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Original Article

Correlation of CA125, CA153, and CEA levels in the diagnosis and prognosis of triple-negative breast cancer

Weijun Lou

Department of Emergency Surgery, Medical Communities of People's Hospital of Fenghua District, Ningbo, Zhejiang Province, China

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Abstract: Objective: The aim of the current study was to investigate correlation levels of CA125, CA153, and CEA in the diagnosis and prognosis of triple-negative breast cancer (TNBC). Methods: A total of 342 patients with breast cancer were selected for the present study, including 107 patients with TNBC (TNBC group) and 235 patients with non-TNBC (non-TNBC group). Postoperative cancer antigen 125 (CA125), cancer antigen 153 (CA153), and carcinoembryonic antigen (CEA) levels were detected. Moreover, correlation analysis of these levels in the diagnosis and prognosis of TNBC was conducted. Results: Positive rates and levels of CA125 and CA153 in the TNBC group were higher than those in the non-TNBC group (all $P<0.05$), while there were no differences in positive rates and levels of CEA between the two groups (both $P>0.05$). An ROC curve of the combination of preoperative CA125, CA153, and CEA levels in the diagnosis of TNBC showed that AUC, sensitivity, and specificity levels were 0.803, 0.991, and 0.706, respectively. Mean overall survival (OS) of the TNBC group (43.2 months) was lower than that of the non-TNBC group (53.2 months; $\chi^2=24.160$, $P<0.001$). In the TNBC group, the mean OS of CA125 and CA153 positive patients after the operation was shorter than that of CA125 and CA153 negative patients (39.7 vs. 47.7 months, $\chi^2=7.790$, $P=0.005$; 39.0 vs. 59.3 months, $\chi^2=15.638$, $P<0.001$). Conclusion: The combination of serum CA125, CA153, and CEA has certain value in the diagnosis of TNBC, with high levels of CA125 and CA153 after the operation in TNBC patients indicating poor prognosis.

Keywords: Triple-negative breast cancer, cancer antigen 125, cancer antigen 153, carcinoembryonic antigen, diagnosis, prognosis

Introduction

Breast cancer (BC) is the most common cancer in women. Incidence of this disease has maintained an upward trend in China, seriously endangering the health of women. Annual occurrence and death cases of BC in China account for 12.2% and 9.6% of total cases worldwide [1]. Triple-negative breast cancer (TNBC) refers to a special type of BC in which estrogen receptors, progesterone receptors, and human epidermal growth factor receptor 2 are all negative [2]. It has been reported that incidence of TNBC accounts for about 10.6-29.5% of all BCs [3, 4]. The particularity of TNBC lies in the negative of the above three receptors, leading to the poor effects of this BC type regarding endocrine therapy, targeted therapy, and chemotherapy [5, 6]. Incidence of TNBC recurrence and metastasis is significantly higher than that of other BC types [7]. Due to the poor effects of conventional and chemotherapy treatment, as well as recurrence and metastasis, the prognosis of TNBC is worse than other BC types [8]. Therefore, it is important for TNBC patients that quick and effective diagnosis is conducted, along with efficacy evaluations and prognosis judgement. Clinical staff members have been searching for simple and effective evaluation indicators [9]. Previous studies have indicated that the combination of serological tumor associated indicators provides good guiding significance for the diagnosis and prognosis of BC [10, 11]. However, some studies have suggested that monitoring of serological tumor associated indicators comes with limitations, being widely disputed [12]. At present, there are few studies concerning the combination of serological indicators in the diagnosis and prognosis of TNBC. Cancer

antigen 125 (CA125), cancer antigen 153 (CA153), and carcinoembryonic antigen (CEA) are serum markers for BC in clinic [13]. The application value of CA125, CA153, and CEA in the diagnosis and prognosis of TNBC was explored in the current study.

Materials and methods

General information

General information of 342 BC patients, admitted to Department of Breast Surgery of Medical Communities of People's Hospital of Fenghua District, from January 2013 to January 2017, was collected for retrospective analysis. Patients were aged 38-72 years, with an average age of 54.9±8.6 years. These patients were divided into two groups, the TNBC group (n= 107, aged 53.8±9.2 years old) and non-TNBC group (n=235, aged 55.3±8.1 years old). The present study was approved by the Ethics Committee of Medical Communities of People's Hospital of Fenghua District, with all patients providing informed consent.

Inclusion criteria: Patients met diagnostic criteria of BC and TNBC [14]; Patients were aged 18-75 years old; Patients received radical mastectomy and postoperative regular chemotherapy procedures.

Exclusion criteria: Patients with incomplete clinical data; Patients with serious heart, liver, and kidney disease, as well as other diseases; Patients with mental illness or cerebrovascular disease; Patients with other cancers or non-primary BC.

Clinical and pathological staging

Clinical and pathological staging was evaluated according to *The 7th edition of UICC/AJCC diagnostic criteria* [15].

Methods

One week after the operation, a total of 5 mL venous blood was extracted, on an empty stomach, 8 hours before chemotherapy. Blood samples were stored in a sterile tube of ethylenediamine tetra-acetic acid (Shanghai Hengyuan Biological Technology Co., Ltd., China). After 15 minutes of storage at 4°C, the blood samples were centrifuged at 3,300 rpm to separate the serum. The serum was added to 40 μL phosphate buffer solution with protease inhibitor (Shanghai Hengyuan Biological Technology Co., Ltd., China) and stored at -80°C. Levels of CA125, CA153, and CEA were determined using the Roche Electrical Chemiluminescence Automatic Immunoassay System (E170; Roche, Switzerland). The operation process was performed in strict accordance with instrument and reagent instructions.

Outcome measures

Overall survival (OS): From the time after the operation to the time of death of the patient or the time of observation in this study.

Detection results: CA125 >35 U/mL, CA153 >25 U/mL, and CEA >5 ng/mL were considered as positive [16].

Statistical analysis

SPSS 17.0 statistical software was used to analyze present data. Measurement data were tested for normality. Data in line with normal distribution are expressed by mean ± standard deviation ($\bar{\chi} \pm SD$); In contrast, expressed by M (P25, P75). Data following a normal distribution and homogeneity of variance were compared using t-tests and expressed by t.Conversely, data not following normal distribution was analyzed by rank sum tests and χ^2. Count data were analyzed by Pearson's Chi-square tests and expressed by χ^2. ROC curves were used to evaluate diagnostic value, drawn using Medcalc software. The Kaplan-Meier method was used for survival analysis, while log-rank tests were used for prognostic univariate analysis. $P<0.05$ indicates statistical significance.

Results

General information and baseline data

There were no statistical differences in age and tumor size between the two groups (both $P>0.05$). However, statistical differences were found in grading, lymphatic metastasis, recurrence, and survival rates between the two groups (all $P<0.05$). See **Table 1**.

Postoperative positive rates and levels of CA125, CA153, and CEA

Positive rates and levels of CA125 and CA153 in the TNBC group were higher than those in the non-TNBC group (all $P<0.05$). There were no differences in positive rates and levels of CEA

Table 1. Comparison of general information and baseline data ($\bar{X}$ ± SD, case)

	TNBC group (n=107)	Non-TNBC group (n=235)	χ^2/t	P
Age (years old)	53.8±9.2	55.3±8.0	1.448	0.149
Tumor size (cm)			0.770	0.380
>3 cm	36	68		
≤3 cm	71	167		
Grading			19.678	<0.001
1	10	67		
2	33	78		
3	64	90		
Lymphatic metastasis			7.439	0.006
Positive	45	64		
Negative	62	171		
Recurrence			4.794	0.029
Yes	54	89		
No	53	146		
Survival			4.603	0.032
Yes	67	188		
No	30	47		

Note: TNBC, triple-negative breast cancer.

Table 2. Comparison of positive rates of CA125, CA153, and CEA (case)

	TNBC group (n=107)	Non-TNBC group (n=235)	χ^2	P
CA125			7.883	0.005
Positive	46	65		
Negative	61	170		
CA153			14.653	<0.001
Positive	51	60		
Negative	56	165		
CEA			0.080	0.777
Positive	24	56		
Negative	83	179		

Note: TNBC, triple-negative breast cancer; CA125, cancer antigen 125; CA153, cancer antigen 153; CEA, carcinoembryonic antigen.

Table 3. Comparison of postoperative levels of CA125, CA153, and CEA

	TNBC group (n=107)	Non-TNBC group (n=235)	t	P
CA125	22.39 (12.90, 173.21)	14.90 (11.22, 54.23)	2.734	0.007
CA153	23.49 (15.34, 48.02)	15.02 (10.12, 26.14)	3.758	<0.001
CEA	1.93 (1.27, 3.64)	1.90 (1.39, 4.12)	0.870	0.138

Note: TNBC, triple-negative breast cancer; CA125, cancer antigen 125; CA153, cancer antigen 153; CEA, carcinoembryonic antigen.

between the two groups (both P>0.05). See **Tables 2**, **3**.

Preoperative CA125, CA153, and CEA levels in the diagnosis of TNBC

The ROC curve of preoperative CA125, CA153, and CEA levels in the diagnosis of TNBC showed that AUC, sensitivity, and specificity levels were (0.644, 0.686, 0.154), (0.701, 0.701, 0.677), and (0.621, 0.570, 0.677), respectively. The ROC curve of the combination of preoperative CA125, CA153, and CEA levels in the diagnosis of TNBC showed that AUC, sensitivity, and specificity levels were 0.803, 0.991, and 0.706, respectively. See **Figure 1**.

OS

The mean OS of the TNBC group (43.2 months) was lower than that of the non-TNBC group (53.2 months; χ^2=24.160, P<0.001). See **Figure 2**.

Predictive value of CA125, CA153, and CEA levels in TNBC patients after the operation

In the TNBC group, mean OS values of CA125 and CA153 positive patients after the operation were shorter than those of CA125 and CA153 negative patients (39.7 vs. 47.7 months, χ^2= 7.790, P=0.005; 39.0 vs. 50.3 months, χ^2=15.638, P<0.001). Mean OS values of CEA positive patients after the operation were shorter than those of CEA negative patients (41.7 vs. 44.1 months, χ^2=0.245, P=0.614). See **Figures 3**-**5**.

Discussion

Tumor proliferation is crucial in the process of tumor growth [17]. After uncontrolled proliferation

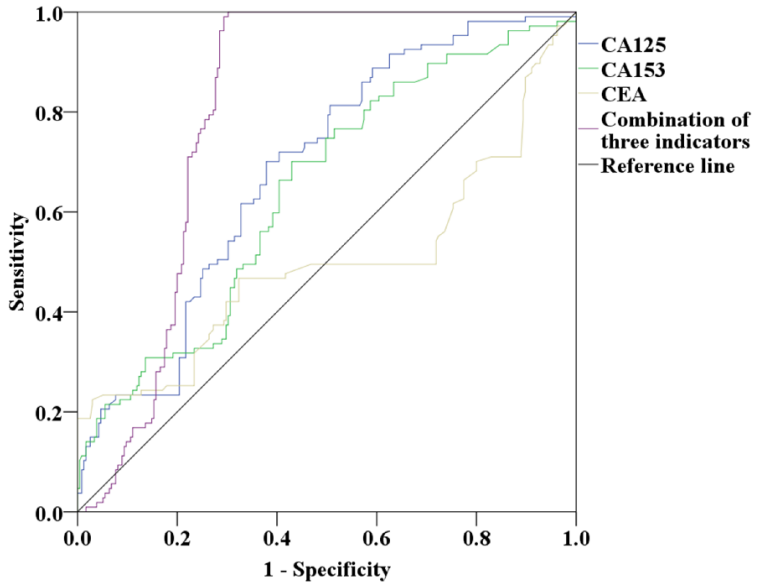

Figure 1. ROC curve of preoperative CA125, CA153, and CEA levels in the diagnosis of TNBC. TNBC, triple-negative breast cancer; CA125, cancer antigen 125; CA153, cancer antigen 153; CEA, carcinoembryonic antigen.

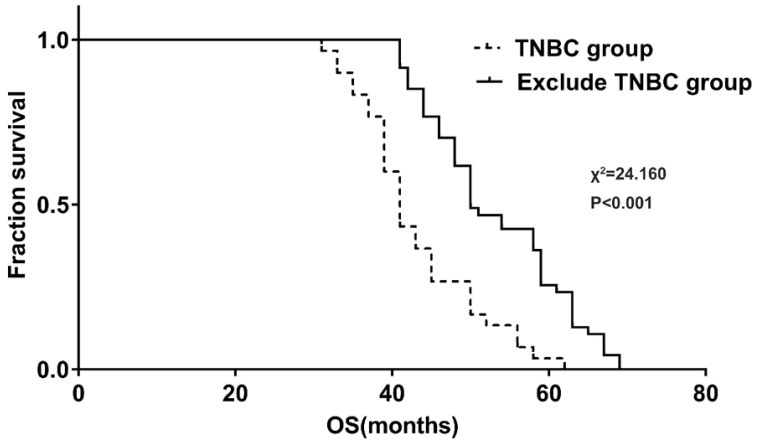

Figure 2. Comparison of mean OS between TNBC group and non-TNBC group. OS, overall survival; TNBC, triple-negative breast cancer.

and differentiation of tumor cells, the probability of tumor cell invasion and metastasis increases [18]. Thus, early detection of cancer and appropriate control of cancer tissues have a positive and important significance. TNBC is a special type of breast cancer with rapid proliferation, as well as easy invasion and metastasis. Its poor response to chemotherapy drugs causes poor prognosis [19]. The current study found that TNBC patients had higher grades, lower survival rates, and shorter OS values. They were also more prone to lymphatic metastasis and recurrence, compared with non-TNBC patients, in accord with previous studies.

Serum tumor markers play a key role in early diagnosis, recurrence, and metastasis of tumors. CA125 is a glycoprotein detected in the ovarian cancer antigen. Previous studies have shown that CA125 plays an important role in the diagnosis and prognosis of ovarian cancer [20]. In-depth studies have shown that CA125 is expressed abnormally in the early stages of BC and is increased in serum. Therefore, results suggested a correlation between the levels of CA125 and diagnosis of BC. The increase was more obvious in cases of breast cancer metastasis [21]. CA153 has been recognized as the most specific serum marker in the diagnosis of BC. However, in recent years, the diagnostic value of CA153 in BC has been questioned. One study found that the sensitivity of CA153 in the diagnosis of BC was poor [22], while another study suggested that monitoring of CA153 provides good prediction in the prognosis of BC [11]. CEA is a broad-spectrum tumor marker with abnormal expression in many tumors. In recent years, it has been reported that CEA can be found in the secretions of breast ducts. Thus, it is of great significance in the diagnosis and prognosis of BC [23]. It has been shown that positive rates and levels of CA125, CA153, and CEA were higher in TNBC patients than in patients with other types of BC. This may be related to increased expression levels of serum tumor markers due to easy tissue infiltration and metastasis, as well as stronger invasion of tumor cells in TNBC [7, 19]. Previous studies concerning disease diagnosis have suggested that the use of a single tumor marker for tumor diagnosis effects is not ideal, even CA153, a specific serum marker in the diagnosis of BC. Therefore, a combination with

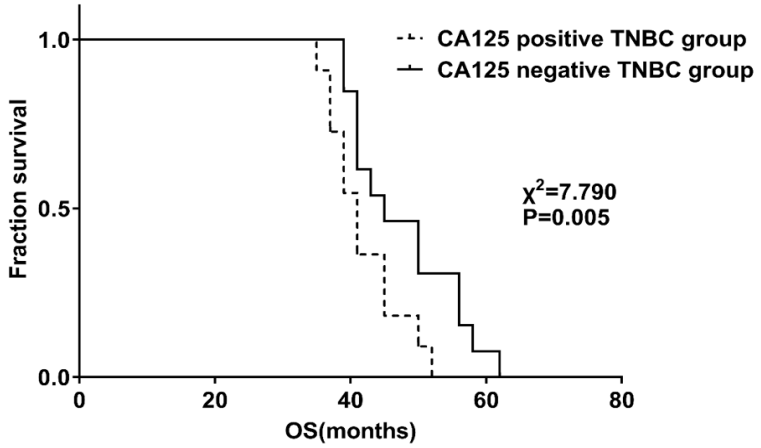

Figure 3. Comparison of mean OS between different CA125 levels in the TNBC group. OS, overall survival; TNBC, triple-negative breast cancer; CA125, cancer antigen 125.

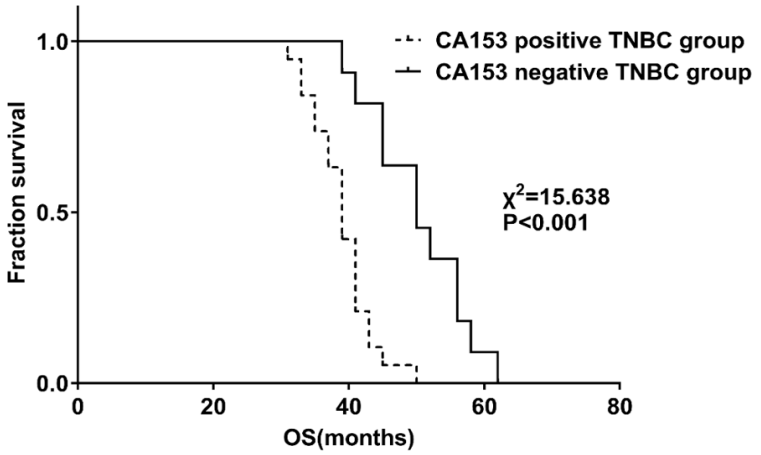

Figure 4. Comparison of mean OS between different CA153 levels in the TNBC group. OS, overall survival; TNBC, triple-negative breast cancer; CA153, cancer antigen 153.

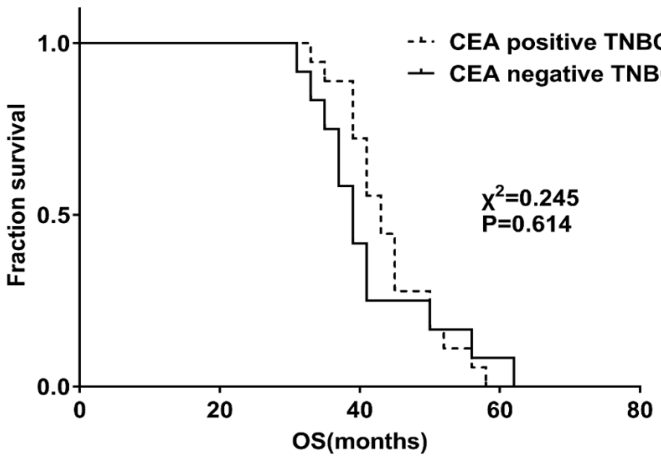

Figure 5. Comparison of mean OS between different CEA levels in the TNBC group. OS, overall survival; TNBC, triple-negative breast cancer; CEA, carcinoembryonic antigen.

the three tumor markers has been recommended to improve diagnostic efficiency [24].

In the present study, the combination of preoperative CA125, CA153, and CEA levels in the diagnosis of TNBC showed that AUC, sensitivity, and specificity levels were 0.803, 0.991, and 0.706, respectively. Diagnostic efficiency of the combination was significantly higher than that of a single indicator. This was consistent with previous studies. Studies concerning the determination of prognosis by serum tumor markers have found that many serum tumor markers have guiding significance in the determination of prognosis in patients with BC after the operation [25]. In TNBC patients, higher expression levels of CA125 and CA153 followed worse prognosis. No differences were seen in prognosis between patients with increased CEA expression levels and those with normal CEA expression levels.

The current study had some limitations. The sample size of the study was quite small. Future studies should be expanded. Moreover, the current study was retrospective in nature, with many external influencing factors, including chemotherapy regimens, chemotherapy effects, and surgical lesion clearance. Therefore, multi-center randomized controlled studies should be conducted in the future, aiming to verify present results.

In summary, the combination of serum CA125, CA153, and CEA provides certain value in the diagnosis of TNBC, with high levels of CA125 and CA153 after the operation in TNBC patients indicating poor prognosis.

Disclosure of conflict of interest

None.

Address correspondence to: Weijun Lou, Department of Emergency Surgery, Medical Communities of People's Hospital of Fenghua District, No. 36 Gongyuan Road, Jinping Street, Fenghua District, Ningbo 315500, Zhejiang Province, China. Tel: +86-13780066621; E-mail: louweijunfh1h@163.com

References

[1] Ye J, Wang W, Xin L, Owen S, Xu L, Duan X, Cheng Y, Zhang H, Zhang S, Li T and Liu Y. The clinicopathological factors associated with disease progression in luminal a breast cancer and characteristics of metastasis: a retrospective study from a single center in China. Anticancer Res 2017; 37: 4549-4556.

[2] Tubtimhin S, Promthet S, Suwanrungruang K and Supaattagorn P. Molecular subtypes and prognostic factors among premenopausal and postmenopausal thai women with invasive breast cancer: 15 years follow-up data. Asian Pac J Cancer Prev 2018; 19: 3167-3174.

[3] Liu Y, Tan S, Zhang H, Kong XJ, Ding LL, Shen J, Lan Y, Cheng C, Zhu T and Xia WD. Selective effects of non-thermal atmospheric plasma on triple-negative breast normal and carcinoma cells through different cell signaling pathways. Sci Rep 2017; 7: 7980.

[4] Pusztai L, Foldi J, Dhawan A, DiGiovanna MP and Mamounas EP. Changing frameworks in treatment sequencing of triple-negative and HER2-positive, early-stage breast cancers. Lancet Oncol 2019; 20: e390-e396.

[5] Planes-Laine G, Rochigneux P, Bertucci F, Chrétien AS, Viens P, Sabatier R and Gonçalves A. PD-1/PD-L1targeting in breast cancer: the first clinical evidences are emerging. A literature review. Cancers (Basel) 2019; 11: E1033.

[6] Walsh EM, Shalaby A, O'Loughlin M, Keane N, Webber MJ, Kerin MJ, Keane MM, Glynn SA and Callagy GM. Outcome for triple negative breast cancer in a retrospective cohort with an emphasis on response to platinum-based neoadjuvant therapy. Breast Cancer Res Treat 2019; 174: 1-13.

[7] Marra A, Viale G and Curigliano G. Recent advances in triple negative breast cancer: the immunotherapy era. BMC Med 2019; 17: 90.

[8] McCann KE, Hurvitz SA and McAndrew N. Advances in targeted therapies for triple-negative breast cancer. Drugs 2019; 79: 1217-1230.

[9] Kashiwagi S, Asano Y, Goto W, Takada K, Takahashi K, Noda S, Takashima T, Onoda N, Tomita S, Ohsawa M, Hirakawa K and Ohira M. Use of tumor-infiltrating lymphocytes (TILs) to predict the treatment response to eribulin chemotherapy in breast cancer. PLoS One 2017; 12: e0170634.

[10] Fang C, Cao Y, Liu X, Zeng XT and Li YR. Serum CA125 is a predictive marker for breast cancer outcomes and correlates with molecular subtypes. Oncotarget 2017; 8: 63963-63970.

[11] Fujimoto Y, Higuchi T, Nishimukai A, Miyagawa Y, Kira A, Ozawa H, Bun A, Imamura M and Miyoshi Y. High levels of serum CA15-3 and residual invasive tumor size are associated with poor prognosis for breast cancer patients with non-pathological complete response after neoadjuvant chemotherapy. J Surg Oncol 2018; 118: 228-237.

[12] Loke SY and Lee ASG. The future of blood-based biomarkers for the early detection of breast cancer. Eur J Cancer 2018; 92: 54-68.

[13] Molina R, Filella X, Alicarte J, Zanon G, Pahisa J, Munoz M, Farrus B and Ballesta AM. Prospective evaluation of CEA and CA 15.3 in patients with locoregional breast cancer. Anticancer Res 2003; 23: 1035-1041.

[14] Chinese Anti-Cancer Association. Guidelines and specifications for breast cancer diagnosis and treatment (2013 Edition). Zhongguo Aizhegn Zazhi 2013; 637-684.

[15] Edge SB, Byrd DR, Carducci MA, Compton CC, Fritz A and Greene F. AJCC cancer staging manual. Springer New York 2010.

[16] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D and Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228-247.

[17] Xu J, Jiao J, Xu W, Ji L, Jiang D, Xie S, Kubra S, Li X, Fu J, Xiao J and Zhang B. Mutant p53 promotes cell spreading and migration via ARHGAP44. Sci China Life Sci 2017; 60: 1019-1029.

[18] Li Y, Weng Y, Zhong L, Chong H, Chen S, Sun Y, Li W and Shi Q. VEGFR3 inhibition chemosensitizes lung adenocarcinoma A549 cells in the tumor-associated macrophage microenvironment through upregulation of p53 and PTEN. Oncol Rep 2017; 38: 2761-2773.

[19] Aydinlik S, Erkisa M, Cevatemre B, Sarimahmut M, Dere E, Ari F and Ulukaya E. Enhanced cytotoxic activity of doxorubicin through the inhibition of autophagy in triple negative breast cancer cell line. Biochim Biophys Acta Gen Subj 2017; 1861: 49-57.

[20] Lubowicka E, Gacuta E, Zajkowska M, Głażewska EK, Przylipiak A, Chrostek L, Zbucka-Krętowska M and Ławicki S. The plasma levels and diagnostic utility of matrix metalloproteinase-9 and CA 125 in cervical cancer patients. Pol Merkur Lekarski 2017; 43: 10-14.

[21] Norum LF, Erikstein B and Nustad K. Elevated CA125 in breast cancer--a sign of advanced disease. Tumour Biol 2001; 22: 223-228.
[22] Wang G, Qin Y, Zhang J, Zhao J, Liang Y, Zhang Z, Qin M and Sun Y. Nipple discharge of CA15-3, CA125, CEA and TSGF as a new biomarker panel for breast cancer. Int J Mol Sci 2014; 15: 9546-9565.
[23] Tang S, Zhou F, Sun Y, Wei L, Zhu S, Yang R, Huang Y and Yang J. CEA in breast ductal secretions as a promising biomarker for the diagnosis of breast cancer: a systematic review and meta-analysis. Breast Cancer 2016; 23: 813-819.
[24] Li X, Xu Y and Zhang L. Serum CA153 as biomarker for cancer and noncancer diseases. Prog Mol Biol Transl Sci 2019; 162: 265-276.
[25] Li L, Gao Q, Xu G, Shi B, Ma X, Liu H, Li Q, Tian T, Tang J and Niu H. Postoperative recurrence analysis of breast cancer patients based on clinical serum markers using discriminant methods. Cancer Biomark 2017; 19: 403-409.