

Determination of the prognostic value of preoperative CA15-3 and CEA in predicting the prognosis of young patients with breast cancer

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Abstract. To the best of our knowledge, no previous study has investigated the association of carcinoembryonic antigen (CEA) and cancer antigen 15-3 (CA15-3) with the prognosis for young patients (≤ 40 years) with breast cancer. In the present study, preoperative CEA and CA15-3 serum levels were evaluated in the prediction of the prognosis for young patients with breast cancer. In total, 699 patients were recruited, for which the CEA and CA15-3 serum levels had been measured prior to surgery via a blood sample. The optimal cut-off high and low values were determined using receiver operating characteristic curve analysis and Youden's index. The value of CEA and CA15-3 in predicting overall survival (OS) and disease-free survival (DFS) were measured using univariate and multivariate Cox's regression analyses. The cut-off values were 3.38 ng/ml and 12.32 U/ml for CEA and CA15-3, respectively. It was identified that CEA, but not CA15-3, was a predictor for the prognosis of the young patients with breast cancer. Multivariate analysis confirmed that CEA, but not CA15-3, was an independent prognostic marker for all young patients with breast cancer. In total, 623 young patients exhibited decreased levels of CEA; in these patients, CA15-3 with a cut-off value of 12.48 U/ml was an independent prognostic factor for OS and DFS. Preoperative serum CEA may thus serve as an independent predictor of poor prognosis for young patients with

breast cancer. However, for low-risk patients with decreased CEA levels, serum CA15-3 may supplement the prediction of overall prognosis.

Introduction

Breast cancer has the highest incidence rate in women, and has increased steadily in incidence in China in recent years (1-4). Young patients (≤ 40 years) are estimated to account for ~6-7% of all patients with breast cancer (5). The biological and clinical characteristics of breast cancer between younger and older patients vary. For example, breast cancer in younger patients typically exhibits the following features: More malignant in nature, usually diagnosed at advanced tumor stage, increased tumor grade, larger tumor size and higher lymph node-positive rates, compared with older patients (6-9). Therefore, prediction methods and treatment strategies for patients with breast cancer should be altered according to the age of the patient. Identifying the most comprehensive and credible prognostic factors to assist in decision-making for young patients with breast cancer is essential in improving the impact of therapy.

Currently, the most commonly used pathological factors include tumor size, lymph node status, tumor grade, and estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER-2) status (10,11). Serum tumor markers have attracted increasing attention for their use in the screening and monitoring of different types of cancer. Among several tumor markers, CEA and CA15-3 are the two most widely used for breast cancer. Numerous studies have been performed to quantitatively evaluate the serum levels of these two tumor markers, which have identified a wide range of cut-off values for predicting the prognosis of poor survival in breast cancer (12-21). At present, the predictive abilities of CEA and CA15-3 remain unclear. Ebeling *et al* (22) investigated 1,046 patients with breast cancer and identified via multivariate analysis that CA15-3 was not a predictor for poor outcome; however, as reviewed by Duffy (23), increased CA15-3 may be associated with a poor outcome in patients with breast cancer. Despite CEA exhibiting a lower positive rate (positive CEA values ranged from 1.99-10 ng/ml, and positive CEA levels ranged from 7.1-36%) in breast cancer,

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there are fewer large-scale studies investigating its prognostic ability (12,24-27).

To the best of our knowledge, no previous studies have demonstrated any potential prognostic values of CEA and CA15-3 in young patients with breast cancer. In the present study, clinicopathological data and preoperative serum CEA and CA15-3 levels of young patients with breast cancer were retrospectively analyzed in order to explore whether these tumor markers could be used to predict the prognosis of patients with breast cancer. Furthermore, the associations between clinicopathological parameters and these two tumor markers were also analyzed.

Patients and methods

Study population. All patients in the retrospective study were treated between January 2008 and December 2012 at the Sun Yat-Sen University Cancer Center (Guangzhou, China) and were diagnosed with invasive breast cancer. Patient data collected for the present study included clinicopathological information, treatment modalities and details of patient outcome. The inclusion criteria for the study were as follows: i) Invasive breast cancer defined using histological examination; ii) no other types of cancer diagnosed or serious disease prior to diagnosis; iii) non-metastatic breast cancer at the time of diagnosis; iv) patients received surgery which completely removed the tumor; v) available and complete clinicopathological and follow-up data; vi) testing of CEA and CA15-3 levels prior to surgery; and vii) no neoadjuvant chemotherapy or radiotherapy prior to surgery. Patients with stage IV tumors or carcinoma *in situ* without invasive lesions were excluded.

Clinical data collection. Basic characteristics collected included age, surgery method, tumor size, axillary lymph node status, and ER, PR and HER-2 status. Tumor-node-metastasis (TNM) staging was based on the American Joint Committee on Cancer criteria, 7th edition (28). The disease subtypes were defined as follows: Luminal A (ER and/or PR-positive, HER-2-negative and Ki-67<14%), luminal B (ER and/or PR-positive alone with HER-2-positive or Ki-67>14%), HER-2 overexpressing (ER and PR all negative, HER-2-positive) and triple-negative breast cancer (ER, PR and HER-2-negative). HER-2 positivity was defined as 3+ in immunohistochemical tests, which were performed using a polyclonal human c-erbB-2/neu antibody, and >30% of the tumor cells were stained (29). Fluorescence *in situ* hybridization (FISH) tests were performed to determine the status of the HER-2 gene when the immunohistochemical score was 2+ (immunohistochemistry demonstrated 10-30% tumor cell staining) according to a protocol described previously (30). If a FISH test was not performed, the cases of 2+ were regarded as missing data. A complete blood count and levels of CEA and CA15-3 tumor markers were performed as part of the routine clinical evaluation prior to surgery.

Study endpoints. The first day of follow-up was considered as the day of confirmed pathological diagnosis. The follow-up consisted of the reexamination of records or phone calls, and included medical history, physical and

laboratory examinations, and radiological imaging tests to detect metastasis or relapse. Overall survival (OS) was calculated as from the day of pathological confirmation to the day of the follow-up endpoint or mortality from any cause. Disease-free survival (DFS) was calculated as from the time of pathological confirmation to the time of first recurrence (local recurrence, distant metastasis or patient mortality).

Statistical analyses. Comparisons between different variables were made using Pearson's χ^2 -square test or Fisher's exact test. The clinical significance and the optimal cut-off value of CEA and CA15-3 were determined using ROC curve analysis. The highest Youden's index was used to stratify patients into 2 ranges according to the cut-off value. The OS and DFS were determined using the Kaplan-Meier method and log-rank test. The influence of potential factors on OS and DFS were determined using univariate and multivariate Cox proportional hazards analyses. The relative risk of each factor was demonstrated using hazard ratios (HRs) and 95% corresponding confidence intervals (CIs). Significance in univariate analyses was regarded as $P<0.1$, whereas $P<0.05$ was considered to indicate a statistically significant difference for other results. All statistical analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics. In total, out of 699 cases in the present retrospective study, 81 (11.6%) patients were 20-30 years, 181 (25.9%) patients were 30-35 years and 437 (62.5%) patients were 35-40 years at the time of the histopathological diagnosis of invasive breast cancer. The median age of the patients was 36. The basic clinicopathological characteristics are presented in Table I. The mean follow-up time was 56 months. The number of patients with stage I, II and III tumors were 239 (34.2%), 308 (44.1%) and 152 (21.7%), respectively. Among all cases, the identified sub-types were luminal A (134, 19.2%), luminal B (364, 52.1%), triple-negative (89, 12.7%), HER2-positive (78, 11.1%) and unknown type (34, 4.9%).

Optimal cut-off values for CEA and CA15-3. The optimal cut-off values for CEA and CA15-3 were determined using ROC curve analysis (Fig. 1). The areas under the curves (AUCs) for CEA and CA15-3 were 0.695 ($P<0.001$) and 0.531 ($P=0.504$), respectively, for all patients. Using the highest Youden's index value, the cut-off values for CEA and CA15-3 were set as 3.38 ng/ml and 12.31 U/ml, respectively. Patients were stratified into 2 levels (low-CEA and high-CEA or low-CA15-3 and high-CA15-3) according to their respective cut-off values: 76 (10.9%) of the patients exhibited high CEA, and 623 (89.1%) low CEA; 295 (42.2%) of the patients exhibited high CA15-3 and 404 (57.8%) low CA15-3.

The associations between CEA or CA153 with clinicopathological characteristics are presented in Table I. CEA was significantly associated with the surgery method ($P=0.032$), TNM stage ($P=0.079$), tumor size ($P<0.001$), axillary lymph node status ($P=0.001$) and HER-2 status ($P=0.004$). However,

Table I. Association of clinicopathological characteristics with CEA and CA15-3 level in young patients with breast cancer.

Variables	CEA, n (%)		P-value	CA15-3, n (%)		P-value
	Low	High		Low	High	
Age, years			1.000			0.752
≤35	234 (89.3)	28 (10.7)		149 (56.9)	113 (43.1)	
>35	389 (89.0)	48 (11.0)		255 (58.4)	182 (41.6)	
Surgical option			0.032			0.151
Modified radical mastectomy	492 (87.9)	68 (12.1)		316 (56.4)	244 (43.6)	
Conserving surgery	131 (94.2)	8 (5.8)		88 (63.3)	51 (36.7)	
Tumor stage			<0.001			0.022
T1	312 (91.2)	30 (8.8)		208 (60.8)	134 (39.2)	
T2	280 (90.0)	31 (10.0)		178 (57.2)	133 (42.8)	
T3	15 (60.0)	10 (40.0)		12 (48.0)	13 (52.0)	
T4	16 (76.2)	5 (23.8)		6 (28.6)	15 (71.4)	
Lymph node metastasis			0.001			0.050
N0	348 (92.3)	29 (7.7)		231 (61.3)	146 (38.7)	
N1	155 (86.1)	25 (13.9)		105 (58.3)	75 (41.7)	
N2	77 (90.6)	8 (9.4)		42 (49.4)	43 (50.6)	
N3	43 (75.4)	14 (24.6)		26 (45.6)	31 (54.4)	
TNM stage			0.079			0.036
I	218 (91.2)	21 (8.8)		145 (60.7)	94 (39.3)	
II	277 (89.9)	31 (10.1)		185 (60.1)	123 (39.9)	
III	128 (84.2)	24 (15.8)		74 (48.7)	78 (51.3)	
ER			0.595			1.000
Positive	444 (89.5)	52 (10.5)		287 (57.9)	209 (42.1)	
Negative	179 (88.2)	24 (11.8)		117 (57.6)	86 (42.4)	
PR			0.793			0.455
Positive	431 (88.9)	54 (11.1)		285 (58.8)	200 (41.2)	
Negative	192 (89.7)	22 (10.3)		119 (55.6)	95 (44.4)	
HER-2			0.004			0.053
Positive	173 (84.0)	33 (16.0)		107 (51.9)	99 (48.1)	
Negative	439 (91.8)	39 (8.2)		287 (60.0)	191 (40.0)	
Intrinsic subtypes			0.115			0.376
Luminal A	126 (94.0)	8 (6.0)		83 (61.9)	51 (38.1)	
Luminal B	318 (87.4)	46 (12.6)		204 (56.0)	160 (44.0)	
Triple-negative	83 (93.3)	6 (6.7)		48 (53.9)	41 (46.1)	
HER-2 overexpression	67 (85.9)	11 (14.1)		45 (57.7)	33 (42.3)	
Missing data	29 (85.3)	5 (14.7)		24 (70.6)	10 (29.4)	
Adjuvant chemotherapy			0.472			0.980
Yes	563 (89.1)	69 (10.9)		366 (57.9)	266 (42.1)	
No	53 (91.4)	5 (8.6)		33 (56.9)	25 (43.1)	
Missing data	7 (77.8)	2 (22.2)		5 (55.6)	4 (44.4)	
Adjuvant radiotherapy			0.222			0.973
Yes	214 (91.5)	20 (8.5)		134 (57.3)	100 (42.7)	
No	362 (87.4)	52 (12.6)		240 (58.0)	174 (42.0)	
Missing data	47 (92.2)	4 (7.8)		30 (58.9)	21 (41.1)	
Endocrine therapy			0.503			0.151
Yes	439 (88.3)	58 (11.7)		296 (59.6)	201 (40.4)	
No	124 (91.9)	11 (8.1)		68 (50.4)	67 (49.6)	
Missing data	60 (89.6)	7 (10.4)		40 (59.7)	27 (40.3)	

Table I. Continued.

Variables	CEA, n (%)		P-value	CA15-3, n (%)		P-value
	Low	High		Low	High	
Overall survival outcome			<0.001			0.034
Surviving	599 (91.0)	59 (9.0)		387 (58.8)	271 (41.2)	
Deceased	24 (58.5)	17 (41.5)		17 (41.5)	24 (58.5)	

P-values were determined using the χ^2 test. TNM, tumor-node-metastasis; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor-2.

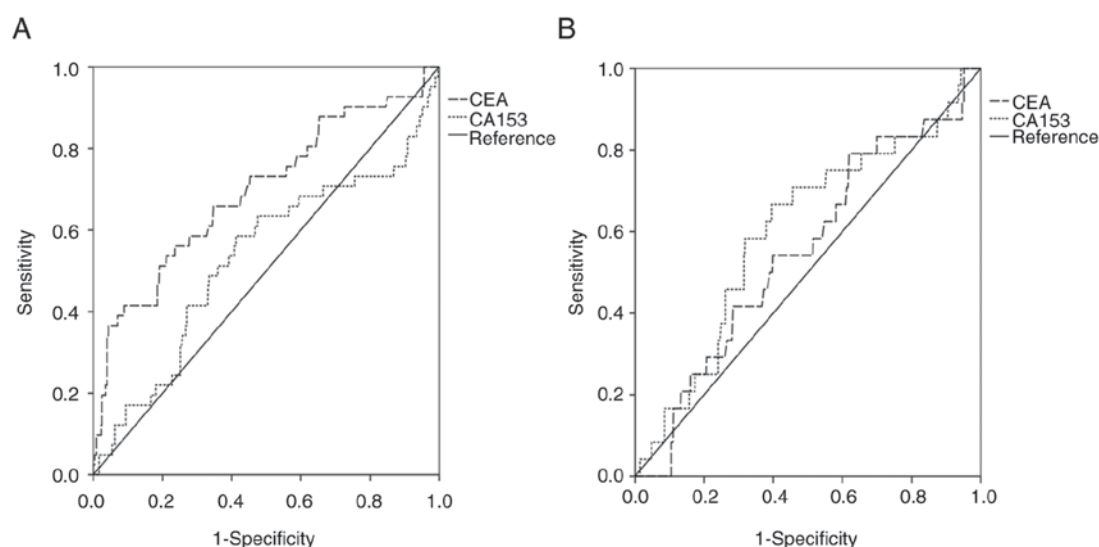


Figure 1. ROC curve for CEA and CA15-3. (A) ROC curve of CEA and CA15-3 for all patients. CEA AUC=0.695, $P<0.001$; CA15-3 AUC=0.531, $P=0.504$. (B) ROC curve of CEA and CA15-3 in low CEA patients. CEA AUC=0.551, $P=0.399$; CA15-3 AUC=0.600, $P=0.098$. ROC, receiver operating characteristic; CEA, carcinoembryonic antigen; CA, cancer antigen; AUC, area under the curve.

CEA was not significantly associated with ER status, PR status, molecular sub-type or follow-up treatment method (all $P>0.05$; Table I). CA153 was only significantly associated with TNM stage ($P=0.036$) and tumor size ($P=0.022$). From the 623 low patients with CEA, the AUCs for CEA and CA15-3 were 0.551 ($P=0.399$) and 0.600 ($P=0.098$), respectively, and the cut-off values were 1.085 ng/ml and 12.48 U/ml.

Association between CEA or CA15-3 and survival outcomes in all young patients with breast cancer. In the present study, the OS rate was 94.1% and the DFS rate was 82.4% for all patients. As demonstrated by the Kaplan-Meier curves, high CEA and CA15-3 were associated with poor OS and DFS in the young patients with breast cancer (Fig. 2). Univariate analysis indicated that patient OS may have been associated with age, surgical method, TNM stage, ER, CEA and CA15-3 levels ($P<0.1$). Multivariate analysis indicated that CEA was an independent prognostic factor for OS ($P<0.001$) with a HR of 2.732 (95% CI, 1.792-4.164). Other identified prognostic factors for OS included age, ER status and TNM stage (Table II). Univariate analysis revealed that DFS was associated with age, TNM stage, CEA and CA15-3 levels ($P<0.1$). Multivariate analysis identified that CEA and TNM stage were

independent prognostic factors for DFS (Table II). However, CA15-3 was not an independent prognostic marker for OS or DFS in the multivariate analysis (Table II).

Association between CA15-3 and survival outcomes in low-CEA patients. The 623 patients with low CEA had an OS rate of 96.1% and a DFS rate of 84.8%. As demonstrated with Kaplan-Meier curves, high CA15-3 within the low CEA group was associated with poor OS and DFS. Relatively high CEA was associated with DFS, and not with OS, in the low-CEA young breast cancer patients (Fig. 3). Furthermore, a univariate analysis demonstrated that OS in this group was associated with age, TNM stage, PR, CEA and CA15-3 levels ($P<0.1$). Multivariate analysis demonstrated that age, TNM stage, PR and CA15-3 levels were independent prognostic factors for OS in this group ($P<0.05$). Multivariate analysis for DFS demonstrated that TNM stage and CA15-3 were independent predictive markers (Table III).

Discussion

A definitive definition for young patients with breast cancer remains controversial. Based on a search of the MEDLINE

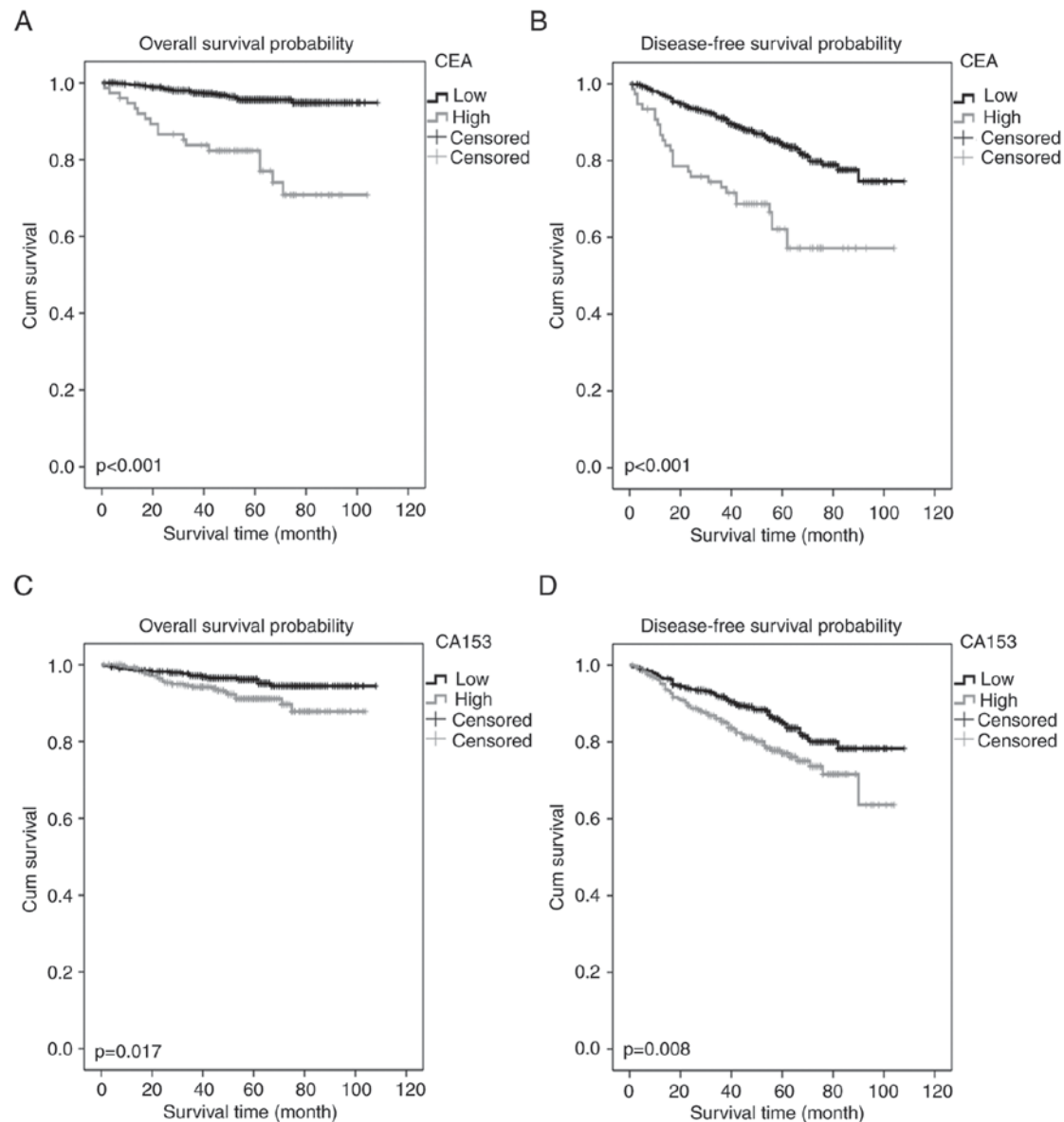


Figure 2. Kaplan-Meier estimator curves of survival rates for young patients with breast cancer. (A) Overall survival and (B) disease-free survival for the young patients with breast cancer stratified by the CEA cut-off level. (C) Overall survival and (D) disease-free survival for all young patients with breast cancer according to the CA15-3 cut-off level. CEA, carcinoembryonic antigen; CA, cancer antigen.

and Cancer Lit databases for the definition of 'young age' in breast cancer, one study defined this as between 35 and 40 years of age (31). Other studies defined young patients with breast cancer as <40 years of age (8,9,32-34). Despite recent improvements in cancer treatment, the OS and DFS rates for younger patients (≤ 40 years) are markedly lower than for older patients (> 40 years) with breast cancer (35). This is potentially due to differences in the biological and physiological parameters of the disease, including the increased likelihood of aggressive subtypes of breast cancer in younger patients (33,36). Despite these differences, the standard treatment is similar for both young and old breast cancer patients. In the present study, patients that were aged ≤ 40 years were considered 'young patients'. The median age of the 699 patients included in the present study was 36 years. However, it is notable that previous studies which divided patients into groups <35 years and >35 years demonstrated that age had

no predictive value for OS and DFS (21,35). Despite this, in the present study, multivariate analysis identified that age had independent prognostic value for OS. Consequently, as age may be an independent prognostic marker, breast cancer in young patients may potentially be regarded as a separate disease subtype.

Blood samples were obtained from each patient prior to surgery to test CEA and CA15-3 levels. CEA and CA15-3 are the most investigated tumor markers in breast cancer, and when the acquisition of tissue specimens is not possible, these markers may offer useful information about the disease phenotype in the early stages (13). However, their sensitivity and specificity may differ according to the cut-off value used. In our hospital (Sun Yat-sen University Cancer Center), the cut-off values for CEA and CA15-3 are usually 5 ng/ml and 25 U/ml, respectively; these cut-off values are the most commonly used (21,37). The value of tumor markers varies

Table II. Univariate and multivariate analysis of factors for OS and DFS in all patients.

A, Association of factors with OS				
Variable	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (>35/≤35 years)	0.457 (0.246-0.846)	0.013	0.403 (0.215-0.775)	0.005
Surgical option (conserving surgery/ modified radical mastectomy)	0.321 (0.099-1.041)	0.058	0.572 (0.170-1.921)	0.366
TNM stage				
I	1 (reference)		1 (reference)	
II	4.281 (1.247-14.692)	0.021	3.960 (1.152-13.616)	0.029
III	13.297 (3.978-44.443)	<0.001	11.026 (3.219-37.771)	<0.001
ER (-/+)	1.821 (0.978-3.391)	0.059	2.415 (1.272-4.588)	0.007
PR (-/+)	1.416 (0.749-2.675)	0.284		
HER-2 (-/+)	0.648 (0.343-1.226)	0.182		
CEA (high/low)	6.128 (3.291-11.409)	<0.001	4.962 (2.647-9.302)	<0.001
CA15-3 (high/low)	2.100 (1.127-3.911)	0.019	1.765 (0.930-3.351)	0.082
B, Association of factors with DFS				
Variable	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (>35/≤35 years)	0.728 (0.510-1.039)	0.08	0.702 (0.491-1.003)	0.052
Surgical option (conserving surgery/ modified radical mastectomy)	0.800 (0.495-1.292)	0.361		
TNM stage				
I	1 (reference)		1 (reference)	
II	1.290 (0.805-2.068)	0.29	1.236 (0.771-1.983)	0.379
III	3.440 (2.164-5.468)	<0.001	3.206 (1.945-4.960)	<0.001
ER (-/+)	1.268 (0.869-1.849)	0.218		
PR (-/+)	1.119 (0.763-1.642)	0.565		
HER-2 (-/+)	0.785 (0.536-1.149)	0.214		
CEA (high/low)	2.732 (1.792-4.164)	<0.001	2.451 (1.599-3.756)	<0.001
CA15-3 (high/low)	1.608 (1.129-2.291)	0.009	1.389 (0.970-1.988)	0.073

P<0.1 was considered to indicate statistical significance for univariate analysis, and P<0.05 for multivariate analysis. OS, overall survival; DFS, disease-free survival; CI, confidence interval; HR, hazard ratio; TNM, tumor-node-metastasis; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor-2; CEA, carcinoembryonic antigen; CA, cancer antigen.

depending on the molecular sub-group. To determine the cut-off value with the strongest prognostic ability, several different cut-off values have previously been applied for CEA (2-10 ng/ml) and CA15-3 (21.8-60 U/ml) (12,14,18,38-41). In the present study, CEA and CA15-3 were identified as prognostic predictors for young patients with breast cancer according to ROC curve analysis. Multivariate analysis revealed that CA15-3 was not an independent prognostic factor, whereas CEA could independently predict the prognosis. These results differ from previous studies that have

identified CA15-3 as an independent prognostic marker for breast cancer (19,21,37). This difference may be due to the relatively powerful prognostic ability of CEA in young patients with breast cancer, or because CEA and CA15-3 have a strong collinear association in young patients with breast cancer that influences the predictive function of CA15-3.

Based on the highest Youden's index value, the present study selected 3.38 ng/ml CEA and 12.31 U/ml CA15-3 as the optimal cut-off values. These cut-offs were more

Table III. Univariate and multivariate analysis.

A, Association of factors with OS

Variable	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (>35/≤35 years)	0.358 (0.157-0.819)	0.015	0.303 (0.131-0.701)	0.005
Surgical option (conserving surgery/ modified radical mastectomy)	0.339 (0.080-1.443)	0.143		
TNM stage				
I	1 (reference)		1 (reference)	
II	9.086 (1.173-70.380)	0.035	8.855 (1.140-68.765)	0.037
III	23.040 (2.995-177.235)	0.003	25.538 (3.292-198.121)	0.002
ER (-/+)	1.8982 (0.840-4.262)	0.124		
PR (-/+)	2.068 (0.925-4.622)	0.077	2.445 (1.086-5.507)	0.031
HER-2 (-/+)	0.681 (0.291-1.595)	0.377		
CEA (high/low) ^a	2.332 (0.871-6.246)	0.092	2.316 (0.853-6.287)	0.099
CA15-3 (high/low) ^a	3.143 (1.345-7.347)	0.008	2.970 (1.263-6.986)	0.013

B, Association of factors with DFS

Variable	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (>35/≤35 years)	0.807 (0.537-1.213)	0.302		
Surgical option (conserving surgery/ modified radical mastectomy)	0.900 (0.539-1.504)	0.688		
TNM stage				
I	1 (reference)		1 (reference)	
II	1.356 (0.797-2.305)	0.261	1.326 (0.779-2.255)	0.298
III	3.442 (2.029-5.839)	<0.001	3.196 (1.879-5.435)	<0.001
ER (-/+)	1.189 (0.768-1.840)	0.438		
PR (-/+)	1.238 (0.806-1.904)	0.330		
HER-2 (-/+)	0.866 (0.551-1.361)	0.532		
CEA (high/low) ^a	1.625 (1.040-2.539)	0.033	1.471 (0.940-2.302)	0.091
CA15-3 (high/low) ^a	1.753 (1.171-2.623)	0.006	1.635 (1.092-2.449)	0.017

^aCut-off value using the highest Youden's index value from the ROC curve of low-CEA patients. P<0.1 was considered to indicate statistical significance for univariate analysis, and P<0.05 for multivariate analysis. OS, overall survival; DFS, disease-free survival; CI, confidence interval; HR, hazard ratio; TNM, tumor-node-metastasis; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor-2; CEA, carcinoembryonic antigen; CA, cancer antigen.

selective than the 5 ng/ml for CEA and 25 U/ml for CA15-3 typically used for breast cancer. This may be because only primary early stage (I-III) patients were included; CEA and CA15-3 levels may increase significantly in metastatic or recurrent breast cancer (24,42-44). Therefore, in order to get the best predictive value, it may be necessary to use different cut-off values of these markers depending on the TNM stage. The multivariate analysis conducted in the present study revealed that CEA was an independent predictor for OS and

DFS for all included patients. The present study categorized patients into low or high CEA groups, and demonstrated that patients in the high CEA group had relatively poor outcomes.

The results regarding CA15-in the present study were similar to Ebeling *et al* (22), as the study also suggested that CA15-3 was not an independent prognostic factor for poor overall survival. However, in the low-CEA group, CA15-3 could independently predict the patient prognosis. Collectively,

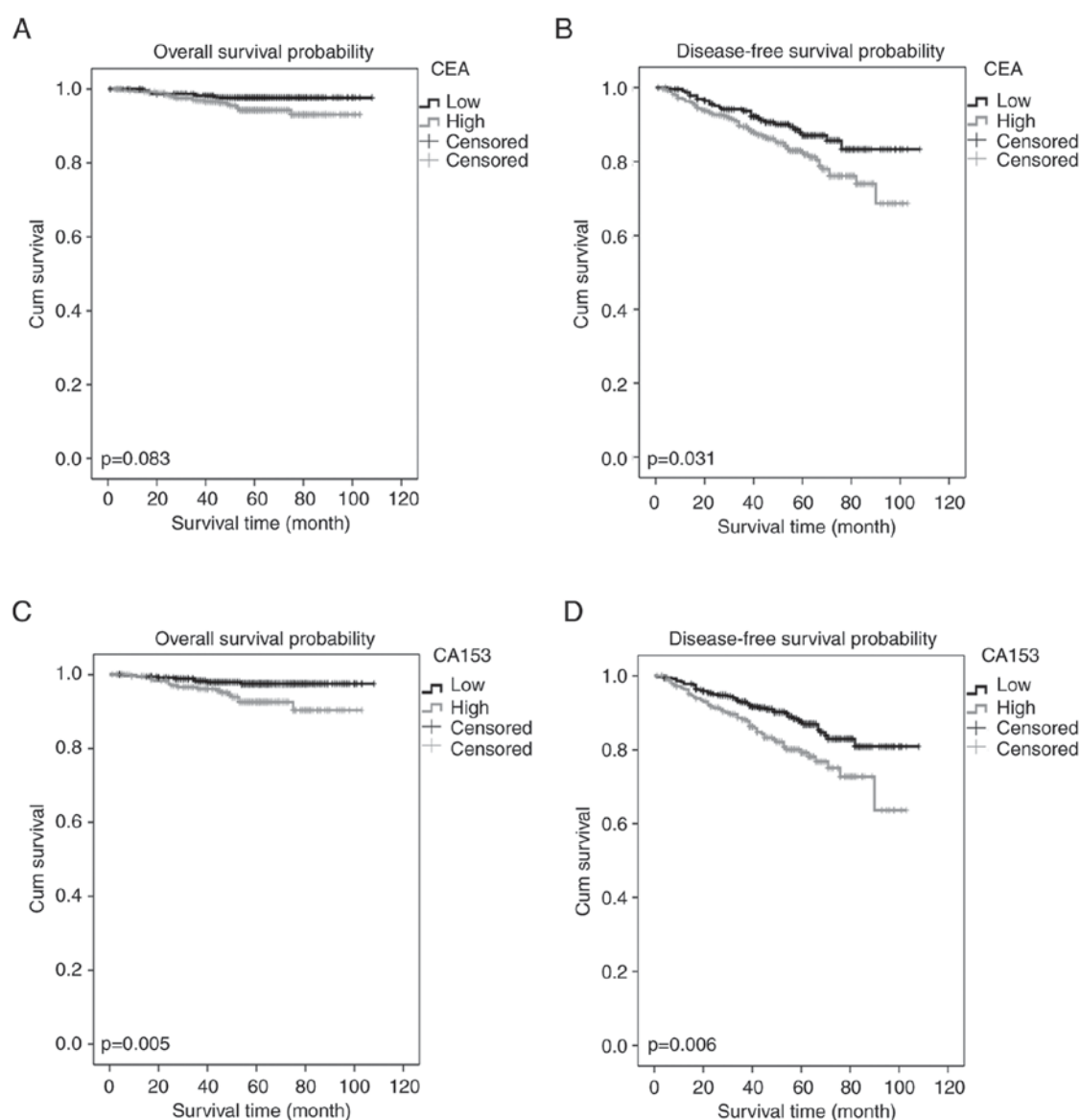


Figure 3. Kaplan-Meier estimator curves of survival rates for patients with low CEA levels. (A) Overall survival and (B) disease-free survival for the young patients with breast cancer according to the CEA cut-off level for the low CEA group. (C) Overall survival and (D) disease-free survival for the young patients with breast cancer according to the CA15-3 cut-off level for the low CEA group. CEA, carcinoembryonic antigen; CA, cancer antigen.

the data suggested that if preoperative serum CEA is elevated in young patients with breast cancer, it may not be necessary to test CA15-3 levels; however, if CEA is not elevated, the level of CA15-3 may provide additional prognostic information. These results are inconsistent with data presented by Harris *et al* (45), as results demonstrated that CEA may be supplementary to CA15-3.

In young patients with breast cancer, the CEA levels were decreased in patients who underwent breast-conserving surgery. This may be because conservation surgery is selected in cases with a decreased tumor burden, including a decreased tumor size and fewer metastatic lymph nodes. In the present study, patients exhibited no significant difference in adjuvant chemotherapy, radiotherapy and endocrine therapy depending on their CEA and CA15-3 levels. As preoperative levels of CEA and CA15-3 lack organ and tumor specificity, and exhibit low sensitivity, they may not be useful in guiding follow-up treatment after surgery (45,46).

There were limitations to the present retrospective study. For example, it was a single-institution retrospective analysis, and despite the formulation of inclusion and exclusion criteria to minimize selective bias, it cannot be avoided completely. Furthermore, results were based on a relatively small database as it focused on a small sub-group (young patients with breast cancer) that constitutes 6-7% of all breast cancer cases. Therefore, applying the results of the present study to all patients will require further consideration.

In conclusion, the present study demonstrated that a relatively high preoperative level of CEA was an independent prognostic factor, and that relatively high CA15-3 was an independent prognostic factor in the patients with low CEA levels, by applying univariate and multivariate analyses. Combining CEA and CA15-3 with other factors may help clinicians assess the risks of metastasis and mortality after surgery in young patients with breast cancer. Further prospective studies will be essential for the validation of these results.

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