Implications of Pretreatment Serum Carcinoembryonic Antigen Levels and Perineural Invasion with Staging, Prognosis, and Management in Stage I-III Colon Cancer after Surgery: A Retrospective Cohort Study in the SEER Database

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Background: Pretreatment levels of serum carcinoembryonic antigen (CEA) and perineural invasion (PNI) are related to poor prognosis in colon cancer. We analyzed the CEA and PNI (defined as incorporation of carcinoembryonic antigen and perineural invasion (CP)-stage), which are included in the Tumor-Node-Metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC), and evaluated the survival prognosis of patients treated with surgery in I-III stage colon carcinoma.

Materials and Methods: We employed a retrospective study for eligible colon carcinoma patients obtained from the Surveillance, Epidemiology, and End Results (SEER) database between 2010 and 2015. Kaplan-Meier curve and Multivariate Cox regression analysis were used to analyze different TNM-CP stages for the cancer-specific survival (CSS) probabilities in colon cancer.

Result: In our study, CEA levels and PNI were significant prognostic factors ($p < 0.05$), and the newly proposed CP-stage was an independent prognostic index in stage I-III colon carcinoma after surgery. Multivariate Cox regression analyses indicated that CP1-stage was related to a 63.9% increased risk of cancer-specific mortality (hazard ratio (HR): 1.639, 95% confidence interval (CI): 1.544–1.739, $p < 0.001$), compared with CP0-stage in colon cancer. In respective TNM stages, the CP0-stage had an advantage over the CP1-stage for CSS ($p < 0.001$). Moreover, CP1-stage patients with node-negative colon cancer were contacted with similar or worse survival in comparison to CP0-stage patients with node-positive.

Conclusion: For postoperative patients with stage I-III colon cancer, our study indicated that the CP stage is a significant prognostic factor for CSS, which deserves more clinical attention. It's worth noting that including the CP stage in the AJCC TNM staging system of colon carcinoma is beneficial to the survival prediction and clinical treatment.

Keywords: CEA; perineural invasion; TNM staging system; colon cancer; prognosis; SEER

Introduction

Colon cancer is one of the most common cancers and the fifth leading cause of cancer-related deaths in the world [1]. Furthermore, colon cancer is the third most common cause of cancer-related death in the United States [2]. Carcinoembryonic antigen (CEA) is an important tumor marker for patients with colon cancer [3]. In 2000, the American Joint Committee on Cancer (AJCC) colorectal working group suggested adding serum CEA level in the traditional AJCC colon cancer Tumor-Node-Metastasis (TNM) installment system [4]. CEA can accelerate tumor invasion, support colon cancer cells attached to the metastatic site, and is related to unfavorable long-term survival. Therefore, CEA is determined to be prognostic and high-risk factor for patients with colon cancer [5,6]. Zhang *et al*. [7] proposed that the positive lymph nodes of colon cancer patients with elevated colon cancer are higher than those of patients with normal CEA, so the increasing number of colon cancers with CEA has more aggressive biological characteristics.

Perineural invasion (PNI) [8] describes tumors' invasion of tumors to the nerve structure and the dissemination of their subsequent nerve sheath. The research found that the predictive factors of colorectal cancer combined PNI including lymphoma invasion, low tumor staging, poor differentiation, and elevation of CEA levels [9,10]. Zhang *et al*. [11] showed that PNI is a risk factor for the prognosis of colon cancer.

Currently, it's recommended that the AJCC-TNM system be used in clinical practice to provide the survival prognosis and effective treatment strategies for various cancers, including the colon cancer. AJCC-TNM staging usually consists of the T stage (extent of primary tumor involvement), the N stage (extent of regional lymph node involvement), and the M stage (with and without distant metastasis). According to the above definition, colon cancer is divided into stages I-IV: stage I (primary tumor in subserosal negative regional lymph nodes), stage II (primary tumor in negative regional lymph nodes other than subserosa), stage III (positive regional lymph nodes and the inexistence of distant metastases), and stage IV (the existence of distant metastasis) [12]. In the TNM staging system, despite the anatom-

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ical extent of malignant tumors and survival analysis has been implemented, which is based on different stages of cancer patients, the clinical treatment and survival prediction of colon cancer are incomplete [13,14].

To improve the survival prediction effect of colon cancer, some previous studies [15,16,17] have incorporated certain biological indicators into the conventional staging system (TNM staging), which can better show the survival prognosis performance than conventional staging alone. However, other biological factors that affect the survival prognosis of colon cancer, including perineural invasion (PNI) [18], tumor deposition (TD) [19], microsatellite instability (MSI) [20], etc. Considering the existence of these factors, we speculate on incorporating different biological factors into the conventional TNM staging system to verify whether it can further improve the survival prediction ability of colon cancer and effectively guide clinical treatment.

We attempted to integrate pretreatment serum CEA and PNI into a novel stage (defined as incorporation of carcinoembryonic antigen and perineural invasion (CP)-stage). Using the Surveillance, Epidemiology, and End Results (SEER) database, we identified 32564 colon cancer patients treated with surgery in the I-III stage and analyzed the survival prognosis after including the CP-stage in the TNM staging system according to the AJCC criterion (Fig. 1). Moreover, we also investigated the survival effect of including the CP-stage in the N-stage on postoperative patients with colon cancer.

Materials and Methods

Research Data Source and Patient Selection

Research data about patients diagnosed with colon cancer from the SEER database (https://seer.cancer.gov/; Incidence—SEER 18 Regs Research Data). In the USA, it is an authoritative database that records cancer incidence and survival data. We extracted patients diagnosed with colon carcinoma from January 1, 2010 to December 31, 2015 by SEER*Stat 8.3.6.1 software (https://seer.cancer.gov/seerstat/).

Patients who met the following criteria were included: (a) histological codes were limited to colon cancer (ICD-O-3: 8140, 8210, 8261, 8263, 8480, 8481, 8490). (b) Tumor-Node-Metastasis (TNM) staging is stage I-III. (c) The follow-up materials are complete treatment with surgical resection. Patients who met the following criteria were excluded: (a) Not first tumor. (b) Tumor size/Race/Marital status unknown. (c) CEA/Tumor/Deposits unknown. (d) Surgery performed unknown e. Other tumors are death and unknown causes of death. Finally, a total of 32,564 colon cancer patients were extracted from the SEER database. Among all colon cancer patients (N = 32,564), 19,130 patients were CP0 stage, and 13,434 patients were CP1. The CP group is the sample group, and the CP1 group is used as a control group.

The following variables were included in the analysis: sex; race; marital status at diagnosis; age at diagnosis; histology grade; TNM stage; radiation therapy; chemotherapy; surgical resection; carcinoembryonic antigen (CEA) levels; perineural invasion (PNI); Patients with race included white, black, or other (Asian/Pacific Islander, American Indian/Alaska Native); patients were divided into two age groups: <60 years old and ≥ 60 years old; chemotherapy included two groups: yes and no/unknown; radiotherapy included two groups: yes and no; only patients with undergoing surgery were enrolled; marital status was defined as: “married”, “divorced/separated”, “widowed”, and “single”; and tumor size was classified as “<5 cm”, “≥ 5 cm”. The pretreatment serum CEA level was coded in the SEER database; we only included “positive/elevated”, and “negative/normal” in the analysis. The perineural invasion was classified as “Yes” and “No” according to the definition of codes. Ultimately, a total of 32,564 colon carcinoma patients were identified in this study.

CP-Stage and Statistical Analysis

Based on prognostic factors obtained by univariate analysis. we performed multivariate analysis and calculated hazard ratios (HRs) using 95% confidence intervals (CIs). In addition, CEA levels and PNI were incorporated into the TNM staging system according to the AJCC standard.

First, we obtained the values of HRs corresponding to each state of CEA and PNI in the patient by multivariate analysis in Table 1, and the value of HRs was defined as the score values. After that, the total prognostic scores of all colon cancer patients were calculated by the sum of score values of CEA and PNI. The status of CEA and PNI in each patient, the corresponding score, and the range of total prognostic scores are shown in Fig. 2A. Similar methods have been used in these studies [12,13]. In our study, the total prognosis scores ranged from 2 to 2.939. Next, the X-tile software calculated the best cutoff value (2.410) of the total prognostic score. Then, all the patients were divided into two groups according to the best cutoff value, patients with lower scores were assigned to the CP0 group, and patients with the higher scores were transferred to the CP1 stage. For example, for a colon cancer patient who is CEA negative and PNI positive, the corresponding values were “1.000” and “1.411”, respectively, and the total prognostic score was 2.411. Then this patient will be designated to the CP1 group. TNM-CP stage was obtained by combining the TNM staging system (including I, IIA, IIB, IIC, IIIA, IIIB, IIIC) with CP0 or CP1 stages, respectively. Finally, a novel staging system (i.e., the TNM-CP stage) was established for evaluating patient survival outcomes.

Statistical analysis represents the characteristics of patients with the number and percentage. We used Kaplan-Meier survival curves to identify the survival prediction performance of various factors and Multivariate Cox regression analysis to compare the risks of cancer-specific survival

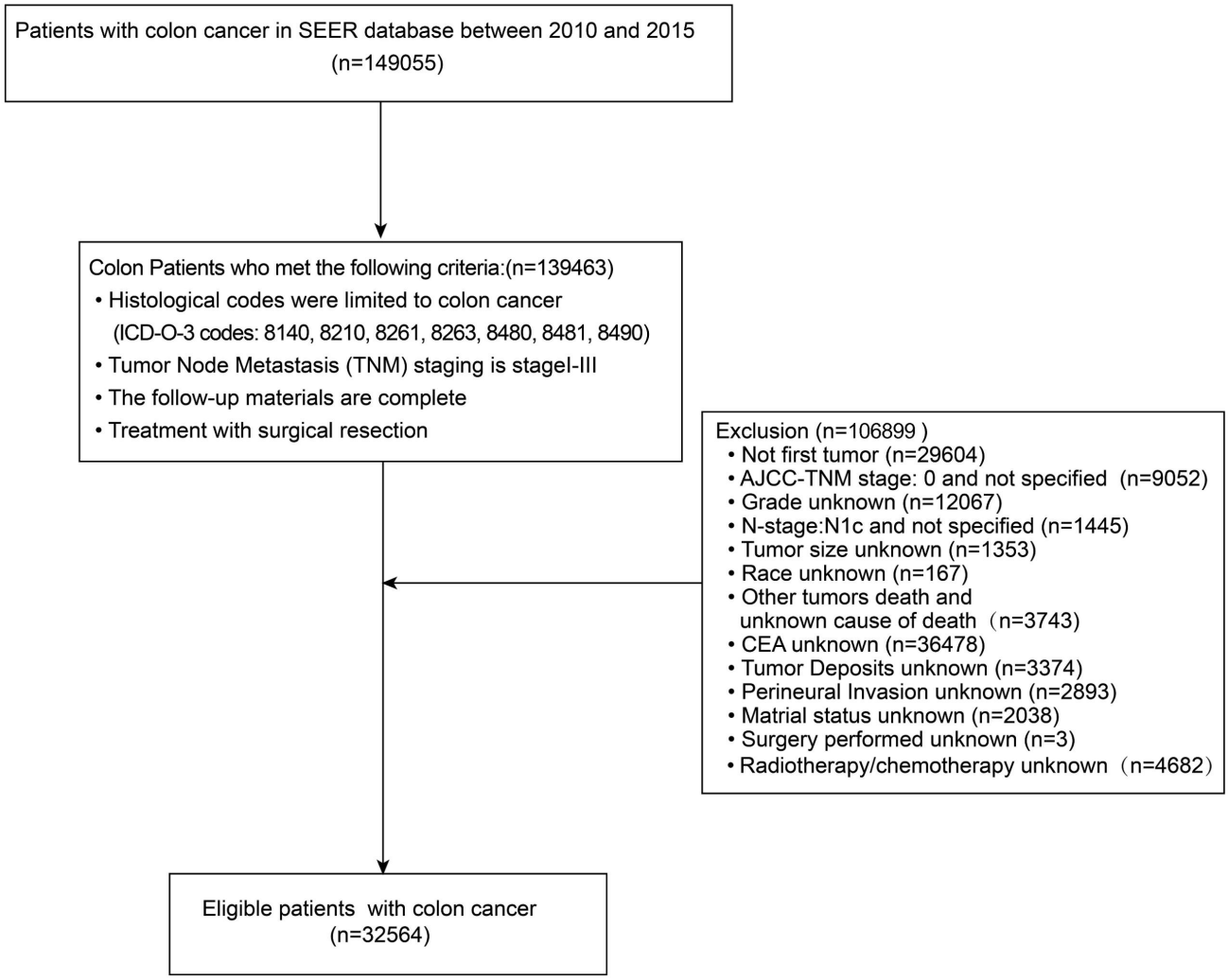

Fig. 1. The flowchart for selecting eligible patients with colon cancer. SEER, the Surveillance, Epidemiology, and End Results; AJCC, American Joint Committee on Cancer; TNM, Tumor-Node-Metastasis; CEA, carcinoembryonic antigen.

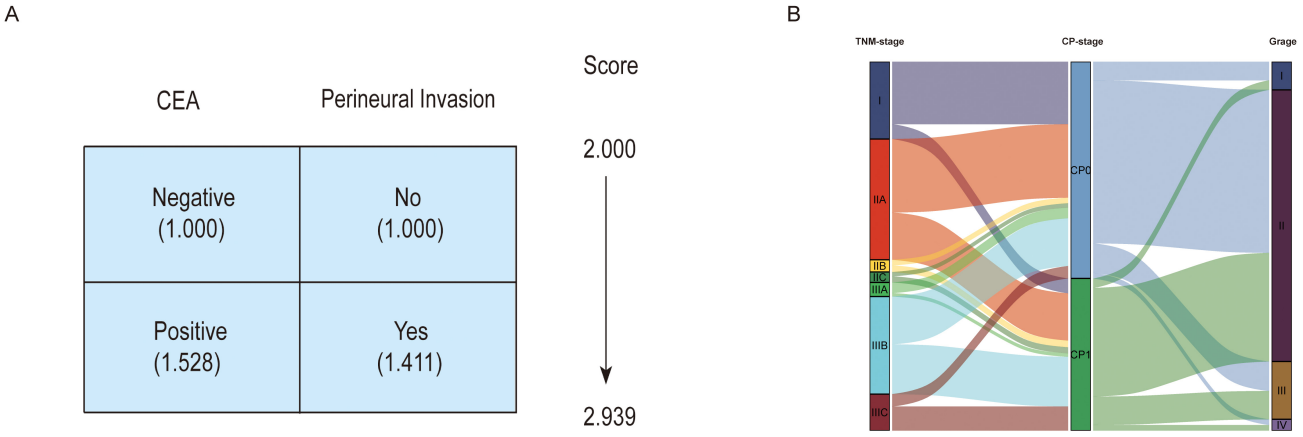

Fig. 2. Patient prognostic score in colon cancer: risk-stratifications. (A) Patient prognostic score and risk stratifications in colon cancer. (B) The Sankey distribution diagram in TNM stage, CP stage, and histology grade, respectively. CP, incorporation of carcinoembryonic antigen and perineural invasion.

(CSS) among the TNM-CP stage. The Pearson χ^2 test was used to assess baseline demographics and tumor characteristics of patients with CP0 and CP1. We used IBM SPSS Statistics, Version 25.0 (SPSS, Inc., IBM Corp., Ar-

Table 1. Univariate and multivariate analysis of independent prognostic factors in colon cancer.

Variable	Univariate analysis		Multivariate analysis	
	Log- rank χ^2	*p* Value	HR (95% CI)	*p* Value
Sex	4.505	<0.001		<0.001
Male			Reference	
Female			0.872 (0.822–0.925)	
Age	338.817	<0.001		<0.001
<60			Reference	
≥60			1.759 (1.634–1.893)	
Race	22.414	<0.001		<0.001
White			Reference	
Black			1.158 (1.067–1.257)	
Other *			0.909 (0.824–1.003)	
Marital status	489.057	<0.001		<0.001
Married			Reference	
Single			1.282 (1.182–1.390)	
Divorced/Separated			1.264 (1.154–1.385)	
Widowed			1.599 (1.482–1.724)	
Grade	746.389	<0.001		<0.001
I			Reference	
II			1.122 (0.979–1.284)	
III			1.518 (1.315–1.753)	
IV			1.786 (1.497–2.129)	
TNM stage	3738.142	<0.001		<0.001
I			Reference	
IIA			2.099 (1.834–2.402)	
IIB			5.862 (4.910–6.997)	
IIC			7.156 (5.955–8.599)	
IIIA			2.652 (2.073–3.392)	
IIIB			7.249 (6.337–8.292)	
IIIC			16.891(14.653–19.470)	
Radiotherapy	20.138	<0.001		0.098
Yes			Reference	
No			0.853(0.706–1.030)	
Chemotherapy	15.827	<0.001		<0.001
Yes			Reference	
No/Unknown			2.228 (2.085–2.381)	
Tumor Size	298.987	<0.001		<0.001
<5 cm			Reference	
≥5 cm			1.052 (0.992–1.116)	
Carcinoembryonic antigen	827.696	<0.001		<0.001
Negative			Reference	
Positive			1.537 (1.451–1.628)	
Perineural invasion	712.459	<0.001		<0.001
No			Reference	
Yes			1.440 (1.340–1.548)	

Abbreviations: HR, hazard ratio; CI, confidence interval; SE, standard error; TNM, Tumor-Node-Metastasis.

*Other includes American Indian/Alaskan Native, Asian/Pacific Islander.

monk, NY, USA) to perform statistical analyses. Forest plots showing univariate and multivariate analysis results and Kaplan-Meier survival curves were drawn using GraphPad Prism 8 (GraphPad Software, Inc., San Diego, CA, USA). The Sankey diagram with the relevant package was drawn using R (version R 4.0.2, R Foundation for Statistical Computing, Vienna, Austria). p values < 0.05 were considered statistically significant.

Table 2. Comparison of colon cancer patients with CP0 and CP1 stage.

Characteristic	No. (%) of Patients			χ^2	*p* Value
	All (*N* = 32,564)	CP0 (*N* = 19,130)	CP1 (*N* = 13,434)		
Sex				52.744	<0.001
Male	16,104 (49.5%)	9783 (51.1%)	6321 (47.1%)		
Female	16,460 (50.5%)	9347 (48.9%)	7113 (52.9%)		
Age				23.064	<0.001
<60	10,303 (31.6%)	6251 (32.7%)	4052 (30.2%)		
≥60	22,261 (68.4%)	12,879 (67.3%)	9382 (69.8%)		
Race				195.737	<0.001
White	25,203 (77.4%)	15,309 (80.0%)	9894 (73.6%)		
Black	4066 (12.5%)	2037 (10.6%)	2029 (15.1%)		
Other*	3295 (10.1%)	1784 (9.4%)	1511 (11.2%)		
Marital status				183.760	<0.001
Married	18,547 (57.0%)	11,480 (60.0%)	7067 (52.6%)		
Single	5310 (16.3%)	2947 (15.4%)	2363 (17.6%)		
Divorced/Separated	3622 (11.1%)	2003 (10.5%)	1619 (12.1%)		
Widowed	5085 (15.6%)	2700 (14.1%)	2385 (17.8%)		
Grade				232.408	<0.001
I	2476 (7.6%)	1638 (8.6%)	838 (6.2%)		
II	23,981 (73.6%)	14,391 (75.2%)	9590 (71.4%)		
III	5108 (15.7%)	2604 (13.6%)	2504 (18.6%)		
IV	999 (3.1%)	497 (2.6%)	502 (3.7%)		
TNM stage				2882.194	<0.001
I	6819 (20.9%)	5509 (28.8%)	1310 (9.8%)		
IIA	10,662 (32.7%)	6491 (33.9%)	4171 (31.0%)		
IIB	1080 (3.3%)	490 (2.6%)	590 (4.4%)		
IIC	914 (2.8%)	378 (2.0%)	536 (4.0%)		
IIIA	1250 (3.8%)	945 (4.9%)	305 (2.3%)		
IIIB	8609 (26.4%)	4220 (22.1%)	4389 (32.7%)		
IIIC	3230 (9.9%)	1097 (5.7%)	2133 (15.9%)		
N stage				2538.366	<0.001
N0	19,375 (59.8%)	12,868 (67.3%)	6607 (49.2%)		
N1a	3963 (12.2%)	2238 (11.7%)	1725 (12.8%)		
N1b	4060 (12.5%)	1994 (10.4%)	2066 (15.4%)		
N1c	533 (1.6%)	261 (1.4%)	272 (2.0%)		
N2a	2491 (7.6%)	1044 (5.5%)	1447 (10.8%)		
N2b	2042 (6.3%)	725 (3.8%)	1317 (9.8%)		
Radiotherapy				73.937	<0.001
Yes	470 (1.4%)	185 (1.0%)	285 (2.1%)		
No	32,094 (98.6%)	18,945 (99.0%)	13,149 (97.9%)		
Chemotherapy				549.951	<0.001
Yes	11,813 (36.3%)	5938 (31.0%)	5875 (43.7%)		
No/Unknown	20,751 (63.7%)	13,192 (69.0%)	7559 (56.3%)		
Tumor Size				871.442	<0.001
<5 cm	18,658 (57.3%)	12,258 (64.1%)	6400 (47.6%)		
≥5 cm	13,906 (42.7%)	6872 (35.9%)	7034 (52.4%)		

Abbreviations: CP, incorporation of carcinoembryonic antigen and perineural invasion.

*Other includes American Indian/Alaskan Native, Asian/Pacific Islander.

Results

In our study, we extracted data on 149,055 patients with colon carcinoma from the SEER database. Finally, a total of 32,564 eligible colon carcinoma patients were included in our research after deleting the data (Fig.1).

Association of CEA and PNI with CSS in Colon Cancer

For the above-mentioned single-factors analysis, the meaningful variables of it incorporated into the multi-variable Cox regression analysis show that the CSS of colon cancer patients <60 years old was better than that of patients who

Table 3. Multivariate survival analysis for cancer-specific survival in colon cancer.

Variable	Reference	Characteristic	HR (95% CI)	Cancer-Specific Survival		
				SE	β	p value
Race	White	Black	1.167 (1.075–1.267)	0.042	0.154	<0.001
		Other*	0.914 (0.828–1.008)	0.050	–0.090	0.071
Sex	Male	Female	0.871 (0.821–0.924)	0.030	–0.138	<0.001
Grade	I	II	1.124 (0.982–1.287)	0.069	0.117	0.090
		III	1.527 (1.322–1.763)	0.073	0.423	<0.001
		IV	1.833 (1.538–2.185)	0.090	0.606	<0.001
Age	<60	≥60	1.754 (1.630–1.887)	0.037	0.562	<0.001
TNM stage	I	IIA	2.089 (1.825–2.392)	0.069	0.737	<0.001
		IIB	5.851 (4.901–6.985)	0.090	1.767	<0.001
		IIC	7.138 (5.939–8.578)	0.094	1.965	<0.001
		IIIA	2.641 (2.064–3.378)	0.126	0.971	<0.001
		IIIB	7.280 (6.364–8.327)	0.069	1.985	<0.001
		IIIC	17.384 (15.092–20.024)	0.072	2.856	<0.001
Radiotherapy	No	Yes	0.865 (0.716–1.045)	0.096	–0.145	0.133
Chemotherapy	Yes	No/Unknown	2.225 (2.082–2.378)	0.034	0.800	<0.001
Tumor Size	<5 cm	≥5 cm	1.048 (0.988–1.111)	0.030	0.047	0.117
CP-Stage	CP0	CP1	1.639 (1.544–1.739)	0.030	0.494	<0.001
Marital status	Married	Single	1.288 (1.188–1.396)	0.041	0.253	<0.001
		Divorced/Separated	1.267 (1.156–1.388)	0.047	0.236	<0.001
		Widowed	1.594 (1.478–1.719)	0.039	0.466	<0.001

*Other includes American Indian/Alaskan Native, Asian/Pacific Islander.

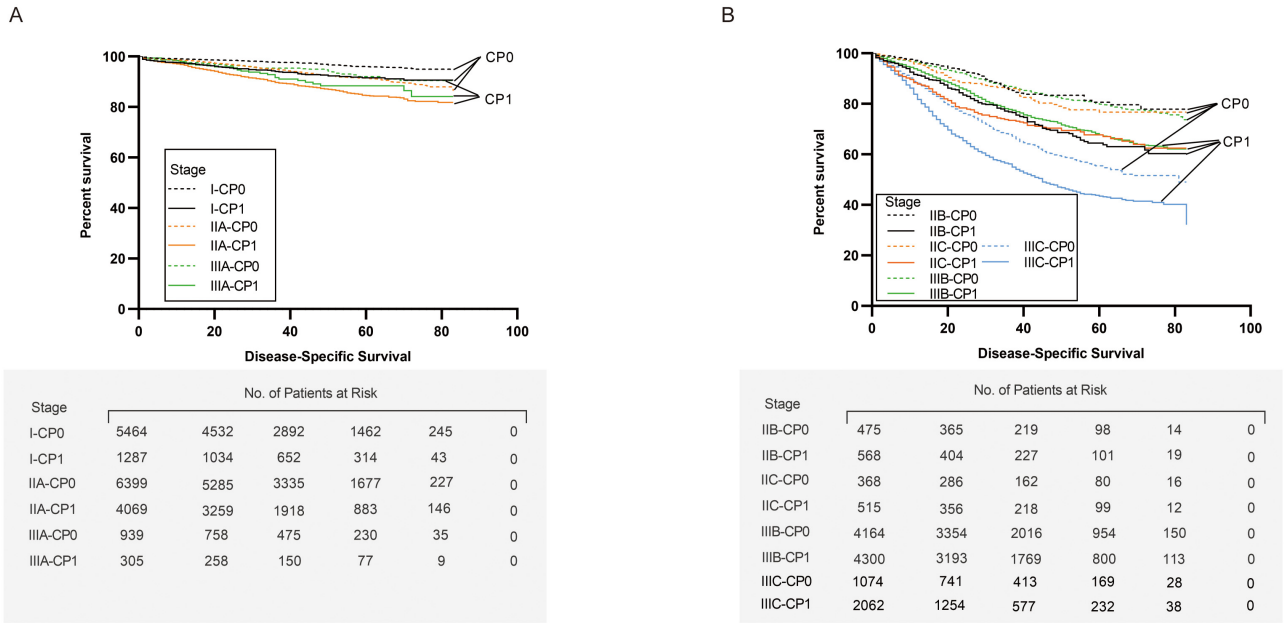

Fig. 3. Kaplan-Meier survival curves of tumor-node-metastasis-carcinoembryonic antigen- perineural invasion (TNM-CP stage). (A) Cancer-specific survival (CSS) of I-CP0 stage, I-CP1 stage, IIA-CP0 stage, IIA-CP1 stage, IIIA-CP0 stage, and IIIA-CP1 stage. (B) CSS of IIB-CP0 stage, IIB-CP1 stage, IIC-CP0 stage, IIC-CP1 stage, IIIB-CP0 stage, and IIIB-CP1 stage, IIIC-CP0 stage, and IIIC-CP1 stage (all p value < 0.001).

are ≥60 years old and the death risk of black people was higher than that of white people (hazard ratio (HR) = 1.158, 95% confidence interval (CI): 1.067–1.257, $p < 0.001$), in terms of marital status, married is used as a comparison, divorced/separated (HR = 1.264, 95% CI: 1.154–1.385, $p < 0.001$), single (HR = 1.282, 95% CI: 1.182–1.390, $p < 0.001$) and being widowed (HR = 1.599, 95% CI: 1.482–1.724, $p < 0.001$) are risk factors. Among them, widowed colon cancer patients are at the highest risk of death, which is 1.599 times that of married patients. For the histologi-

Stage	No. of patients	Univariate analysis			Multivariate analysis	
		5-year CSS	Log rank χ2	P value	HR (95%CI)	P value
I-CP0	5509	95.6%	Reference		Reference	
I-CP1	1310	90.3%	53.203	<0.001	2.423 (1.898-3.094)	<0.001
IIA-CP0	6491	90.6%	Reference		2.236 (1.884-2.654)	<0.001
IIA-CP1	4171	83.3%	94.683	<0.001	4.108 (3.469-4.865)	<0.001
IIB-CP0	490	79.0%	Reference		5.176 (3.955-6.775)	<0.001
IIB-CP1	590	62.7%	24.029	<0.001	10.082 (8.156-12.463)	<0.001
IIC-CP0	378	75.2%	Reference		6.036 (4.567-7.977)	<0.001
IIC-CP1	536	65.7%	15.917	<0.001	10.760 (8.689-13.325)	<0.001
IIIA-CP0	945	91.7%	Reference		1.851 (1.372-2.498)	<0.001
IIIA-CP1	305	88.3%	3.358	0.067	2.816 (1.891-4.193)	<0.001
IIIB-CP0	4220	79.1%	Reference		5.079 (4.310-5.986)	<0.001
IIIB-CP1	4389	66.6%	130.890	<0.001	8.777 (7.500-10.272)	<0.001
IIIC-CP0	1097	54.4%	Reference		13.696 (11.521-16.281)	<0.001
IIIC-CP1	2133	42.2%	43.406	<0.001	20.649 (17.574-24.261)	<0.001

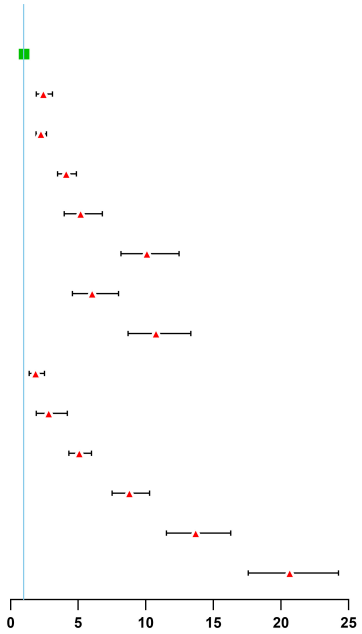

Fig. 4. Prognosis of TNM-CP stage in colon cancer. Abbreviations: CSS, cancer-specific survival.

cal grading, high differentiation was used as the comparison, moderate differentiation (HR = 1.122, 95% CI: 0.979–1.284, $p < 0.001$), and poorly differentiated (HR = 1.518, 95% CI: 1.315–1.753, $p < 0.001$), undifferentiated (HR = 1.786, 95% CI: 1.497–2.129, $p < 0.001$) is a risk factor. The risk of death in patients with positive CEA levels (HR = 1.537, 95% CI: 1.451–1.628, $p < 0.001$) was higher than that of patients with negative CEA and positive PNI (HR = 1.440, 95% CI: 1.340–1.548, $p < 0.001$) and the prognosis is worse than that of patients with negative PNI. Age, gender, race, marital status, histological grade, TNM stage, chemotherapy, CEA, PNI and tumor size (all $p < 0.001$) were independent of CSS prognostic factors. For the rest of the information, check (Table 1).

Comparison of Patients with CP0 and CP1 Stage

Among all colon cancer patients (N = 32,564), 19,130 patients were CP0 stage, and 13,434 patients were CP1. A comparison of patients with baseline demographics and pathological characteristics between the CP0 and CP1 stages is shown in Table 2. The results show that two groups are ≥60 years old, and white and married people account for the majority of the research groups. Regarding histological grading, both groups are common in moderately differentiated patients, with 75.2% (14,391 cases) of medium differentiation patients in the CP1 group and the minimized poorly differentiated patients, only 2.6 (497 cases) in the CP1 group. Patients with the CP1 stage presented more at the IIIB stage and were poorly differentiated (Fig. 2B) than those with the CP0 stage.

CP-Stage as a Prognostic Factor in Colon Carcinoma

Analysis of the Multivariate COX regression analysis shows that CP-stage is an independent prognosis of CSS patients with colon cancer (Table 3). Compared with the CP0 stage, CP1 stage, and cancer-specific death risk increased by 63.9% independent (HR: 1.639, 95% CI: 1.544–1.739), $p < 0.001$). Race, age, gender, marriage status, tumor level, TNM staging, chemotherapy, and marriage status are the independent prognoses of CSS patients with colon cancer. In subsequent treatment, compared with patients not receiving radiotherapy, the risk of cancer-specific deaths in patients who received radiotherapy decreased by 13.5% independent (HR: 0.865, 95% CI: 0.716–1.045, $p = 0.133$) (Table 3).

Prognostic Prediction of TNM-CP Stage in Colon Cancer

In this research, compared with the concordance index (C-index) of the TNM stage (C-index: 0.711, 95% CI: 0.7031–0.7188), the TNM-CP stage (**Supplementary Table 1**) showed better (C-index: 0.729, 95% CI: 0.7212–0.7368), and combining CEA or PNI alone with TNM stage, the consistency indices are (C-index: 0.720, 95% CI: 0.7121–0.7278) (C-index: 0.716, 95% CI: 0.7081–0.7238), therefore, it further illustrates that incorporating biological factors into TNM stage can better predict the prognosis of colon cancer patients.

We used Kaplan-Meier curves to assess prognosis of patients' after combining AJCC TNM stages with CP stages (stages I-CP0, I-CP1, IIA-CP0, IIA-CP1, and so on). As shown in Fig. 3, compared with patients with CP0-stage, patients with CP1-stage had a worse survival outcome

within each AJCC TNM stage, such as patients with stage I-1 showed a worse CSS than patients with stage I-0 and so on. Moreover, we also found that CP1 patient with a lower TNM stage had similar or worse prognosis than CP0 patients with higher TNM stage. For example, the CSS of patients with stage I-1 was lower than those patients with stage IIIA-0.

The above phenomenon was better demonstrated in univariate and multivariate Cox regression analyses. The HRs in each TNM-CP stage illustrated this result. As shown in Fig. 4, patients with TNM-CP0 stage indicated lower HRs than their counterparts with TNM-CP1 stage, and it also showed a comparatively higher 5-year CSS. For instance, patients with IIB-CP0 stage (79.0%) for 5-year CSS were better than that of patients with IIB-CP1 stage (62.7%), and the HRs of patients with IIB-CP0 stage (HR: 5.176, 95% CI: 3.955–6.775) were lower than that patients with IIB-CP1 stage (HR: 10.082, 95% CI: 8.156–12.463). When using stage I-CP0 as the reference, compared with patients with stage TNM-CP0 who had higher TNM stages, patients with stage TNM-CP1 of lower TNM stages showed higher HRs. For example, HRs of patients with stage IIC-CP1 (HR: 10.760, 95% CI: 8.689–13.325) were higher than that of patients with stage IIIA-CP0 (HR: 1.851, 95% CI: 1.372–2.498) (Fig. 4).

In addition, we incorporated CP-stage into the N-stage to obtain various combinations. We analyzed the prognosis of patients with colon carcinoma to understand the relationship between lymph node status and CP status (**Supplementary Fig. 1**). Similarly, we found that patients with CP0 of the respective nodal stage for prognosis had an advantage over patients with CP1. Moreover, compared to patients with CP0 of higher nodal stage, patients with CP1 who had lower nodal stages showed a similar or worse survival prognosis.

Discussion

Our research suggested that CP-stage was an independent prognostic indicator for CSS among postoperative patients with stage I-III colon cancer, and CP1-stage increased the risk of cancer-specific mortality by 62.1% compared with CP0 stage. We found that CP1-stage patients had worse survival outcomes within each TNM stage than compared with CP0-stage patients. Moreover, CP1-stage patients with negative lymph nodes of colon cancer were associated with a similar or worse prognosis than CP0-stage patients with node-positive.

The National Comprehensive Cancer Network (NCCN) [14] and Japanese guidelines [15] for CRC treatment indicated that postoperative serum CEA levels could predict the recurrence of CRC. Nevertheless, these guidelines did not reflect the clinical implication of preoperative serum CEA was not reflected in these guidelines. Up to now, there has been much previous research [16,17,18,19] that showed that preoperative serum CEA is related to poor survival in CRC patients treated with surgery. In 2000 TNM staging strategy revision, it was also suggested that neoplasm should be divided into elevated CEA and normal CEA groups [20]. Moreover, a study [6] found that positive preoperative serum CEA increased the overall rate and disease-specific mortality (51% and 59%, respectively) compared with normal CEA. The results suggested that the level of CEA should be added to the TNM staging system to improve the prognosis of colon cancer. The above suggestion was also proposed in Dienstmann's research [17]. Although the above studies have included preoperative serum CEA in the TNM staging system to improve the prognosis of colon carcinoma, few studies bave included a combination of multiple biological factors in the TNM staging system. In our study, preoperative biological indicators and postoperative pathological results were combined into TNM staging to improve the prognosis outcome of postoperative patients with colon cancer.

Many prognostic indicators that can affect the survival outcome after colon cancer surgery, and PNI is one of them. Most studies [21,22,23,24] reported that the incidence of PNI was about 11.2%, and PNI was also a risk factor that could influence overall survival (OS) and disease-free survival (DFS). Moreover, the AJCC staging manual also showed that it could affect the recurrence and prognosis of patients with colon carcinoma.

We combined CEA levels and PNI into a stage (i.e., the CP-stage). We evaluated the effect of CP-stage and the inclusion of the CP stage into the TNM stage on the prognosis of colon carcinoma after surgery. Multivariate regression analyses indicated that the CP-stage was an independent prognostic index, and the CP1-stage more showed poorer prognosis than the CP0-stage. We found that the CSS of patients with CP0 and CP1 was significantly different in each AJCC TNM stage, with a few exceptions. Furthermore, we noted that CP1-stage enhanced the risk of cancer-specific mortality by 62.1% in comparison with CP0-stage in colon cancer. The above results showed that CEA levels and PNI had great clinical significance as predictive tools for the prognosis of colon carcinoma after surgery, and it could make the clinical prediction function of the conventional TNM staging system more perfect after including the CP-stage.

Patients without lymph node invasion (TNM stage I/II) usually receive surgery only in current treatment strategies. In addition, adjuvant chemotherapy could be considered in patients with stage II colon carcinoma who are associated with high-risk indicators (i.e., less than 12 lymph nodes, poorly differentiated carcinoma, vascular or lymphatic invasion, bowel obstruction, localized perforation, and close or positive margins) according to the NCCN guidelines [14]. However, in this study, we found that patients with node-negative (IIB-CP1, IIC-CP1) exhibited a poorer prognosis than patients with node-positive (IIIA, IIIB). Adjuvant chemotherapy is not recommended for these patients with

node-negative (IIB-CP1, IIC-CP1) according to the current clinical treatment pattern. Moreover, previous studies [25,26,27] had no clear evidence that stage II patients with colon carcinoma could profit from adjuvant chemotherapy. Nevertheless, according to our research, we suggest that such CP1 patients with stage II colon cancer may be considered for adjuvant chemotherapy. In other words, it also indicates that the CP1 stage could be a high-risk feature for stage II colon cancer. A previous retrospective study [28] indicated that adjuvant chemotherapy was required in stage II colon carcinoma patients with preoperative elevation of serum CEA level. A report by Chen *et al*. [21] showed that stage II colon carcinoma patients with PNI tended to have a worse survival prognosis and recommended the adoption of adjuvant chemotherapy. Moreover, previous literature [23] found that PNI was associated with poor survival in patients with stage II adenocarcinoma of colon cancer, and adjuvant chemotherapy may be a protective specifically when the presence of PNI. The above studies also support our findings of this study to a certain extent.

Surgical treatment and adjuvant chemotherapy are often required in patients with positive lymph nodes (TNM stage III). In this study, certain lymph positive stage patients with CP0 (IIIA-CP0; 91.7%) showed better 5-year CSS outcomes compared with lymph negative stage patients with CP1 (I-CP0, IIA-CP1, IIB-CP1, IIC-CP1; 90.3%, 83.3%, 62.7%, 65.7%; respectively). According to the treatment strategy of traditional TNM staging, patients with IIIA-CP0 who are associated with poorer TNM staging and lymphatic positivity and should have a poorer prognosis. Interestingly, our study showed that patients with IIIA-CP0 had lower HRs, which suggested that postoperative patients with IIIA-CP0 may require less adjuvant chemotherapy or no chemotherapy. On the contrary, adjuvant chemotherapy may need to be considered for high-risk patients with colon cancer (especially stage II colon cancer with CP1). Undoubtedly, it indicated that CP0 is a protective factor for the prognosis of patients suffering who have colon cancer.

There are some potential limitations in this study. Firstly, although the total population samples were relatively large in our study, some subgroups existed with a small number of samples after the addition of the CP stage and TNM staging system, which may lead to a bias in the study results. In addition, not all patients diagnosed with colon cancer underwent a test for pretreatment serum CEA, which also limits the sample size to some extent. Secondly, other factors associated in with the prognosis of colon carcinoma were not included in the TNM-CP stage due to missing or unregistered information on the SEER database, such as MSI [29,30], DNA mismatch repair [31] status, and so on. Thus, the role of the CP-TNM stage should be further explored in future studies. Thirdly, our research population was sourced from the SEER database in the United States, so these results may not apply to populations in other regions.

Conclusion

Despite the importance of the CP-stage in the prognosis of postoperative sufferers with colon carcinoma based on our study in the SEER database, our results will be need to be confirmed by a longer follow-up time.

Based on our results, we indicated that the CP stage is an independent prognostic indicator, which has important prognostic significance in postoperative patients with I-III colon carcinoma. We believe that routine preoperative CEA testing and the determination of PNI are necessary, especially for stage II colon cancer. Combination of CP-stage and the current AJCC TNM staging system is conducive to improving the prediction of survival prognosis and strengthening the guidance of adjuvant chemotherapy.

Availability of Data and Materials

The datasets used or analyzed during the present study are available from the corresponding author on reasonable request.

Author Contributions

QZ carried out the data retrieval and extraction, LW and RS performed the data analysis and statistics, JG and TL checked the raw data, confirmed the authenticity of all the raw data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.62713/aic.3296.

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