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A new prognostic factor of breast cancer: High carboxyl ester lipase expression related to poor survival

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ABSTRACT

Objective: The enzyme carboxyl ester lipase (CEL), known as bile salt-dependent lipase (BSDL) or bile salt-stimulated lipase (BSSL), is mainly expressed in pancreatic acinar cells and lactating mammary glands. To investigate the link between CEL expression of breast cancer (BC) tissues and the survival of BC patients by analyzing The Cancer Genome Atlas Breast Carcinoma (TCGA-BRCA) level 3 data.
Methods: The clinical information and RNA-sequencing (RNA-Seq) expression data were downloaded from TCGA. Patients were divided into a high CEL expression group and a low CEL expression group using the optimal cutoff value (5.611) identified from the ROC curve. Chi-square test and Fisher exact test were used to find the correlation between the expression of CEL and clinicopathologic features. To assess the diagnostic capability, the receiver operating characteristic (ROC) curve of CEL was drawn. The survival differences between high and low CEL expression groups were compared by Cox regression analysis. Log-rank test was applied to the calculation of p values and the comparison of the Kaplan–Meier curves. Furthermore, Gene Expression Omnibus (GEO) datasets were used for external data validation.
Results: Analysis of 1104 cases of tumor data showed that CEL was over-expressed in breast cancer. There were relationships between high CEL expression and clinicopathologic features. The high CEL expression group had a lower survival. By analyzing the area under the ROC curve (AUC) of CEL, it was found to have a limited diagnostic capability. CEL expression may be an independent prognostic factor for breast cancer survival through the multivariate analysis. The validation in GEO datasets also showed that CEL expression was higher in breast tumor tissues than in normal breast tissues. High CEL expression was associated with the poor overall survival of breast cancer.
Conclusions: High CEL expression may be an independent prognostic factor for the poor survival of breast cancer.

Introduction

Breast cancer is a common disease which morbidity and mortality rates have been rising over the past 50 years [1]. At present, the treatment of breast cancer is comprehensive and guided by tissue factors which includes tumor size, lymph node status, histological classification, and molecular classification [2]. The diagnosis and prognosis of breast cancer are also in the process of continuous development and improvement. In general, breast cancer has the best proven markers, including ER, PR, HER-2 [1]. Studies have also shown that DNA mutation testing (including measurement of ctDNA) and microRNAs have a great potential in the diagnostic, predictive and prognostic processes of breast cancer patients [3–6]. In addition, prognostic tests based on multiple gene expression are on the rise rapidly [2].

Carboxyl ester lipase (CEL) is an enzyme found in all vertebrates so far [3,7–9]. It had a high expression in the exocrine pancreas of mouse, as well as pregnant and lactating mammary mouse glands [8]. Similarly, a lipolytic enzyme called carboxyl ester lipase (CEL) which is known as bile salt-stimulated lipase (BSSL) is also produced in human pancreas and lactating mammary gland [10]. It can hydrolyze dietary fat, cholesteryl esters and fat-soluble vitamins in the duodenum [7]. Moreover, the expression of CEL

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(or BSDL) variations was found in the pancreas of patients who suffered from MODY-8 (maturity-onset diabetes of the young type 8), chronic pancreatitis and pancreatic cancer [7,9]. Most of the previous studies have focused on the relationship between CEL and pancreatic diseases. The association between CEL expression and breast diseases, especially breast cancer, is unclear.

Here, to make a preliminary judgment on whether CEL can be a factor affecting the prognosis of breast cancer, we investigated the link between CEL expression in BC tissues and clinicopathologic features, as well as the survival of BC patients through an analysis of TCGA-BRCA level 3 data. GEO datasets were applied for the validation.

Materials and methods

Data mining of TCGA database

The clinical information and the RNA-Seq expression data for breast cancer patients were downloaded from TCGA (https://cancergenome.nih.gov/). The RNA-Seq by Expectation-Maximization (RSEM) expression values were applied in the analysis process. GEO datasets were downloaded from the GEO database (https://www.ncbi.nlm.nih.gov/geo/).

Statistical analysis

The expression difference of discrete variables was visualized by using the ggplot2 package in R into boxplots. Patients were divided into a high CEL expression group and a low CEL expression group using the optimal cutoff value (5.611) identified from the ROC curve. We used Chi-square test and Fisher exact test to find the correlation between the expression of CEL and clinicopathologic features in R (version 3.5.2). Through the application of pROC package, the ROC curve of subjects was drawn to assess the diagnostic capability. Using the survival package of R, the differences in the overall survival (OS) and relapse free survival (RFS) between two groups were compared by the Kaplan–Meier curves. Log-rank test was applied to the calculation of p values. The relevant clinicopathologic features were screened by univariate analysis and multivariate analysis was then applied in the effects of CEL expression on the survival of BC patients.

Results

Patient characteristics

According to the downloaded TCGA-BRCA level 3 data, the preliminary analysis was done. The clinical characteristics, including histological type, molecular subtype, ER, PR, HER-2, TNM stage, clinical stage, lymph node status, vital status and sample type, were shown in Table 1.

CEL expression in breast cancer

CEL expression was higher in tumor tissues (n = 1104) than in normal tissues (n = 114; p = 0.04). In addition, differences in CEL expression were shown in boxplots according to clinical stage, molecular subtype (p = 1.9e-05), patient age, ER (p = 4.6e−06), PR (p = 3.6e−05), HER-2, vital status (p = 0.021), T classification, N classification (p = 0.024), M classification (Fig. 1). Through the validation in microarray GSE21422 (p = 0.014), CEL expression was higher in breast tumor tissues than in normal breast tissues (Fig. S1).

Table 1
Clinical characteristics of TCGA-BRCA level 3 Cohort.

Characteristics	Numbers of cases (%)
CEL	
High	217(19.66)
Low	887(80.34)
Age	
<60	589(53.35)
>=60	513(46.47)
NA	2(0.18)
Gender	
Female	1090(98.73)
Male	12(1.09)
NA	2(0.18)
Histological type	
Infiltrating Ductal Carcinoma	790(71.56)
Infiltrating Lobular Carcinoma	204(18.48)
Other	107(9.69)
NA	3(0.27)
Molecular subtype	
Basal	142(12.86)
HER-2	67(6.07)
Lum A	422(38.22)
Lum B	194(17.57)
Normal	24(2.17)
NA	255(23.1)
ER	
Indeterminate	2(0.18)
Negative	239(21.65)
Positive	813(73.64)
NA	50(4.53)
PR	
Indeterminate	4(0.36)
Negative	345(31.25)
Positive	704(63.77)
NA	51(4.62)
HER-2	
Equivocal	180(16.3)
Indeterminate	12(1.09)
Negative	565(51.18)
Positive	164(14.86)
NA	183(16.58)
T classification	
T1	281(25.45)
T2	640(57.97)
T3	138(12.5)
T4	40(3.62)
TX	3(0.27)
NA	2(0.18)
N classification	
N0	516(46.74)
N1	367(33.24)
N2	120(10.87)
N3	79(7.16)
NX	20(1.81)
NA	2(0.18)
M classification	
M0	917(83.06)
M1	22(1.99)
MX	163(14.76)
NA	2(0.18)
Stage	
I	182(16.49)
II	626(56.7)
III	252(22.83)
IV	20(1.81)
X	14(1.27)
NA	10(0.91)
Lymph node status	
No	28(2.54)
Yes	697(63.13)
NA	379(34.33)
Vital status	
Deceased	155(14.04)
Living	947(85.78)
NA	2(0.18)
Sample type	
Metastatic	7(0.63)
Primary tumor	1097(99.37)

Abbreviation: NA, not available.

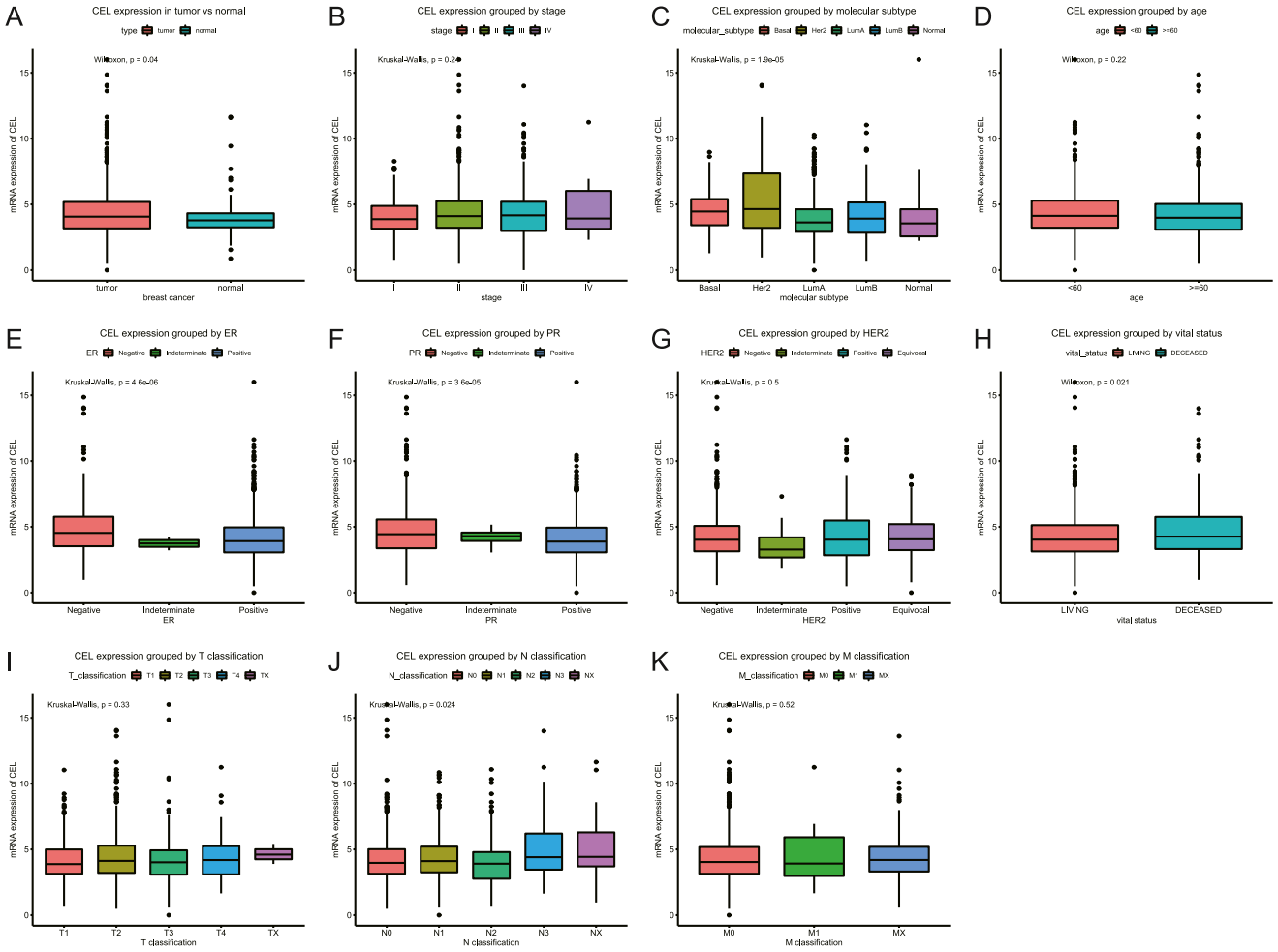

Fig. 1. Differences in CEL expression were shown in boxplots according to type (A), clinical stage (B), molecular subtype (C), patient age (D), ER (E), PR (F), HER-2 (G), vital status (H), T classification (I), N classification (J), M classification (K).

The correlation between CEL expression and clinicopathologic features in breast cancer

The optimal cutoff value (5.611) was obtained from ROC curve (Fig. S2) and the high and low CEL expression groups were determined. Chi-square test and Fisher exact test were used. The results revealed that there were many clinicopathologic features significantly correlated with high CEL expression, including histological type ($p = 0.0014$), molecular subtype ($p = 0.0002$), ER ($p = 0.0075$), PR ($p = 0.0257$), N classification ($p = 0.0325$), lymph node status ($p = 0.0222$) and vital status ($p = 0.0047$) (Table 2).

The diagnostic capability of CEL expression

The ROC curve of CEL was drawn to assess the diagnostic capability and the AUC was 0.558, which meant that it had a limited diagnostic capability. The subgroup analyses of different stages also showed diagnostic capability to some extent (AUC: stage I, 0.518; stage II, 0.570; stage III, 0.557; stage IV, 0.543) (Fig. 2).

CEL expression in association with breast cancer survival

We used the Kaplan–Meier curves to show the association between CEL expression and breast cancer survival. The log-rank tests revealed that high CEL expression had relations with the poor overall survival ($p = 0.0020$) (Fig. 3) and poor relapse free survival ($p = 0.0220$) (Fig. 4). Subgroup analyses indicated that high CEL expression had relations with poor overall survival in patients with ER ($p = 0.0037$) positive tumors, PR ($p = 0.0300$) positive tumors, HER-2 positive tumors ($p = 0.0011$), luminal B tumors ($p = 0.0057$) and infiltrating ductal carcinoma ($p = 0.0019$) (Fig. 3). The analyses also indicated that high CEL expression was related to poor relapse free survival in patients with ER positive tumors ($p = 0.0230$), luminal B tumors ($p = 0.0014$) and infiltrating ductal carcinoma ($p = 0.0071$) (Fig. 4). The validation in microarray GSE88770 showed that high CEL expression was associated with the poor overall survival of breast cancer (Fig. S3).

High CEL expression as an independent prognostic factor of breast cancer

The relevant clinicopathologic features were screened by univariate analysis and multivariate analysis was then applied in the effects of CEL expression on the survival of BC patients. Univariate analysis indicated that the poor overall survival was related to age, HER-2, clinical stage and CEL expression (Table 3). Similarly, ER, PR, clinical stage and CEL expression were related to the poor relapse free survival (Table 4). Then the multivariate analyses were executed, it can be demonstrated that high CEL expression was an independent prognostic factor related to the poor overall survival ($p = 0.023$; HR: 1.87, 95% CI: 1.09–3.20) (Table 3) and poor relapse free survival ($p = 0.034$; HR: 1.67, 95% CI: 1.04–2.68) (Table 4).

Table 2
Correlations of CEL expression in BC tissues with clinicopathologic features.

Clinical characteristics	Variable	No. of cases	CEL expression		$\chi 2$	p value
			High n (%)	Low n (%)		
Age	<60	589	116(19.69)	473(80.31)	0	1
	>=60	513	101(19.69)	412(80.31)		
Gender	Female	1090	217(19.91)	873(80.09)	1.8491	0.1739
	Male	12	0(0)	12(100)		
Histological type	Infiltrating Ductal Carcinoma	790	169(21.39)	621(78.61)	13.1071	**0.0014**
	Infiltrating Lobular Carcinoma	204	22(10.78)	182(89.22)		
	Other	107	26(24.3)	81(75.7)		
Molecular subtype	Basal	142	28(19.72)	114(80.28)	21.928	**0.0002**
	Her2	67	25(37.31)	42(62.69)		
	LumA	422	60(14.22)	362(85.78)		
	LumB	194	37(19.07)	157(80.93)		
	Normal	24	3(12.5)	21(87.5)		
ER	Indeterminate	2	0(0)	2(100)	9.7879	**0.0075**
	Negative	239	64(26.78)	175(73.22)		
	Positive	813	145(17.84)	668(82.16)		
PR	Indeterminate	4	0(0)	4(100)	7.319	**0.0257**
	Negative	345	84(24.35)	261(75.65)		
	Positive	704	125(17.76)	579(82.24)		
HER2	Equivocal	180	33(18.33)	147(81.67)	2.4154	0.4908
	Indeterminate	12	2(16.67)	10(83.33)		
	Negative	565	101(17.88)	464(82.12)		
	Positive	164	38(23.17)	126(76.83)		
T classification	T1	281	51(18.15)	230(81.85)	2.2506	0.6898
	T2	640	134(20.94)	506(79.06)		
	T3	138	24(17.39)	114(82.61)		
	T4	40	8(20)	32(80)		
	TX	3	0(0)	3(100)		
N classification	N0	516	94(18.22)	422(81.78)	10.5189	**0.0325**
	N1	367	73(19.89)	294(80.11)		
	N2	120	19(15.83)	101(84.17)		
	N3	79	24(30.38)	55(69.62)		
	NX	20	7(35)	13(65)		
M classification	M0	917	176(19.19)	741(80.81)	2.3304	0.3119
	M1	22	7(31.82)	15(68.18)		
	MX	163	34(20.86)	129(79.14)		
Stage	I	182	27(14.84)	155(85.16)	6.3833	0.1723
	II	626	130(20.77)	496(79.23)		
	III	252	50(19.84)	202(80.16)		
	IV	20	7(35)	13(65)		
	X	14	2(14.29)	12(85.71)		
Lymph node status	No	28	11(39.29)	17(60.71)	5.2335	**0.0222**
	Yes	697	137(19.66)	560(80.34)		
Vital status	Deceased	155	44(28.39)	111(71.61)	7.9963	**0.0047**
	Living	947	173(18.27)	774(81.73)		
Sample type	Metastatic	7	3(42.86)	4(57.14)	1.1503	0.2835
	Primary Tumor	1097	214(19.51)	883(80.49)		

Abbreviations: Bold values of $p < 0.05$ indicate statistically significant correlations.
Note: High n (%) and low *n* (%) added up to 100% in each subgroup. For example, high LCN1 expression n (%) of "Age < 60" =116/589 = 19.69%; low CEL expression *n* (%) of "Age < 60" = 473/589 = 80.31%.

Table 3
Univariate and multivariate analyses of overall survival in breast cancer patients.

Parameters	Univariate analysis			Multivariate analysis		
	HR	95%CI	p value	HR	95%CI	p value
Age	1.91	1.39-2.63	0	2.22	1.39-3.54	**0.0010**
Histological type	0.93	0.74-1.17	0.543			
Molecular subtype	1.01	0.88-1.16	0.901			
ER	0.85	0.71-1.02	0.074			
PR	0.87	0.73-1.03	0.096			
HER-2	1.29	1.05-1.57	0.013	1.17	0.94-1.46	0.1530
Stage	1.64	1.4-1.91	0	2.13	1.62-2.81	**0.0000**
Lymph node status	1.1	0.93-1.3	0.274			
CEL	1.73	1.22-2.47	0.002	1.87	1.09-3.20	**0.0230**

Abbreviations: HR Hazard Ratio, CI confidence interval, bold values of $p < 0.05$ indicate statistically significant correlations.

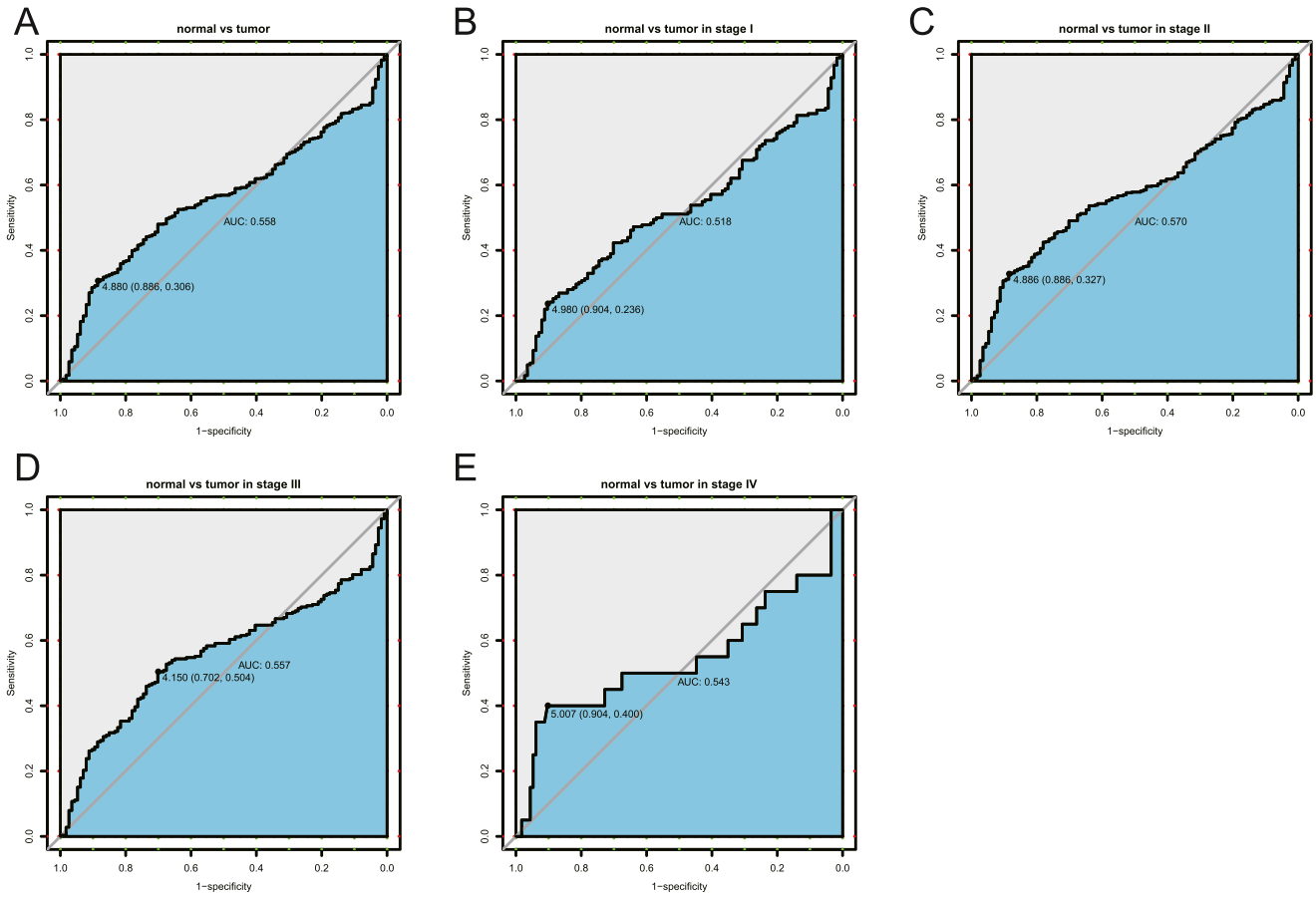

Fig. 2. The ROC curve of CEL in breast carcinoma cohort.
Normal and tumor samples (A). The AUC (0.558) indicated a limited diagnostic capability. Subgroup analyses: Stage I(B), Stage II(C), Stage III(D), Stage IV(E).
Abbreviations: AUC, area under the curve; ROC, receiver operating characteristic.

Table 4
Univariate and multivariate analyses of relapse free survival in breast cancer patients.

Parameters	Univariate analysis			Multivariate analysis		
	HR	95%CI	*p* value	HR	95%CI	*p* value
Age	1.45	0.97–2.16	0.072			
Histological type	0.86	0.65–1.14	0.29			
Molecular subtype	0.99	0.82–1.2	0.945			
ER	0.78	0.63–0.97	0.026	0.86	0.62–1.20	0.3870
PR	0.78	0.64–0.96	0.019	0.86	0.63–1.17	0.3220
HER-2	0.93	0.7–1.22	0.596			
Stage	1.71	1.4–2.08	0	1.6	1.29–2.00	**0.0000**
Lymph node status	0.86	0.7–1.06	0.159			
CEL	1.69	1.07–2.67	0.024	1.67	1.04–2.68	**0.0340**

Abbreviations: HR Hazard Ratio, CI confidence interval, bold values of $p < 0.05$ indicate statistically significant correlations.

Discussion

Our team has been exploring the novel biomarkers for diagnosis and prognosis in the field of oncology [11–17]. According to the findings based on TCGA database, the expression of CEL was higher in tumor tissues than in normal tissues. High CEL expression had relations with the poor survival and it was also proved that CEL expression could become an independent prognostic factor of breast cancer. The expression and survival analyses of CEL were also validated in GEO datasets. As far as we know, this is the first time that CEL expression is identified to be related to breast cancer survival through TCGA database mining.

The human CEL gene is located on the chromosome 9q34.3 and the last exon of CEL gene has the variable number of tandem repeat (VNTR) region which gives the gene a high degree of polymorphism [10,18]. As we know, alterations that occur in the VNTR sequence can lead to pancreatic disease [19]. By analyzing the patients' cancer tissues or blood samples, it was found that SNP rs488087 in VNTR could be used to predict pancreatic cancer [20]. There were reports that mRNAs specific to BSDL (or CEL) was found in HepG2 cells (a human hepatoma cell line) [21], SOJ-6 cells and Mia PaCa-2 cells (human pancreatic tumoral cell lines) [22,23]. Another study found that CEL gene expressed higher in nasopharyngeal cancer samples than in normal nasopharyngeal

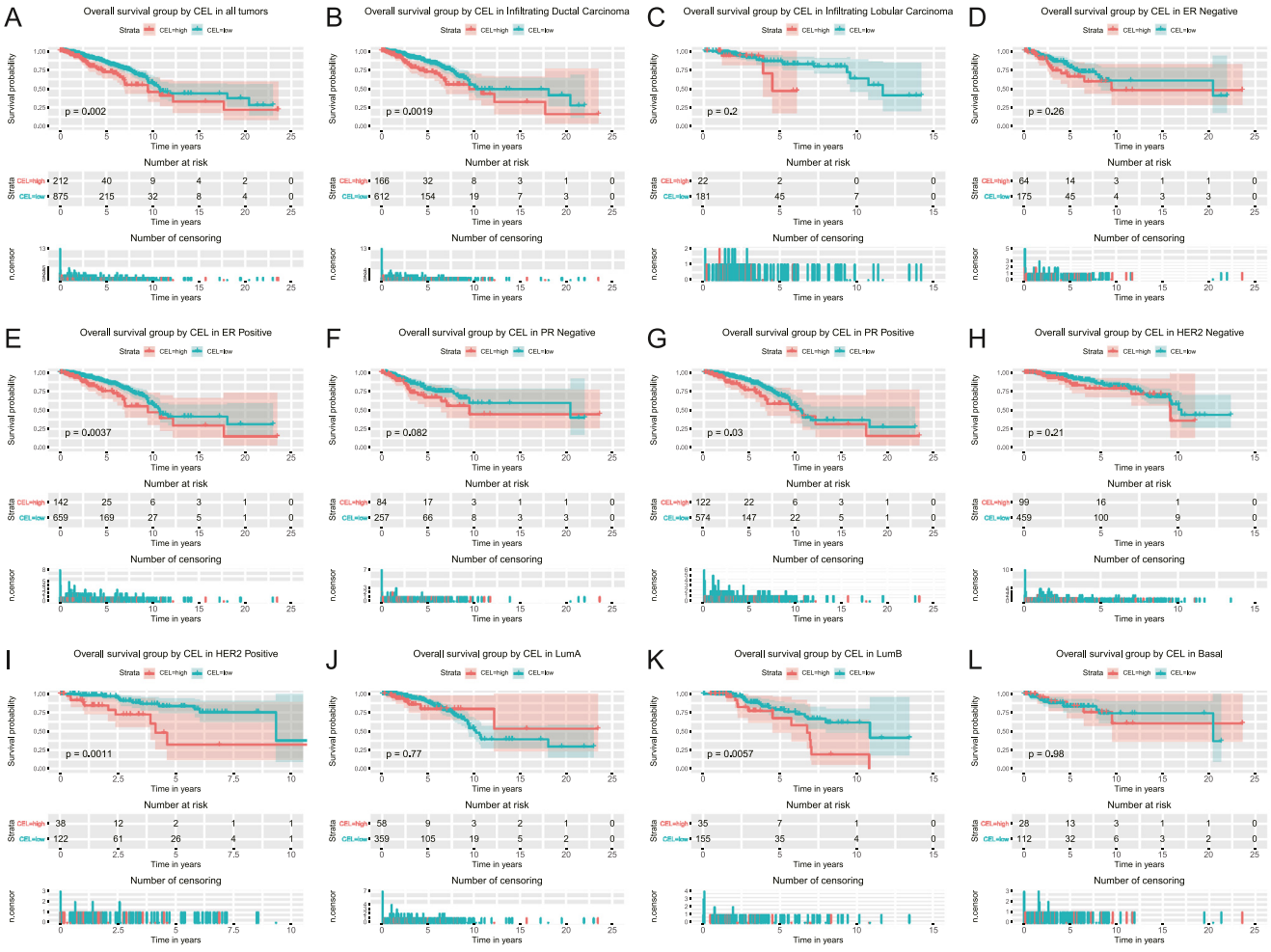

Fig. 3. Kaplan–Meier curves of overall survival in breast cancer according to CEL expression in breast cancer tissues. Overall survival analysis and subgroup analyses of histological type (B and C), ER (D and E), PR (F and G), HER-2 (H and I) and molecular subtype (J, K and L). High CEL expression had relations with the poor overall survival ($p = 0.0020$) (A).

samples, and it was speculated to be a biomarker for nasopharyngeal carcinoma [24]. Our study also showed that the expression of CEL in breast cancer tissues was higher than that in normal tissues based on the analyses of TCGA database and microarray GSE21422. The high CEL expression was associated with many clinicopathologic features, including histological type, molecular subtype, ER, PR, N classification, lymph node status and vital status. It's recognized that the features have great significance for the treatment and prognosis of breast cancer [25,26]. The results urged us to conduct further research on CEL and breast cancer.

The present study revealed that high CEL expression had relations with both poor overall survival and relapse free survival in breast cancer, especially patients with ER (estrogen receptor) positive tumors, luminal B tumors. As we know, estrogens play an important role in the etiology of breast cancer [27]. It was demonstrated that CEL expressed in normal pituitary gland and pituitary adenomas and the researchers speculated that CEL may regulate hormone secretion by inactivating ceramides [28] which was suggested to play an important role in the regulation of GHRH (growth hormone releasing hormone)-stimulated responses [29]. The change of CEL expression level may lead to the corresponding change of hormone level. Therefore, we may link CEL with breast cancer to some extent. However, further study is needed to prove this hypothesis. Gene expression profiling is the main basis for the classification of breast cancer and it was usually called intrinsic subtypes which conclude luminal A, luminal B, basal-like and HER-2-enriched [30]. Luminal A breast cancer is recognized as having a more favorable clinical outcome. On the contrary, luminal B breast cancer is considered to have an aggressive clinical behavior, and its prognosis is similar to that of HER-2-enriched and basal-like groups [31]. There may be some relationships between CEL and the prognosis of breast cancer.

Our study found that high CEL expression was associated with the poor survival of breast cancer in patients with infiltrating ductal carcinoma. It is recognized that the mammary gland secretes milk through the contraction of myoepithelial cells to drive the milk out from the acinus and through the ducts. Researchers found that infiltrating ductal carcinoma of the breast originated from the luminal epithelium and the milk fluidity prevented cancer cells from existing in the breast tissue, thus the milk deposition may lead to the breast cancer, in the same way that constipation increased the incidence of colon cancer [32]. Infiltrating ductal carcinoma may be correlated with the low milk fluidity caused by the milk deposition. A study revealed that the up-regulation of the CEL gene was correlated with an increase in the number of differentiated epithelial cells [33]. CEL was one of the most highly expressed genes involved in milk synthesis [34]. In this way, CEL may have associations with infiltrating ductal carcinoma. Moreover, milk

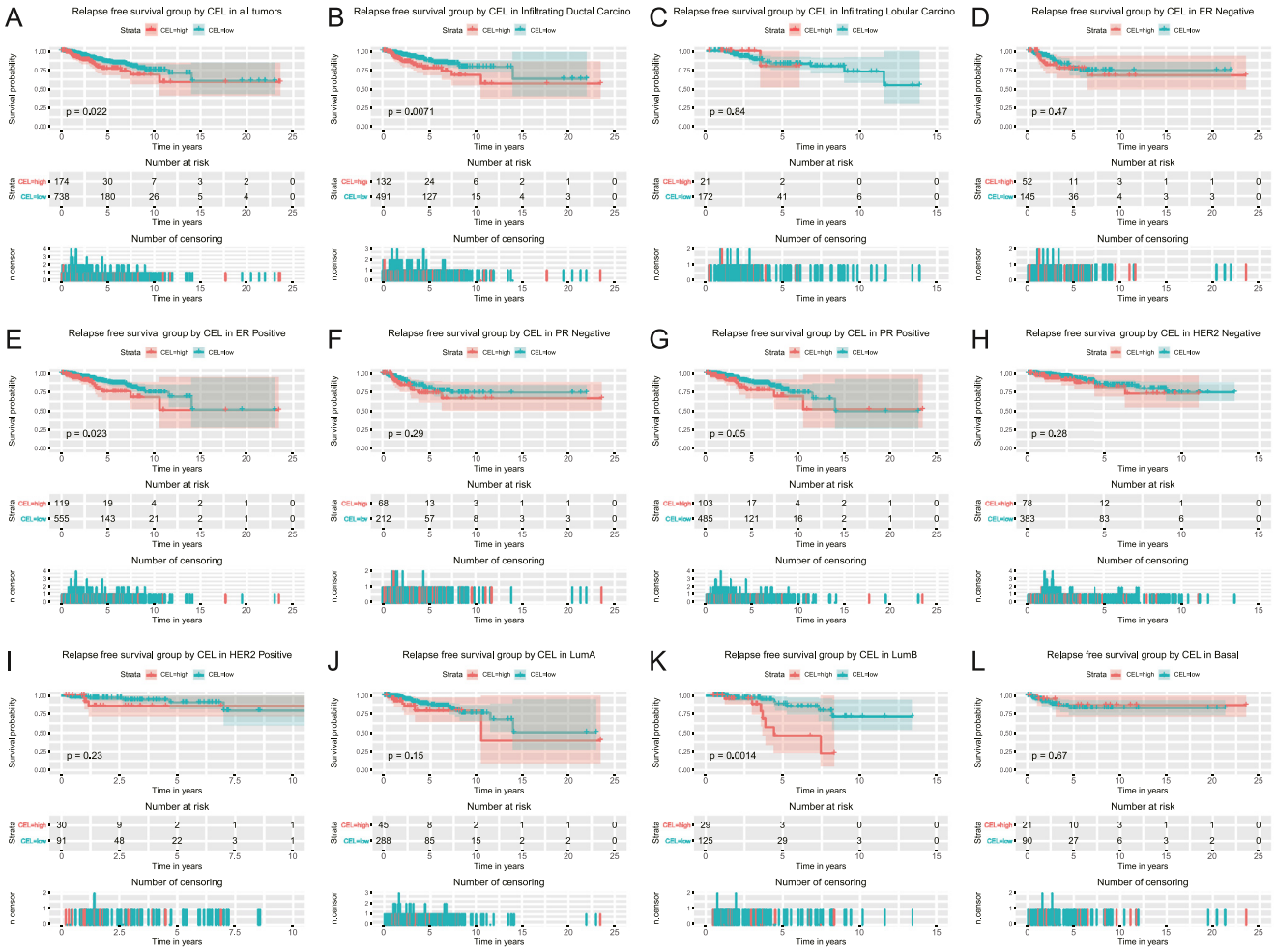

Fig. 4. Kaplan–Meier curves of relapse free survival in breast cancer according to CEL expression in breast cancer tissues. Relapse free survival analysis and subgroup analyses of histological type (B and C), ER (D and E), PR (F and G), HER-2 (H and I) and molecular subtype (J, K and L). High CEL expression had relations with the poor relapse free survival ($p = 0.0220$) (A).

stasis is one of the causes of the mastitis [35]. There were evidences supported the link between inflammation and breast cancer [36]. Carboxyl ester lipase was identified as a hydrolase of fatty acid esters of hydroxy fatty acids (FAHFAs) which possess anti-inflammatory abilities. High CEL expression may reduce FAHFAs level and cause inflammation, which might result in an increased risk of cancer. Nevertheless, the further research is needed.

It was demonstrated that high CEL expression could become an independent prognostic factor related to the poor survival of breast cancer though the multivariate analyses in the present study. In addition, the ROC curve of CEL revealed its limited diagnostic capability by analyzing the AUC. A previous study suggested that the separate detection of serum BSDL levels, or combined with CA19-9 antigen detection, contributes to the diagnosis of pancreatic cancer and the identification of malignant diseases and pancreatitis [37]. From this, we need to verify the association between breast cancer and the expression of CEL in blood samples or other specimens. The combination of CEL expression and other biomarkers may improve its limited diagnostic capability.

Our study preliminarily explored the value of CEL expression for being an independent prognostic factor of breast cancer through data analysis. As the number of samples is limited, we still need exploration based on the data of large samples to provide an accurate prognostic factor for breast cancer patients. The further experimental verifications are necessary as well.

In conclusion, we determined the link between CEL expression and breast cancer through the analysis based on TCGA database and the validation in GEO datasets. The results showed that high CEL expression could be regarded as an independent prognostic factor related to the poor survival of breast cancer.

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Ethical standards

This article does not contain any studies with human participants or animals performed by any of the authors.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cancergen.2019.09.005.

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