Online ISSN: 2682-2628
Print ISSN: 2682-261X

IJCBR

International Journal of Cancer and Biomedical Research

https://jcbr.journals.ekb.eg

Editor-in-chief
Prof. Mohamed Labib Salem, PhD

EMMPIRRIN (CD147) and matrix-matrix metalloproteinase-9 (MMP9) immunohistochemical expression in breast carcinoma: relationship with clinicopathological parameters

Shorouk M. Mowafy and Basma S. Amer

EKB Egyptian Knowledge Bank بنك المعرفة المصري

PUBLISHED BY
EACR EGYPTIAN ASSOCIAN FOR CANCER RESEARCH
Since 2014

International Journal of Cancer & Biomedical Research
(IJCBR) https://jcbr.journals.ekb.eg

IJCBR is an Int. journal published by the Egyptian Society of Cancer Research (EACR, established in 2014, http://eacr.tanta.edu.eg) and sponsored by the Egyptian Knowledge Bank (EKB: www.ekb.eg).

IJCBR has been approved by the Supreme Council of Universities, Egypt with score 7 (http://egjournal.scu.eg). The journl is cited by google scholar and registered by Publons (https://publons.com). The journal has recently been evaluated in 2020 by Nature Springer with a good standing.

Scope of IJCBR

- Drug discovery from natural and synthetic resources
- BioMedical applications of nanotehnology
- Sem cell biology and its application
- Basic and applied biotechnology
- Inflammation and autoimmune diseases
- In slico models and bioinformatics
- In vitro and In vivo preclinical animal models
- Cellular and molecular cancer biology
- Cancer Immunology and Immunotherapy
- New methods for prediction, early detection, diagnosis prognosis and treatment of dieases.
- Immunology in health and dieases
- Anti-microbial defense mechanisms
- Cellular and molecular physhiology and pahthology of diseases

IJCBR Editor,
Prof. Mohamed Labib Salem, PhD
Professor of Immunology
Faculty of Science, Tanta Universiy, Egypt

INTERNATIONAL JOURNAL OF CANCER AND BIOMEDICAL RESEARCH (IJCBR)

RESEARCH ARTICLE

EMMPIRRIN (CD147) and matrix-matrix metalloproteinase-9 (MMP9) immunohistochemical expression in breast carcinoma: relationship with clinicopathological parameters

Shorouk M. Mowafy and Basma S. Amer

Department of Pathology, Faculty of Medicine, Tanta University, Egypt

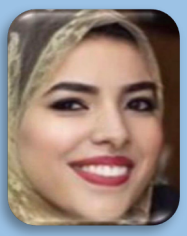
ABSTRACT

Background: Breast cancer is one of the leading causes of cancer mortality in women worldwide. Despite significant advances in cancer treatment, mortality results from local invasion and/or distant metastasis. **Aim:** To evaluate EMMPIRIN (CD147) and matrix metalloproteinase-9 (MMP9) immunohistochemical expressions significance in invasive ductal breast carcinoma cases in relation to other clinicopathological parameters. **Materials and Methods:** The study included 50 specimens of surgically resected breast carcinomas in which the expression of CD147and MMP9 was assessed. The results were compared statistically with chi-square ($\chi 2$) and Fisher exact test. **Results:** CD174 overexpression showed significant association with poorly differentiated tumors, staging, presence of nodal metastasis and high Ki67 expression. There was a significant correlation between high MMP9 expression and pathological variables as tumor staging, positive nodal metastasis, low ER expression and high HER2 expression. **Conclusion:** The results of this study suggest that high expressions of EMMPRIN and MMP9 correlate to poor prognostic parameters. Targeted therapy might improve the prognosis of patients with CD147 and MMP-9 overexpression.

Keywords: EMMPIRIN, Matrix metalloproteinase 9, Breast carcinoma, Immunohistochemistry (IHC)

Editor-in-Chief: Prof. M.L. Salem, PhD - Article DOI: 10.21608/JCBR.2020.26206.1015

ARTICLE INFO



Article history

Received: March 19, 2020
Revised: April 11, 2020
Accepted: April 14, 2020

Correspondence to:

Dr. Basma Saed Amer
Department of Pathology
Faculty of Medicine
Tanta University
Tanta, Egypt
Tel. +20- 01016660737
E-mail:
Basmasaedamer@yahoo.com

INTRODUCTION

Breast cancer is the most common malignancy and one of the most common causes of cancer-related deaths in females worldwide (Siegel et al., 2019). Invasive ductal carcinoma is the most frequent histological subtype, which accounts for 70% to 80% of all cases (Siziopikou 2013). Using prognostic factors alone or combined to predict a worse outcome of patients with early advanced treatment may improve patient survival. Identifying more available and new factors are very important (Li et al., 2018).

EMMPRIN (extracellular matrix metallo-proteinase inducer, EMN, (CD147) is a highly glycosylated transmembrane glycoprotein that is widely expressed in hematopoietic and nonhematopoietic cell lines and belongs to the immunoglobulin superfamily (Muramatsu 2016). CD147 is a multifunctional protein, which has an important role in the development and progression of different tumor types, including breast cancer. CD147 was shown to stimulate surface expression of matrix metalloproteases in adjacent tumor cells or fibroblast (Liu et al., 2018). Additionally, EMN influences cancer cell proliferation, migration, invasion and metastasis (Knutti et al., 2015).

CD147 is regarded as a risk factor for the recurrence and metastasis of breast cancer. The expression of CD147 protein is significantly

higher in those with distant metastasis (Nagashima et al., 2014). EMN was associated with the progression of several cancer types. It has been proposed to be an important potential therapeutic target (Xin et al., 2016).

Matrix metalloproteinases (MMPs) are a family of, zinc- and calcium-dependent extracellular enzymes that play a critical role in the degradation of extracellular matrix and basement membrane (Rawlings et al., 2018). MMP-9 degrades the collagen-rich extracellular matrix, which has been related to cancer invasiveness, metastasis, and recurrence of various malignant neoplasms (Shen et al., 2017).

Gelatinase matrix metalloprotease (MMP-9) may be involved in breast cancer initiation and growth through the interaction with tumor suppressor genes involved in the early stage of tumorigenesis (Skerenova et al., 2017). It was a biomarker for the aggressive subtype of breast cancer as elevated tissue levels of MMP-9 were found to be associated with poor prognosis, regional node metastases, shorter time to relapse, and reduced survival (Yousef et al., 2014). Thus, controlling MMP-9 in tumors is considered a promising strategy for inhibiting metastasis and improving the survival of breast cancer patients (Hong et al., 2018).

MATERIALS & METHODS

This retrospective study included 50 primary breast carcinoma specimens. Formalin-fixed paraffin-embedded blocks were provided from the Pathology Department during the period from March 2018 to August 2019. This study included patients who had pathologically confirmed invasive ductal breast carcinoma of no special type, proper histologic specimens with sufficient tumor tissue, and complete clinicopathologic data. Patients who received chemotherapy or radiotherapy before surgery were excluded. Clinicopathologic data and hormone receptor status of these patients were obtained from their medical reports. All included cases were classified as invasive carcinoma of no special type according to the 2019 World Health Organization (WHO) criteria (Hoon Tan et al., 2020). Nottingham grading system was used to determine tumor grade (Elston and Ellis, 1998). TNM staging was assessed according to the American Joint Committee on Cancer (Giuliano et al., 2018).

Immunohistochemical staining

Sections (5 um thick) were prepared on positively charged slides and then left to dry for 30 min at 37 °C. Dako PT Link unit was applied for deparaffinization and antigen retrieval. Both high and low pH EnVisionTM FLEX Target Retrieval Solutions were used reaching 97 °C for 20 min. Immunostaining was carried out with Dako Autostainer Link 48. Antibodies included in this study were mouse monoclonal antibody anti-Cd147 (Clone: 8D6:sc21746; dilution 1:200; Santa cruz Biotechnology Inc., Texas, USA) and mouse monoclonal anti-MMP-9 (Clone: GE-213; 1:200 dilution; Thermo Fisher Scientific Inc., Fremont, CA). Slides were left in Peroxidase-Blocking Reagent for 5 min, incubated with primary antibodies for 20–30 min, horseradish peroxidase (HRP) polymer reagent for 20 min, and diaminobenzidine (DAB) chromogen/ substrate working solution for 10 min. Finally, counterstaining with hematoxylin was done.

Interpretation of immunostaining

The tumor cells with membranous or cytoplasmic staining were considered positive for expression of CD147 or MMP-9. Staining for CD147 and MMP-9 was assessed using the following scoring method: The staining intensity was scored on a scale of 0–3 as negative (0), weak (1), medium (2) or strong (3). The percentage of positive staining areas of cancer cells was scored on a scale of 0–4 as the following: 0, <10 %; 1, 10–25 %; 2, 26–50 %; 3, 50–75 %and 4, ≥76 %. The sum of the staining-intensity and staining-extent scores was used as the final staining score for CD147 and MMP-9 (0–7). For statistical analysis, final staining scores of 0–5 and 6–7 were considered to be a low and high expression, respectively (Zhao et al., 2013).

Statistical analysis

Statistical analysis was performed using statistical package for the social sciences (SPSS version 23, IBM corp., Armonk, New York, USA). Categorical variables were expressed as frequencies and percentages, whereas mean±SD was used to express continuous variables. Chi-squaree ($\chi 2$) Test was performed for comparing categorical variables. Fisher's

exact test was applied when one of the expected frequencies was up to 5. P values of less than 0.05 were considered statistically significant.

RESULTS

Clinicopathologic characteristics:

Mean age of the studied breast carcinoma cases was 60.06+ 6.454 years. In 34 (68%) cases, tumor measured <5 cm in its greatest dimension. GII tumors constituted 30 (60%) cases whereas 20 (40%) cases were poorly differentiated. Regarding tumor stage, 26(52%) cases were Stage III, 20 (40%) cases were stage II, while only 4 (8%) cases were stage I. Positive nodal metastasis was detected in 31 (62%) cases, whereas positive vascular invasion was identified in 33(66%) cases. As regards hormone receptor status, 40 (80%) cases were ER-positive and 36 (72%) positively expressed PR. Forty (80%) cases were negative for HER-2 expression. Ki-67 proliferation index was <20% in 35(70%) cases and >20% in 15 (30%) cases. Clinicopathologic characteristics of the studied cases were illustrated in Table (1).

The relation between CD147 expression and clinicopathologic parameters

CD147 expression was noted as membranous and cytoplasmic staining in tumor cells. Twenty-six (52%) cases out of the 50 studied breast carcinoma exhibited low CD147 expression (Figs.1 and 2), while 24 cases (48%) cases exhibited high expression for CD147 protein (Fig. 3). We assessed the relationship between CD147 expression and various clinicopathological parameters as illustrated in Table (2). Regarding tumor grade, CD147 expression showed a significant correlation (p-value = 0.002). There was a significant correlation between CD147 expression and nodal metastasis (p value = 0.016). CD147 expression showed highly positive significant association with tumor staging (p-value < 0.001) and Ki67 expression (p-value < 0.001). There was no significant correlation between CD147 expression and other clinicopathological parameters such as age (p value=0.567), tumor size (p-value =0.159), vascular invasion (p value = 0.924), ER expression (p-value = 0.119), PR expression (p value=0.151) and HER2 expression (p value=0.396).

Table 1. Clinicopathological characteristics of the studied cases

Variable	Total=50
Age (years) mean ± SD	60.06± 6.454
Size	Number (%)
< 5 cm	34(68)
≥ 5 cm	16(32)
Grade	
GII	30(60)
GIII	20(40)
Nodal metastasis	
Negative	19(38)
Positive	31(62)
Staging	
I	4(8)
II	26(52)
III	20(40)
Vascular invasion	
Negative	17(34)
Positive	33(66)
ER	
Negative	10(20)
Positive	40(80)
PR	
Negative	14(28)
Positive	36(72)
Her2	
Negative	40(80)
Positive	10(20)
Ki67	
<20	35(70)
>20	15(30)

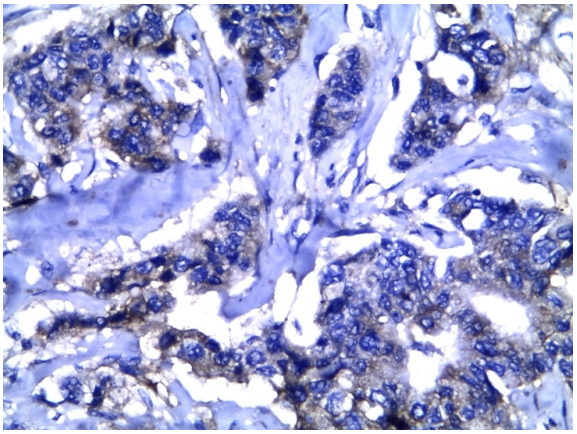


Figure 1. Grade (II) case showing low CD147cytoplasmic and membranous immunostaining (score 3) (x400).

Table 2. CD147 expression in relation to clinicopathologic variables. *significant (p value < 0.05)

		CD147 expression		
		Low expression N=26 (52)%	High expression N=24(48)%	P-value
Age (years) mean ± SD		58.73±6.017	61.5±6.724	0.567
Size				
< 5 cm	34	20(58.8)	14(41.2)	0.159
≥ 5 cm	16	6(37.5)	10(62.5)	
Grade				
GII	30	21(70)	9(30)	0.002*
GIII	20	5(25)	15(75)	
Nodal metastasis				
Negative	19	14(73.7)	5(26.3)	0.016*
Positive	31	12(38.7)	19(61.3)	
Staging				
I	4	4(100)	0(0)	< 0.001*
II	26	19(73.1)	7(26.9)	
III	20	3(15)	17(85)	
Vascular invasion				
Negative	17	9(52.9)	8(47.1)	0.924
Positive	33	17(51.5)	16(47.1)	
ER				
Negative	10	3(30)	7(70)	0.119
Positive	40	23(57.5)	17(42.5)	
PR				
Negative	14	5(35.7)	9(64.3)	0.151
Positive	36	21(58.3)	15(41.7)	
Her2				
Negative	40	22(55)	18(45)	0.396
Positive	10	4(40)	6(60)	
Ki67				
<20	35	24(68.6)	11(31.4)	< 0.001*
>20	15	2(13.3)	13(86.7)	

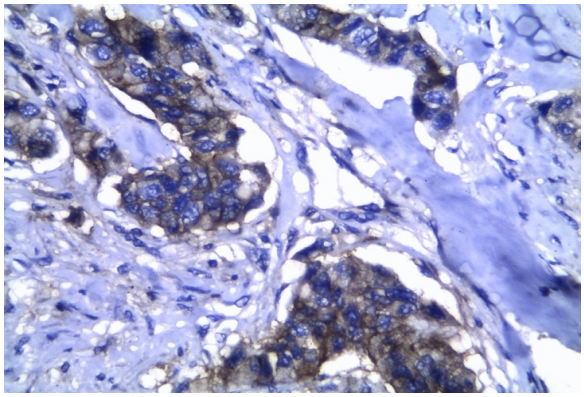


Figure 2. Grade (II) case showing low CD147 cytoplasmic and membranous immunostaining (score 5) (x400).

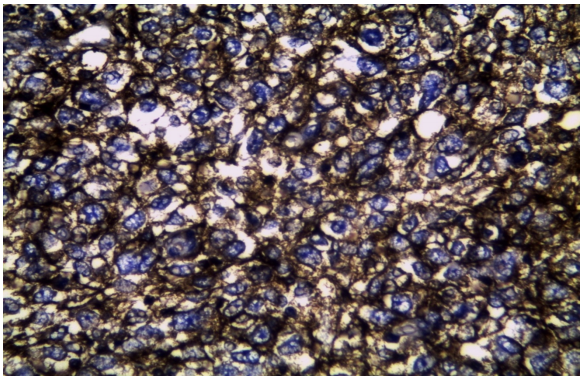


Figure 3. Grade (III) case showing high CD147 cytoplasmic and membranous immunostaining (score 7) (x400).

Table 3. MMP9 expression in relation to clinicopathologic variables. *significant (p value < 0.05)

		MMP9 expression		
		Low expression N=20 (40)%	High expression N=30 (60)%	P-value
Age (years) mean ± SD		59.05±6.716	60.73±6.297	0.998
Size				
< 5 cm	34	16(47.1)	18(52.9)	0.137
≥ 5 cm	16	4(25)	12(75)	
Grade				
GII	30	14(46.7)	16(53.3)	0.239
GIII	20	6(30)	14(70)	
Nodal metastasis				
Negative	19	11(57.9)	8(42.1)	0.043*
Positive	31	9(29)	22(71)	
Staging				
I	4	4(100)	0(0)	0.002*
II	26	13(50)	13(50)	
III	20	3(15)	85(17)	
Vascular invasion				
Negative	17	9(52.9)	8(47.1)	0.180
Positive	33	11(33.3)	22(66.7)	
ER				
Negative	10	1(10)	9(90)	0.030*
Positive	40	19 (%47.5)	21 (%52.5)	
PR				
Negative	14	5(35.7)	9(64.3)	0.700
Positive	36	15(41.7)	21(58.3)	
Her2				
Negative	40	19(47.5)	21(52.5)	0.030*
Positive	10	1(10)	9(90)	
Ki67				
<20	35	17(48.6)	18(51.4)	0.059
>20	15	3(20)	12(80)	

The relation between MMP9 expression and clinicopathologic parameters

MMP9 expression was noted as cytoplasmic staining in tumor cells. Twenty cases (40%) showed low expression for MMP9 protein (Fig. 4), whereas 30 (60%) cases exhibited high expression (Figs. 5 and 6). We assessed the relationship between MMP9 expression and various clinicopathological parameters as illustrated in Table (3). There was a significant correlation between MMP9 expression and tumor staging (p value=0.002). MMP9 expression showed positive significant association with lymph node metastasis (p-value = 0.043), ER expression (p value=0.030), HER2 expression (p-value = 0.030). There was no significant correlation between MMP9 expression and other clinicopathological parameters such as age (p-value = 0.998), tumor size (p-value = 0.137), tumor grade (p value = 0.239), vascular invasion (p-value = 0.180), PR expression (p-value = 0.700) and Ki67 expression (p-value = 0.059).

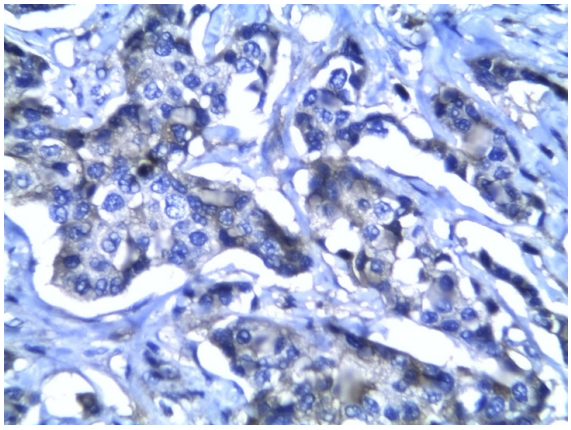


Figure 4. Grade (II) case showing low MMP9 cytoplasmic immunostaining (score 5) (x400).

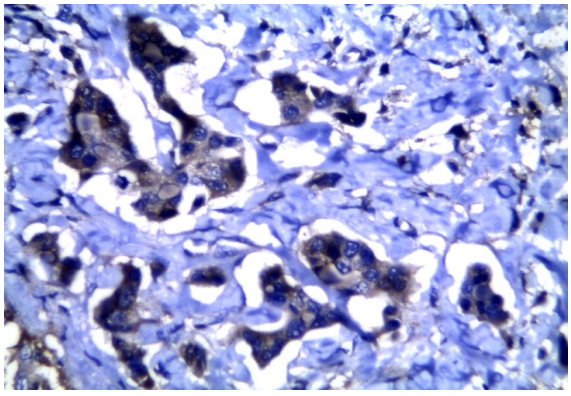


Figure 5. Grade (II) case showing High MMP9 cytoplasmic immunostaining (score 6) (x400).

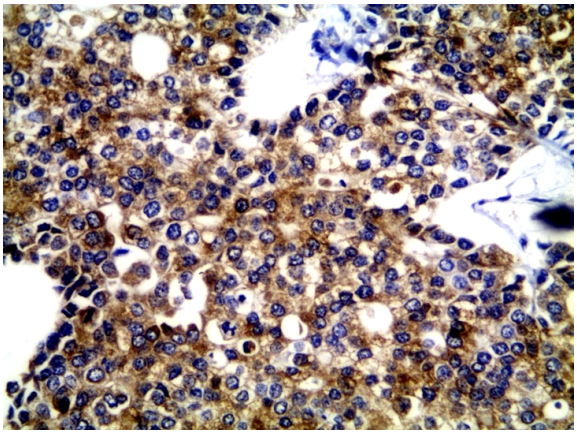


Figure 6. Grade (III) case showing High MMP9 cytoplasmic immunostaining (score 7) (x400).

DISCUSSION

CD147 is an adhesive molecule found on the surface of tumor cells, overexpressed on the surface of malignant cells. It was thought that CD 147 is MMPs inducer and plays important roles in the malignant transformation, invasion, metastasis of tumors and angiogenesis in tumor transformation (AbdRabh et al., 2019).

Earlier detection of cancer can greatly increase the opportunity for successful treatment. Identify new prognostic biomarkers can be useful for cancer clinical and therapeutic management. An increasing number of studies have shown CD147 as a promising biomarker for predicting prognosis in many cancers (Fan et al., 2017).CD147 expression in primary breast cancer tissue correlates with tumor size and staging and is predictive of poor prognosis. It has been shown that CD147 overexpression is associated with secretion of MMPs proteins in the invasion and metastasis of malignant neoplasia. Transfection of antisense RNA of CD147 into hepatocellular carcinoma cells decreases the secretion of MMP-9 and inhibits tumor cells invasion and metastasis (Li et al., 2003). CD147 has been proposed as a marker of poor prognosis in some carcinomas, for example, HCC and colorectal carcinoma. (Davidson et al., 2003).

In this study, we aimed to investigate the significance of CD147 and MMP9 immunohistochemical expression in invasive ductal carcinomas (IDC) not otherwise specified in relation to other clinicopathological parameters. CD147 is expressed in

hematopoietic and nonhematopoietic cell transmembrane glycoproteins. (Wang et al., 2019). It was observed that CD 147 positivity was significantly higher in poorly differentiated carcinoma than in well-differentiated carcinoma. These results are in agreement with those of Li, Zhang, et al., 2018 and Liu et al., 2018 who reported that CD147 expression was significantly increased with increasing tumor grade. These findings are inconsistent with those obtained by Tian et al., 2015 who reported that CD147 expression was insignificantly increased with increasing tumor grade.

In agreement with Xiong et al., 2016 the present study reported significant relations between CD147 expression with increasing TNM stage and vascular invasion. Similarly, Zhao et al., 2013 showed a significant relation between CD147 expression and lymph node metastasis. CD147 is a glycoprotein involved in cancer progression by several mechanisms in particular, by the control of glycolysis and also by its well-known ability to induce proteinases leading to matrix degradation, tumor cell invasion and angiogenesis. Tumor invasion depends on a complex mechanism involving cell adhesion, migration and matrix degradation. (Landras et al., 2019).

The present study reported a significant relation between CD147 expressions with increasing ki 67 index. This was following the study of Liu et al., 2018. On the contrary to this study, Liu et al., 2010 found a negative significant relation between CD147 expression with ER and PR expressions. They found also a positive significant relation between CD147 expression and HER2 expression.

Tumor invasion and metastasis are the major causes of treatment failure for carcinoma patients. The ways of action of CD147 for tumor invasion are two different ways; one involving an MMP-mediated cleavage of surface-bound CD147 and a second is based on the release of microvesicles, containing full-length of CD147 molecules (Sidhu et al., 2004).

CD147 stimulates the adhesion effect between tumor cells, or between tumor cells and stromal cells. It can also stimulate the activation of matrix metalloproteinase on the surface of tumor cells and stimulates the tumor cells and interstitial cells to produce MMP-2 and MMP-9. Degradation of extracellular matrix components and basement membrane by tumor cells is an important step in the metastasis of tumor. MMPs are a group of ion-dependent endopeptidases. Among them, type IV collagenase (MMP-2, MMP-9) plays an important role in disease progression and high expression has been found with metastasis and in relation with poor prognostic parameters of several types of carcinoma, such as colorectal cancer, gastric carcinoma, lung cancer, prostatic carcinoma and head and neck cancer (Jiang et al., 2018).

MMPs are regarded to be relevant to the prognosis of breast cancer. Numerous studies have confirmed the association between MMPs and tumor growth, invasion and metastasis in breast cancer. However, their prognostic values for survival in patients with breast cancer still remain controversial. Hence, this study was performed to clarify a more accurate estimation of the role of MMPs on the prognosis of breast cancer patients (Ren et al., 2015).

In accordance to Yang et al., 2018, this study revealed a significant relation between MMP9 expression and staging. However, there was no significant relation between MMP9 and grading in this study. MMPs degrade the components of the extracellular matrix removing the barrier between tumor cells and normal tissue and initiating the metastatic process (Cymbaluk-Płoska et al, 2017).

This study reported a significant relation between MMP9 expression and Lymph node metastasis. High MMP9 expression was significantly correlated with low ER expression and High HER2 expression. These results were similar to those of Yousef et al., 2014.

On the contrary, Thammineni et al., 2019 showed a positive correlation between MMp9 expression and vascular invasion. MMP-9 involves in diverse aspects of cancer progression, ranging from initiation and early progression to dissemination, invasion and motility, metastatic niche formation, angiogenesis.

In conclusion, this study showed that the high-grade tumors, tumors with stage III, the presence of nodal metastasis were associated with high CD147 and MMP9 expressions. MMP-9 and its inducer CD147 maybe participate in invasion and metastasis of breast cancer as their high expressions may be in relation with poor prognostic parameters. Prospective studies are necessary to determine the clinical value of the approach. Using these markers as a target might become a specific treatment of choice.

References

AbdRabh, RM, Zafer NS, Emara NM, Aal, EMA (2019). Immunohistochemical study of extracellular matrix metalloproteinase inducer expression and nuclear morphometry in endometrial hyperplasia and endometrioid adenocarcinoma. Egyptian Journal of Pathology 16(1): 141.

Cymbaluk-Płoska A, Chudecka-Głaz A, Pius-Sadowska E, Sompolska-Rzechuła, A., Chudecka K, Bulsa M, Menkiszak J (2017). Clinical relevance of NGAL/MMP-9 pathway in patients with endometrial cancer. *Disease markers*. Article ID 6589262.

Davidson B, Goldberg I, Berner A (2003). EMMPRIN (extracellular matrix metalloproteinase inducer) is a novel marker of poor outcome in serous ovarian carcinoma. Clin Exp Metastasis 20:161–169

Elston CW and Ellis IO (1998): Assessment of histological grade. In Elston, CW and Ellis IO (eds), The breast. Vol. 13. Churchill Livingstone, Edinburgh; New York;356–84.

Fan H, Yi W, Wang C, Wang J (2017). The clinicopathological significance and prognostic value of EMMPRIN overexpression in cancers: Evidence from 39 cohort studies. *Oncotarget* , *8*, 82643–82660.

Giuliano AE, Edge SB, Hortobagyi GN (2018). Eighth Edition of the AJCC Cancer Staging Manual: Breast Cancer. Ann Surg Oncol: 25(7):1783–5.

Hong O, Youn HJ, Jang H, Jung SH, Noh E, Chae HS, Jeong Y, Kim W, Kim C, Kim J (2018).Troglitazone Inhibits Matrix Metalloproteinase-9 Expression and Invasion of Breast Cancer Cell through a Peroxisome Proliferator-Activated Receptor γ- Dependent Mechanism. J Breast Cancer Mar: 21(1): 28–36.

Hoon Tan P, Ellis I, Allison K, Brogi E, Fox SB, Lakhani S, Lazar AJ, Morris EA, Sahin A, Salgado R, Sapino A, Sasano H, Schnitt S, Sotiriou C, van Diest P, White VA, Lokuhetty D, Cree IA; WHO Classification of Tumours Editorial Board (2020): The 2019 WHO classification of tumours of the breast. Histopathology. 2020 Feb 13. doi: 10.1111/his.14091.

Jiang Z, Zhang H, Liu C (2018): β3GnT8 promotes colorectal cancer cells invasion via CD147/MMP2/Galectin3 axis. *Frontiers in Physiology*, *9*, 588.

Knutti N, Kuepper M, Friedrich K (2015). Soluble extracellular matrix metalloproteinase inducer (EMMPRIN, EMN) regulates cancer-related cellular functions by homotypic interactions with surface CD147. FEBS J 282:4187–4200.

Landras A, Reger de Moura C, Jouenne F, Lebbe C, Menashi S, Mourah, S (2019). CD147 Is a Promising Target of Tumor Progression and a Prognostic Biomarker. *Cancers*, *11*(11), 1803.

Li Y, Shang P, Qian AR (2003). Inhibitory effects of antisense RNA of HAb18G/CD147 on invasion of hepatocellular carcinoma cells in vitro. World J Gastroenterol. ;9:2174–2177.

Li X, Dai D, Chen B, Tang H, Xie X, Wei W (2018): Clinicopathological and Prognostic Significance of Cancer Antigen 15-3 and Carcinoembryonic Antigen in Breast Cancer: A Meta-Analysis including 12,993 Patients. Dis Markers. 9863092.

Li F, Zhang J, Guo J, Jia Y, Han Y, Wang Z (2018). RNA interference targeting CD147 inhibits metastasis and invasion of human breast cancer MCF-7 cells by downregulating MMP-9/VEGF expression. Acta Biochimica et Biophysica Sinica, 50(7), 676-684.

Liu F1, Cui L, Zhang Y, Chen L, Wang Y, Fan Y, Lei T, Gu F, Lang R, Pringle GA, Zhang X, Chen Z, Fu L (2010). Expression of HAb18G is associated with tumor progression and prog nosis of breast carcinoma. Breast Cancer Res Treat 24(3):677-88.

Liu M, Tsang JYS, Lee M, Ni YB, Chan SK, Cheung SY, Hu J, Hu H, Tse GMK (2018). CD147 expression is associated with poor overall survival in chemotherapy treated triple negative breast cancer. J. Clin. Pathol. 71, 1007–1014.

Muramatsu T (2016). Basigin (CD147), a multifunctional transmembrane glycoprotein with various binding partners. J Biochem 159:481–490

Nagashima S, Sakurai K, Suzuki S, Hara Y, Maeda T, Hirano T, Enomoto K, Amano S, Koshinaga T (2014). CD147 expression in non-invasive and invasive breast carcinoma. Gan To Kagaku Ryoho 41(10):1267–9.

Rawlings ND, Barrett AJ, Thomas PD, Huang X, Bateman A, Finn RD (2018). The MEROPS database of proteolytic enzymes, their

substrates and inhibitors in 2017 and a comparison with peptidases in the PANTHER database. Nucleic Acids Res 46: D624–D632.

Ren F, Tang R, Zhang X, Madushi WM, Luo D, Dang Y, Chen G (2015). Overexpression of MMP family members functions as prognostic biomarker for breast cancer patients: a systematic review and meta-analysis. *PloS one 10*(8): e0135544.

Shen Z, Zhu D, Liu J, Chen J, Liu Y, Hu C, et al. (2017) .27-Hydroxycholesterol induces invasion and migration of breast cancer cells by increasing MMP9 and generating EMT through activation of STAT-3. Environ Toxicol Pharmacol 51:1–8.

Sidhu S, Mengistab T, Tauscher N, LaVail J, Basbaum, C (2004). The microvesicle as a vehicle for EMMPRIN in tumor stromal stromalinteractions. *Oncogene*, *23*: 956.

Siegel RL, Miller KD, Jernal A (2019). Cancer statistics. CA CANCER J CLIN 2019; 69:7–34.

Siziopikou KP (2013). Ductal carcinoma in situ of the breast: current concepts and future directions. Arch Pathol Lab Med 137:462-6.

Skerenova M, Mikulova V, Capoun O, Zima T, Tesarova P (2017). Circulating tumor cells and serum levels of MMP-2, MMP-9 and VEGF as markers of the metastatic process in patients with high risk of metastatic progression. Biomed. Pap. Med. Fac. Univ. Palacky Olomouc Czech Repub 161: 272–280.

Thammineni KL, Thakur GK, Kaur N, Banerjee BD (2019). Significance of MMP-9 and VEGF-C expression in North Indian women with breast cancer diagnosis. *Molecular* and cellular biochemistry 457(1-2): 93-103.

Tian X, Ye C, Yang Y, Guan X, Dong B, Zhao M, Hao C (2015). Expression of CD147 and matrix metalloproteinase-11 in colorectal cancer and their relationship to clinicopathological features. Journal of translational medicine 13(1): 337.

Wang C, Xu C, Niu R, Hu G, Gu, Z, Zhuang Z (2019). MiR-890 inhibits proliferation and invasion and induces apoptosis in triple-negative breast cancer cells by targeting CD147. *BMC* Cancer 19(1): 577.

Xin X, Zeng X, Gu H, Li M, Tan H, Jin Z, Hua T, Shi R, Wang H (2016). CD147/EMMPRIN overexpression and prognosis in cancer: A systematic review and meta-analysis. Sci Rep 6: 32804

Xiong L, Ding L, Ning H, Wu C, Fu K, Wang Y, Zhou L (2016). CD147 knockdown improves the antitumor efficacy of trastuzumab in HER2-positive breast cancer cells. Oncotarget 7(36): 57737.

Yang J, Min KW, Kim DH, Son BK, Moon KM, Wi YC5, Bang SS, Oh YH2, Do SI, Chae SW, Oh S, Kim YH, Kwon MJ (2018). High TNFRSF12A level associated with MMP9 overexpression is linked to poor prognosis in breast cancer: Gene set enrichment analysis and validation in large-scale cohorts. PLoS One. 2018 Aug 24; 13(8):e0202113.

Yousef EM, Tahir MR, St-Pierre Y, Gaboury LA (2014). MMP-9 expression varies according to molecular subtypes of breast cancer. BMC Cancer 14, 609.

Zhao S, Ma W, Zhang M, Tang D, Shi Q, Xu S, Zhang, Q (2013). High expression of CD147 and MMP-9 is correlated with poor prognosis of triple-negative breast cancer (TNBC) patients. Medical Oncology, 30(1), 335.

Egyptian Association for Cancer Research (EACR)
http://eacr.tanta.edu.eg/

EACR is an NGO society that was declared by the Ministry of Social Solidarity (Egypt) No. 1938 in 19/11/2014 based on the initiative of Prof. Mohamed Labib Salem, the current Chairman of EACR. EACR aims primarily to assist researchers, in particular young researchers in the field of cancer research through workshops, seminars and conferences. Its first international annual conference entitled "Anti-Cancer Drug Discovery" was successfully organized in April 2019 (http://acdd.tanta.edu.eg). Additionally, EACR aims to raise the awareness of the society about the importance of scientific research in the field of cancer research in prediction, early diagnosis and treatment of cancer. EACR is also keen to outreach the scientific community with periodicals and news on cancer research including peer-reviewed scientific journals for the publication of cutting-edge research. The official scientific journal of EACR is "International Journal of Cancer and biomedical Research (IJCBR: https://jcbr.journals.ekb.eg) was successfully issued in 2017 and has been sponsored by the Egyptian Knowledge Bank (EKB: www.ekb.eg).

EACR **Chairman,**
Prof. Mohamed Labib Salem, PhD
Professor of Immunology
Faculty of Science, Tanta Universiy, Egypt

International Journal of Cancer & Biomedical Research
(IJCBR) Online ISSN 2682-2628

Editor-in-Chief

Mohamed Labib Salem, PhD
Tanta University, Egypt

Managing Editor

Nehal Elmashad, MD
Tanta University, Egypt

Nabil Mohy Eldin, PhD
Kafrelsheikh University, Egypt

Doaa Al-Ghareeb, PhD
Alexandria University, Egypt

Abdel-Aziz Zidan, PhD
Damanhour University, Egypt

Wesam Meshrif, PhD
Tanta University, Egypt

Rasha Eraky, MD
Tanta University, Egypt

Associate Editor

Hesham Tawfik
Tanta University, Egypt

Mostafa El-Sheekh
Tanta University, Egypt

Yousry Albolkiny, PhD
Tanta University, Egypt

Gamal Badr
Assuit University, Egypt

Elsayed Salim
Tanta University, Egypt

Essam Elshiekh
Tanta Cancer Center, Egypt

Editorial Board

Alberto Montero
Taussig Cancer Center, Cleveland, USA

Marcela Diaz
Cleveland Clinic Foundation, USA

Yi Zhang
Zhengzhou University, China

Shengdian Wang
Chinese Academy of Sciences, China

Faris Alenzi
Prince Sattam bin Abdulaziz University, KSA

Mark Robunstein
Medical University of South Carolina, USA

Mamdooh Ghoneum, DSc
Charles Drew University of Medicine & Science, USA

Natarajan Muthusamy, DVM
The Ohio State University, USA

Hideki Kasuya MD, PhD, FACS
Nagoya University, Japan

Sherif El-Khamisy, MD
Sheffield University, UK

Mohamed Abou-El-Enein, MD
Charité Universitätsmedizin Berlin, Germany

Alaa Eldin Almostafa, MD
McGill University, Canada

Amr Amin
United Arab Emirates University, UAE

AbdelRahman Zekri
National Cancer Institute, Egypt

Mohamed Attia, MD
Tanta University, Egypt

Mohamed Elshanshory, MD
Tanta University, Egypt

Hussein Khamis
Alexandria University, Egypt

Magdy Mahfouz
Kafr Elsheikh University, Egypt

Ehab Elbedewey
Tanta University, Egypt

Abeer Badr
Cairo University, Egypt

Nadia Hamdy, PharmD
Ain Shams University, Egypt

Ibrahim El-Sayed
Menoufia University, Egypt

Tarek Aboul-Fadl, PharmD
Assiut University, Egypt

Mohamed Noureldin
Banaha University, Egypt

Haiam Abou Elela
National Institute of Oceanography and Fisherie, Egypt

Sameh Ali, MD
Nationa Liver Institute, Egypt

Maha EL-Demellawi
City for Scientific Research & Technology Applications, Egypt

Desouky A Abd-El-Haleem
City for Scientific Research & Technology Applications, Egypt

Ashraf Tabll
National Research Center, Egypt

Wael Lotfy, MD
Alexandria University, Egypt

Olfat Gadallah, MD
Tanta University, Egypt

Nahla Shoukry
Suez University, Egypt

Medhat Eldenary
Tanta University, Egypt

Nagla Sarhan, MD
Tanta University, Egypt

Naglaa Fathy, MD
Zagazik University, Egypt

Azza Hasan Mohamed
Menufia University, Egypt

Nanees Gamal Eldin
Tanta University, Egypt

Mohamed Mansour, UK

Sabbah Hammoury
Alexandria Ayadi Almostaqbal Oncology Hospital, Egypt

Nehal Aboulfotoh
Zewail City for Science and Technology, Cairo, Egypt

Amir Elkhami
Galaxo, San Francisco, USA

Rabab Khairat
National Research Center, Giza, Egypt

Ahmed Alzohairy
Zagazi University, Egypt

Wgady Khalil
National Research Center, Egypt

Sayed Bakry
Alazhar University, Egypt

Mohamed Ghanem, MD
Kafr Elshikh University, Egypt

Mohamed Salama, MD
Mansoura University, Egypt

Mona Marie, MD
Alexandria University, Egypt

For more information, contact

Hamdi Kandil
Tanta University, Egypt
Email: Ijcbr100@gmail.com