



Original article

# Diagnosis Delay and Predicated Factors in Libyan Women with Breast Cancer

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## Abstract

**Aims.** To investigate the diagnosis-related delay time and its predicating factors as well as impacts of this delay on stages of disease. **Methods.** A total of 400 women, aged 19 to 80 years with breast cancer diagnosed during 2020–2021 were interviewed about the period from the first discovering of symptoms to final histology diagnosis of breast cancer. This timed (diagnosis related time) was divided into three arms: 1) less than 3 months, 2) 3–6 months, and 3) more than 6 months. If diagnosis related time took longer than three months, considered delayed. Patient related time was the calculated time from the date of the discovering of symptoms to the date of the first medical advice. If this time took longer than two months, considered delayed. Systemic related time, the calculated time from the date of first medical advice to the date of final histology diagnosis. Systemic related time considered delayed if took longer than 1 month. Retrospective preclinical and clinical data were collected on a form (questionnaire) during an interview with each patient and from patient's records. **Results.** The median of diagnosis related time was 6 months, 25 months as the maximum. 40.5% of patients were diagnosed within a period less than 3 months after symptoms and 10.3% of patients from 3 to 6 month, while 49.2% of patients within a period longer than 6 months. A several factors predicted patient-related delay time: Symptoms were not considered serious enough in 18% of patients. Alternative therapy was applied in 17.7% of the patients, while fear and shame prevented the visit to the doctor in 7.7% and 4.3% of patients, respectively. Patient-related delay time was also associated with old age ( $p < 0.0001$ ), with rural residence ( $p < 0.0001$ ), with illiteracy ( $p < 0.0001$ ), with comorbidity ( $p < 0.0001$ ), with women who had used oral contraceptive pills longer than 5 years ( $p < 0.0001$ ), with unawareness of breast cancer ( $p < 0.0001$ ), with women who did not report monthly self-examination ( $p < 0.0001$ ), with initial breast symptom(s) that did not include a lump ( $p < 0.0001$ ), and with past history of benign fibrocystic disease ( $p = 0.049$ ). Failure of medical practitioners to act on presenting findings with inappropriate reassurance that the lump was benign was an important reason for prolongation the systemic related time. At the time of diagnosis, the stage distribution was as follows: 13% stage I, 27.5% stage II, 47.2% stage III and 12.3% stage IV. Diagnosis-related delay time was associated to larger tumour size ( $p < 0.0001$ ), to positive lymph nodes ( $p < 0.0001$ ), and to a higher rate of advanced stages ( $p < 0.0001$ ). **Conclusion.** The present study shows a significant relationship between late diagnosis and advanced stage of breast cancer. In Libya, late diagnosis of breast cancer is still a large serious health problem. It was related to a complex interaction between patient and systemic predicating factors, which resulting in a high risk of advanced stage of breast cancer with lower survival rate. Therefore, public awareness programs and training of general practitioners are highly recommended to reduce breast cancer mortality by promoting early detection.

**Keywords:** Breast Cancer, Diagnosis Delay, Advanced Stages, Predicting Factors.

## Introduction

Globally, breast cancer (BC) is the most common invasive cancer in women (1). According to a recent WHO report, along with lung cancer, BC is the most common diagnosed cancer globally with over two million cases were diagnosed in 2018, responsible for more than

400,000 deaths worldwide (2,3). BC forms about 30% of invasive cancer in women and 16% of all women cancers (3,4). The incidence of BC is increasing worldwide, but varies from areas of high incidence (United States, Western Europe and Australia) to areas of low incidence (Japan, Asia, Latin America, and African countries) (5). Although, the incidence rate of BC is higher in developed countries than developing countries, the majority of related deaths occur in developing countries (6). The studies reported that more than 70% of BC patients in high income countries are diagnosed at early stages (i.e., stage 1 and 2), corresponding estimation in low-income countries is about 20%-50% (7). Additionally, about 50% of BC patients were diagnosed with metastatic disease in Africa, corresponding proportion in United States is about only 19% (8). These differences may be related to the healthcare setting or be explained by difference in other aspects such as biology and genetic background (9,10).

In Libya as in many African countries, management of BC forms a large medical, social and economic issues. BC patients in those countries often present with younger age, premenopausal status, have early disease recurrence, late stage and are associated with poor survival (9,11-13). Despite advances in BC treatments, the mortality rate is still high. So, it is very important to secure a good cancer control program through different aspects, by improvements in early detection and treatment as an important aspect, and to go thoroughly to study of genetic and biology behavior of this cancer, which applied with traditional factors can predict the outcome of the individual patient and allow selection of appropriate therapy (14,15).

We can improve the early detection through knowledge more about the extent and reasons behind diagnosis delay in Libyan women with BC. To improve outcome and survival, early detection remains the cornerstone of BC control, through better understanding of the predicting factors and causes for treatment delay (16). Early detection of cancer is important because delay is preventable and earlier treatment can lead to improved patient outcome. Late detection has been associated with late stages and poor survival as well as negative implication on cost and treatment choice (17-20).

The association between diagnosis-related delay time (which includes both patient and systemic delays) and its predicating factors has been investigated in numerous studies as well as impacts of this delay on stage of disease and patient's outcome. Diagnosis delay and treatment of BC are significantly associated with low survival, and one the most important causes of significant differences in the mortality rate in various countries as reported in many studies (15,17,21). Numerous predicating factors are found to be associated with delay in diagnosis and treatment, including socioeconomic status, minority ethnicity, age, health insurance, menopause, tumor type, breast cancer awareness, breast self-examination, and marital status (21). Patient-related delay time was also associated with lighter symptoms, fear of diagnosis, negative attitude toward medical practitioners (22). Failures of medical practitioners to act on presenting findings, and false-negative mammogram or fine needle aspiration cytology (FNAC) were the main reasons for system-related delay time (23,24).

Delay in diagnosis and treatment of BC is divided into three categories: patient-related delay time (the duration between the date of the beginning of symptoms to the date of the first medical advice), systemic-related delay time (from the first medical advice to the definite histopathological diagnosis), and diagnosis-related delay time (from the date of the discovery of symptoms to the date of final BC diagnosis based on histology examination) (15,25,26). Diagnosis time was considered delayed if it took longer than 3 months after symptoms to reach the final diagnosis of BC, which is associated with late stage and low survival (20).

We conducted this study to learn more regarding the reasons of diagnosis delay in Libyan women with BC and the impacts of this delayed on stage of disease for promoting earlier diagnosis of BC in Libya.

### Methods

The present study was included 400 Libyan women with BC diagnosed at the National Cancer Institute (NCI, Misurata) and the National Cancer Institute (NCI Sabratha) during the period from January 1st, 2020 to December 31st, 2021. All patients who were diagnosed and registered during that period were targeted for this study. Obtainable patients who were treated at both centers during that period were included. Only the patients who were diagnosed within a period less than 2 months were selected for the interview. The patients were asked to be interviewed and the collection of data was stopped after 400 interviews had been completed.

**Data collection**

Retrospective preclinical data was collected on a form (questionnaire) during an interview with each patient. A validated questionnaire was used for assessment of diagnosis-related delay time (15). Structured face-to-face interviews were conducted by trained doctors (MG, EE, IA, HA) and required 15 to 20 minutes to complete it. The arrangement of participations for interview was either during the first registration due to BC (40%) or during follow-up in the outpatient department (60%). 35.5% of all interviews took place within 4 weeks after diagnosis and 64.5% within 8 weeks after diagnosis.

The obtained information was included socio-demography, medical and obstetric history, symptoms related questions, and medical consultation related questions. Date of the entire chronological event (i.e., first detection of symptoms, first medical consultation, and referral). In addition, estimate the duration between first symptoms and the first medical advice (patient-related time), between the first medical advice and histopathological diagnosis (system-related time) and between the first symptoms and histopathological diagnosis to the date of final BC diagnosis based on histology examination (diagnosis-related time). The content was including age at diagnosis, place of residence (urban and rural), education (literate and illiterate), occupation (employed and housewife), marital status (single and married), age at first childbirth (< 20 years, 20-30 years, >30 years and no pregnancy), body mass index (BMI) (kg/m<sup>2</sup>) (underweight, normal, overweight and obese), menopausal status (pre and post-menopausal), comorbidity, breast feeding, oral contraceptive, BC awareness, regular practices of breast self-examination, family history of BC, and history of benign breast disease. First symptoms were defined as lump, symptoms other than lump, and symptoms not related to the breast (i.e. back pain, headache). The participants were asked about previous use of alternative therapy. Complementary alternative therapy was defined as any therapy using methods and products not included in conventional modern medicine. In order to minimize recall bias, the participants were reminded of events in the calendar year, such as religious and national occasions, school holidays and birth dates, to help them remember important dates relative to their medical history. Data regarding tumor stage relied on histopathological and clinical data including TNM stage (27) were collected from patient files.

**Patient-related time, systemic-related time and diagnosis-related time**

Patient-related time (consultation time) was measured from the date of the discovery of first symptoms to the date of the first medical advice. This time was categorized into 3 arms: <2 months, 2-6 months, and >6 months. Patient-related time was considered delayed (patient delay) if it took longer than 2 months after symptoms. Systemic-related time that took place between the first medical advice and the definite histopathological diagnosis. Systemic-related delay time was occurring if it took longer than one month between the first medical advice and the final histopathological diagnosis. Diagnosis related time (diagnosis time) was measured from the date of the discovery of symptoms to the date of final BC diagnosis based on histology examination. Diagnosis-related time was categorized into 3 arms: < 3 months, 3-6 months, and > 6 months. Diagnosis time was considered delayed if it took longer than 3 months after symptoms to reach the final diagnosis of BC (13,22).

Factors related to patient delay (i.e., symptoms were considered not serious, using of alternative therapy, fear of diagnosis and/or treatment, and shame) and/or systemic-related delay factors (i.e., patient inappropriately reassured after first medical visit that the lump was benign, non-specific medical treatment without control, a negative fine-needle aspiration biopsy, surgical excision without pathological tissue, not oriented to specialized service, lack of information, and appointment delay were collected.

**Statistical analysis**

The variables of the material were grouped into logical classes and descriptive statistics calculated for the continuous variables using SPSS 26.0 for Windows (SPSS, Inc., Chicago, USA). Frequency tables were analysed using the Chi-square test, with likelihood ratio (LR) to assess the significance of the correlation between the categorical variables. The p value <0.05 was considered to indicate statistical significance.

**RESULTS****Study population**

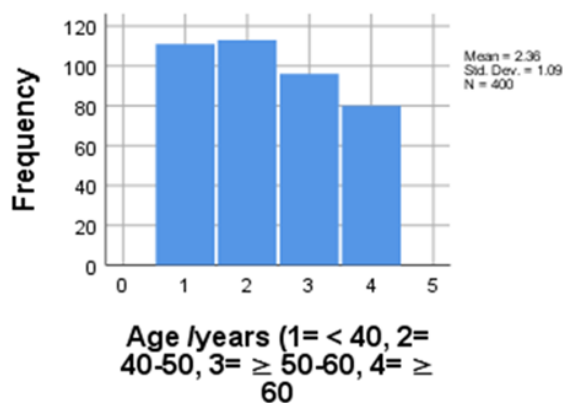
The characteristics of the study population (n=400) are shown in Table 1. A total of 400 patients were interviewed. The mean age of women was 48.6 years (range 19- 80 years) Figure 1. There were 238 patients (59.5 %) resided in urban areas and 332 patients (83%)

were literate. Three hundred fifty-eight patients (88%) were married, multi-parous, and had fed their babies. Sixty patients (15%) had taken oral contraceptive pills, 17.8% did not have any children, and 43.5% were post-menopausal. Only 7.5% had a family history of breast cancer and 36.8% had previous benign breast diseases. In this cohort, 252 (63%) patients with breast carcinoma noted lumps in respective breasts as accidental findings, while 32 (8%) patients detected lumps during breast self-examination. Other symptoms of the breast such as skin changes, nipple discharge or bleeding were reported less frequently (24.7%). Systemic involvements as the first symptoms reported in 49 (12.3%) patients.

**Table 1:** Description of study population (n=400)

| Socio-economic factors, health behavior and tumor related factors |                 | Number of patients | Percent (%) |
|---|-----------------|--------------------|-------------|
| Age / years   | <50             | 215                | 53.8        |
|   | ≥50             | 185                | 46.2        |
| Place of residence  | Urban           | 238                | 59.5        |
|   | Rural           | 162                | 40.5        |
| Education   | Literate        | 332                | 83.0        |
|   | Illiterate      | 68                 | 17.0        |
| Occupation  | House wife      | 235                | 58.8        |
|   | Employed        | 165                | 41.2        |
| Marital status  | Married         | 352                | 88.0        |
|   | Single          | 48                 | 12.0        |
| Age at first childbirth   | < 20 year       | 29                 | 7.2         |
|   | Year            | 214                | 53.5        |
|   | > 30 year       | 86                 | 21.5        |
|   | No pregnancy    | 71                 | 17.8        |
| BMI   | Under weight    | 42                 | 10.5        |
|   | Normal weight   | 184                | 46.0        |
|   | Over weight     | 94                 | 23.5        |
|   | Obese           | 80                 | 20.0        |
| Menopausal status   | Pre-menopausal  | 226                | 56.5        |
|   | Post-menopausal | 174                | 43.5        |
| Co-morbidity  | Yea             | 121                | 30.2        |
|   | No              | 279                | 69.8        |
| Breast feeding  | Yes             | 341                | 85.2        |
|   | No              | 59                 | 14.8        |
| Oral contraceptive  | Yes <5 years    | 23                 | 5.8         |
|   | Yes ≥ 5 years   | 37                 | 9.2         |
|   | No              | 340                | 85.0        |
| Breast cancer awareness   | Yes             | 89                 | 22.2        |
|   | No              | 311                | 77.8        |
| Breast Self-Examination   | Yes             | 32                 | 8.0         |
|   | No              | 368                | 92.0        |

|                                  |                  |     |      |
|----------------------------------|------------------|-----|------|
|                                  |                  |     |      |
| Family history                   | Positive         | 30  | 7.5  |
|                                  | Negative         | 370 | 92.5 |
| History of benign breast disease | Yes              | 147 | 36.8 |
|                                  | No               | 253 | 63.2 |
| Symptoms                         | Lump             | 252 | 63.0 |
|                                  | Nipple discharge | 45  | 11.2 |
|                                  | Skin changes     | 54  | 13.5 |
|                                  | Systemic         | 49  | 12.3 |
| Symptoms                         | Lump             | 252 | 63.0 |
|                                  | Others           | 148 | 37.0 |
| Site                             | Right            | 284 | 71.0 |
|                                  | Left             | 116 | 29.0 |



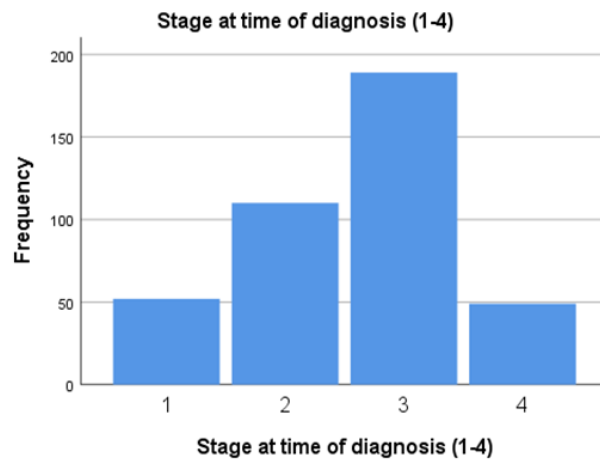
**Figure 1:** Age distribution among 400 Libyan women with breast cancer at time of diagnosis (2020-2021).

***Clinicopathological variables of patients and staging at time of diagnosis***

Clinicopathological variables of patients and staging at time of diagnosis are shown in Table 2 and Figure 2. With regards to the anatomical site, right BC was the most frequent presenting site (71%) and invasive ductal carcinoma type was reported in 81% of patients. The less frequent T stage was T1 (10.3%), while T2, T3 and T4 in increasing frequency (31.2%, 28.5%, and 30.0% respectively). Two hundred eighty-seven patients (71.8%) had positive lymph nodes and negative lymph nodes reported in 113 patients. Most of patients were presented with histological grade 2 and 3 (40.8% and 36.8% respectively). In terms of AJCC staging, 49 patients were stage IV (12.3 %), 189 (47.3%) were stage III, 110 (27.4%) were classified as stage II, and 52 (13%) were staged as I.

**Table 2:** Staging at the diagnosis in 400 Libyan women with breast cancer 2020-2021.

| Tumour characteristics |                           | Number of patients | Percent (%) |
|------------------------|---------------------------|--------------------|-------------|
| Clinical stage         | Stage 1                   | 52                 | 13.0        |
|                        | Stage 2                   | 110                | 27.5        |
|                        | Stage 3                   | 189                | 47.2        |
|                        | Stage 4                   | 49                 | 12.3        |
| Clinical stage         | Early stage (1 and 2)     | 162                | 40.5        |
|                        | Late stage (3 and 4)      | 238                | 59.5        |
| T                      | T 1                       | 41                 | 10.3        |
|                        | T 2                       | 125                | 31.2        |
|                        | T 3                       | 114                | 28.5        |
|                        | T 4                       | 120                | 30.0        |
| Lymph node             | Positive                  | 287                | 71.8        |
|                        | Negative                  | 113                | 28.2        |
| N                      | N 0                       | 113                | 28.2        |
|                        | N 1                       | 86                 | 21.5        |
|                        | N 2                       | 101                | 25.3        |
|                        | N 3                       | 100                | 25.0        |
| M                      | M 0                       | 351                | 87.8        |
|                        | M 1                       | 49                 | 12.2        |
| Histological type      | Invasive ductal carcinoma | 224                | 81.0        |
|                        | Other types               | 76                 | 19.0        |
| Histological grade     | 1                         | 91                 | 22.8        |
|                        | 2                         | 163                | 40.7        |
|                        | 3                         | 146                | 36.4        |

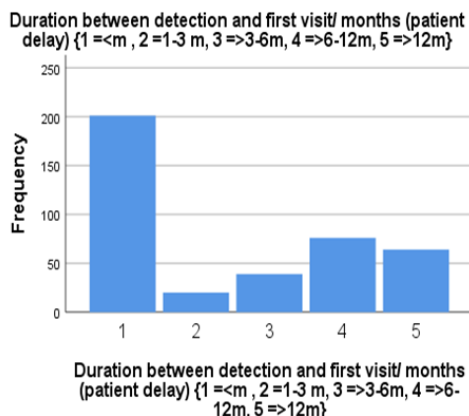


**Figure 2:** TNM staging distribution among 400 Libyan women with breast cancer at time of diagnosis (2020-2021)

**Diagnosis-related time**

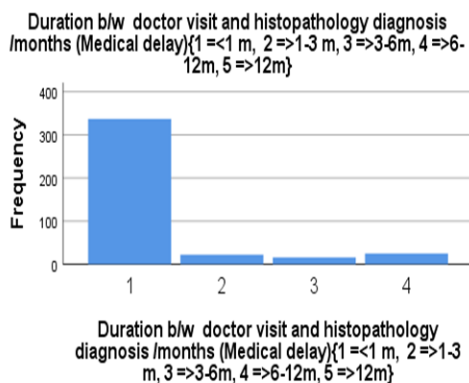
Patient-related time (consultation time), systemic-related time (medical time) and diagnosis-related times (diagnosis time) are shown in Figures 3, 4 and 5 respectively.

The median consultation time was 2 months, 24 months as the maximum. Two hundred-nine patients (52.2%) had medical advice within two months after discovering symptoms, while 51 (12.8%) within 2-6 months after symptoms. One hundred forty patients (35%) had consultation later than 6 months after first symptoms Figure 3.



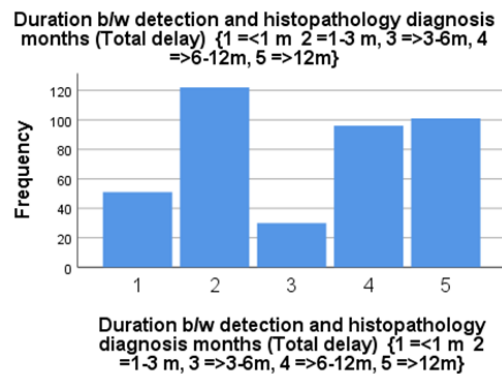
**Figure 3:** Patient-related time (consultation time) from the first symptoms to first doctor visit among 400 Libyan women with breast cancer (2020-2021).

The majority of patients (337 patients, 84.2%) were diagnosed within one month after the first medical advice while thirty-eight patients (9.5%) were diagnosed from 2 to 6 months after the first medical advice. Twenty-five (6.3 %) patients had waited more than 6 months for final diagnosis after the first medical consultation Figure 4.



**Figure 4:** Systemic-related time (medical time) from the first consultation to histopathology diagnosis among 400 Libyan women with breast cancer (2020-2021).

The median diagnosis time was 6 months, 25 months as the maximum. One hundred sixty-two patients (40.5%) were diagnosed within a period less than 3 months after discovering symptoms. Forty-one patients (10.3%) were diagnosed within a period from 3 to 6 months. One hundred ninety-seven patients (49.2%) within a period longer than 6 months Figure 5.



**Figure 5:** Diagnosis-related time (from the first symptoms to histopathology diagnosis) among 400 Libyan women with breast cancer (2020-2021).

**Diagnosis-related delay time and predicating factors**

Predicating factors of patient related delay time are shown in Table 3 and Figure 6. This study observes that symptoms were not considered serious enough in 18% of patients, which delayed the seeking medical advice for more than 2 months. Alternative therapy was applied in 17.7% of the patients, while fear and shame prevented the Doctors visit in 7.7% and 4.3% respectively, of the patients Figure 6.

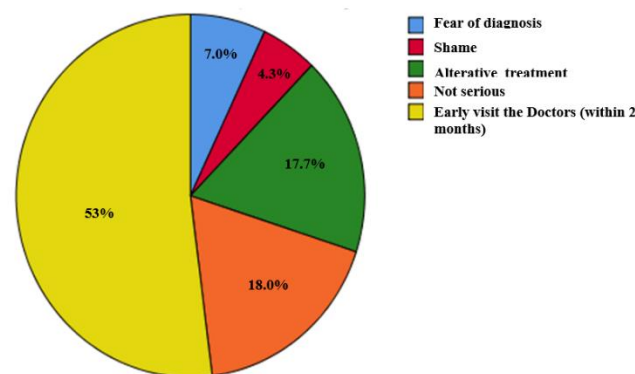
**Table 3:** Patient-related time in Libyan women with breast cancer by socio-economic factors, health behavior and tumor related factors.

| Predicting factors       |                | N*  | Proportions of patients according to patient- related time (%) |            |            | p-value |
|--------------------------|----------------|-----|--|------------|------------|---------|
|                          |                |     | < 2 months   | 2-6 months | > 6 months |         |
| Age years                | < 50           | 215 | 65.5   | 9.8        | 24.7       | <0.0001 |
|                          | ≥ 50           | 185 | 36.8   | 16.2       | 47.0       |         |
| Place of residence       | Urban          | 238 | 63.9   | 13.9       | 22.2       | <0.0001 |
|                          | Rural          | 162 | 35.2   | 11.1       | 53.7       |         |
| Education                | Literate       | 332 | 56.4   | 9.6        | 34.0       | <0.0001 |
|                          | Illiteracy     | 68  | 32.4   | 27.9       | 39.7       |         |
| Occupation               | Housewife      | 235 | 51.1   | 11.9       | 37.0       | 0.535   |
|                          | Employed       | 165 | 57.6   | 10.3       | 32.1       |         |
| Marital status           | Married        | 352 | 52.2   | 13.4       | 34.4       | 0.673   |
|                          | Single         | 48  | 52.1   | 8.3        | 39.6       |         |
| Age at first child-birth | < 30 year      | 192 | 51.6   | 12.5       | 35.9       | 0.276   |
|                          | ≤ 30 year      | 136 | 48.5   | 16.2       | 35.3       |         |
|                          | No pregnancy   | 72  | 61.2   | 6.9        | 31.9       |         |
| Body mass index          | Under weight   | 42  | 64.2   | 4.8        | 31.0       | 0.074   |
|                          | Normal weight  | 184 | 53.8   | 15.8       | 30.4       |         |
|                          | Over weight    | 94  | 44.6   | 12.8       | 42.6       |         |
|                          | Obese          | 80  | 51.2   | 10.0       | 38.8       |         |
| Menopausal status        | Pre-menopausal | 226 | 67.7   | 10.2       | 22.1       |         |



|                                  |                 |     |      |      |      |         |
|----------------------------------|-----------------|-----|------|------|------|---------|
|                                  | Post-menopausal | 174 | 32.2 | 16.1 | 51.7 | <0.0001 |
| Cor-morbidity                    | Yes             | 121 | 20.6 | 11.6 | 67.8 | <0.0001 |
|                                  | No              | 279 | 65.9 | 13.3 | 20.8 |         |
| Breast feeding                   | Yes             | 341 | 51.0 | 13.8 | 35.2 | 0.414   |
|                                  | No              | 59  | 59.3 | 6.8  | 33.9 |         |
| Oral contraceptive               | Yes <5 years    | 23  | 26.1 | 17.4 | 56.5 | <0.0001 |
|                                  | Yes ≥5 years    | 37  | 18.9 | 27.0 | 54.1 |         |
|                                  | Not used        | 340 | 55.6 | 10.9 | 33.5 |         |
| Breast cancer awareness          | Yes             | 89  | 86.5 | 3.4  | 10.1 | <0.0001 |
|                                  | No              | 311 | 48.4 | 13.6 | 38.0 |         |
| Breast self-examination          | Yes             | 32  | 96.9 | 3.1  | 0.0  | <0.0001 |
|                                  | No              | 386 | 49.7 | 12.3 | 30.0 |         |
| Family history                   | Positive        | 30  | 53.3 | 10.0 | 36.7 | 0.992   |
|                                  | Negative        | 370 | 52.2 | 13.0 | 34.8 |         |
| History of benign breast disease | Yes             | 147 | 46.9 | 22.5 | 30.6 | 0.049   |
|                                  | No              | 253 | 55.3 | 7.1  | 37.6 |         |
| Symptoms                         | Lump            | 252 | 71.8 | 13.9 | 14.3 | <0.0001 |
|                                  | Others          | 148 | 18.9 | 10.8 | 70.3 |         |
| Site                             | Right           | 284 | 51.8 | 12.6 | 35.6 | 0.725   |
|                                  | Left            | 116 | 53.5 | 12.9 | 33.6 |         |

\* Number of patients



**Figure 6:** Predicated factors of late a seeking medical advice

This study also notes that patient-related delay time was associated with old age ( $p<0.0001$ ), with women who live in rural ( $p<0.0001$ ), with illiteracy ( $p<0.0001$ ), with comorbidity ( $p<0.0001$ ), with women who had used oral contraceptive pills longer than 5 years ( $p<0.0001$ ), and with history of benign fibrocystic disease ( $p=0.049$ ). In addition, this study also noted that patient-related delay time tended to be higher among women who did not awareness of BC and did not report monthly breast self-examination ( $p<0.0001$ ) and ( $p<0.0001$ ) respectively). Also, first breast symptoms without lump were strongly associated with patient-related delay time ( $p<0.0001$ ).

Occupation, age at the first childbirth, body mass index, breast feeding, family history of breast cancer, and anatomical site of breast cancer (right / left) did not show a significant association with patient related time delay Table 3.

Regarding the systemic-related delay time, sixty-three women (15.8%) were inappropriately reassured after first medical visit that the lump was benign. This was an important reason for the prolongation of the systemic-related time as well as the diagnosis-related time.

**Correlation between diagnosis-related delay time and TNM staging**

Diagnosis-related delay time (patient and systemic delays) and risk of advanced stage are shown in Table 4. In this study, Late stage (stage 3 and 4) breast cancer was found in 238 patients (59.5%) and it tended to be more frequent among women with diagnosis-related delay time >6 months (82.8%) than among women who diagnosed within a period less than 3 months after onset of symptoms (5.4%; p<0.0001).

Diagnosis-related delay time was strongly associated with larger tumour size (T3 and T4; p< 0.0001) and with N2 and N3 positive lymph nodes (P< 0.0001). Forty-nine patients (12.3%) presented with metastasis at time of diagnosis, all of those had diagnosis within a period more than 6 months (p< 0.0001) after symptoms.

**Table 4:** Diagnosis-related time and risk of advanced stage among Libyan women with breast cancer (N=400)

| Tumour characteristics |              | N*  | Proportions of diagnosis accordance to related time (percent) |            |            |          |                        |            |            |          |                         |            |            |          |
|------------------------|--------------|-----|---|------------|------------|----------|------------------------|------------|------------|----------|-------------------------|------------|------------|----------|
|                        |              |     | Patient -related time   |            |            | P- value | Systemic- related time |            |            | p- value | Diagnosis- related time |            |            | P- value |
|                        |              |     | < 2 months  | 2-6 months | > 6 months |          | < 1 month              | 1-3 months | > 3 Months |          | <3 months               | 3-6 months | > 6 months |          |
| Stage                  | Stage 1      | 52  | 100.0   | 0.0        | 0.0        | <0.0001  | 88.5                   | 11.5       | 0.0        | <0.0001  | 94.2                    | 5.8        | 0.0        | <0.0001  |
|                        | Stage 2      | 110 | 96.4  | 3.6        | 0.0        |          | 92.7                   | 7.3        | 0.0        |          | 90.9                    | 9.1        | 0.0        |          |
|                        | Stage 3      | 189 | 24.9  | 24.3       | 50.8       |          | 79.4                   | 1.6        | 19.0       |          | 6.9                     | 14.3       | 78.8       |          |
|                        | Stage 4      | 49  | 8.2   | 2.0        | 89.8       |          | 79.6                   | 10.2       | 10.2       |          | 0.0                     | 2.0        | 98.0       |          |
| Stage                  | Early stages | 162 | 97.5  | 2.5        | 0.0        | <0.0001  | 91.4                   | 8.6        | 0.0        | <0.0001  | 92.0                    | 8.0        | 0.0        | <0.0001  |
|                        | Late stages  | 238 | 21.4  | 19.8       | 58.8       |          | 79.4                   | 3.4        | 17.2       |          | 5.4                     | 11.8       | 82.8       |          |
| T                      | T 1          | 41  | 100.0   | 0.0        | 0.0        | <0.0001  | 92.7                   | 7.3        | 0.0        | 0.001    | 92.7                    | 7.3        | 0.0        | <0.0001  |
|                        | T 2          | 125 | 94.4  | 5.6        | 0.0        |          | 86.4                   | 7.2        | 6.4        |          | 84.0                    | 12.0       | 4.0        |          |
|                        | T 3          | 114 | 24.6  | 30.7       | 44.7       |          | 79.8                   | 1.8        | 18.4       |          | 6.2                     | 14.0       | 79.8       |          |
|                        | T 4          | 120 | 18.3  | 7.5        | 74.2       |          | 83.3                   | 6.7        | 10.0       |          | 10.0                    | 5.8        | 84.2       |          |
| N                      | N 0          | 113 | 96.5  | 3.5        | 0.0        | <0.0001  | 91.2                   | 8.8        | 0.0        | <0.0001  | 91.2                    | 8.8        | 0.0        | <0.0001  |
|                        | N 1          | 86  | 48.8  | 27.9       | 23.3       |          | 95.3                   | 3.5        | 1.2        |          | 47.7                    | 12.8       | 39.5       |          |
|                        | N 2          | 101 | 32.7  | 13.9       | 53.4       |          | 73.3                   | 7.9        | 18.8       |          | 11.9                    | 15.8       | 72.3       |          |
|                        | N 3          | 100 | 25.0  | 9.0        | 66.0       |          | 78.0                   | 1.0        | 21.0       |          | 6.0                     | 4.0        | 90.0       |          |
| M                      | M 0          | 351 | 58.4  | 14.2       | 27.4       | <0.0001  | 84.9                   | 4.8        | 10.3       | 0.395    | 46.2                    | 11.4       | 42.4       | <0.0001  |
|                        | M 1          | 49  | 8.2   | 2.0        | 89.8       |          | 79.6                   | 10.2       | 10.2       |          | 0.0                     | 0.0        | 100.0      |          |

|                             |             |     |      |      |      |         |      |     |      |         |      |      |      |         |
|-----------------------------|-------------|-----|------|------|------|---------|------|-----|------|---------|------|------|------|---------|
| His-<br>tol-<br>ogy<br>type | IDC         | 324 | 51.8 | 13.6 | 34.6 | 0.566   | 83.0 | 5.9 | 11.1 | 0.347   | 38.9 | 11.1 | 50.0 | 0.470   |
|                             | Oth-<br>ers | 76  | 53.9 | 9.3  | 36.8 |         | 89.5 | 3.9 | 6.6  |         | 47.4 | 6.6  | 46.0 |         |
| Grade                       | Grade<br>1  | 91  | 62.6 | 22.0 | 15.4 | <0.0001 | 93.4 | 2.2 | 4.4  | <0.0001 | 58.2 | 12.1 | 29.7 | <0.0001 |
|                             | Grade<br>2  | 163 | 66.9 | 12.9 | 20.2 |         | 83.4 | 9.8 | 6.8  |         | 54.6 | 12.3 | 33.1 |         |
|                             | Grade<br>3  | 146 | 29.5 | 6.8  | 63.7 |         | 79.5 | 2.7 | 17.8 |         | 13.7 | 6.8  | 79.5 |         |

\* Number of patients

## DISCUSSION

In Libya, BC is an important public health problem. Breast carcinoma is the most common malignant tumor in women and the incidence is 18.8 new case per 100,000 women per year (28). The patients are often younger than Europe, presented with late disease, have early disease recurrence, and are associated with low survival (11-13 and 15). With respects to the genetic and biological behavior of BC, perhaps this trend can be attributed to low awareness of health issues among women, to poor information campaigns that address warning signs of BC in Libya, and to the absence of screening programs for early detection of breast cancer.

Delay of diagnosis and treatment of BC are correlated with a lower survival and one of the important reasons for the significances different in the mortality rate of BC among countries (15, 17 and 21). Because diagnosis delay is preventable and has major impacts on disease stage and patient's outcome, it is very important to study diagnosis-related delay time and to understand the reasons of delay to promote early detection.

This work shows that the diagnosis-related delay time is still a serious health problem in Libya. The average time before medical advice and diagnosis was long, and the time of the delay was even in line with developing countries, but higher than developed countries (15, 29-32). Among European patients the median diagnosis related time is less than one month. Perhaps this tends that the diagnosis delay is a big serious health problem in Libya as well as other developing countries.

This study observed that there is a correlation between the patient predicated factors and the expected delay. The association between the patient-predicated factors (psychology and/or sociology) and delayed presentation of symptoms was an important predictor of delay. The patients assumed that symptoms were benign (harmless and temporary) and would disappear without and any medical intervention (33). This reflects poor knowledge of women regarding importance of these warning signs and symptoms of breast cancer, the seriousness of these symptoms can attain with the time, being irreversible, and even progress to be fatal in advanced stages. In our study, 18% of patients often considered symptoms as benign and probable to fade without any medical intervention. This was the most important reason given by women for delay in a seeking medical advice after discovering the symptoms. These results were in agreement with other studies (25,30,34).

In the present study, 17.7% of patients had taken alternative therapy before seeking any medical advice, this is in agreement with other studies which observed that using of unconventional and alternative therapies before seeking any medical advice as an important reason for patient-related delay time [11,12,35]. Most of the patients used alternative treatment as a method to keep away from the surgery and some believed that there was no effective treatment for BC treatment, or that traditional medicine is better than modern medicine. Although, the majority of patients experienced worsening of symptoms, which eventually led to more advanced stage after using alternative therapy. Anyhow, patients often had strong beliefs on traditional medicine and used it as the last hope chance (33). Thus, it might be worthwhile to encourage women to keep away from this bad wrong belief.

In addition, this study also observed that a fear of cancer diagnosis and/or treatment and shame to appearance the symptoms are important reasons for patient-related delay time as in the developing countries (13,30,25). Negative information on BC diagnosis and treatment causes delay. Some patients believed that BC is means the death and there is no way for

curability, so there was no difference of having it diagnosed and treated (36). Diagnosis-related delay time was also associated with a negative idea such as a belief that mastectomy causes disfigurement and disability, which lead to the fear and refusal of therapy.

We observed that older age women, illiterate, who live in rural and with other-morbidity were waited longer than younger women, literate, who live in urban and without comorbidity for presenting their symptoms to a physician. These observations confirmed the same findings in other studies (13,17-19,37-40).

Since, older age women are a risk for both developing BC and subsequent delayed presentation (38). Any intervention program should target older women regarding this issue.

The association between role of education and delays has been reported in several studies [13,38]. The finding suggests that lack of knowledge about BC is an important factor of delays in developing countries and there is a need for public educational programs especially for low educated women.

A significant difference in the diagnosis and treatment of BC between women who live in urban areas and rural worldwide, women who live in rural areas were associated with both diagnosis delay and a high risk of advanced stage at diagnosis (18,39). This may be attributed to limited facilities in rural areas to diagnostic services (40). Rural areas need to empower in terms of awareness and improvement in access to health services regarding a particular emphasis on breast cancer.

Women with comorbidity were more likely to be diagnosed late and at advanced stage of breast cancer (19), in agreement with our results. Patients with other morbidity are likely to attribute breast cancer symptoms to their comorbidities, thus, may decrease the chances for early detection. However, the evidence is still weak and further research is required.

The awareness of breast cancer and performing of breast self-examination are clearly associated with early diagnosis and early stage of BC as observed in our study. The role of breast self-examination on early detection of BC is controversial. Some studies showed no clear evidence of an association between lack of breast self-examination and patient-related delay time (41). The risk of delays and late stages reduces in women who regular breast self-examination (17). The results suggest that breast self-examination could be a primary method for early detection of BC, because women will be aware of their physical changes earlier. Anyhow, these studies revealed poor awareness of women regarding this method (21,42)

One of important findings in this work was regarding the symptoms and signs of BC, we observed that the first breast symptoms that did not include a lump were strongly associated with patient-related delay time. In the agreement with other which also noted that the discovering of breast lump as initial symptoms was associated with early diagnosis of breast cancer (43,44). The findings suggest that women need to be educated about the different types of breast cancer symptoms to assist symptom recognition as well as encouragement to seek medical advice if a symptom is mysterious.

Women with past medical history of benign breast disease were associated with diagnosis-related delay time, which observed in this study. Patients with BC often consider breast problems as benign, which is an important cause of patient-related delay time (13). Anyhow, breast symptoms also were significantly associated with doctor's delay (45,46). Explanation is that former episodes of breast tissue changes, if considered by physicians nonmalignant is also later considered benign. Thus, it might be worthwhile to encourage women with known benign breast disease to present new breast symptoms immediately. Physicians also should understand that new symptoms should be evaluated as potential new risks for BC.

On other hand, previous studies have observed that late diagnosis is related with advanced stage of the disease that may occur by doctors. About 40% of women who were diagnosed with cancer, were inappropriately reassured after the first doctor visit that a malignant lump was benign as noted by Unger-Saldana and colleagues (46). This could lead to loss of patient confidence in healthcare system. In our study, failures of medical practitioners to act on presenting findings with inappropriate reassurance that the lump was benign was an important reason for prolongation the systemic-related time resulting in twenty-five (6.3%) patients had waited more than 6 months for final diagnosis, after the first doctor's visit. Caution for health professionals about 'warning symptoms' which is rarely the cause of cancer should be considered (29). As a result, improved quality of primary care, prompt hospital referral system, improved patient information and doctors' education and training are a highly recommended to promote early detection of BC (29). The treatment guidelines should pay more attention to the early phases of BC. Especially, guidelines for good practices in managing detectable tumors are necessary.

Diagnosis-related delay time strongly impacts on stage of disease and potentially on survival as reported in this work. Similar to previous studies (13,19,29,46), our findings indicated that diagnosis-related delay time was strongly associated with larger tumors size, with a positive lymph node with poorly differentiation of tumors, and with a high incidence of advanced stages.

Interestingly, Comparison between this work and others from developed countries in light of the difference in African and American BC (47). These differences may be related to healthcare or be explained by differences in other aspects such as biology and genetics. The observations in both studies suggest that the diagnosis-related delay time is clearly associated with advanced stage of disease at diagnosis. In the Libyan patients, the median of diagnosis-related time was 180 days and 55.5% of patients waited longer than 3 months for diagnosis after the symptom. Among American patients the median of diagnosis-related time was 23 days. The big difference in these results may reflect the difference in health care and/or be related to other demographic, social, and patient associated factors. With respect to health care, differences in the biology of BC may also be involved. African American women with breast cancer are more likely to be diagnosed at advanced stage and have BC markers of bad prognosis (10).

Comparison between this work and other one from Libya (48) is also very interesting in light of improvement early detection of Libyan women with breast cancer since 10 years ago. A total of 200 Libyan women aged 22 to 75 years with breast cancer diagnosed during 2008-2009 were interviewed about the period from the first symptoms to the final histological diagnosis of breast cancer were studied by Ermiah and colleagues concluded that the median of diagnosis time was 7.5 months. Only 30.0% of patients were diagnosed within 3 months after symptoms. 14% of patients were diagnosed within 3-6 months and 56% within a period longer than 6 months. Our study confirms these results as well as the diagnosis delay still a large health serious problem in Libya without any intervention regarding this issue.

### **Conclusion**

The present study shows a significant relationship between late diagnosis and advanced stage of breast cancer. In Libya, late diagnosis of breast cancer is still a large serious health problem. It was related to a complex interaction between patient and systemic predicating factors, which resulting in a high risk of advanced stage of breast cancer with lower survival rate. Therefore, public awareness programs and training of general practitioners are highly recommended to reduce breast cancer mortality by promoting early detection.

### **Authors' contributions**

MG performed designed the present study, drafted manuscript and the writing. MG, EE, IA and HA making patients interview. AA, FO, AL, MF and AE analyzed data and review the manuscript. AE and MA performed data interpretation and analysis, drafting and proof reading and discussions. EE make the statistical analysis. AB prepared the figures and Tables and reviewed the study, interpreted data and aided in drafting and proof reading of the manuscript. All authors critically reviewed and approved the final version of the manuscript.

### **Approval and consent to participate**

The study was done under research ethics approval by ethical committee at the National Cancer Institute, Misurata (Ethical Approval Number: 8/2022). All participants in this study were gave oral consent, after explain to them about the study in detail.

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