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ORIGINAL ARTICLE

Preoperative serum carcinoembryonic antigen elevation in stage I colon cancer: improved risk of mortality in stage T1 than in stage T2

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Abstract

Purpose This study aimed to investigate the implications of preoperative serum carcinoembryonic antigen (CEA) elevation in cause-specific survival (CSS) of patients diagnosed with stage I (T1N0M0 and T2N0M0) colon cancer.

Methods Eligible patients diagnosed with stage I colon cancer from the Surveillance, Epidemiology, and End Results (SEER) database from January 2004 to December 2010 were included in this respective and propensity score–matched (PSM) study. Some Cox proportional hazards models were constructed to identify prognostic factors associated with oncologic outcomes of colon cancer. Pearson's chi-squared tests and Kaplan–Meier methods were performed.

Results The median follow-up time of the whole cohort was 79 months. A total of 16,659 patients diagnosed with stage I colon cancer were identified from the SEER database. Multivariate Cox analyses showed that stage T1N0M0 in the context of serum CEA elevation (T1, CEA+) presented up to 158.4% increased risk of colon cancer-specific mortality compared with stage T1N0M0 in the context of normal serum CEA [hazard ratio (HR) = 2.584, 95% confidence interval (CI) = 2.167–3.082, $P < 0.001$]. After PSM, Kaplan–Meier survival curves of stage T1N0M0 colon cancer showed that 5-year CSS rates of normal and elevated CEA were 94.8% and 96.6% ($P < 0.001$).

Conclusions This large population-based and propensity score–matched study with long follow-up time provides the first evidence that stage T1N0M0 colon cancer with the elevation of preoperative serum CEA would be a surrogate of aggressive tumor biology and predict poor prognosis. In addition, this subgroup of colon cancer might need to be paid more attention of clinicians.

Keywords Stage I · Colon cancer · Carcinoembryonic antigen · Propensity score–matched

Introduction

Colorectal cancer is the third most prevalent malignancy among men and women in the USA [1]. At present, based on the American Joint Cancer Commission (AJCC) tumor-node-metastasis (TNM) staging system which is widely used as a guideline for staging and prediction of prognosis, colon cancer patients are grouped as stage I (node-negative tumors within the submucosa), stage II (node-negative tumors beyond subserosa), stage III (node-positive nonmetastatic tumors), and stage IV (any metastases) colon cancers [2]. However, the AJCC staging system is not perfect in the prognostic prediction and clinical management, and patients with the same stage of colon cancer might present evidently different oncologic outcomes [3, 4].

As a 201-kDa highly glycosylated antigen and a member of the immunoglobulin gene superfamily, carcinoembryonic antigen (CEA) is normally produced during prenatal development [5, 6]. After birth, CEA blood levels are normally very low or undetectable. However, diagnosis with some carcinomas especially colorectal cancer often causes the elevation of serum CEA levels. Therefore, CEA testing is recommended in patients suspected to be associated with colorectal cancer [7].

Recent studies have suggested that tumor metastasis that occurs at an early point of tumor progression could be a surrogate of aggressive tumor biology and predict poor oncologic outcomes [8–10]. And CEA-producing tumors have been demonstrated to have a higher ability for metastasis in mouse models [11, 12]. Therefore, we have the assumption that early-

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stage (stage T1) colon cancer with elevated level of serum CEA might predict unexpected poor prognosis. It was reported by Wanebo et al. in 1978 that the CEA level was a strong prognostic factor in colorectal cancer [13]. In 2000, based on the results of several studies showing the stage-independent prognostic value of serum CEA in colorectal cancer, the Colorectal Working Group of the AJCC even proposed that the serum level of CEA (C-stage) could be included in the conventional TNM staging system [4]. Later, many other studies confirmed the unfavorable prognosis of serum CEA elevation in patients diagnosed with colorectal cancer [4, 14–17].

To the best of our knowledge, however, no study was reported to investigate the association of T-stage and preoperative serum CEA level in predicting the prognosis of stage I colon cancer. We conducted this study to examine the implications of preoperative serum CEA elevation in cause-specific survival (CSS) of patients diagnosed with stage I (T1N0M0 and T2N0M0) colon cancer.

Patients and methods

Patients in Surveillance, Epidemiology, and End Results database

The Surveillance, Epidemiology, and End Results (SEER) database is an authoritative source of information on the most recent cancer incidence, mortality, prevalence, and lifetime risk statistics in SEER-participating areas and covering approximately 28% of the US population. Then, the National Cancer Institute's SEER*Stat software (Surveillance Research Program, National Cancer Institute SEER*Stat software, www.seer.cancer.gov/seerstat) (Version 8.3.5) was used to select eligible patients from SEER database.

Shown in Fig. 1, of 41,194 patients with a diagnosis of stage I colon cancer between the years 2004 and 2010 identified from the SEER Registry, those lack of positive histological confirmation or with unknown race or non-adenocarcinoma histologies or not active follow-up were excluded from our analyses. We identified patients diagnosed in these years because the information of preoperative serum CEA was recorded starting from 2004 and we wanted to ensure adequate follow-up time. Then, a total of 16,659 patients with known preoperative serum CEA level (normal or elevated, for nonsmokers, CEA elevation was more than 2.5 ng/ml, for nonsmokers, CEA elevation was more than 5 ng/ml) were eligible for the present study, including 8007 stage T1N0M0 colon cancer and 8652 stage T2N0M0 colon cancer patients.

Propensity-score matching

As a retrospective study, there could be significant bias introduced by inherent differences between patients based on the level of serum CEA. And propensity-score matching (PSM) is most commonly applied to match two groups, a treatment group and a control groups, according to several covariates in quasi-experimental settings [18]. To adjust for significant clinicopathologic covariates between CEA-normal (CEA−) and CEA-elevated (CEA+) groups in the present study, a propensity-score matching process using a logistic regression model based on the following baseline characteristics: histology, tumor grade, race, gender, age at diagnosis, tumor location, year of diagnosis, and no. of lymph nodes dissected. Patients with normal preoperative serum CEA were matched on a one-to-one basis with patients with elevated CEA. Matching was performed based on nearest-neighbor matching; CEA-normal and CEA-elevated patients were matched within their respective risk groups. The caliper used for matching was set at 0.01. Propensity scores reflect the probability that patients with normal or elevated preoperative serum CEA were based on their baseline characteristics (Fig. 1). Then, PSM was utilized in stage T1N0M0 and T2N0M0 patients, respectively. After propensity score matching, patient demographics, surgical data, pathological data, and follow-up status were re-evaluated (Tables 3 and 4).

Statistical analyses

In this study, we compared different clinicopathologic factors between the CEA-normal and CEA-elevated groups using Pearson's chi-squared test for different variables. Several Cox proportional hazards models were built to identify independent prognostic variables. All the hazard ratios were shown with 95% confidence intervals (CI). Variables which showed prognostic significance (log rank, $P < 0.20$) in univariate analysis were entered in multivariate analysis. The Kaplan–Meier method with a log-rank test was used to evaluate the prognostic prediction of different factors. The primary outcome of interest used in our study was CSS, which was calculated from the date of diagnosis to the date of colon cancer death. Overall survival (OS) was also used to validate our findings. Patients who died of other causes were censored at the date of death. In the present study, we also designed a variable combining T-stage (T1 or T2-stage) and serum CEA level (CEA-normal of CEA-elevated) to compare the interaction between these two characteristics in patients with stage I colon cancer. All tests were two sided, and P values less than 0.05 were considered statistically significant. Statistical analysis was performed using SPSS version 22 (SPSS Inc., IL, USA).

Results

Patient characteristics of the overall cohort

A total of 16,659 patients diagnosed with stage I colon cancer were identified from the SEER database, including

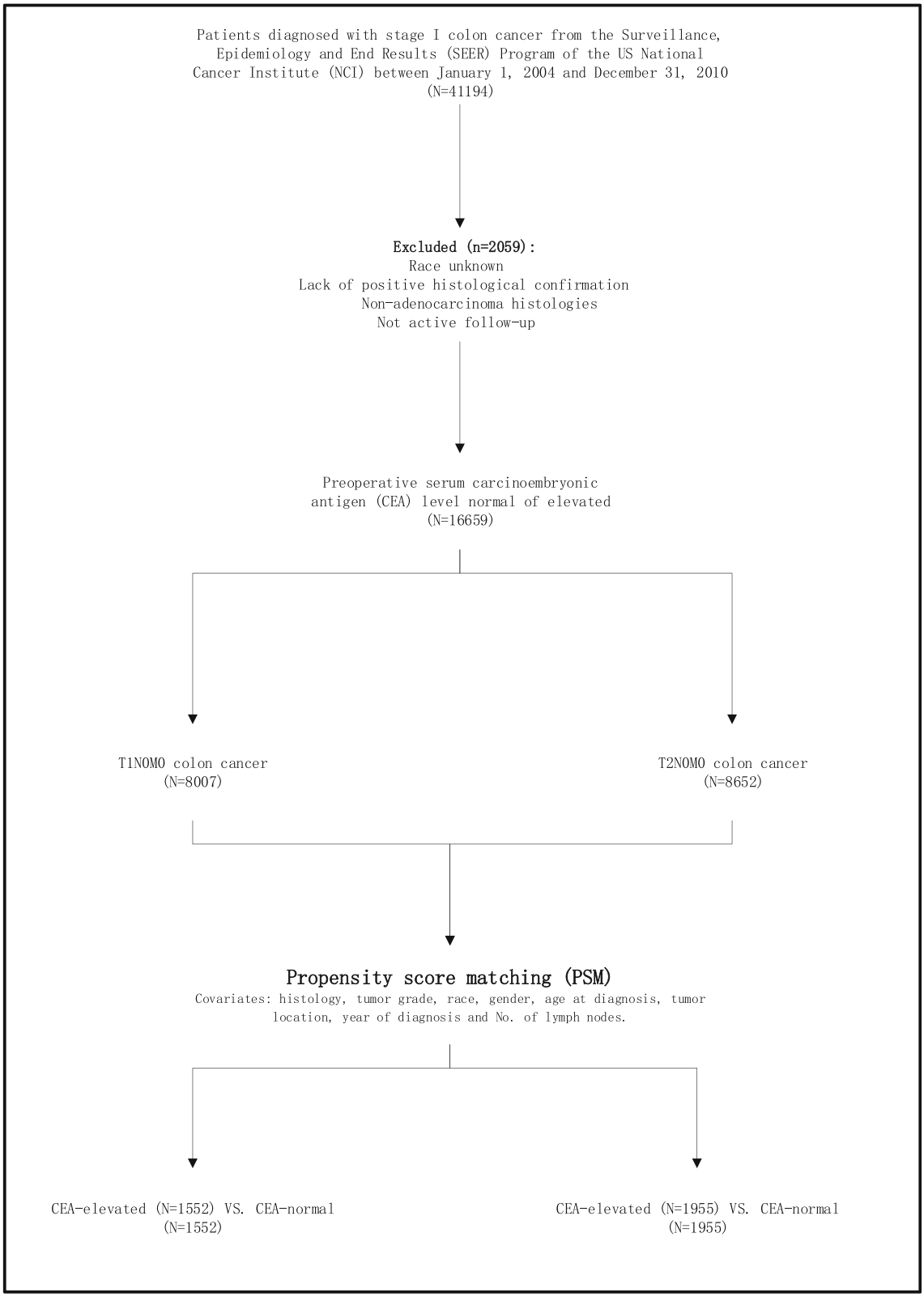

Fig. 1 Flow diagram of eligible patients selected from SEER database

stage T1N0M0 ($N = 8007$) and stage T2N0M0 ($N = 8652$). Of all, 13,123 patients (78.8%) were stratified into the CEA-normal group, and 3536 patients (21.2%) were stratified into the CEA-elevated group. The median follow-up time of the whole cohort was up to 79 months. At the end of the follow-up time, only 1092 (6.6%) patients died of colon cancer.

The baseline demographic characteristics of the patients are summarized in Table 1. Stage T2, aggressive histology, black race, female, older patients, right colon and no. of lymph nodes ≥ 12 were more likely to be associated with preoperative serum CEA elevation ($P < 0.001$). Differences in other characteristics were not obvious.

Prognosis of patients diagnosed with stage I colon cancer combined with preoperative serum CEA level before PSM

A total of six variables including tumor grade, race, age at diagnosis, year of diagnosis, no. of lymph nodes dissected, and T-stage and CEA level were entered in multivariate analyses. In the multivariate Cox analysis, a significant interaction was found between T-stage and preoperative serum CEA level in determining CSS ($P < 0.001$, Table 2). It was found that the variable of "T-stage and CEA level" was independently associated with CSS of 16,659 stage I colon cancer patients. Moreover, the subgroup of T1, CEA+ presented up to 158.4% increased risk of colon cancer-specific mortality

Table 1 Comparison of baseline characteristics of stage I colon cancer by the serum CEA level

Variable	No. of patients (%)		*P*
	CEA-normal ($N = 13,123$)	CEA-elevated ($N = 3536$)	
T-stage			< 0.001
T1	6446 (49.1)	1561 (44.1)	
T2	6677 (50.9)	1975 (55.9)	
Histology			
Adenocarcinoma	12,562 (95.7)	3309 (93.6)	< 0.001
Mucinous adenocarcinoma/ signet ring cell carcinoma	561 (4.3)	227 (6.4)	
Tumor grade			0.379
Grade I/II	11,042 (84.1)	2953 (83.5)	
Grade III/IV	1111 (8.5)	297 (8.4)	
Unknown	970 (7.4)	286 (8.1)	
Race			
White	10,790 (82.2)	2780 (78.6)	< 0.001
Black	1341 (10.2)	477 (13.5)	
Other	992 (7.6)	279 (7.9)	
Gender			< 0.001
Male	6775 (51.6)	1683 (47.6)	
Female	6348 (48.4)	1853 (52.4)	
Age at diagnosis (years)			< 0.001
≤ 65	4870 (37.1)	937 (26.5)	
> 65	8253 (62.9)	2599 (73.5)	
Tumor location			< 0.001
Right colon	7677 (58.5)	2141 (60.5)	
Left colon	5446 (41.5)	1395 (39.5)	
Year of diagnosis			0.139
2004–2006	5205 (39.7)	1451 (41.0)	
2007–2010	7918 (60.3)	2085 (59.0)	
No. of lymph nodes dissected			< 0.001
1–11	5551 (42.3)	1689 (47.8)	
≥ 12	7572 (57.7)	1847 (52.2)	

compared with T1, CEA− [hazard ratio (HR) = 2.584, 95% CI = 2.167–3.082, $P < 0.001$, using T1, CEA− as the reference]. By contrast, T2, CEA+ was only associated with 79.6% increased risk of colon cancer-specific mortality compared with T1, CEA− (HR = 1.796, 95%CI = 1.489–2.168, $P < 0.001$, using T1, CEA− as the reference). We also identified some other parameters as prognostic factors, including tumor grade, race, age at diagnosis, and no. of lymph nodes dissected.

In addition, Kaplan–Meier survival curves were used to analyze the prognosis of stage I colon cancer combined with preoperative serum CEA level. Shown in Fig. 2a, T1, CEA+ was associated with the worst 5-year CSS rate compared with other subgroups (86.5% for T1, CEA+; 95.3% for T1, CEA−; 95.7% for T2, CEA−; and 91.6% for T2, CEA+, respectively; $P < 0.001$). Also, T1, CEA+ was associated with the worst 5-year OS rate compared with other subgroups (50.7% for T1, CEA+; 78.6% for T1, CEA−; 77.8% for T2, CEA−; and 62.0% for T2, CEA+, respectively; $P < 0.001$, Fig. 2b), again confirming the unfavorable prognosis of T1, CEA+.

CSS of preoperative serum CEA level in stage T1N0M0 and T2N0M0 colon cancer after PSM

Histograms of propensity score before and after PSM procedure in stages T1N0M0 and T2N0M0 are shown in Supplementary Fig. 1–2. In stage T1N0M0 colon cancer, PSM produced 1552 patients in the CEA-normal group and

Table 2 Multivariate Cox regression analyses of CSS in stage I colon cancer

Variable	University analysis		Multivariate analysis	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Histology		0.547		
Adenocarcinoma	Reference			
Mucinous adenocarcinoma/ signet ring cell carcinoma	0.914 (0.682–1.224)			
Tumor grade		0.027		0.040
Grade I/II	Reference		Reference	
Grade III/IV	1.225 (1.003–1.495)	0.047	1.272 (1.041–1.554)	0.019
Unknown	1.241 (1.004–1.533)	0.046	1.136 (0.914–1.413)	0.250
Race		< 0.001		< 0.001
White	Reference		Reference	
Black	1.566 (1.330–1.845)	< 0.001	1.613 (1.367–1.902)	< 0.001
Other	0.969 (0.769–1.220)	0.789	1.011 (0.803–1.274)	0.925
Gender		0.333		
Male	Reference			
Female	0.943 (0.838–1.062)			
Age at diagnosis (years)		< 0.001		< 0.001
≤ 65	Reference		Reference	
> 65	2.138 (1.856–2.462)		2.066 (1.791–2.384)	
Tumor location		0.904		
Right colon	Reference			
Left colon	0.904 (0.801–1.020)			
Year of diagnosis		0.115		0.538
2004–2006	Reference		Reference	
2007–2010	0.906 (0.801–1.025)		1.040 (0.917–1.180)	
No. of lymph nodes dissected		< 0.001		< 0.001
1–11	Reference		Reference	
≥ 12	0.554 (0.492–0.625)		0.579 (0.510–0.657)	
T-stage and CEA level		< 0.001		< 0.001
T1, CEA−	Reference		Reference	
T1, CEA+	2.940 (2.467–3.503)	< 0.001	2.584 (2.167–3.082)	< 0.001
T2, CEA−	1.024 (0.886–1.184)	0.746	1.099 (0.946–1.277)	0.218
T2, CEA+	1.773 (1.476–2.130)	< 0.001	1.796 (1.489–2.168)	< 0.001

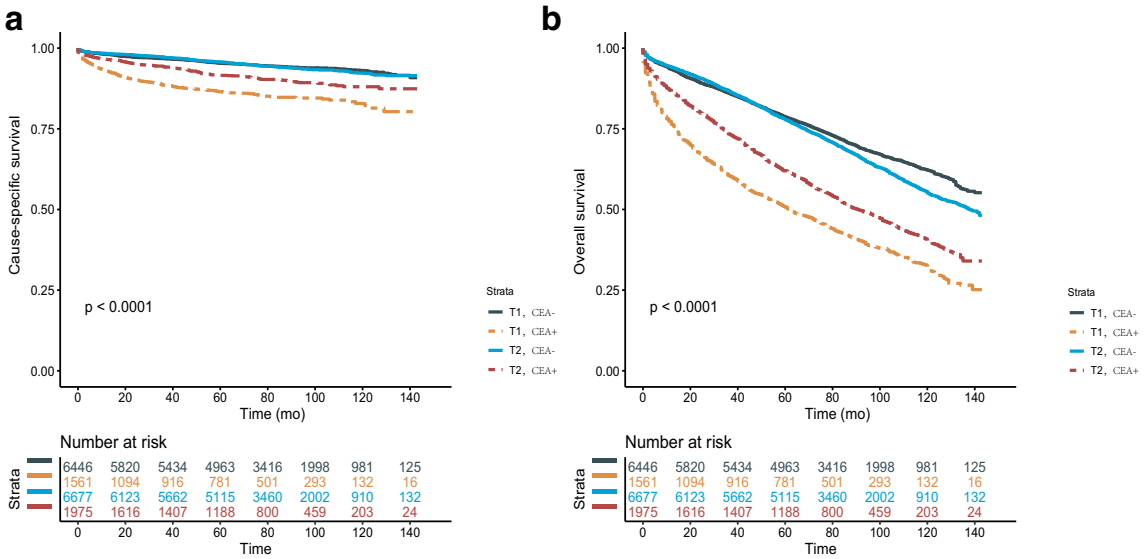

Fig. 2 Kaplan–Meier survival curves of stage T1N0M0 and stage T2N0M0 colon cancer with the combination of preoperative serum CEA level before PSM in **a** CSS and **b** OS

1552 patients in the CEA-elevated group. Then, all the tumor and patient characteristics showed no statistical differences between the two groups ($P > 0.05$, Table 3). Kaplan–Meier CSS curves showed that 5-year CSS rates of normal and elevated CEA were 94.8% and 86.6% ($P < 0.001$, Fig. 3a). In univariate Cox proportional hazards regression analysis, the cancer-specific mortality risk of CEA elevation in stage T1N0M0 colon cancer after PSM was increased by 158.1% (HR = 2.581, 95%CI = 2.010–3.315, $P < 0.001$). In stage T2N0M0 colon cancer, PSM produced 1955 patients in the CEA-normal group and 1955 patients in the CEA-elevated group. Then, all the tumor and patient characteristics showed no statistical differences between the two groups ($P > 0.05$, Table 4). Kaplan–Meier CSS curves showed that 5-year CSS rates of normal and elevated CEA were 95.9% and 91.5% ($P < 0.001$). In univariate Cox proportional hazards regression analysis, the cancer-specific mortality risk of CEA elevation in stage T1N0M0 colon cancer after PSM was increased by 72.6% (HR = 1.726, 95%CI = 1.356–2.196, $P < 0.001$, Fig. 3b).

Discussion

Traditionally, cancer cells gain the ability to metastasize as it grows to a larger size [19]. However, Wo et al. reported that very small tumors with four or more positive lymph nodes may have poorer prognosis compared with larger tumors in breast cancer and they believed very small tumor size in the context of node-positive disease may be a surrogate for biologically aggressive disease [8]. Later, two similar findings were observed in prostate cancer and colon cancer [9, 10]. The three studies suggested that early-stage tumors in the presence of metastasis may be a surrogate for inherent biologic aggressiveness.

As the single most important and reliable independent prognostic biomarker in colorectal cancer, CEA-producing tumors have been demonstrated to have a higher ability for metastasis in mouse models [11, 12]. Then, we have the reasonable assumption that, in stage I colon cancer, the elevation of preoperative serum CEA in stage T1N0M0 might be a surrogate for biologically aggressive disease compared with stage T2N0M0 in the context of serum CEA elevation.

In 2000, based on the results of several studies showing serum CEA to be a stage-independent poor prognostic factor in CRC, the Colorectal Working Group of the AJCC proposed the incorporation of C-stage to further refine the conventional AJCC TNM staging system [4, 20]. Later, however, as C-stage has not been validated and clear analyses of its implications in patient care are lack, it is yet to be incorporated in colon cancer staging. In 2011, Thirunavukarasu et al. reported that C-stage was an independent prognostic factor for colon cancer and supported the inclusion of C-stage in the conventional TNM staging of colon cancer [4]. Also using SEER database, in their study, they found that elevated preoperative serum CEA was associated with poorer prognosis compared with normal preoperative serum CEA in stage I, which was consistent with our analyses. Unfortunately, they did not further investigate the prognostic value of serum CEA elevation in stages T1NM0 and T2N0M0.

In the present study with long follow-up time (the median follow-up time reached up to 79 months), not only Cox proportional hazard analyses but also Kaplan–Meier survival analyses showed the unexpected poor prognosis of stage T1N0M0 colon cancer in the context of preoperative serum CEA elevation. In multivariate Cox analyses, the subgroup of

Table 3 Comparison of baseline characteristics of stage T1N0M0 colon cancer by the serum CEA level after PSM

Variable	No. of patients (%)		*P*
	CEA-normal (*N* = 1552)	CEA-elevated (*N* = 1552)	
Histology			0.919
Adenocarcinoma	1502 (96.8)	1503 (96.8)	
Mucinous adenocarcinoma/ signet ring cell carcinoma	50 (3.2)	49 (3.2)	
Tumor grade			0.631
Grade I/II	1180 (76.0)	1194 (76.9)	
Grade III/IV	124 (8.0)	110 (7.1)	
Unknown	248 (16.0)	248 (16.0)	
Race			0.937
White	1200 (77.3)	1194 (76.9)	
Black	218 (14.0)	225 (14.5)	
Other	134 (8.6)	133 (8.6)	
Gender			0.858
Male	796 (51.3)	791 (51.0)	
Female	756 (48.7)	761 (49.0)	
Age at diagnosis (years)			0.873
≤ 65	432 (27.8)	423 (27.6)	
> 65	1120 (72.2)	1124 (72.4)	
Tumor location			0.719
Right colon	827 (53.3)	817 (52.6)	
Left colon	725 (46.7)	735 (47.4)	
Year of diagnosis			0.884
2004–2006	645 (41.6)	641 (41.3)	
2007–2010	907 (58.4)	911 (58.7)	
No. of lymph nodes dissected			0.870
1–11	1005 (64.8)	1004 (54.7)	
≥ 12	547 (35.2)	548 (35.3)	

T1, CEA+ presented up to 158.4% increased risk of colon cancer-specific mortality compared with T1, CEA−. By contrast, T2, CEA+ was only associated with 79.6% increased risk of colon cancer-specific mortality compared with T1, CEA−. Kaplan–Meier survival curves showed that T1, CEA+ was associated with the worst 5-year CSS (86.5% for T1, CEA+; 95.3% for T1, CEA−; 95.7% for T2, CEA−; 91.6% for T2, CEA+, respectively) and OS (50.7% for T1, CEA+; 78.6% for T1, CEA−; 77.8% for T2, CEA−; 62.0% for T2, CEA+, respectively) rates compared with other subgroups. This finding was consistent with our previous hypothesis that early-stage colon cancer with elevated level of serum CEA could predict unexpected poor prognosis. We have also made a secondary analysis comparing the oncologic outcomes between normal and elevated serum CEA using PSM, in stages T1N0M0 and T2N0M0, respectively. After PSM, univariate Cox analysis showed that the cancer-specific mortality risk of CEA elevation in stage T1N0M0 colon cancer was increased by 72.6%. By contrast, the cancer-specific mortality risk of CEA elevation in stage T1N0M0 colon cancer was increased by up to 158.1%, which as in line with the aforementioned analyses. The 5-year CSS rate of T1, CEA+ was only 50.7%, even worse than T2, CEA+ (62.0%).

The difference in colon cancer-specific mortality between stage T1 and T2 CEA-elevated tumors was present even after adjusting for other clinicopathological characteristics, which suggested that the increased biological aggressiveness of stage T1N0M0 CEA-elevated tumors could provide some undetected prognostic information beyond what is captured by conventional clinicopathological variables. This could help to identify additional markers that have not yet been identified, which may be related to the metastatic potential of colon tumors.

Our findings suggested that early-stage tumors with serum CEA elevation might experience relatively early acquisition of genetic changes in the pathways involved in metastasis. And some previous studies identified the alterations in the expression of certain genes including BamBi, DGKζ, soCs1, DaCh1, and C5a that impact the metastatic potential of colon

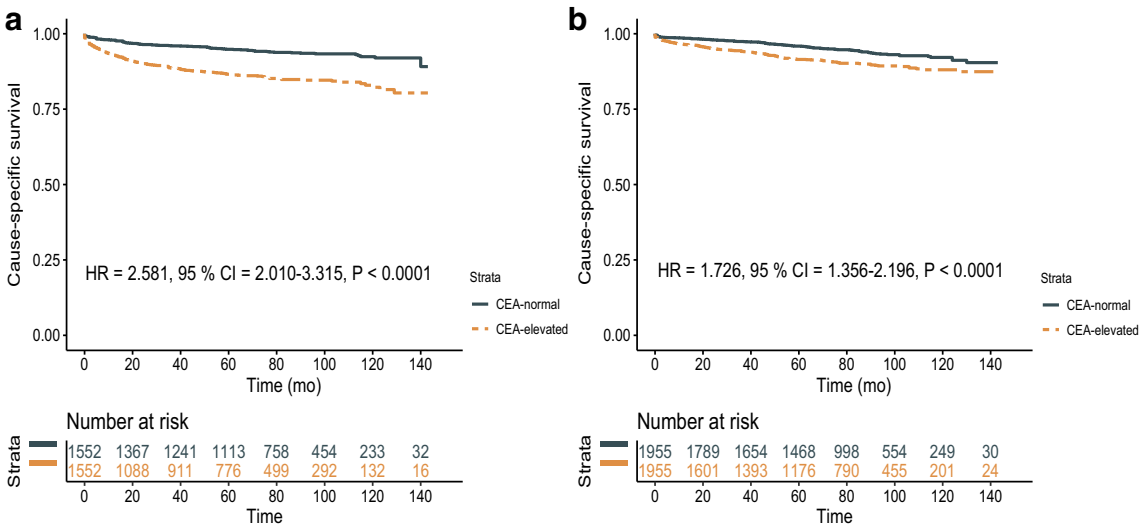

Fig. 3 Kaplan–Meier CSS curves of preoperative serum CEA level after PSM in stages **a** T1N0M0 and **b** T2N0M0 colon cancer

Table 4 Comparison of baseline characteristics of stage T2N0M0 colon cancer by the serum CEA level after PSM

Variable	No. of patients (%)		*P*
	CEA-normal ($N = 1955$)	CEA-elevated ($N = 1955$)	
Histology			0.641
Adenocarcinoma	1791 (91.6)	1799 (92.0)	
Mucinous adenocarcinoma/ signet ring cell carcinoma	164 (8.4)	156 (8.0)	
Tumor grade			0.986
Grade I/II	1751 (89.6)	1754 (89.7)	
Grade III/IV	176 (9.0)	173 (8.8)	
Unknown	28 (1.4)	28 (1.4)	
Race			0.258
White	1603 (82.0)	1573 (80.5)	
Black	211 (10.8)	244 (12.5)	
Other	141 (7.2)	138 (7.1)	
Gender			0.699
Male	867 (44.3)	879 (45.0)	
Female	1088 (55.7)	1076 (55.0)	
Age at diagnosis (years)			0.884
≤ 65	507 (25.9)	503 (25.7)	
> 65	1448 (74.1)	1452 (74.3)	
Tumor location			0.892
Right colon	1302 (66.6)	1306 (66.8)	
Left colon	653 (33.4)	649 (33.2)	
Year of diagnosis			0.720
2004–2006	788 (40.3)	799 (40.9)	
2007–2010	1167 (59.7)	1156 (59.1)	
No. of lymph nodes dissected			0.893
1–11	675 (34.5)	671 (34.3)	
≥ 12	1208 (65.5)	1284 (65.7)	

cancer cells [21–25]. Early-stage tumor-activating pathways such as these earlier in cancer progression might then contribute to the elevation of preoperative serum CEA elevation though the primary tumor is very small. These tumors are more likely to be associated with aggressive tumor biology and present a poor prognosis.

Moreover, our study identified a subgroup of stage I colon cancer patients with dismal prognosis, which need to be paid more attention to. According to the National Comprehensive Cancer Network (NCCN) guidelines, stage I colon cancer was treated with surgical resection alone because of the favorable prognosis. The present study indicated that some stage I colon cancer such as stage T1N0M0 in the context of serum CEA elevation might be candidates for intensification of adjuvant treatment.

Still, there are also some limitations in the present study. First, data on microsatellite instability (MSI) which was proved to be a strong prognostic factor was unavailable from SEER database. Second, though our analyses were based on a large population with long follow-up time (the median follow-up time reached up to 79 months) using propensity score matching, it was merely a retrospective one, and prospective clinical studies concerning our findings are also needed to be conducted. Finally, the SEER database lacked the data on local recurrence. Local recurrence is an important factor that is associated with the survival of colon cancer. Yet this would have minimal impact on this study as stage I colon cancer has very low possibility of tumor relapse.

In conclusion, this large population-based and propensity score–matched study with long follow-up time provides the first evidence that stage T1N0M0 colon cancer with the elevation of preoperative serum CEA would be a surrogate of aggressive tumor biology and predict poor prognosis. In addition, this subgroup of colon cancer needs to be paid more attention in clinical practice. Our study would also provide the researchers a better understanding of tumor biology and elicit further investigation on the prognostic markers related to the metastatic potential of colon tumors.

Compliance with ethical standards

Competing interests The authors declare that they have no conflict of interest.

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