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*Original Article*

# Expression of CD147 after neoadjuvant chemotherapy and its relationship with prognosis in patients with triple negative breast cancer

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**Abstract:** Background: Triple-negative breast cancer (TNBC) has rapid development and a worse prognosis, without special treatment. It is necessary to explore targeted treatment. Objective: To explore the significance of CD147 and matrix metalloproteinase-9 (MMP-9) in TNBC and their influence on prognosis. Methods: 81 TNBC patients admitted to our hospital and 86 healthy individuals undergoing physical examination from August 2014 to August 2016 were included. The concentrations of serum CD147 and MMP-9, their diagnostic value, and their relationship with clinicopathologic features were analyzed. A 3-year follow-up visit was conducted to assess the prognostic effect of CD147. Its effect on the biologic behavior of breast cancer cells was also determined. Results: Higher serum CD147 and MMP-9 levels were found in TNBC patients than healthy individuals (P<0.05). CD147 and MMP-9 were closely related to the pathologic stage, metastasis, and differentiation of the tumors (P<0.05). A positive correlation between CD147 and MMP-9 was detected before chemotherapy (n=127, r=0.609, P<0.01), with similar expression rates of CD147 (76.9%) and MMP-9 (80.67%) (P>0.05). The 2 markers were independent risk factors for poor prognosis in TNBC ($P_{CD147}$=0.023; $P_{MMP-9}$=0.015), and increased CD147/MMP-9 expression was significantly related to treatment failure. After chemotherapy, the expression of CD147 in TNBC patients decreased, and higher expression predicted death (P<0.05). The sensitivity and specificity of CD147 for death in 3-year follow-up were 76.92% and 88.89%, and the expression of CD147 in breast cancer cells was increased (P<0.001). Interfering with CD147 can decrease the proliferation and invasion of breast cancer cells and increase apoptotic rate (P<0.05). Conclusion: CD147 can promote the proliferation and invasion of breast cancer cells, which underlines its value in the diagnosis and treatment of TNBC.

**Keywords:** CD147, breast cancer, prognosis, proliferation, invasion

## Introduction

Breast cancer is one of the most common female malignant tumors, with an increasing incidence in recent years [1]. According to statistics, 278,800 new cases of breast cancer were reported in China in 2013 [2]. At present, the pathogenesis of breast cancer has not been clearly defined. Studies have claimed that heredity and abnormal hormone secretion are the main inducing factors for breast cancer [3]. Triple-negative breast cancer (TNBC) is a common type of breast cancer, which refers to breast cancer with negative estrogen receptor (ER), progesterone receptor (PR), and proto-oncogene Her-2, accounting for about 10%-20% of all breast cancers [4]. Compared with other types of breast cancer, TNBC has more serious development and an extremely poor prognosis due to its relatively high risk for distant metastasis [5]. According to statistics, among the 1.7 million patients with TNBC, 520,000 died within 5 years [6]. At present, there is no special clinical treatment for TNBC, and it is usually treated conventionally [7]. This, which may be a reason for the poor prognosis of TNBC. Therefore, finding a targeted treatment for TNBC by fully understanding its pathogenesis is currently receiving attention but is a difficult issue in clinical research.

Molecular targeted therapy has gradually become a focus of modern tumor therapy [8-10]. Tumor metastasis is closely related to abnormal activation of matrix metalloproteinases in the body [11]. CD147 molecule, also known as an extracellular matrix metalloproteinase inducer (EMMPRIN), can stimulate fibroblasts to produce a large amount of matrix metalloproteinase to promote tumor cell invasion and metastasis [12]. Recently, it has been continuously verified to be closely correlated with female malignant tumor diseases such as cervical cancer and ovarian cancer [13, 14], but its relationship with TNBC is not clear. Matrix metalloproteinase-9 (MMP-9) may play an important role in TNBC. It is a secretory multidomain enzyme that can be produced by many types of cells, including keratinocytes, monocytes, macrophages, polymorphonuclear leukocytes, and many types of malignant tumor cells. Compared with non-invasive tumors, invasive tumors have significantly higher expression and activity of MMP-9. CD147 and MMP-9 play important roles in the metastasis of many cancers, but their expression in TNBC and their clinical significance are not clear. We suspect that both CD147 and MMP-9 have significance in TNBC, which has strong invasion and metastasis ability. In order to verify our conjecture, this experiment will explore the relationship between CD147 and MMP-9 in patients with TNBC, aiming to provide a new reference for clinical diagnosis and treatment of TNBC.

## Materials and methods

### *Data of patients*

Totally 81 patients with TNBC admitted to our hospital and 86 healthy individuals undergoing physical examination in our hospital from August 2014 to August 2016 were selected for prospective study. These were the research group and the control group, respectively. This study was approved by the ethics committee of our hospital with an ethics approval number of 2013-12-11, and all study subjects above signed an informed consent.

### *Inclusion and exclusion criteria*

Inclusion criteria were as follows: Patients with breast cancer diagnosed by biopsy in the department of pathology in our hospital; negative results of ER, PR, and Her-2; and patients met the indications for neo-adjuvant chemotherapy; patients with complete clinical data; aged 30-70 years old. Exclusion criteria were as follows: Complicated by other tumors; other cardiovascular or cerebrovascular diseases, autoimmune deficiency diseases, severe infectious diseases, or severe liver or kidney dysfunction; patients who received surgery, radiotherapy, chemotherapy, or antibiotic drugs half a year before admission; patients whose survival time was expected to be less than 1 month; patients who had poor treatment compliance due to mental disorders; patients in pregnancy or lactation period, and referred patients.

### *Cell lines*

Human breast cancer cells MCF7, MX-1, and human normal breast epithelial cells MCF-10A were purchased from Beina Science and Technology Co., Ltd., with batch numbers of BNCC337656, BNCC100280, and BNCC33-7734, respectively.

### *Methods*

*Therapies:* All patients in the research group received weekly paclitaxel (EC-wP, CSPC Ouyi Pharmaceutical Co., Ltd., NMPA Approval Number H20183044) chemotherapy after admission, 90 mg/m$^2$ epirubicin (Zhejiang Hisun Pharmaceutical, NMPA Approval Number YPBH872) + 600 mg/m$^2$ cyclophosphamide (Tonghua Maoxiang Pharmaceutical Co., Ltd., NMPA Approval Number H22022673). Specifically, an intravenous drip was given on the first day, with 21 days per cycle. After 4 cycles of treatment, 80 mg/m$^2$ paclitaxel was sequentially applied for intravenous drip, which was completed within 1 hour, with 7 days per cycle, for a total of 12 cycles of treatment. Thirty min before administration, 10 mg dexamethasone (Guangdong Huanan Pharmaceutical Group Co., Ltd., NMPA Approval Number H44024469) was routinely given to prevent allergic reaction, with proton pump inhibitors (Haikou Kellett Pharmaceutical Co., Ltd., NMPA Approval Number H2005939) to inhibit acid, and serotonin inhibitor (Suzhou Yushi Pharmaceutical Co., Ltd., NMPA Approval Number H20093454) to prevent vomiting. When the absolute value of neutrophils was less than 2×10$^9$/L, recombinant human granulocyte col-

ony-stimulating factor was injected subcutaneously (Chugai Pharmaceutical Co., Ltd., NMPA Approval Number S20000018). Liver function was detected during chemotherapy, and liver protection was enacted when the level of glutamic-pyruvic transaminase or glutamic-oxalacetic transaminase (GOT) was 1.5 times higher than normal. When the cumulative dose of anthracyclines exceeded 300 mg/m$^2$, dexrazoxane (Shanghai Abbott Pharmaceutical Co., Ltd., NMPA Approval Number H20023659) was given for cardiac protection. In addition, a B-ultrasound and physical examination were performed on each patient once per chemotherapy cycle to assess the patient's vital signs.

*Detection of CD147 and MMP-9 in peripheral blood:* Fasting venous blood (4 ml) was sampled from each patient in the research group at the time of admission and after the completion of chemotherapy, respectively. 4 ml of it was sampled from each individual in the control group in the morning. The sampled blood was put into pro-coagulation tubes and centrifuged for 10 min (400×g) to collect serum after being placed at room temperature for 30 min. The concentrations of CD147 and MMP-9 in the collected serum were detected by enzyme-linked immunosorbent assay (ELISA) with a kit purchased from Shanghai Yuanmu Biotechnology Co., Ltd. (batch number: YM-EM9185). Procedures were strictly carried out in a sterile environment in accordance with the kit instructions. Immunohistochemically stained tissue sections were scored by two histopathologists. The staining intensity was graded as 0-3 points: 0 points for a negative result, 1 point for weak, 2 points for moderate, and 3 points for strong. The positive degree was defined as the percentage of the area of positively stained malignant tumor cells or fibrous tissue cells relative to the whole tissue area, and the degree was graded as 0-4 points: 0 points for a percentage <10%, 1 point for percentage between 10% and 25%, 2 points for percentage between >25% and 50%, 3 points for percentage between >50% and 75%, and 4 points for percentage >75%. The sum of staining intensity and staining degree score was taken as the final staining score of CD147 and MMP-9 (0-7 points). For statistical analysis, total staining scores of 0-5 and 6-7 were considered to be low expression and high expression, respectively.

*Follow-up for understanding prognosis:* Patients in the research group were followed up for 3 years by hospital reexamination, and the survival of the patients during 3 years was recorded.

*Cell culture and transfection:* MCF7, MX-1, and MCF-10A cells were cultured in Dulbecco modified Eagle medium (DMEM, Thermo Fisher, 11550043) containing 10% fetal bovine serum (FBS, Thermo Fisher) and penicillin-streptomycin mixed solution at 37°C and 5% $CO_2$. Cells in good growth status were selected for transfection after 2-3 times of stable passage. According to the instructions, CD147 was interfered with RNA (si-CD147: S-GGUUGUGGUUUCUCGAUCAdTdT; As-UGAUCGAGAAACCACAACCdTdT) with ExFect 2000 Transfection Reagent, and negative control group (si-NC: S-UUCUCCGAACGUGUCACGUdTdT; As-ACGUGACACGUUCGGAGAAdTdT) was adopted.

*Outcome measures*

Outome measures were the concentration of CD147 in peripheral blood of the research group and control group, the diagnostic value of CD147 for TNBC and its influence on the prognosis of patients with TNBC, the relative expression of CD147 protein in breast cancer cells, and the effect of CD147 on the biologic behavior of breast cancer cells.

*Statistical analysis*

SPSS22.0 (Shanghai Yuchuang Network Technology Co., Ltd.) was applied for data analysis and Graphpad8 software (Shanghai Yuchuang Network Technology Co., Ltd.) for graph drawing of the data results. Counted data were recorded in the form of (%), and compared between groups using the chi-square test. Measured data were recorded in the form of (mean ± standard deviation) and compared between groups using the independent sample t-test. In addition, the paired t-test was used for comparison before and after treatment, and the repeated measurement analysis of variance and Bonferroni backtesting was used for comparison among multiple time points. Moreover, a receiver operating characteristic (ROC) curve was applied to analyze the predicted value. The survival rate was calculat-

**Table 1.** Comparison of general data between the two groups

| Index | Research group (n=81) | Control group (n=86) | $t/\chi^2$ | P |
|---|---|---|---|---|
| Age (years) | 56.36±10.14 | 55.99±9.98 | 0.314 | 0.536 |
| BMI (kg/m$^2$) | 23.65±4.75 | 24.11±5.31 | 0.394 | 0.845 |
| Gender | | | 0.536 | 0.757 |
| Male | 40 | 43 | | |
| Female | 41 | 43 | | |

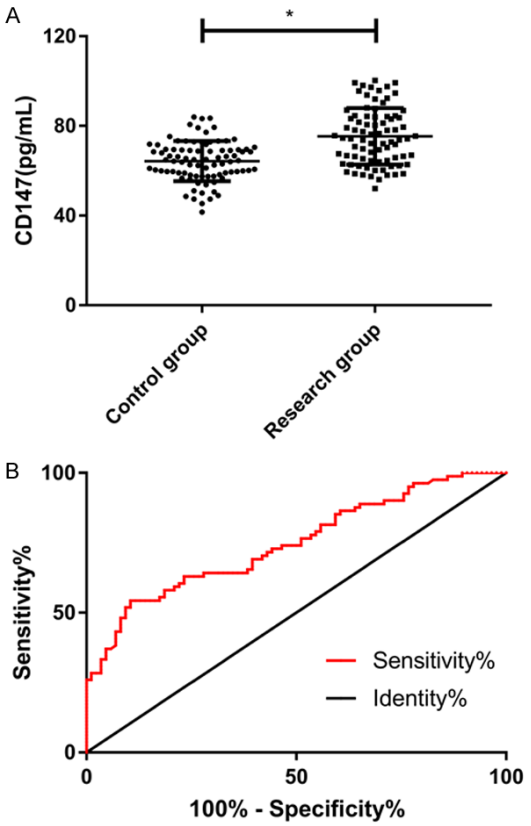


**Figure 1.** Clinical significance of CD147 in TNBC. A. The total serum concentration of CD147 in the research group was higher than that of the control group, *P<0.05. B. ROC curve of CD147 in serum for predicting TNBC.

ed by the Kaplan-Meier method, and the survival rate was compared by the Log-rank test. P<0.05 was considered significant.

## Results

*Comparison of general data*

There was no statistical difference in general data such as age and body mass index (BMI) between the two groups (all P>0.050, See **Table 1**).

*Clinical significance of CD147 and MMP-9 in TNBC*

After detection, we found that the concentrations of CD147 and MMP-9 in the serum of the research group were higher than those of the control group before chemotherapy (both P<0.050). ROC curve analysis showed that the predictive sensitivities and specificities of CD147 and MMP-9 in serum before chemotherapy for TNBC were 54.32% and 89.53% (sensitivity; AUC: 0.747, 95% CI: 0.673-0.821, P<0.001) and 56.45% and 90.14% (specificity; AUC: 0.787, 95% CI: 0.612-0.893, P<0.001), respectively, with the cut-off values of 73.520 and 73.67. See **Figures 1** and **2**.

*Relationship between CD147/MMP-9 and clinical pathology of TNBC*

By comparing the relationship between serum CD147/MMP-9 and clinicopathologic features before chemotherapy in the research group, we found that the concentrations of CD147 and MMP-9 in TNBC patients were not related to age, BMI, marital status, residence, and nationality (all P>0.050), but closely related to pathologic staging, metastasis, and differentiation degree (all P<0.050). See **Table 2**.

*Comparison of correlation before neo-adjuvant chemotherapy*

A significant positive correlation between the expression of CD147 and MMP-9 in cases with TNBC before neo-adjuvant chemotherapy was detected (n=127, r=0.609, P<0.01). See **Figure 3**.

*Correlation analysis between CD147/MMP-9 and prognosis of patients*

To further evaluate the prognostic value of CD147 and MMP-9 on the survival rate of all patients, postoperative chemotherapy and radiotherapy were carried out. The results of Kaplan-Meier estimation showed that TNBC patients with higher expression of CD147 and MMP-9 had significantly lower survival rates than those with lower expression ($P_{CD147}$= 0.039. Median survivals were 36.3 months vs.

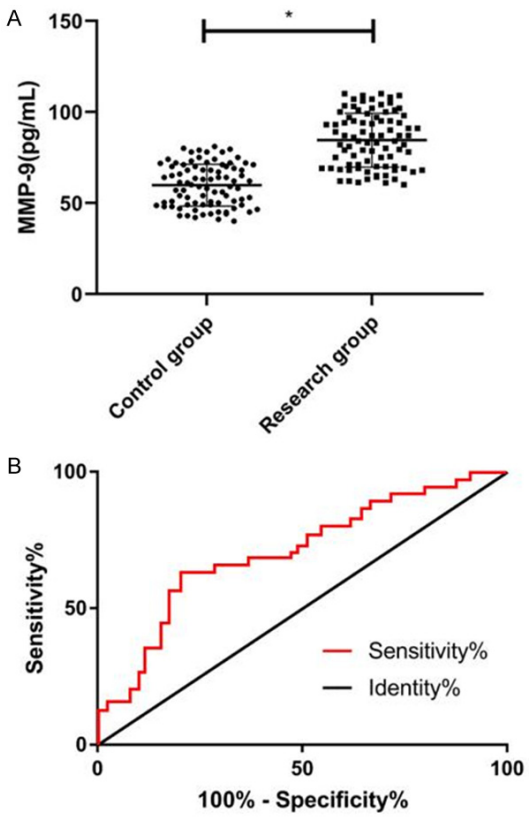


**Figure 2.** Clinical significance of MMP-9 in TNBC. A. The total serum concentration of MMP-9 in the research group was higher than that in the control group, *P<0.05. B. ROC curve of MMP-9 in serum for prediction in TNBC.

46.7 months. $P_{MMP-9}$=0.037, and the median survivals were 34.9 months vs. of 47.4 months). See **Figure 4**. Multivariate analysis revealed that in addition to tumor size, tumor grade, and lymph node metastasis, CD147 and MMP-9 were independent risk factors for poor prognosis of patients with TNBC ($P_{CD147}$= 0.023; $P_{MMP-9}$=0.015). See **Table 3**. According to these results, an increased ratio of CD147/MMP-9 expression was significantly correlated with treatment failure.

*Expression of CD147 and MMP-9 by immunohistochemistry*

The expression rates of CD147 and MMP-9 in 81 cases of TNBC were 76.9% and 80.67%, respectively, with no significant difference (P> 0.05). See **Figures 5**, **6**.

*Changes of CD147 before and after chemotherapy*

According to detection results, after chemotherapy, the concentration of CD147 in the serum of patients in the research group decreased (P<0.05). See **Figure 7**.

*Effect of CD147 on prognosis of patients with TNBC*

76 patients in the research group were successfully followed up for 3 years, with a follow-up success rate of 93.83%. The total mortality rate in the research group was 17.11% (13/76) during the 3 years of follow-up. The concentration of CD147 after chemotherapy was higher in patients who died than that in the survivors (P<0.05). ROC curve analysis revealed that when the cut-off value of CD147 was set at 68.730, the sensitivity and specificity of CD147 concentration in the serum of patients after chemotherapy to their prognostic death within 3 years were 76.92% and 88.89%, respectively (AUC: 0.854, 95% CI: 0.738-0.969, P<0.001). The patients were further divided into a high CD147 group (CD147 ≥68.73 pg/ml, n=17) and a low CD147 group (CD147 <68.73 pg/ml, n=59) according to the cut-off value after chemotherapy. By observing the 3-year survival curve of the two groups, the survival rate of the high CD147 group was notably lower than that of the low CD147 group (P=0.002). See **Figure 8**.

## Discussion

In recent years, the incidence of breast cancer has increased. The most serious type, triple negative breast cancer (TNBC) poses an increasing threat to patients [15]. Fully understanding the pathogenesis of TNBC and finding a new reliable and effective method for diagnosis and treatment are the most effective approach to TNBC. CD147 is a marker for various tumor diseases, but its impact on breast cancer and its relationship with TNBC were uncertain. This study explored the relationship between TNBC and CD147.

Results showed that CD147 was markedly increased in serum of patients with TNBC, suggesting that CD147 may be involved in the occurrence and development of TNBC. By referring to previous studies, we found that CD147 also showed an increase in patients with hepatocellular carcinoma and thyroid cancer [16, 17], which also supports our experimental results. However, according to ROC curve analysis, the predictive sensitivity and specificity of detecting CD147 for patients with TNBC were 54.32% and 89.53%, respective-

**Table 2.** Relationship between CD147/MMP-9 and Clinical pathology of TNBC

| Index | n | CD147 (ng/mL) | MMP-9 (U/L) | t | P |
|---|---|---|---|---|---|
| Age (years) | | | | 0.297 | 0.767 |
| <60 | 24 | 75.16±11.86 | 501.87±398.85 | | |
| ≥60 | 57 | 74.24±13.05 | 500.98±389.77 | | |
| BMI (kg/m$^2$) | | | | 0.073 | 0.942 |
| <24.9 | 32 | 75.06±12.62 | 502.45±367.41 | | |
| ≥24.9 | 49 | 74.86±11.57 | 501.96±387.14 | | |
| Marital status | | | | 0.562 | 0.576 |
| Married | 69 | 75.84±11.54 | 502.45±367.41 | | |
| Unmarried | 12 | 73.75±13.84 | 501.84±357.23 | | |
| Residence | | | | 0.175 | 0.862 |
| Town | 72 | 74.16±12.84 | 511.15±312.36 | | |
| Countryside | 9 | 74.94±10.76 | 512.47±309.68 | | |
| Nationality | | | | 0.183 | 0.855 |
| Han | 76 | 75.05±11.52 | 510.45±371.36 | | |
| Minority | 5 | 74.06±14.63 | 509.36±369.21 | | |
| Staging | | | | 2.759 | 0.007 |
| I-II | 24 | 71.63±8.92 | 502.45±367.41 | | |
| III-IV | 57 | 79.42±12.54 | 530.36±375.36 | | |
| Metastasis | | | | 4.271 | <0.001 |
| With | 22 | 82.34±8.63 | 536.45±312.39 | | |
| Without | 59 | 70.52±11.84 | 502.36±304.91 | | |
| Grade of Differentiation | | | | 2.835 | 0.006 |
| Medium and high | 54 | 71.16±9.05 | 502.45±367.41 | | |
| Low | 27 | 78.64±14.62 | 524.53±317.63 | | |

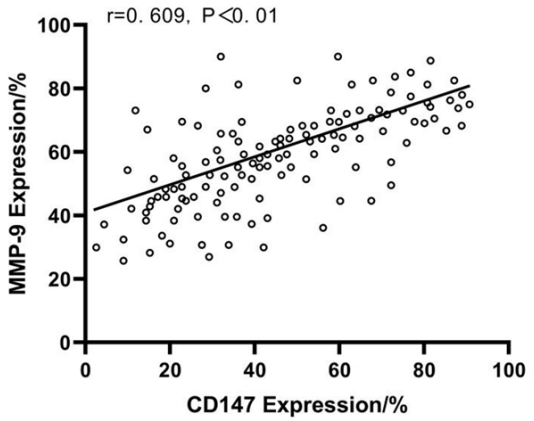


**Figure 3.** Correlation between expression of CD147 and MMP-9 in breast tumor tissues of TNBC patients before neoadjuvant chemotherapy.

ly, suggesting that CD147 is beneficial in the diagnosis of TNBC. Currently, tumor markers commonly used in clinical practice, such as CEA and CA125, are generally characterized by high sensitivity but insufficient specificity [18]. The research results of CD147 can make up for the deficiency of current tumor markers and contribute to better clinical diagnosis of TNBC, allowing early diagnosis to provide treatment as soon as possible, and better prognosis. By analyzing the relationship between CD147 and clinical pathology of TNBC, we found that CD147 was closely related to pathologic staging, metastasis, and differentiation degree, which further confirmed its involvement in TNBC development. This reinforced our above results. Moreover, we found that CD147 in patients decreased after chemotherapy, which also showed that CD147 changed after the recovery of patients. According to follow-up results, the concentration of CD147 in patients who later died was also higher than that in survivors after chemotherapy, and it had a good predictive value for mortality within 3 years. The results suggest CD147 is useful to measure in TNBC. In addition, one study by Peng et al. [19] suggests that CD147 can be used as a marker for poor prognosis in liver

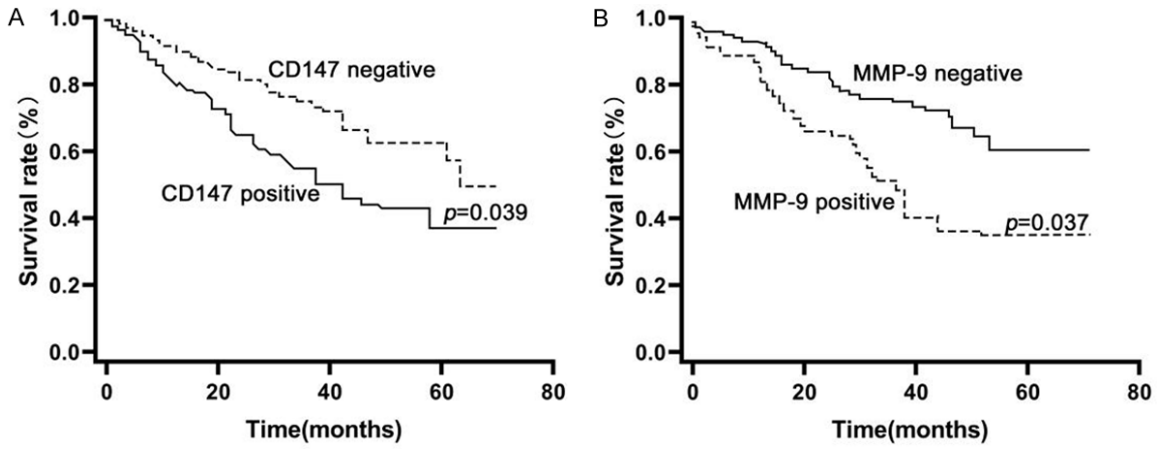


**Figure 4.** Correlation between CD147 and MMP-9 and prognosis in patients with TNBC.

**Table 3.** Prognostic factors for patients with TNBC according to multivariate analysis

| Measure | Hazard ratio | *P*-value | 95% CI |
|---|---|---|---|
| Tumor >2 cm | 1.731 | 0.001 | 1.056-2.869 |
| Lymph node metastasis | 3.092 | 0.002 | 1.769-5.364 |
| Tumor grade | 1.856 | 0.004 | 1.257-2.364 |
| High expression of CD147 | 2.847 | 0.014 | 1.212-7.096 |
| High expression of MMP-9 | 1.834 | 0.015 | 1.365-2.967 |

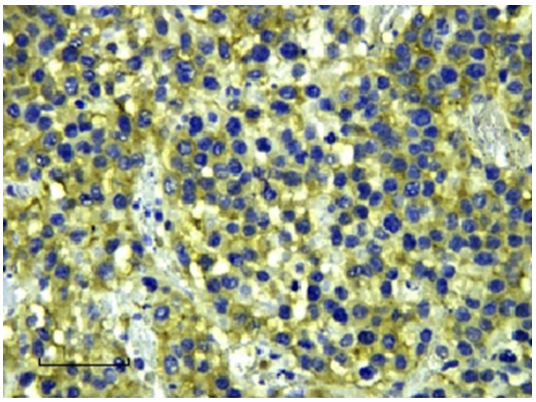

**Figure 5.** MMP-9 in TNBC (×400).

cancer, which also indicates its significance. Accordingly, we analyzed the survival of the high CD147 group and low CD147 group, and revealed that the higher the CD147, the greater the risk of death. This indicates that CD147 may be a therapeutic target for future TNBC treatment, but further experiments are needed.

Some researchers claim that CD147, as a transmembrane immunoglobulin, can promote tumor invasion by regulating cell-cell and cell-matrix adhesion and degrading the related adhesion proteins [20, 21]. For example, studies of Dana et al. [22] and Zheng et al. [23] suggest that CD147 promotes the invasion and migration of cholangiocarcinoma cells and gastric cancer cells, but its effect on breast cancer was uncertain. TNBC has extremely strong invasion ability. We speculate that the mechanism of CD147 may be achieved by regulating tumor invasion ability. Therefore, we analyzed the effect of CD147 on breast cancer cell lines. The results showed that the expression of CD147 protein in breast cancer cells was significantly increased. By interfering with CD147, the proliferation and invasion ability of breast cancer cells decreased, and the apoptosis rate increased. These results suggest that CD147 plays a role in promoting breast cancer, which is also in line with the experimental results obtained by Zhang et al. [24] and Suzuki et al. [25], verifying our hypothesis and further confirming the clinical significance of CD147 in breast cancer and TNBC. Before neoadjuvant chemotherapy, there was a significant positive correlation between the expression of CD147 and MMP-9 in TNBC tissues. The expression rates of CD147 and MMP-9 in 81 cases of TNBC were 76.9% and 80.67%, respectively, with no significant difference. In addition, both CD147 and MMP-9 were independent risk factors for poor prognosis in patients with TNBC, and the increased ratio of CD147/MMP-9 expression was significantly associated with treatment failure in patients with TNBC.

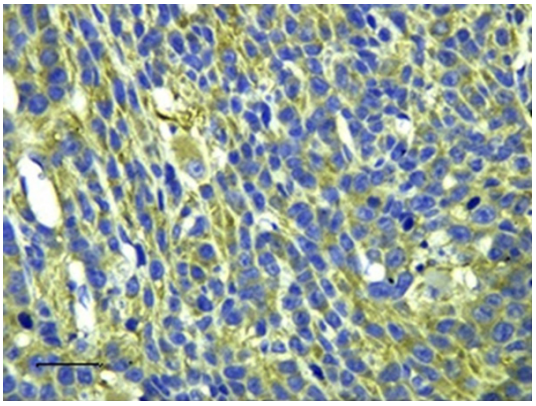

Figure 6. CD147 in TNBC (×400).

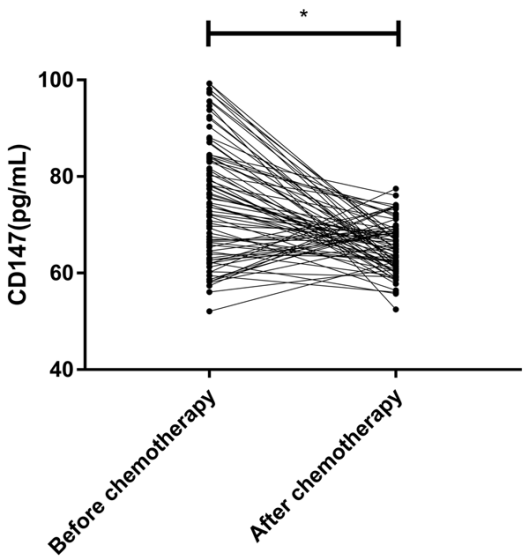


Figure 7. Changes in CD147 concentration before and after chemotherapy in the research group. After chemotherapy, the CD147 concentration decreased. *P<0.05.

This study has some limitations. For example, we did not include patients with conventional breast cancer in this experiment, so it is not clear how CD147 behaves in conventional breast cancer. Moreover, the relevant signaling pathway of CD147 affecting breast cancer cells is still unclear, and requires more in-depth experiments. We will refine the design of the study as soon as possible to address the above deficiencies, and conduct a longer follow-up for the prognosis of the subjects in this study to obtain the best experimental results for clinical reference.

In summary, CD147 is upregulated in TNBC cases, but decreases after chemotherapy, and a higher CD147 concentration indicates a greater risk of death. In addition, biologic behavior analysis shows that CD147 can promote the proliferation and invasion of breast cancer cells and inhibit their apoptosis.

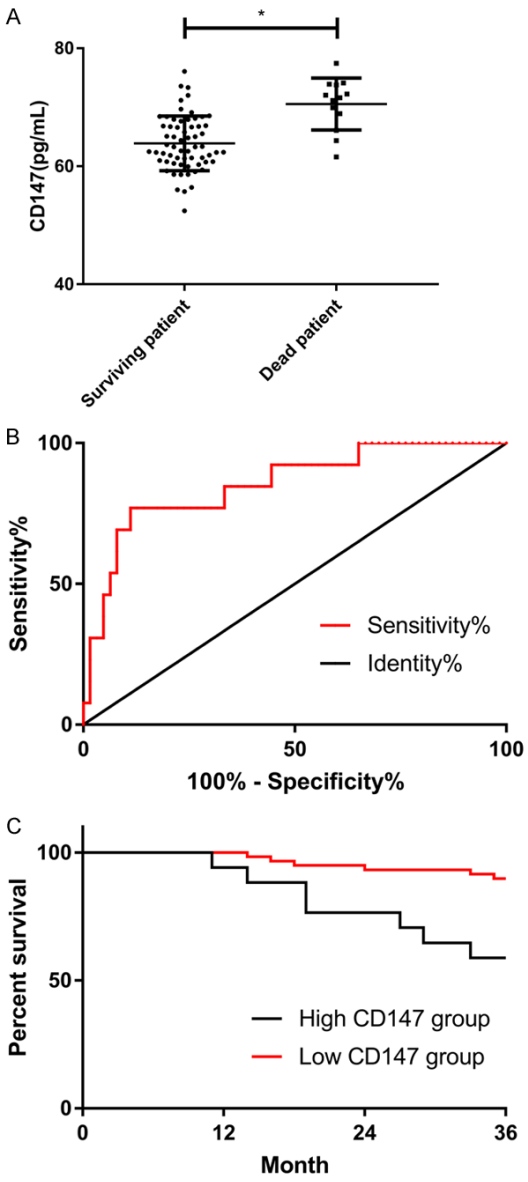


Figure 8. Effect of CD147 on prognosis of TNBC patients. A. After 3 years of follow-up, the level of CD147 of dying patients and survivors was compared, and that of dying patients was higher than in survivors, *P<0.050. B. ROC curve of CD147 concentration in serum after chemotherapy for predicting the death of patients within 3 years. C. 3-year survival curve of the high CD147 group and low CD147 group. The survival rate of the high CD147 group was lower than that of the low CD147 group, P=0.002.

## Disclosure of conflict of interest

None.

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