas, determined in the same manner as performed for TB,^{7,36} and patients were divided into TIPa (expansile + intermediate) and TIPb (infiltrative) subgroups as in previous studies.^{7,36} All the parameters were read by 2 independent senior pathologists who were blinded to the clinical information of the cohort.

Calculating for LMR

Routine laboratory tests were performed between 6:00 and 9:00 am by peripheral venous blood collection within 1 week before surgery. The LMR was calculated as previously reported.³⁷

Definition of Relapse-Free Survival (RFS) and Overall Survival (OS) Intervals

Follow-up was performed by telephone, WeChat or visit as per the hospital medical records at intervals of 3 to 6 months for the first 3 years and 6 to 12 months for the subsequent 3 years. The RFS interval was defined as the time between the date of surgery and the date of the first recurrence at any location, disease progression identified by imaging or death from any cause. The OS interval

was defined from the date of surgery until the date of death from any cause. The latest follow-up date was in June 2020.

Statistical Analysis

All statistical analyses were conducted by using SPSS 20.0 (SPSS Inc.). A receiver operating characteristic (ROC) curve analysis was used to determine the optimal discriminator value for LMR. The areas under the curve (AUCs) were compared by MedCalc v19.0.7 (MedCalc Software Ltd). The differences in clinicopathological parameters among low or high TB/TSR/LMR and TIPa or TIPb subgroups were calculated by χ^2 -test or Fisher's exact test or Student's *t* where appropriate. The associations among these markers were determined by Spearman's correlation analysis, Kaplan–Meier (K-M) survival curves were applied to compare patients in different subgroups, and significance was determined by log-rank tests. Univariate and multivariate analyses were conducted by using the Cox proportional hazards model. A two-sided $P < .05$ was considered statistically significant.

Results

Demographic Characteristics and the Differences in Clinicopathological Parameters Among TB, TIP, and LMR Subgroups

In total, 147 colorectal adenocarcinoma patients staged I to IV (according to the seventh edition of the AJCC) were enrolled (Figure 1). There were 57 female and 90 male patients, and the mean age of the patients was 59.87 years (range: 24–85 years) with a medium follow-up time of 48.81 m (range: 1.00–91.00 m). In the ROC analysis, both TB and TIP, but not

Table 1. Differences of TB, TIP, and LMR Among Different Clinicopathological Parameters.

	No.	TB			TIP			LMR		
		Low	High	<i>P</i>	a	b	<i>P</i>	Low	High	<i>P</i>
Age (y)				.81			.98			.48
<60	67	39	28		37	30		19	48	
≥60	80	45	35		44	36		27	53	
Gender				.38			.84			.08
Female	57	30	27		32	25		13	44	
Male	90	54	36		49	41		33	57	
Tumor location				.43			.10			.98
Right	35	18	17		15	20		11	24	
Left	112	66	46		66	46		35	77	
Histological grade				.02			.01			<.01
Well + moderate	118	73	45		71	47		31	87	
Poor	29	11	18		10	19		15	14	
CEA level				.09			.05			.06
Normal	93	58	35		57	36		24	69	
Elevated	54	26	28		24	30		22	32	
CA19-9 level				<.01			<.01			.06
Normal	119	77	42		74	45		33	86	
Elevated	28	7	21		7	21		13	15	
TSR				.37			.48			.20
Low	130	76	54		73	57		43	87	
High	17	8	9		8	9		3	14	
Invasive depth				<.01			<.01			.05
T ₁₊₂	34	28	6		29	5		6	28	
T ₃₊₄	113	56	57		52	61		40	73	
Maximum tumor diameter (cm)	147	4.04 ± 1.58	4.71 ± 2.16	.04	3.95 ± 1.39	4.79 ± 2.27	.01	5.12 ± 2.22	3.96 ± 1.58	<.01
Node involvement				<.01			<.01			.49
N ₀	86	60	26		61	25		25	61	
N ₁₊₂	61	24	37		20	41		21	40	
M stage				.26			.10			.09
0	137	80	57		78	59		40	97	
1	10	4	6		3	7		6	4	
TNM stage				<.01			<.01			.64
I + II	84	58	26		57	27		25	59	
III + IV	63	26	37		24	39		21	42	
Adjuvant therapies				<.01			<.01			.83
Received	78	34	44		32	46		25	53	
None	69	50	19		49	20		21	48	
BMI (kg/m ²)	147	23.50 ± 3.82	22.88 ± 3.28	.31	23.55 ± 3.68	22.86 ± 3.49	.25	23.04 ± 3.98	23.32 ± 3.43	.66

Abbreviations: TB, tumor budding; TSR, tumor stroma ratio; TIP, tumor infiltrating pattern; LMR, lymphocyte-to-monocyte ratio; BMI, body mass index; No., number of the patients.

TSR (Figure 2), were useful for predicting survival (Figure 3A), and the LMR had a sensitivity of 50.00% and specificity of 79.40% at the cutoff point of 3.15 (Figure 3B). However, subsequent comparison of the AUCs for TB, TIP, and LMR displayed no significant differences ($P > .05$). Patients with a poor histological grade and large tumor diameter were more likely to present with high TB and TIPb and low LMR; in addition, those with advanced T, N, and TNM stages as well as elevated CA199 displayed high TB and TIPb (Table 1).

Correlation among TB, TSR, TIP, and LMR

Spearman correlation analyses of TB, TSR, TIP, and LMR indicated no significant correlations among TB, TSR, and LMR,

and only TB and TIP showed statistically significant correlations ($r = .63, P < .01$). Patients with low TB (82.14%) were more commonly found to have TIPa; whereas those with high TB (80.95%) more commonly had TIPb, as revealed by further analysis.

Predictive Value of TB, TIP, and LMR for Survival Outcomes

In the K-M analyses, patients with high TB or TIPb had significantly worse RFS (TB low vs high: 49.92 ± 20.30 m vs 38.19 ± 24.98 m, $P < .01$; TIP a vs b: 50.83 ± 18.88 m vs 37.61 ± 25.71 m, $P < .01$) and OS (TB low vs high: 52.90 ± 18.54 m vs 43.33 ± 22.05 m, $P < .01$; TIP a vs b: 52.80 ± 16.63 m vs

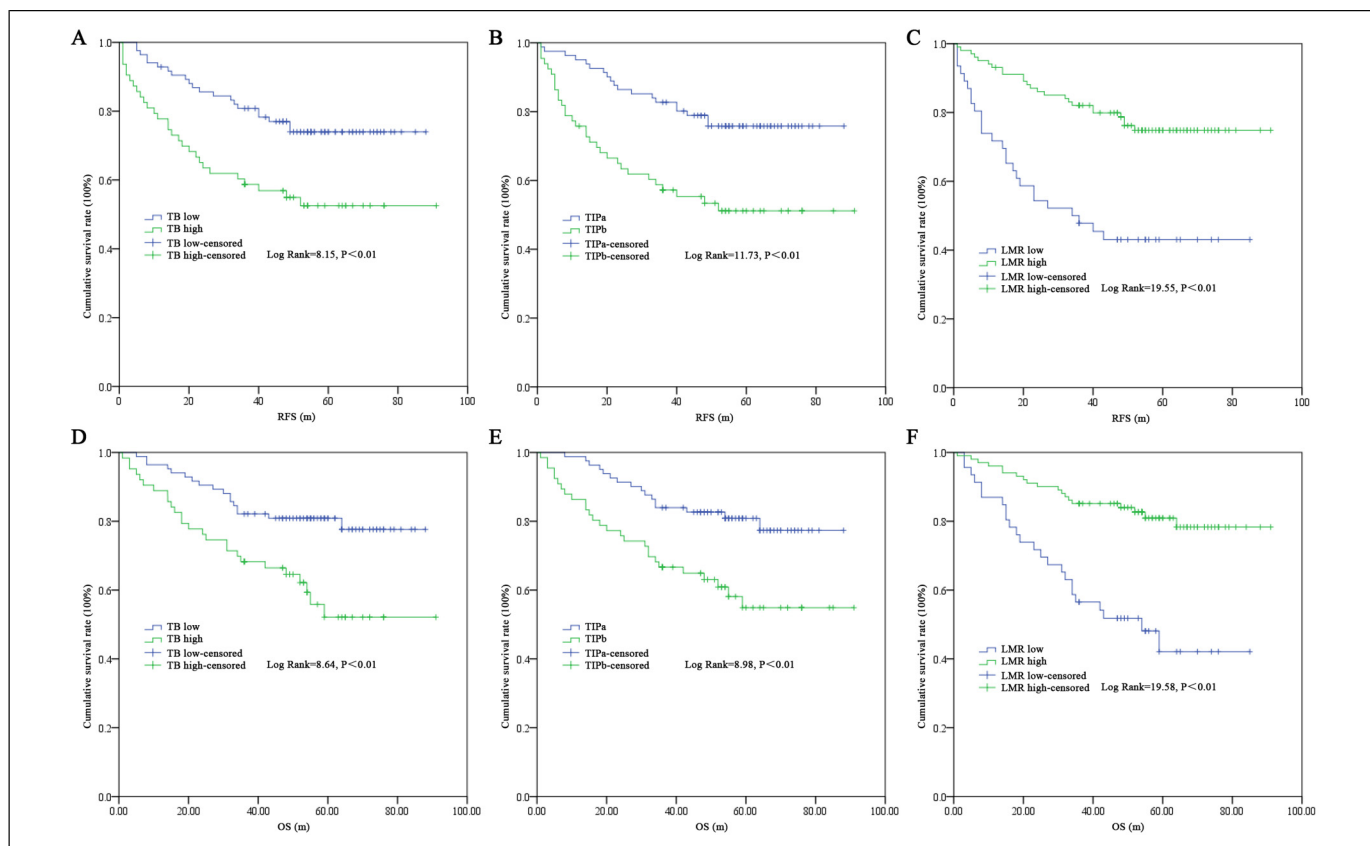


Figure 4. Impact of low or high TB; TIPa or TIPb; and LMR on RFS and OS outcomes in patients.

Abbreviations: TB, tumor budding; TIP, tumor infiltrating pattern; LMR, lymphocyte-to-monocyte ratio; RFS, relapse-free survival; OS, overall survival.

43.89 ± 23.84 m, $P < .01$) outcomes than those of patients with low TB or TIPa; in contrast, patients with high LMR had significantly poorer RFS (low vs high: 33.11 ± 24.45 m vs 50.26 ± 20.40 m, $P < .01$) and OS (low vs high: 39.17 ± 21.65 m vs 19.11 ± 24.45 m, $P < .01$) outcomes (Figure 4).

Univariate and Multivariate Analyses of the Prognostic Factors for RFS and OS Outcomes

Univariate tests revealed that TB, TIP, and LMR were significant prognostic factors for RFS (Table 2) and OS outcomes (Table 3); multivariate tests revealed that TB and LMR were independent prognostic factors for RFS outcomes (Table 2), but only LMR was an independent factor for the OS outcome (Table 3).

Discussion

In the present study, we found that TB, TIP, and LMR, but not TSR, were useful markers for predicting the survival outcomes of CRC patients. Patients with a poor histological grade and large tumor diameter are likely to present with high TB and TIPb and low LMR. In addition, although both TB and LMR were independent prognostic factors for RFS outcomes, the

LMR was the only independent factor for OS outcomes among these markers.

Previously, TB, TSR, and TIP were reported to be important prognostic factors in CRC. Oh et al¹⁸ conducted a study including 4196 staged I to III patients and found that high TB was associated with several adverse clinicopathological parameters, such as advanced stages and poor histological grade, as well as inferior disease-free survival (DFS) and OS outcomes. Similarly, Nagata et al¹² conducted a study of 371 stage IV patients and found that those with a high TB had poor OS outcomes. In addition, TIP has also been reported to a robust indicator of local or distant recurrence^{14,20} and of OS outcomes (confined to stage I-III patients) in CRC patients.³⁶ Our results regarding TB and TIP were in line with those of these reports.^{12,18,36} In addition, the TSR has been found to be an important prognostic marker in CRC, but with conflicting results; for example, Mesker et al.'s³⁵ study revealed that DFS and OS outcomes in patients with a high TSR were remarkably superior, but other reports yielded opposite conclusions.^{13,19,38} Nonetheless, the TSR failed to predict survival outcomes in our study, even though we excluded stage IV patients according to the recommendations in previous reports.^{13,19,35,38} We speculate that these findings may be attributable to the relatively low proportion of high TSR levels in our study cohort (11.56%) compared to that reported by others (70.8%,¹³ 73.00%,³⁵ and 70.51%³⁹).

Table 2. Univariate and Multivariate Analyses of Different Parameters for RFS.

	Univariate			Multivariate		
	<i>P</i>	HR	95%CI	<i>P</i>	HR	95%CI
Age (y)						
<60	1					
≥60	.15	1.53	0.86-2.73			
Gender						
Female	1					
Male	.64	1.15	0.65-2.05			
Tumor location						
Right						
Left	.30	1.47	0.72-3.03			
Histological grade						
Well + moderate	1					
Poor	.04	1.93	1.04-3.59			
CEA level						
Normal	1					
Elevated	.02	1.92	1.10-3.35			
CA19-9 level						
Normal	1					
Elevated	<.01	2.39	1.30-4.39			
TSR						
Low	1					
High	.95	0.97	0.42-2.29			
Invasive depth						
T ₁₊₂	1					
T ₃₊₄	<.01	5.96	1.86-19.18			
Maximum tumor diameter (cm)	.08	1.13	0.99-1.30			
Node involvement						
N ₀	1					
N ₁₊₂	<.01	2.47	1.41-4.34			
M stages						
M ₀	1			1		
M ₁	<.01	8.49	4.03-17.86	<.01	7.48	3.48-16.08
TNM stage						
I + II	1			1		
II + IV	<.01	2.76	1.56-4.90	.04	3.52	1.06-11.68
Adjuvant therapies						
Received	1					
None	.32	0.75	0.43-1.32			
BMI (kg/m ²)	.01	0.90	0.82-0.98	.03	0.90	0.83-0.99
TB	<.01	2.28	1.30-4.00	.05	1.80	1.01-3.19
TIP	<.01	2.60	1.46-4.60			
LMR	.02	0.79	0.65-0.96	.01	0.80	0.67-0.96

Abbreviations: TB, tumor budding; TSR, tumor stroma ratio; TIP, tumor infiltrating pattern; LMR, lymphocyte-to-monocyte ratio; RFS, relapse-free survival; BMI, body mass index; HR, hazard ratio.

Notably, TB, TSR, and TIP are potentially correlated with each other and related to the stroma. For example, a several studies have indicated that TB is associated with TIP,⁴⁰ and both TB and TIP have been suggested to be related to TSR.^{13,39} In addition, TB is a marker of cancer cells that undergo epithelial-to-mesenchymal transition,^{41,42} these cells are supported by key signaling molecules such as twist-related protein 1 (TWIST1) and TWIST2 in the surrounding stroma.⁴³ However, the prognostic potency of these markers may not be identical. Eriksen et al³⁹ conducted a study that included 573

stage II patients and compared the prognostic role of TB and TSR and found that TB had no prognostic value. In our study, we also found a significant correlation between TB and TIP,⁴⁰ both of which are important patient prognostic factors, particularly TB; however, due to the heterogeneity of TSR in our cohort, no correlation was found among TB, TIP, and TSR, and larger study sample sizes are needed in the future.

The preoperative LMR has long been regarded as an important prognostic indicator in CRC. Previously, Stotz et al²⁵ conducted a study of 372 stage II to III patients and reported that an

Table 3. Univariate and multivariate analyses of different parameters for OS.

	Univariate			Multivariate		
	<i>P</i>	HR	95%CI	<i>P</i>	HR	95%CI
Age (y)						
<60	1					
≥60	.02	2.16	1.13-4.15			
Gender						
Female	1					
Male	.43	1.30	0.69-2.46			
Tumor location						
Right						
Left	.39	1.40	0.65-3.01			
Histological grade						
Well + moderate	1					
Poor	.03	2.03	1.06-3.90			
CEA level						
Normal	1					
Elevated	<.01	2.34	1.28-4.26			
CA19-9 level						
Normal	1			1		
Elevated	<.01	2.84	1.52-5.34	<.01	2.44	1.29-4.64
TSR						
Low	1					
High	.77	0.87	0.34-2.21			
Invasive depth						
T ₁₊₂	1			1		
T ₃₊₄	<.01	7.48	1.81-30.94	.02	5.62	1.34-23.57
Maximum tumor diameter (cm)	.03	1.18	1.02-1.36			
Node involvement						
N ₀	1					
N ₁₊₂	.01	2.12	1.16-3.88			
M stages						
M ₀	1			1		
M ₁	<.01	11.03	5.21-23.35	<.01	8.83	4.04-19.28
TNM stage						
I + II	1					
II + IV	<.01	2.81	1.51-5.23			
Adjuvant therapies						
Received	1					
None	.80	0.92	0.51-1.69			
BMI (kg/m ²)	.07	0.92	0.84-1.01			
TB	<.01	2.43	1.32-4.48			
TIP	<.01	2.49	1.34-4.63			
LMR	.03	0.79	0.64-0.98	.03	0.80	0.65-0.98

Abbreviations: TB, tumor budding; TSR, tumor stroma ratio; TIP, tumor infiltrating pattern; LMR, lymphocyte-to-monocyte ratio; RFS, relapse-free survival; BMI, body mass index; HR, hazard ratio; OS, overall survival.

elevated preoperative LMR was significantly associated with increased OS times, but this was limited to stage III patients. Ozawa et al⁴⁴ conducted a study that included 117 stage IV patients and found that LMR was not correlated with DFS outcomes but was linked to cancer-specific survival outcomes in patients who underwent curative resection. Subsequently, Chan et al²⁹ reported in a study of 1623 stage I to IV patients and found that the LMR was superior for predicting OS outcomes in comparison to the results obtained with other

established biomarkers. Recently, Tan et al²⁶ performed a meta-analysis including 11 783 patients and found that a high LMR was a significant predictor of better DFS and OS outcomes and was also associated with tumor invasion depth and tumor size. In our study, the preoperative LMR was also significantly correlated with histological grade and tumor diameter and boundary linked to invasion depth; in addition, the LMR was an independent prognostic factor for DFS and OS outcomes, which was in line with previous reports.^{25,26,29}

Interestingly, the LMR is believed to be an indicator of the inflammatory process not only at the tumor level but also systemically and can be manipulated by several cytokines, growth factors, and other mediators released by tumor cells and tumor-associated stroma.²⁹ From this point of view, TB, TSR, and TIP could potentially be associated with LMR; a typical example is TB featuring increased expression of CXCL12,⁴⁵ which plays an important role in regulating lymphocytes and monocytes.^{46,47} Surprisingly, no significant correlation was found between TB and peritumoral or intratumoral inflammatory infiltration;⁴⁸ additionally, the TSR was not found to be associated with the systemic inflammatory response in a previous report.¹³ In our study, we also failed to find a correlation between LMR and TB, TSR and TIP, and additional studies are still needed in the future.

The present study had some limitations. First, the study was retrospectively performed at a single center, and the limited sample size may have impaired the statistical power and biased the findings; in particular, the relatively small proportion of high TSR in the cohort may have influenced the results. Second, as some patients, in particular those staged III and IV, subsequently received chemotherapy and other therapies after surgery, the final survival outcome of the patients could have been affected by these treatments. Third, the proportion of patients with distant lesions in the cohort was relatively low, and the study of more patients with these characteristics could balance the demographic characteristics. Fourth, some important molecular information, such as MSI and K-Ras status, was lacking. In previous studies, correlations among MSI and TB, TSR, and TIP have been reported.^{16,35,38,49} Ultimately, additional studies with larger sample sizes in the future could attenuate these biases and validate the results of this study.

Conclusion

In conclusion, our results indicate that TB, TIP, and LMR are useful prognostic markers for CRC; however, LMR is likely to be the only independent prognostic factor for both RFS and OS outcomes.

Acknowledgments

The study was conducted with grants from the Chinese Natural Science Foundation (81503391) and Sanya Medical and Health Science Innovation Project (2018YW06 and 2016YW08).

Ethics Statement

The study was approved by the ethics committee of Hainan Hospital of PLA General Hospital (approved ID: 301HLFYLS15), and written informed consent was obtained from the patients or his/her authorized relatives.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship and/or publication of this article.

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