

# Prognostic Value of the Matrix Metalloproteinase-9 and Its Relation to Clinicopathological Features in Women with Invasive Breast Cancer

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## Abstract

**Background:** Invasive breast cancer is the most common type of malignancy in women worldwide. Matrix Metalloproteinase-9 is a member of degrading enzymes required for tumor metastasis. **Aim:** To assess the prognostic significance of the Matrix Metalloproteinase-9 expression in invasive breast cancer and its association with the clinicopathological features. **Patients and Methods:** Cross-sectional study was conducted at the Oncology and Nuclear Therapy Unit, Suez Canal University Hospital. The study involved 33 females that were registered between January 1<sup>st</sup>, 2008 and December, 31<sup>st</sup>, 2012. The eligible participants had a confirmed non-metastatic invasive ductal carcinoma, underwent surgery that their paraffin blocks containing tumor were available. The participants' tissue specimens were immune stained for Matrix Metalloproteinase-9 expression level in the hospital pathology lab. Survival analysis and correlation models were conducted to explore the association between Matrix Metalloproteinase-9 expression level with clinicopathological parameters and survival. **Results:** The mean age of participants was 51.2 ± 9.9 years. The mortality rate was 18.2%. The mean Matrix Metalloproteinase-9 expression was 5.42 (±3.37); 57.6% showed high expression level. There was no significant correlation with clinicopathological features. Nottingham Prognostic Index was a significant predictor of mortality. Overall survival and disease-free survival were insignificantly different among cases with low and

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high MMP-9 expression. **Conclusion:** Tissue Matrix Metalloproteinase-9 expression level does not play a significant role in disease progression. However, Nottingham Prognosis Index is a significant predictor of mortality among studied breast cancer cases.

## Keywords

Prognosis, Ductal Carcinoma, Matrix Metalloproteinase-9

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## 1. Introduction

Breast cancer (BC) accounts for the first leading cause of cancer mortality among women globally. Additionally, BC represents the second most incident cancer type after lung cancer [1]. In Egypt, BC is the most prevalent cancer among females; they represent 32.0% of all cancer cases. Despite the considerable diagnostic and therapeutic advances in recent years, BC is the most common cause of cancer-related mortality among women aged 40 - 49 years [2]. Breast Cancer Foundation of Egypt, 2013 reported that the proportion of females BC was 37.5% of all cancer patients. National Cancer Institute-Cairo University, 2009 highlighted BC as a rapidly spreading cancer among women and estimated its incidence rate to be 24 per 100,000 women [3].

Matrix Metalloproteinases (MMPs) are zinc-dependent endopeptidases that present in the extracellular compartment of various tissues. They are involved in the degradation of Extra-Cellular Matrix (ECM). To date, 26 MMPs have been identified in humans. Most of them have similar structural and functional properties; however, they differ in their substrate specificities [4]. According to the specific structure, MMPs could significantly contribute to cancer invasion and metastasis, angiogenesis and tumorigenesis [5].

Matrix Metalloproteinases-9 (MMP-9) has the ability to degrade Type IV collagen and other essential ECM components. Thus, it joined the 70 genes in the Rosetta poor prognosis signature of BC patients. However, the prognostic significance of MMP-9 expression level was not consistent in relevant published literature [6]. Therefore, this study investigated the tissue MMP-9 expression level in relation to the clinicopathologic features as well as its prognostic value among BC female patients attending Oncology and Nuclear Therapy Unit, Suez Canal University Hospital.

## 2. Patients and Methods

### 2.1. Design

A cross-sectional study was used to identify the tissue MMP-9 expression level among female patients with invasive breast cancer. The tissue level of MMP-9 expression was measured at baseline for all registered patients with IDC in the period between January 1<sup>st</sup>, 2008 and December 31<sup>st</sup>, 2012. The prognostic sig-

nificance of the tissue level MMP-9 expression was then evaluated through follow-up study of the cases for at least 5 years period from baseline.

**Setting:** The study was conducted at Oncology and Nuclear Medicine Unit, Suez Canal University Hospital, Ismailia governorate. The laboratory investigations were carried out at the Pathology lab. of the same hospital. Inclusion criteria were; histologically confirmed Invasive Ductal Breast Carcinoma in females older than 18 years without visceral or bone metastasis underwent surgery and whose paraffin blocks containing tumor were available. Exclusion Criteria were; Metastatic breast cancer females at time of presentation, Patients with comorbidity that interfere with chemotherapy administration (e.g. Cardiomyopathy, renal failure) and who had received neoadjuvant radiation or chemotherapy.

## 2.2. Methods

Data were collected through patient's medical records and the laboratory examination of tumor specimen paraffin blocks. A structural electronic form that was established using Microsoft Excel (version 2013), was used to collect the required data. The age at the diagnosis, histopathological initial diagnosis (e.g. IDC, DCIS) onset, time, and sites of metastasis development were collected from the archived records in the oncology clinic.

Histopathological examination and immunohistochemical study of the tumor specimen paraffin blocks to explore tissues MMP-9 expression level were done in the pathology department. The representative sections containing both normal mammary and tumor tissue were obtained from the archival material of 10% buffered formalin fixed paraffin embedded blocks. Two sections were cut into 5  $\mu$ m thick sections, one was mounted on glass slides for Hematoxylin and Eosin staining (H & E) and the other ones were mounted on positively charged slide for immunohistochemical staining using antigen retrieving techniques. The H & E sections were assessed for the prognostic factors; histological Grade, hormonal receptors and Nottingham prognostic index (NPI).

## 2.3. Immunohistochemistry Study

Anti-MMP9 antibody, mouse monoclonal antibody (5G3) (MA515886) to MMP-9 (No. IL 61105, USA) for assessment of MMP9 expression in specimens diagnosed as IDC. The slides were evaluated according to *Staining intensity score*: Rated as: No staining  $\rightarrow$  0, Weak staining  $\rightarrow$  1, Moderate staining  $\rightarrow$  2, and Strong staining  $\rightarrow$  3.

*The proportion of staining:* This parameter corresponds to the percentage of immunoreactive cells also known as the quantity score (QS). QS was estimated as follows: (no staining was scored as 0, 1% - 10% of cells with positive staining were scored as 1, >10% - 50% as 2, >50% - 70% as 3, and >70% - 100% as 4). The sum of the intensity and proportion score was used as the final staining score (the total IHC score that ranges from 0 to 12). IHC scores of 0 to 4 were considered to represent low levels of expression while the score from >4 to 12 was con-

sidered as high levels of expression [7].

## 2.4. Statistical Analysis

The data were exported to SPSS statistical software (version 22) to conduct the statistical analysis. Firstly, the significance of the relationship between tissue expression level of MMP-9 and clinicopathological parameters were evaluated with bivariate analysis using chi-square test and Fisher's exact probability test. Then, survival analysis was performed using log rank test. The effect of MMP-9 differential expression on postoperative survival rates was assessed using Cox's proportional hazard regression model analysis. The performance of MMP-9 and clinicopathological factors as prognostic factors were assessed and compared using the diagnostic test accuracy parameters: sensitivity, specificity, predictive values and likelihood ratios. A p-value of 0.05 or less was considered statistically significant.

## 2.5. Ethical Consideration

The study proposal was first approved by the research ethics committee of Faculty of Medicine Suez Canal University January 23<sup>rd</sup>, 2016. The official agreements of the general manager of Suez Canal University Hospital and the head of Oncology and Nuclear Therapy Unit were obtained to access the required data from the patient's medical records. Confidentiality of the obtained data was strictly kept; the anonymousness of patient information was ensured throughout the study conduction. Additionally, the accessed data was used for the purpose of this research only.

## 3. Results

Thirty three female cases were included in the present work and followed-up for least 5 years unless the case has died. Follow-up ended on 31/12/2017, with a minimum follow-up time of 1.42 years and a maximum of 8.67 years (Mean  $\pm$  SD: 6.16  $\pm$  1.84). All patients in our study had a confirmed IDC. The enrolled breast cancer patients had a mean age of 51.2 years ( $\pm$ 9.9), and an age range of 33 - 72 years. About 64% had a history of lymph nodes involvement. The mean largest diameter of tumor tissue was 4.0  $\pm$  9.9 cm. The majority of cases had stages IIA, IIB, and IV. Estrogen and Progesterone receptors were positive in 70% of cases as mentioned in **Table 1**. The mean Nottingham Prognostic Index (NPI) was 4.45 ( $\pm$ 0.87) and ranged from 3.1 to 6.0. Based on NPI score, 66.7% had 70% 5-year survival, 18.2% had 50% 5-year survival, and 15.2% had 85% 5-year survival (**Table 2**).

Histopathologic examination of specimens revealed that About 39% had DCIS.

Desmoplastic reaction was positive in about 61% of cases with variable levels. The majority of patients had grade II breast cancer (93.9%) as shown in **Figure 1**.

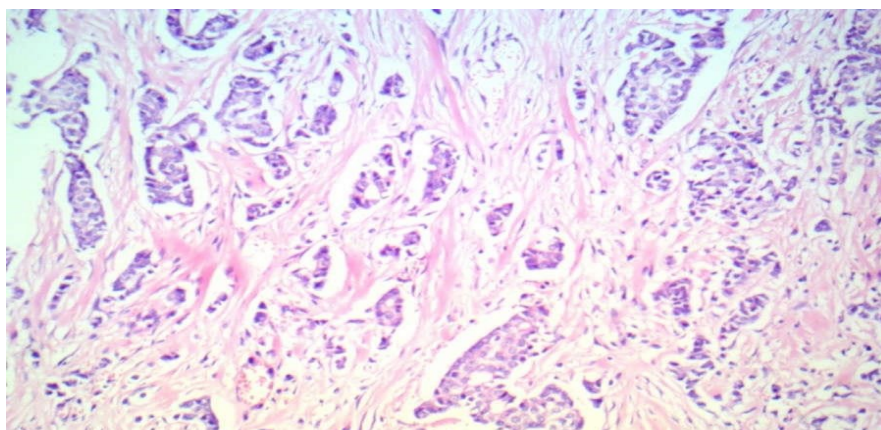
**Immunohistochemistry of MMP9 Expression:** Based on IHC score criterion

**Table 1.** Patients and tumor characteristics among studied population.

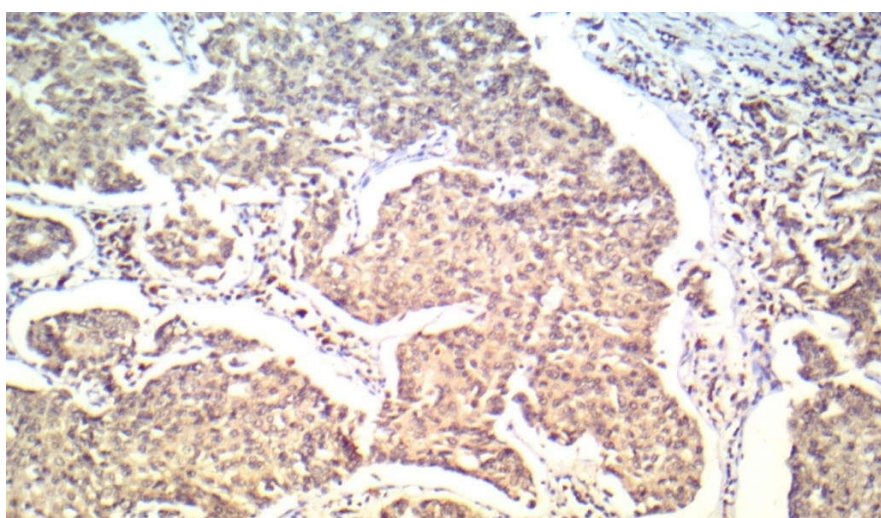
|                                        |               | Frequency                                | %      |
|----------------------------------------|---------------|------------------------------------------|--------|
| Age (years)                            | Mean $\pm$ SD | 51.2 $\pm$ 9.9<br>(Range: 33 - 72 years) |        |
| BMI                                    | Mean $\pm$ SD | 28 $\pm$ 9.4                             |        |
| Residence                              | Urban         | 13                                       | 39.3%  |
|                                        | Rural         | 20                                       | 60.6%  |
| Tumor Type                             | IDC           | 33                                       | 100.0% |
| Ductal carcinoma <i>in situ</i> (DCIS) | No            | 20                                       | 60.6%  |
|                                        | Yes           | 13                                       | 39.4%  |
| Desmoplastic reaction                  | None          | 13                                       | 39.4%  |
|                                        | Mild          | 8                                        | 24.2%  |
|                                        | Moderate      | 7                                        | 21.2%  |
|                                        | Marked        | 5                                        | 15.2%  |
| Lymph Nodes involvement                | No            | 12                                       | 36.4%  |
|                                        | Yes           | 21                                       | 63.6%  |
| Largest Tumor diameters                | Mean (SD)     | 4.0 (2.4)                                |        |
| Tumor Stage                            | IA            | 2                                        | 6.1%   |
|                                        | IIA           | 7                                        | 21.2%  |
|                                        | IIB           | 8                                        | 24.2%  |
|                                        | IIIA          | 3                                        | 9.1%   |
|                                        | IIIC          | 2                                        | 6.1%   |
|                                        | IV            | 11                                       | 33.3%  |
| Tumor Grade                            | I             | 1                                        | 3.0%   |
|                                        | II            | 31                                       | 93.9%  |
|                                        | III           | 1                                        | 3.0%   |
| Estrogen Receptors (ER)                | Negative      | 10                                       | 30.3%  |
|                                        | Positive      | 23                                       | 69.7%  |
| Progesterone Receptors (PR)            | Negative      | 10                                       | 30.3%  |
|                                        | Positive      | 23                                       | 69.7%  |

**Table 2.** Nottingham Prognostic Index (NPI) among studied population (n = 33).

| Nottingham Prognostic Index          | Mean $\pm$ SD | 4.45 $\pm$ 0.87 |       |
|--------------------------------------|---------------|-----------------|-------|
|                                      | Range         | 3.1 - 6.0       |       |
|                                      |               | Frequency       | %     |
| NPI interpretation [5-year survival] | 85%           | 5               | 15.2% |
|                                      | 70%           | 22              | 66.7% |
|                                      | 50%           | 6               | 18.2% |



**Figure 1.** GII invasive duct carcinoma with moderate desmoplastic reaction ( $\times 10$ ).



**Figure 2.** Moderate expression of MMP9 in IDC ( $\times 10$ ).

of  $>4$ , the mean MMP-9 expression was  $5.42 (\pm 3.37)$ ; 42.4% showed low expression level and 57.6% showed high expression level. Most of the studied cases showed moderate cytoplasmic expression of MMP-9 (60.6%) (**Figure 2**). MMP-9 was expressed in more than 70% - 100% of the examined sections in 57.6%.

**Correlations between the MMP9 Expression and Clinicopathological:** Although the clinicopathological characteristics showed variable distribution between high and low MMP-9 expression subgroups, these variations were not statistically significant (**Table 3**). Likewise, the correlation between the quantitative values of NPI and MMP-9 expression (IHC) was weak and statistically insignificant (**Figure 3**).

#### **Survival Analysis:**

The outcomes of interest were metastasis and death. 33.3% of patients developed Mets.

The mean overall survival (OS) was 7.69 years with 88% 5-year survival, while the mean disease-free survival (DFS) was 6.93 years with 78% 5-year survival. There were no statistically significant differences in survival curves of OS & DFS



**Table 3.** Relation between MMP-9 expression and clinicopathological characteristics.

|                              |          | MMP-9 Expression Level |                            |                     |                           | p-value |
|------------------------------|----------|------------------------|----------------------------|---------------------|---------------------------|---------|
|                              |          | Low Level (n= 14)      |                            | High Level (n = 19) |                           |         |
|                              |          | Frequency              | %                          | Frequency           | %                         |         |
| <b>Age</b>                   |          | 14                     | Mean ± SD<br>49.93 ± 10.21 | 19                  | Mean ± SD<br>52.11 ± 9.75 | 0.542   |
| <b>DCIS</b>                  | No       | 6                      | 42.9%                      | 14                  | 73.7%                     | 0.073   |
|                              | Yes      | 8                      | 57.1%                      | 5                   | 26.3%                     |         |
| <b>Desmoplastic reaction</b> | No       | 9                      | 64.3%                      | 4                   | 21.1%                     | 0.079   |
|                              | Mild     | 3                      | 21.4%                      | 5                   | 26.3%                     |         |
|                              | Moderate | 1                      | 7.1%                       | 6                   | 31.6%                     |         |
|                              | Marked   | 1                      | 7.1%                       | 4                   | 21.1%                     |         |
| <b>Tumor mass (T)</b>        | T1       | 2                      | 14.3%                      | 2                   | 10.5%                     | 0.951   |
|                              | T2       | 9                      | 64.3%                      | 12                  | 63.2%                     |         |
|                              | T3       | 2                      | 14.3%                      | 4                   | 21.1%                     |         |
|                              | T4       | 1                      | 7.1%                       | 1                   | 5.3%                      |         |
| <b>LN #</b>                  | N0       | 4                      | 28.6%                      | 8                   | 42.1%                     | 0.674   |
|                              | N1       | 6                      | 42.9%                      | 6                   | 31.6%                     |         |
|                              | N2       | 1                      | 7.1%                       | 3                   | 15.8%                     |         |
|                              | N3       | 3                      | 21.4%                      | 2                   | 10.5%                     |         |
| <b>METs</b>                  | No       | 11                     | 78.6%                      | 11                  | 57.9%                     | 0.278   |
|                              | Yes      | 3                      | 21.4%                      | 8                   | 42.1%                     |         |
| <b>Stage</b>                 | IA       | 1                      | 7.1%                       | 1                   | 5.3%                      | 0.780   |
|                              | IIA      | 3                      | 21.4%                      | 4                   | 21.1%                     |         |
|                              | IIB      | 5                      | 35.7%                      | 3                   | 15.8%                     |         |
|                              | IIIA     | 1                      | 7.1%                       | 2                   | 10.5%                     |         |
|                              | IIIC     | 1                      | 7.1%                       | 1                   | 5.3%                      |         |
|                              | IV       | 3                      | 21.4%                      | 8                   | 42.1%                     |         |
| <b>Grade</b>                 | I        | 1                      | 7.1%                       | 0                   | 0.0%                      | 0.676   |
|                              | II       | 13                     | 92.9%                      | 18                  | 94.7%                     |         |
|                              | III      | 0                      | 0.0%                       | 1                   | 5.3%                      |         |
| <b>ER status</b>             | No       | 3                      | 21.4%                      | 7                   | 36.8%                     | 0.445   |
|                              | Yes      | 11                     | 78.6%                      | 12                  | 63.2%                     |         |
| <b>PR status</b>             | No       | 3                      | 21.4%                      | 7                   | 36.8%                     | 0.445   |
|                              | Yes      | 11                     | 78.6%                      | 12                  | 63.2%                     |         |
| <b>Death</b>                 | No       | 11                     | 78.6%                      | 16                  | 84.2%                     | 0.967   |
|                              | Yes      | 3                      | 21.4%                      | 3                   | 15.8%                     |         |

<sup>a</sup>Fisher's exact test; <sup>b</sup>Chi-square test.

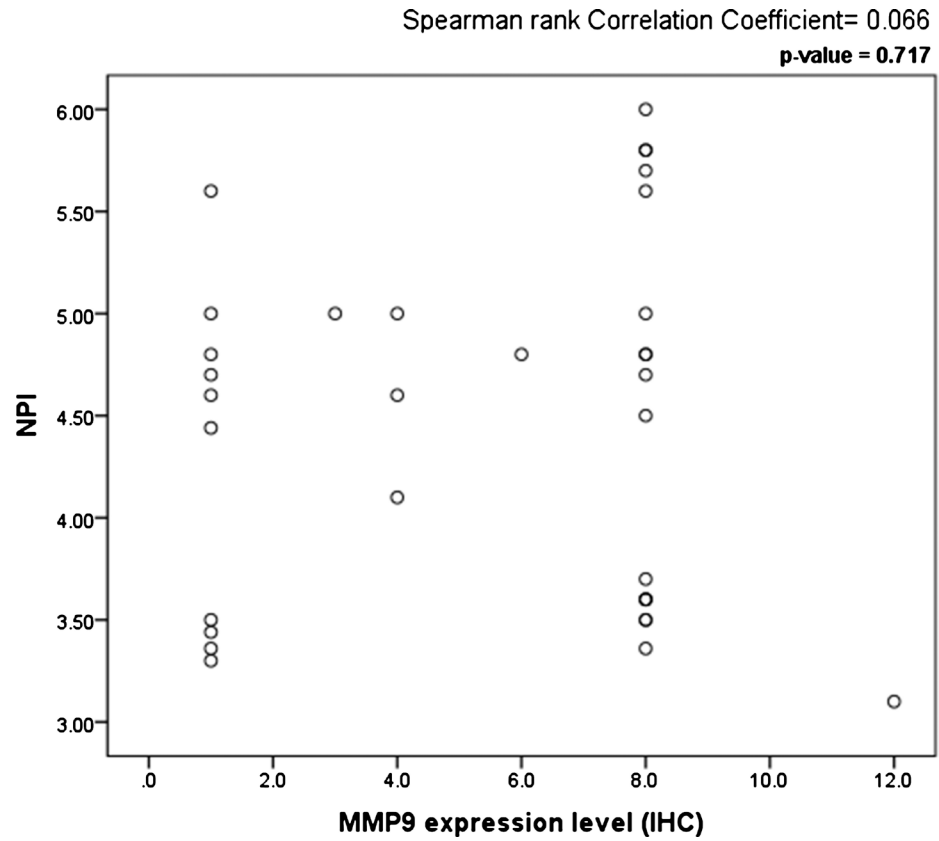


Figure 3. Correlation between MMP-9 expression and NPI.

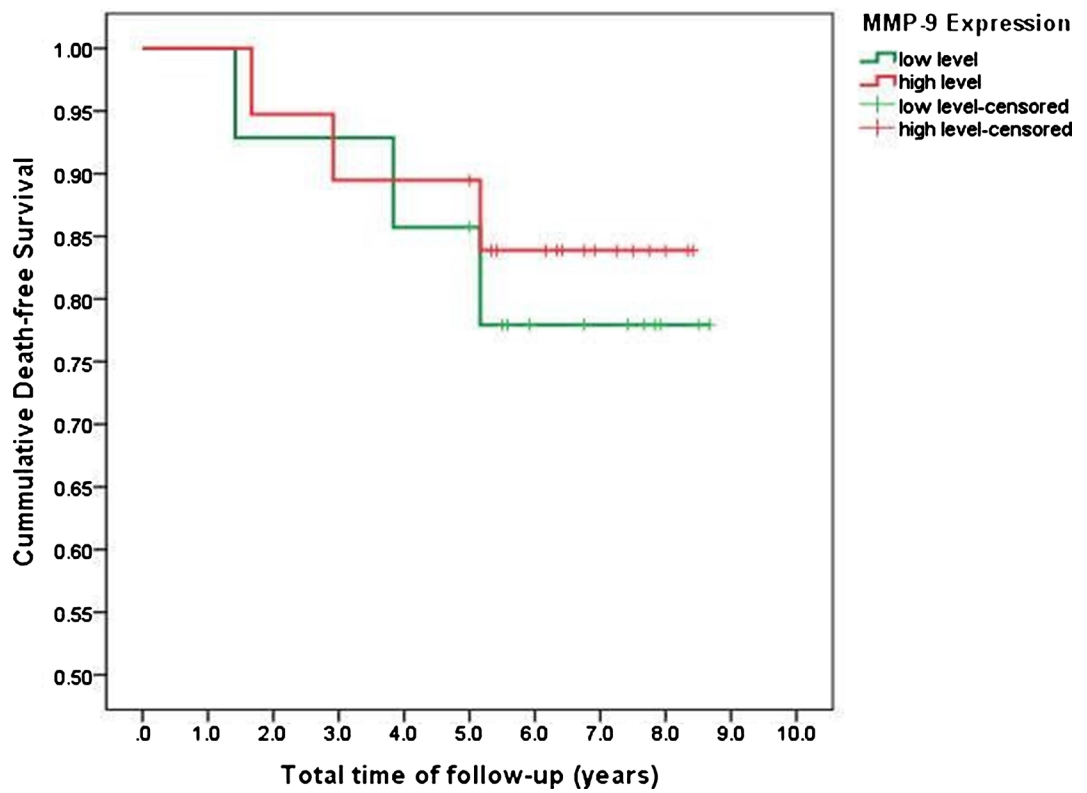


Figure 4. Survival in breast cancer women with low and high MMP-9 expression cases.



between the low and high MMP-9 expression cases. Likewise, the 5-year survival did not show much variation between low and high MMP-9 expression as shown in picture (Figure 4). The mean Mets-free survival was 6.93 years with 78% 5-year survival (Figure 5).

The 5-year survival predicted by NPI was not statistically significantly associated with MMP-9 expression level (p-value = 0.337). Though, high MMP-9 expression showed less 5-year survival compared to low expression (Figure 6).

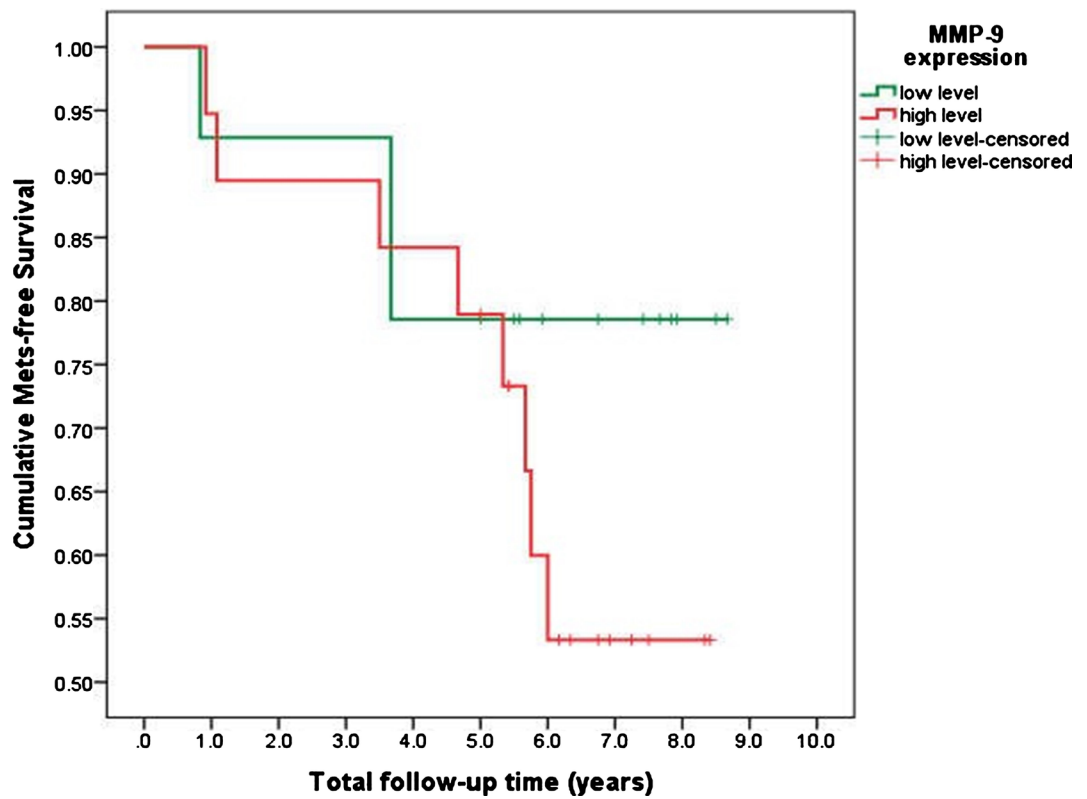


Figure 5. METs-free survival among low and high MMP-9 expression breast cancer cases.

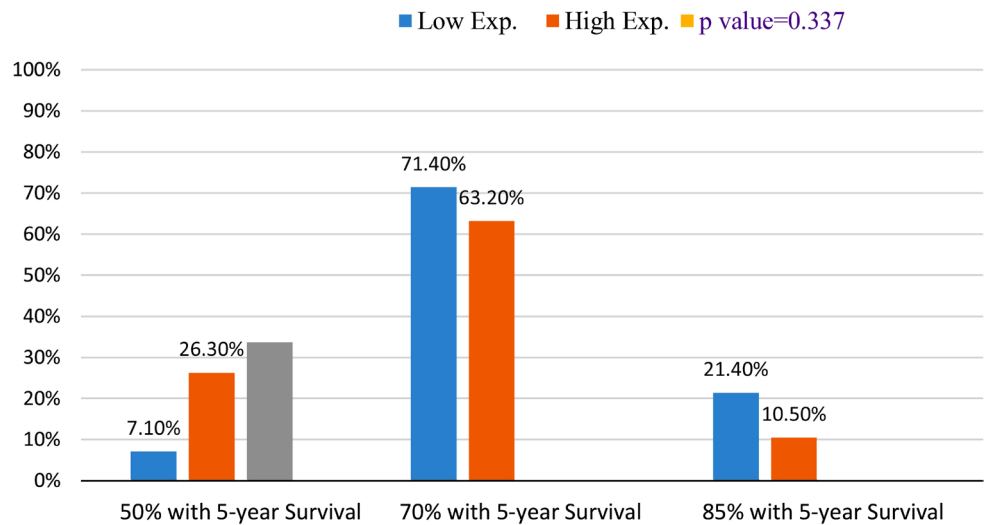


Figure 6. NPI-based prediction of 5-year survival.

According to cox-regression model, the only significant predictor was NPI; every unit increase in NPI score was associated with about 9.5 times increase in mortality rate per unit time (year) (Table 4).

#### 4. Discussion

The mean age of the studied cases were 51.2 years  $\pm$  9.9; more than one third of them (39.4%) were  $\geq$ 55 years old [8]. This was nearly similar to the age distribution found in recent studies. Additionally, the last published incidence rates trend of BC in Egypt (1999 to 2008), found that the women age category (40 - 50 years old) had the peak incidence rate [9].

Regarding histopathological examination of participants' specimens, desmoplastic reaction was positive in 60.6% of patients. This is mainly related to the relatively high representativeness of advanced stage (33.3% of patients were stage IV) among study participants. The majority of patients (63.6%) had their tumor size in the T2 category. The mean of the largest diameter of tumor tissue measured about 4.0 cm. Possible reason for relatively high representativeness of the larger tumor size and stage is this study and other similar studies are attributed to the study setting; usually in general hospitals, patients come at a late stage of the disease. Limited access to screening programs in developing countries could be another indirect explanation. The study found that more than two thirds (69.7%) of participants were ER positive. whereas, (30.3%) were negative ER. This also coincides with the international cancer estimates of increased incidence rates of ER positive BC in most of the age groups [9].

Pertaining to the level of tissue MMP-9 expression, 19 out of 33 study participants showed high expression level. This was detected as a brown cytoplasmic staining of the tumor cells, with total staining score of 5 - 12. Consequently, less than half of the participants (42.4%) had low level of expression (0 - 4 of the total score). Differently higher proportions of expression level were found in previous studies; higher level of tissue MMP-9 was expressed among 85%, and 55.14% of BC specimens [10] [11]. Additionally, the current study findings were similar to other study that found MMP-9 expression was focused mainly in tumor area; normal breast tissue adjacent to the MMP9-positive tumors was not or was minutely stained [11].

**Table 4.** Cox regression analysis for predictors of mortality among breast cancer cases.

|                  | B      | SE    | Sig.   | HR    | 95.0% CI for HR |        |
|------------------|--------|-------|--------|-------|-----------------|--------|
|                  |        |       |        |       | Lower           | Upper  |
| Age (years)      | 0.029  | 0.050 | 0.558  | 1.030 | 0.934           | 1.135  |
| NPI              | 2.250  | 1.112 | 0.043* | 9.489 | 1.074           | 83.855 |
| ER               | -0.777 | 0.867 | 0.370  | 0.460 | 0.084           | 2.514  |
| MMP-9 Expression | -1.643 | 1.181 | 0.164  | 0.193 | 0.019           | 1.959  |

The associations between tissue MMP-9 expression level and the studied pathological features of BC cases were not significant with almost all of the studied clinico-pathological features such as age, histological grade & ER and PR status. Also similar results were obtained from Wu *et al.* (2014) [12]. In contrast to these results, Soliman *et al.* (2017) confirmed correlation between MMP-9 expression and these pathological features [8].

Regarding the association between tissue MMP-9 expression level and lymph node involvement, this study pointed out that the majority of cases (71.4%) in the low MMP-9 expression level group had positive axillary lymph nodes. Relatively lower percentage (57.9%) was found among the high MMP-9 level expression group. However, this difference was not statistically significant. Other studies similarly reported these findings among BC cases [13] [14]. In disagreement with these findings, Mahmood, 2015 [15] and Wu *et al.* [6] identified a significant correlation between tissue levels of MMP-9 and lymph Node metastasis.

Tumor stage was higher (42.1%) among high level cases that were in advanced stages (IV). However, this difference was concluded as insignificant. The same was demonstrated by Mylona *et al.* [13]. Different conclusion of significant positive correlation between advanced stage and tissue MMP-9 expression level was highlighted [8] [6] [11] [15] [16]. These discrepancies may be related to the use of different scoring systems and/or different immunohistochemistry employed antibodies; The type of primary antibody can significantly influence the sensitivity of IHC. Furthermore, there was no standardized cut-off value for classifying the positive MMP-9 expression level in BC patients.

The current study reported that tumor size (T2) was dominant among less than two thirds of cases in the low and high MMP-9 expression level groups; It accounted for (63.2% and 64.3%) of the cases respectively. However insignificant association was concluded. This matched the results of other several studies [12] [14]. On the other hand, recent studies highlighted the significant positive association between high expression of MMP-9 and tumor size [8] [11] [17] [18]. Pellikainen *et al.* exclusively reported the significant association between high MMP-9 expression level and small tumors size [16].

The Nottingham Index was the one used to set the prognosis interpretation of this study. NPI was a statistically significant predictor of mortality among study participants ( $p = 0.043$ , HR = 9.489, 95% CI = 83.855). However, NPI was insignificantly associated with MMP-9 expression level, though high MMP-9 expression showed less 5-year survival compared to low expression. On the contrary, Vizoso *et al.* pointed out a significant association between positive tissue MMP-9 expression level and high NPI [17].

As regards the survival follow-up findings, the study reported that among the (33.3%) patients who developed metastasis during follow up period, 9.1% had the metastasis in liver, 12.1% progressed to multiple organs metastasis. Additionally, the 5-year overall survival was 88.0%. The 5-year Disease Free Survival (DFS) was 78.0% as well. Nevertheless, there were no statistically significant dif-

ferences in overall survival (OS) and DFS between the low and high MMP-9 expression level groups. Puzovic *et al.* reported similar insignificant differences between MMP-9 positive and negative tumors in DFS as well as regarding MMP-9 expression impact on OS and DFS [14].

On the other hand, MMP-9 positive tumors were associated with considerable reduction in risk of relapse and death [6] [7] [16] [17] [18] [19]. These studies depended mainly on classical distinct indicators (e.g. stage, hormonal status, size, grade, KI67, HER2neu and/or co-expression of ETS1, MMP-2 and MMP-9) to predict prognosis and survival. The inconsistency observed between our study and these studies regarding the survival profile and its association with MMP-9 expression level can be explained by the variations in the applied BC management plans; This could have influenced the survival outcome. On the other hand, the demonstrated difference in the baseline characteristics of patients regarding stage, tumor grade and histology, hormone receptor status can also lead to these disagreements. This study explored the tissue MMP-9 expression level and assessed its association with clinicopathological features and survival profile among patients with IDC. The study targeted cases of IDC, in particular, to limit the confounding effect of biological differences among cancer types which may influence the outcome assessment. Additionally, the study depended mainly on a comprehensive composite prognostic indicator (NPI) rather than single component or independent prognostic factors to assess the study variables. This was not found in other studies which used single component indicators to assess the prognosis (e.g. Tumor size and/or lymph node status). Moreover, the study was based on a relatively longer follow-up duration (at least five years) to properly assess the survival profile.

The data were collected using mainly objective tools. However, the current study didn't consider the significance of socioeconomic factors, differences in comorbidities, adherence to high-quality medical care as probable confounders of survival outcome. Additionally, the relatively small number of the eligible cases and hence using a non-probability sampling technique were the limitations of this study.

## 5. Conclusion

Tissue MMP-9 expression level role in carcinogenesis and progression of Breast Cancer could not be established; however, NPI is a significant predictor of mortality among the studied cases.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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