An-Najah National University

Faculty of Graduate Studies

THE RELATIONSHIP BETWEEN SYMPTOM SEVERITY AND SYMPTOM INTERFERENCE, QUALITY OF LIFE, AND TYPE OF TREATMENT IN PALESTINIAN WOMEN WITH BREAST CANCER

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Dedication

The study is dedicated to those who believe in me and show me the path to success, with endless support, assistance, and encouragement, to my mother, my father, my dear husband, and my lovely children I dedicate this work.

Acknowledgment

First and foremost, thank GOD for the blessing, to give me the power, patience, and skills to finish this research.

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I would like to thank the patients who agreed to give me their time to fill out and complete the questionnaire and to be a part of this research.

Declaration

I, the undersigned, declare that I submitted the thesis entitled:

THE RELATIONSHIP BETWEEN SYMPTOM SEVERITY AND SYMPTOM INTERFERENCE, QUALITY OF LIFE, AND TYPE OF TREATMENT IN PALESTINIAN WOMEN WITH BREAST CANCER

I declare that the work provided in this thesis, unless otherwise referenced, is the researcher's own work, and has not been submitted elsewhere for any other degree or qualification.

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Date: 5/3/2024

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Abstract

Background: Breast cancer is one of the most common cancers that affects women more than men and is considered a major cause of cancer death among women. Women with breast cancer experience bothersome symptoms related either to the disease itself or breast cancer treatments that interfere with patients' life activities and affect their quality of life.

Objectives: To provide a comprehensive explanation of the relationship between symptom severity and symptom interference, quality of life and type of treatment.

Methodology: This is a cross-sectional study conducted through the MDASI questionnaire to assess symptom severity and symptom interference and the EQ-5D-5 L questionnaire to assess quality of life among women with a confirmed diagnosis of breast cancer at An-Najah National University Hospital and AL-Watani Hospital. The questionnaire was completed through face-to-face interviews and reviewing patients' medical records.

Results: A cohort of 229 participants was enrolled in the study. Predominantly, patients (34.1%, n=78) fell within the 50-59 years age bracket. Treatment modalities included chemotherapy alone (35.4%, n=81), hormonal therapy (48%, n=110), targeted therapy (9.6%, n=22), and various combination regimens. Specifically, 3.9% (n=9) received hormonal therapy along with targeted therapy, and 3.1% (n=7) underwent combined chemotherapy and targeted therapy. Fatigue emerged as the most prevalent and severe symptom, except for women undergoing chemotherapy plus targeted therapy who reported heightened complaints of sleep disturbances. Pearson correlations between the

MDASI symptom severity total mean score and the MDASI symptom interference total mean score were significant for chemotherapy ($r = 0.685$, $p < 0.05$), hormonal therapy ($r = 0.827$, $P < 0.05$), targeted therapy ($r = 0.922$, $P < 0.05$) and hormonal plus targeted therapy ($r = 0.699$, $P < 0.05$), and not significant for the chemotherapy plus targeted therapy group ($r=0.398$, $p=0.329$). The most robust associations were identified with feelings of sadness ($r=0.792$, $P< 0.05$), fatigue ($r=0.774$, $P< 0.05$), and distress ($r=0.743< P< 0.05$). There were significant differences between study participants in relation to patient age, smoking status and treatment methods (p value<0.05), whereas other sociodemographic and clinical characteristics are not significantly associated with the total mean score of the symptom severity scale. Regarding the EQ-5D-5 L dimensions, the majority of patients reported no issues. The EQ-5D-5 L index score exhibited significant positive correlation with the EQ-VAS score ($r = 0.568$, P value < 0.05). Conversely, it demonstrated significant negative correlations with both the total mean score of symptom severity ($r = -0.664$, P value < 0.05) and the symptom interference total mean score ($r = -0.651$, P value < 0.05).

Conclusions: The most common type of treatment associated with severe symptoms and affecting patients' daily life activities is chemotherapy, which has no significant influence on patients' quality of life. Fatigue was the most severe symptom associated with the breast cancer treatment method.

Keywords: symptom severity, symptom interference, quality of life, and type of treatment.

Chapter One

Introduction

1.1 Background

Breast cancer is a malignancy in the tissue of the breast; it occurs in women as well as in men, but it affects women 100 times more than men [1]. At the end of December 2020, World Health Organization (WHO) statistics results found that 2.3 million women were diagnosed with breast cancer; unfortunately, 685000 died of breast cancer worldwide wild in that year [2].

In recent years, the prevalence of breast cancer among Palestinian women has increased significantly; it is considered the most common type of cancer among Palestinian women, and it was surpassed only by heart disease as a major cause of death among Palestinian women [3]. According to the Palestinian Health Annual Report 2021, the incidence rate of breast cancer was 36.2 cases per 100,000 females, and 513 cases were diagnosed in the West Bank and ranked as the first type of cancer affecting Palestinian women at that time [3].

Due to raising awareness of the importance of early detection and improving efforts toward better understanding, diagnosis, and treatment of cancer, survival rates from breast cancer have improved significantly, especially among younger women [1, 4].

Due to the lack of equipment in developing countries, early detection of breast cancer is less common than in developed countries that have a high level of diagnostic equipment, and the breast cancer incidence rate is higher in developed countries than in developing countries [5].

Daily life activities and the patient's quality of life are adversely affected by bothersome and distressing symptoms that are reported by breast cancer patients, and the appearance of those symptoms is considered to be related either to the disease itself or to the type of treatment regimen decided by the health care providers [6, 7].

1.1.1 Breast cancer risk factors

Epidemiologic studies have found that a variety of risk factors, including sex, age, race, environmental factors, lifestyle factors, lifetime exposure to estrogen, and genetic inheritance, are related to breast cancer development and prognosis [8].

Male breast cancer cases account for only 0.5-1% of breast cancer cases, and the majority of cases occur in females, with a 99% incidence ratio; thus, breast cancer development has a strong association with female sex [2].

As age increases, the breast cancer incidence increases, and older individuals have a higher rate of occurrence than younger individuals [9]. In the United States, black women exhibit a higher prevalence of later-stage diagnosis and a greater incidence of triple-negative tumors (characterized by negativity for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2)), as compared to their white counterparts. This demographic disparity contributes to an elevated mortality rate among black women. The augmented poor prognosis and heightened aggressiveness observed in women with the triple-negative receptor subtype of breast cancer further accentuate the increased fatality associated with this demographic group [10, 11].

In accordance with environmental determinants, the likelihood of developing breast cancer is elevated through exposure to substances such as bisphenol A (BPA), organochlorine pesticides (OCPs), polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs), dioxin (2,3,7,8 tetrachlorodibenzo-p-dioxin), and ionized radiation [12].

Lifestyle elements such as obesity, physical inactivity, and excessive alcohol consumption emerge as noteworthy risk factors for breast cancer. Notably, a heightened body fat composition serves as a substrate facilitating the conversion of androgen into estrogen within adipose tissue. Moreover, obesity and physical inactivity are concomitant contributors to hyperinsulinemia and insulin resistance, both independently recognized as risk factors for breast cancer according to epidemiological investigations [12, 13].

Approximately 3 to 6 drinks per week or more were significantly associated with breast cancer incidence [12].

Early menarche (<12 years), late menopause (>55 years), late first pregnancy, and absence of breastfeeding are associated with higher estrogen exposure during the lifetime, and doubled estradiol levels were seen in women with early menarche compared with women who had menarche 13 years and older [14].

The most important hormone implicated in breast cancer pathogenesis is estrogen, which stimulates the production of various growth factors, such as platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and transforming growth factor alpha (TGFα). All of these growth factors play an important role during puberty, menstruation, and pregnancy in the proliferation of breast epithelial cells, and estrogen stimulates the growth of tumor cells in women with ER-positive breast cancer[15, 16].

A strong family history, particularly a first-degree relative who had been diagnosed with breast cancer, has been shown to increase the risk for breast cancer occurrence [17].

In relation to genetics, breast cancer gene 1 (BRCA1), breast cancer gene 2 (BRCA2), tumor protein 53 (TP53), phosphatase and tensin homolog (PTEN) and human epidermal growth factor receptor 2 (HER2) genes are involved in the pathogenesis of breast cancer, in which double-stranded DNA breaks are repaired through the action of the BRCA1 and BRCA2 genes. TP53 is a guardian of the genome, PTEN is an important negative regulator of the pro-growth phosphoinositide 3-kinase-protein kinase B (PI3K-AKT) pathway, HER2 promotes cell proliferation and opposes apoptosis, and mutation of these genes results in an increased risk for the development of breast carcinogenesis [12].

A total of 80-90% of familial breast cancers and 3-6% of all breast cancers are related to mutations in BRCA1 and BRAC2 genes, and BRCA2 mutations are more frequently associated with male breast cancer [18].

1.1.2 Breast cancer types

Breast cancer is categorized as noninvasive and invasive breast cancer. Noninvasive breast cancer refers to carcinoma in situ, in which the cancer cell is involved only in the ducts (ductal carcinoma) and lobules (lobular carcinoma), whereas invasive breast cancer refers to cancer expanded from ducts and lobules to surrounding breast tissue [19].

The majority of cases are invasive ductal carcinoma, accounting for 40-80% of invasive breast cancer cases [9], and invasive lobular carcinoma accounts for 10-15% [20],whereas tubular carcinoma, carcinoma with medullary features, mucinous carcinoma (colloid carcinoma), and other types account for less than 5% of invasive breast cancer cases [21].

1.1.3 Breast cancer stages

According to the American Cancer Society, the American Joint Committee on Cancer (AJCC) TNM staging system, which assesses tumor size (T), lymph node involvement (N), and distant metastasis (M), is universally used to determine prognosis and assist clinicians with treatment decisions.

The stages are represented as follows:

Early breast cancer:

- Stage 0: carcinoma in situ or disease that did not invade the basement membrane.
- Stage I: primary invasion without lymph node involvement.
- Stage II: regional lymph node involvement.
- Locally advanced breast cancer:
- Stage III: large tumor, extensive nodal involvement in which the tumor or node is fixed to the chest wall without distant metastasis.
- Advanced or metastatic breast cancer:
- Stage IV: tumor metastasis to distant organs.

Staging performed before surgery, which is based on physical examination (tumor size, lymph node involvement), imaging (e.g., mammography, MRI...etc.), and pathological examination (e.g., biopsy result) is called clinical staging, whereas staging performed after surgery based on surgical resection and the addition of further data is called pathological staging [22].

Before 2018, the 7th edition of the AJCC staging manual purely used the TNM anatomical method to assess patient prognosis based on clinical and pathological evaluations. After implementation of the 8th AJCC staging manual in 2018, anatomical staging in addition to prognostic staging (tumor grade, hormone receptors +/-, multigene testing) allowed health care providers to understand why the same stage has a different prognosis among breast cancer patients [23].

Clinical staging and pathological staging are similar for tumor size, which ranges from Tis (ductal carcinoma in situ) to T4 (metastasis), and use the prefix “c” for clinical staging and the prefix “p” for pathological staging. LCIS is not included in the TNM 8th staging manual; it is indicated as benign but still carries a malignancy risk [23, 24].

T1 is divided into Tmi mean tumor size less than 1 mm or less, T1a means tumor size more than 1 mm and 5 mm or less, T1b means tumor size more than 5 mm and 10 mm or less, T1c tumor size more than 10 mm and 20 mm or less, T2 tumor size more than 20 mm and 50 mm or less, T3 tumor size more than 50 mm,T4 subdivided into (T4a, T4b, T4c), T4a tumor with chest wall involvement, T4b mean skin involvement, skin ulceration and/or satellite skin nodules and/or edema, T4c indicated when the criteria of both T4a and T4b are present, and T4d inflammatory carcinoma [23, 24].

The staging category for axillary lymph node involvement (N) ranges from N0 to N3; N0 means that there is no axillary lymph node involvement, N1 means that there is regional metastasis to (one–three) movable ipsilateral lymph nodes at level I and/or level II, N2 is subdivided into N2a and N2b, N2a indicates involvement of four to nine ipsilateral lymph nodes at level I and/or level II, N2b indicates involvement of isolated internal mammary lymph nodes (without axillary lymph node involvement), N3 is divided into N3a,N3b, and N3c, N3a indicates metastasis to ipsilateral infraclavicular axillary lymph nodes (level III) or more than 10 axillary lymph nodes, N3b indicates

ipsilateral internal mammary plus axillary lymph node involvement, and N3c indicates ipsilateral supraventricular lymph node involvement [23-25].

The staging category for metastasis (M), M0 indicates no metastasis, cM0 means there is no clinically or radiologically proven metastasis and pM0 is invalid, and M1 indicates metastases; if there is clinically and radiologically proven metastasis, it is called cM1, and if there is histological detection with a tumor size greater than 0.2 mm, it is called pM1 [24, 26].

1.1.4 Diagnosis of breast cancer

Based on breast physical examination, family history, and breast imaging techniques, such as diagnostic mammography, ultrasound, and MRI, are all diagnostic methods for breast cancer [27].

A biopsy is performed if there is any palpable mass on physical diagnosis or mammographic abnormality [28].

1.1.5 Breast cancer grades

Grade represents the similarity or differences between cancer cells and normal breast cells**.** Given an idea about cancer cell behavior, many features, such as mitotic count, cell arrangement, tubule formation and the extent of similarity with normal breast cells, are used together to identify the grade of breast cancer [29].

The grade ranges from I to III. Grade I is a low-grade breast cancer that looks similar to normal cells under a microscope, is associated with good prognosis, and grows and spreads slowly. Grade II breast cancer is an intermediate grade between grade I and grade III. Grade III is associated with poor prognosis, grows and spreads rapidly and is different from normal cells of the breast tissue under a microscope [29].

1.1.6 Breast cancer treatments

Patients with early-stage breast cancer are considered for surgery. The types of surgery performed are breast-conserving surgery, in which the surgeon removes the tumor and preserves the shape and size of the breast; total mastectomy, in which the surgeon removes the whole breast involving the tumor; or modified radical mastectomy, in which the surgeon removes the tumor and a part of the breast surrounding the tumor.

Neoadjuvant therapy is given before surgery to shrink the tumor and decrease the amount of tissue that needs to be removed during surgery. Adjuvant therapy is given after surgery to kill the cancer cells that were not removed through surgery, and neoadjuvant and adjuvant therapy includes chemotherapy, hormonal therapy, immunotherapy, and targeted therapy [30].

Hormonal therapy is used to stop cancer cell growth by blocking the action of hormones on cancer cells or by decreasing the amount of circulating hormones [31]. The hormone of interest is estrogen, which is produced by the ovaries. The treatment used to stop estrogen production from the ovaries is called ovarian ablation [32].

Tamoxifen is a selective estrogen receptor modulator (SERM) used in women with ER-positive breast cancer and premenopausal and postmenopausal women with a high risk for breast cancer [33] and is also preferred as adjuvant therapy for both invasive breast cancer and noninvasive breast cancer (DCIS) [34].

Tamoxifen is preferred over aromatase inhibitors (AIs) in premenopausal women because AIs are not effective without ovarian suppression therapy [35].

Similar to tamoxifen, toremifene and raloxifene are SERMs, both of which are used in postmenopausal women. Toremifene is approved for metastatic breast cancer, and raloxifene is approved to prevent breast cancer [33].

Fulvestrant is a selective estrogen receptor degrader (SERD) that binds to estrogen receptors more tightly than SREM, which leads to receptor degradation [36].

AIs (anastrozole, letrozole, or exemestane) are used for at least five years in postmenopausal women with ER-positive breast cancer, in which AIs lower estrogen levels by blocking the conversion of endogenous androgenic steroids to estrogen [37].

There is controversy about increasing the risk of osteoporosis for patients receiving AIs. A study published in 2019 showed that there is no association between extended anastrozole use and an increased risk for osteoporosis, in which extended anastrozole use results in a modest decrease in bone mineral density (BMD), and patients receiving AIs must be assessed annually using dual-energy X-ray absorptiometry (DEXA) [38].

Another study showed that extended AI administration did not show any benefits; instead, the patients were more likely to have osteoporosis and bone fracture [39].

Ovarian suppression therapy mainly by luteinizing hormone-releasing hormone (LHRH) agonists, which include goserelin and leuprolide, can be used alone or in combination with other hormonal therapies (tamoxifen, AIs or fulvestrant) in premenopausal women who are at a high risk for cancer recurrence[32].

In premenopausal women, AIs should never be used alone; they can be used only with ovarian suppression therapy [32].

Chemotherapy can be given before surgery as neoadjuvant therapy to reduce the tumor size and is used mainly in locally advanced and inflammatory breast cancer. Chemotherapy is given after surgery as adjuvant therapy to destroy any cancer cells that remain after surgery [40], both neoadjuvant and adjuvant chemotherapy lower the risk of recurrence [40].

Chemotherapy is mainly given when the tumor spreads to distant areas such as the liver, lung, bone, and brain in which surgery cannot be performed and when tumor cells are triple-negative receptors [41].

Anthracyclines, such as doxorubicin and epirubicin; taxanes, such as paclitaxel and docetaxel; antimetabolites, such as 5-fluorouracil (5-FU), capecitabine, and gemcitabine; alkylating agents, such as cyclophosphamide, carboplatin, and cisplatin; mitotic inhibitor alkaloid agents, such as vinorelbine, vincristine, vindesine, and vinblastine; Ixabepilonea microtubule stabilizing agent; and eribulin, an antimirotubule agent, were used as single drugs or in combination [42].

Targeted therapy binds to specific molecules to stop cell signaling pathways within tumor cells to prevent them from growing or destroying them. The targeted molecules of interest are receptor tyrosine kinases (RTKs), steroid receptor coactivators (SRC), mammalian target of rapamycin (mTOR), phosphatidylinositol 3-kinase (PI3K), and poly (ADP-ribose) polymerase (PARP) [43].

HER2, which is a tyrosine kinase receptor, is a target for monoclonal antibodies (trastuzumab, pertuzumab) that prevent cancer cells from growing, and both can be used in early, locally advanced stage and metastatic breast cancer [44].

Margetuximab is another monoclonal antibody that binds to HER2 target sites on cancer cells and is used in metastatic breast cancer that is resistant to conventional monoclonal antibodies [45].

Antibody drug conjugates (ADCs), such as Ado-trastuzumab emtansine and Fam-trastuzumab deruxtecan, are monoclonal antibodies conjugated to chemotherapy, in which monoclonal antibody binding to HER2 protein on cancer cells sends signals to bring chemotherapy directly to cancer cells [45, 46].

In the case of ER-positive, PR-positive, and HER2-negative tumors, certain target drugs (PI3K and CD4/6 inhibitors) are used along with hormone therapy to increase the effectiveness of treatment and prolong survival [47].

CDK4/6 inhibitors, such as palbociclib, ribociclib, and abemaciclib, block cyclin-dependent kinase (CDK) proteins (CDK4 and CDK6) [48]and are given in advanced and metastatic breast cancer along with fulvestrant in patients who have received hormonal therapy or along with AIs as an initial hormonal therapy in both postmenopausal and premenopausal women [49, 50].

Everolimus is a targeted therapy that blocks the mammalian target of rapamycin, a protein that plays a role in cell division and growth, used in postmenopausal women along with exemestane or fulvestrant to treat advanced breast cancer, with ER-positive, PR-positive, HER2-negative, in which cancer growth is not controlled while using letrozole or anastrozole [51].

Alpelisib blocks the PI3K protein in postmenopausal women and is used along with fulvestrant to treat ER-positive, PR-positive, HER2-negative metastatic breast cancer [52].

Sacituzumab govitecan is an antibody drug conjugate (ADC) used in cases of triple-negative or HER2-negative breast cancer, ER-positive, and PR-positive, in which monoclonal antibodies link to the cell-surface antigen trophoblast 2 (Trop-2) on cancer

cells, which acts as a calcium signal transducer, allowing cancer cells to divide and proliferate [53].

Olaparib and talazoparib are poly (ADP-ribose) polymerase inhibitors (PARP inhibitors) that tend to cause more damage to tumor cells and ultimately lead to cancer cell death. PARP proteins are responsible for DNA repair, such as the BRCA1 and BRCA2 genes, but there are few differences between them [54].

Olaparib and talazoparib are given in cases of BRCA mutation and ER-positive, PR-positive, and HER2-negative advanced breast cancer patients who have been treated with chemotherapy or previously received hormonal therapy [55-57].

Programmed death receptor-1 (PD-1), an inhibitory receptor found on tumor infiltrating lymphocytes (TILs), is programmed cell death ligand-1 (PDL-1) found on cancer cells, in which PD-1 binds to PDL-1, which prevents the immune system from attacking and destroying cancer cells [58].

A deficient DNA mismatch repair pathway (DMMR), a pathway that plays an important role in maintaining genome stability, can induce repetitive genomic sequence mutations, microsatellite instability (MSI), and tumors with multiple sequence mutations known as MSI-high (MSI-H) [59].

Colon and endometrial studies have shown that tumors with MSI or DMMR are more sensitive to immune checkpoint blockade (anti-PDL-1/PD-1), but the data are limited for breast cancer [60].

Pembrolizumab is a monoclonal antibody that binds to PD-1 on T cells, preventing the interaction between PD-1 and PDL-1 in cancer cells; in this way, the activity of T cells is restored. Atezolizumab and Avelumab are IgG1 monoclonal antibodies that target PDL-1 on cancer cells. Atezolizumab is more selective for PDL-1 than Avelumab, and all are promising treatments in cases of triple-negative metastatic breast cancer [61].

Radiation therapy is used alone or in combination with surgery to shrink the tumor size or to slow its growth, and radiation can be delivered to cancer cells in two ways: external and internal beam radiation [62].

Hypofractionated radiation to the whole breast mass, followed by breast-conserving surgery, is preferred in early-stage breast cancer. This approach is associated with higher efficacy and fewer side effects. Additionally, patients with unfavorable tumor biology benefit from hypofractionated radiation. Surgery followed by radiation is also recommended in locally advanced breast cancer [63]. Regarding metastatic breast cancer, the role of radiation is under study, and the main role currently is as palliative therapy for systematic lesions. New studies are concerned about the efficacy and safety of combined radiation and immunotherapy, but the results are still obtained from animal models and have not been evaluated in humans. The results are promising, as radiation therapy enhances immunity against cancer cells by recruiting T cells, enhancing antigen presentation by tumor cells, and altering cytokine and chemokine release [64].

Treatment decisions are based on two concepts: the first concept is to reduce local recurrence, which is achieved by surgery alone or surgery plus radiotherapy, and the second concept is to reduce the risk for metastasis, which is achieved by introducing systemic therapy (chemotherapy, hormonal therapy, immunotherapy and targeted therapy) [65].

1.2 Literature review

Women who are receiving breast cancer therapy complain of bothersome symptoms that must be clearly understood by health care providers. Any underestimation of the reported symptoms could adversely affect daily life activities [6, 66, 67]. Efforts are directed not only toward improving treatment but also toward patient rehabilitation, social integration and improving quality of life [68].

A study performed in 2010 using the MD Anderson Symptom Inventory (MDASI) scale found that fatigue, sleep disturbances, and drowsiness were the most prevalent and the most severe symptoms associated with chemotherapy treatment, followed by distress and sadness [66].

Among sociodemographic characteristics, age was not significantly associated with the overall mean score of the symptom severity scale, education was significantly associated with the overall mean score of symptom severity scale, and more highly educated women complained of less severe symptoms [69].

Fatigue is the most common symptom that persists for a long time after breast cancer diagnosis and treatment and adversely affects physical, psychosocial, and socioeconomic patients' lives [68, 70, 71]. Berger et al. were the first to report that sleep disturbances are the most common symptom [72]. Another study in Taiwan found that sleep disturbances had a significantly higher level of severity than other symptom severity among breast cancer survivors [73].

A strong relationship was found between the symptom severity scale and symptom interference scale with daily life activities, especially work and general activity in most cases [74]. The strongest association was found between symptom interference and fatigue, followed by distress, sadness, and drowsiness [66]. Berger et al. found that pain is the most severe symptom interfering with patient function and influencing the severity of other symptoms [72]. Nyrop et al. found that older and younger women perceived symptom interference with activities of daily living to be less concerning than symptom severity [75].

Bothersome symptoms have also been reported by breast cancer survivors with a history of adjuvant chemotherapy, in contrast to survivors without a history of adjuvant chemotherapy[4, 70].

Women who complete chemotherapy have less contact with healthcare providers; unfortunately, at that time, they need more support and have better adjustment difficulties[76].

Stanton et al. did not provide a comprehensive comparison between the chemotherapy regimen and the symptoms experienced by a breast cancer patient who received that regimen [76].

Nyrop et al. found that an anthracycline-based regimen is related to a higher rate of reported symptoms, which ranges from moderately severe to very severe (MSVS) symptoms, in contrast to patients who receive a non-anthracycline-based regimen [75].

Prigozin, Uziely et al. found that patients who completed their treatment with paclitaxel had a lower total mean score on the MDASI symptom severity scale than patients treated with doxorubicin plus cyclophosphamide or doxorubicin plus cyclophosphamide plus fluorouracil [66].

Limited data are available about women who are receiving or had received hormonal, immunotherapy, targeted therapy, or combination treatments compared with studies performed on chemotherapy alone using MDASI scales because the MDASI scale is a specific symptom measurement tool for chemotherapy and is not specific for other therapies [77].

The available data show that women on hormonal therapy experience a low mean score of symptom severity and symptom interference, and women with previous hormonal therapy show a lower score of symptom severity than women who never received hormonal therapy [78].

Hormone-positive breast cancer is more prevalent than hormone-negative breast cancer and is associated with better prognosis and survival [79].

Postmenopausal women who are receiving aromatase inhibitors complain of musculoskeletal pain (arthralgia) and hot flushes. Bone loss is an essential side effect of aromatase inhibitor administration and must be assessed annually to avoid osteoporosis and subsequent fractures [80].

Using the Functional Assessment of Cancer Therapy - Endocrine Symptoms (FACT-ES), women who received SERMs such as tamoxifen complained more of vaginal dryness and loss of sexual interest than women who received aromatase inhibitors, and women who received aromatase inhibitors complained more of joint pain; the quality of life for both women who received SERMs and those receiving aromatase inhibitors was not significantly different [69].

Due to differences in symptom assessment tools that are used among studies to assess symptom severity and interference, the comparison between results is not easy and needs to be treated with caution. The most commonly used tools (Breast Cancer Prevention Trial (BCPT), FACT-ES, MDASI) do not comprehensively assess symptoms associated with hormonal therapy [77].

According to the MD Anderson Symptoms Inventory scale, trastuzumab symptom severity overall mean scores were mild, in which fatigue, sleep disturbances, and numbness were the most severe symptoms reported, with a mild overall mean score for the symptom interference scale [81].

Targeted therapy and hormonal therapy are tolerated therapies in general and show lower side effect profiles and better quality of life than chemotherapy, which is associated with aggressive side effects and a higher rate of side effects [82, 83].

Quality of life was assessed by different studies using the EuroQol 5 Dimension 5 Level (EQ-5D-5 L) measurement scale among breast cancer patients [84, 85].

A higher EQ-5D-5 L index score was seen between noncancer patients, and the index score improved after completing the treatment [86]. Another study found that the treatment method was significantly associated with quality of life [87].

Sociodemographic characteristics such as elderly women, employee women, and women with high income or higher education were associated with higher index scores, meaning better quality of life [88-90]. Another study found that there was no association between sociodemographic characteristics and EQ-5D-5 L index scores among women with breast cancer [91, 92].

The results from an Indian study using the EQ-5D-5 L questionnaire found that the anxiety/depression domain was the most affected domain, followed by the pain/discomfort domain [86]. A study conducted in Malaysia using the same instrument found that the pain/discomfort domain was the most affected domain among Malaysian participants [89], and the results of a Canadian study showed that pain/discomfort was the most affected domain, followed by anxiety/depression [87].

A research investigation was undertaken to assess the quality of life in women diagnosed with advanced-stage breast cancer. The European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) served as the instrument for this evaluation. The findings revealed a noteworthy correlation between the average quality of life measures and distinct breast cancer treatments, including chemotherapy, hormonal therapy, and targeted therapy. Notably, the study observed an enhancement in quality of life associated with hormonal and targeted therapies. Conversely, chemotherapy demonstrated no discernible impact on the overall quality of life for the patients involved [92].

Chemotherapy in other studies significantly affected patient quality of life, and patients on chemotherapy complained of severe symptoms compared with those on hormonal and targeted therapy, in which the degree of severity was much higher for chemotherapy and lowest for targeted therapy than for hormonal therapy [91, 92].

Among hormonal therapies, the older hormonal therapy selective estrogen receptor modulator (e.g., tamoxifen) results in more side effects than newer hormonal therapy, such as aromatase inhibitors and selective estrogen receptor degrader (fulvestrant), and newer hormonal therapy has a favorable quality of life profile in contrast to patients receiving SERMs (tamoxifen) [93].

1.3 Problem statement

Breast cancer is a major public health concern, particularly among Palestinian women, as evidenced by increased rates of occurrence. Individuals diagnosed with breast cancer may experience symptoms that are both directly related to the disease and as a result of its treatments, which have the potential to seriously impair their daily functioning and general well-being. Nonetheless, there is a scarcity of extensive scholarly research on the interconnections of symptom severity, symptom interference, various treatment modalities (particularly hormonal and targeted therapy), and their impact on the quality of life experienced by Palestinian women diagnosed with breast cancer.

Limited studies are available to provide sufficient information regarding the relationships between symptom severity, symptom interference, and the type of treatment (especially hormonal and targeted therapy) using MDASI scales and relation with quality of life using the EQ-5D-5 L tool.

To the best of our knowledge, in Palestine, West Bank, the relationship between symptom severity and symptom interference among women with breast cancer has not been explored and assessed before, and quality of life was evaluated in women who had only undergone surgery and had received chemotherapy [90].

The need to correlate all the results to each other and then provide a cornerstone to understand and manage the complaints from women with breast cancer undergoing or having received breast cancer therapy reduces interference with the patient’s life activities.

1.4 Research questions

What are the most common symptoms related to breast cancer itself or to the breast cancer treatment regimen, and is there a difference in severity between these symptoms among breast cancer patients?

What is the most significant symptom severity that interferes with the patient's life activities?

Is there is a significant relation between symptom severity and symptom interference?

Does the experience of symptom severity adversely affect the quality of life of women with breast cancer?

1.5 Objectives of the study

1.5.1 General Objectives

The aim of this study was to determine the relationship between symptom severity and symptom interference, quality of life, and type of treatment among women with breast cancer.

1.5.2 Specific Objectives

1. To assess the significance of symptom severity on daily life activities.

2. Identifying the relationship between symptom severity and the type of treatment regimen.

3. To provide a good description of how a different type of treatment adversely affects patient quality of life by using a well-validated QOL instrument (EQ-5D-5 L).

1.6 Significance of the study

This study seeks to fill a significant knowledge gap regarding the associations between symptom intensity, symptom interference, quality of life, and treatment modalities among Palestinian breast cancer patients. The significance of the investigation derives from the following factors:

1. The particular significance of the study is identifying the most prevalent and severe symptoms associated with various treatment protocols. This information provide guidance to healthcare practitioners on prescription treatment options that seek to minimize adverse effects and minimize disruption to patients' daily lives.

2. We argue that the study moves the breast cancer treatment forward by undertaking a comprehensive analysis of how symptom severity impacts quality of life. Understanding how specific symptoms impact day-to-day activities will enable healthcare providers to recommend treatments that improve overall quality of life.

3. Our findings enhance the current understanding of the relationships between symptom severity, the degree to which symptoms interfere with daily functioning, and various treatment modalities, such as hormonal and targeted therapies. These findings have the potential to inform the development of tailored therapeutic regimens for individual patients, thereby decreasing the incidence of adverse effects and increasing treatment adherence.

4. The findings of this study have the potential to increase patient satisfaction through the promotion of effective symptom management and a better understanding of the challenges associated with breast cancer treatment. This phenomenon has the potential to facilitate collaborative decision-making and improve the quality of communication between patients and healthcare providers.

In light of the rising incidence of breast cancer, particularly in certain geographic regions, this research study contributes to the existing body of knowledge regarding the unique obstacles Palestinian women face. The aforementioned findings provide significant contributions that can guide future scholarly investigations and initiatives aimed at meeting the unique needs of this particular demographic in an efficient manner.

Chapter Two

Methodology

2.1 Study design

The research is a cross-sectional, observational study conducted by using symptom and quality of life assessment tools.

2.2 Study setting

The study was conducted at the Oncology Department, Day Time Unit at An-Najah National University Hospital and AL-Watani Hospital, Nablus, West Bank, Northern Palestine. Both hospitals are considered major hospitals for cancer treatment in the northern part of the West Bank.

The sample were collected during two period, from March-3 to April-17 2022, and from August-2 to September-1, 2022.

2.3 Study procedure

After approval by the institutional review board (IRB) as shown in appendix B, data were collected at the oncology department of the day care unit by interviewing the patients who met the research criteria (face-to-face interview) in which the researcher explained the security of the patient information and the purpose of the study. If the patient agreed to be a part of the study, the researcher started to complete the research questionnaire.

The patient's medical profile was also reviewed to determine the type of treatment methods that the patient received and the medical situation and to collect other information that could help to improve the results of the study.

2.4 Sample size and sampling technique

According to the 2021 Health Annual Report, 513 newly reported cases were addressed.

The study sample size was calculated by using the Raosoft® sample size calculator by applying a margin of error of 5% and a confidence interval of 95%; the minimum sample size recommended was 220 participants, and 229 participants were collected. The participants were recruited using convenience sampling technique.

2.5 Inclusion criteria

- Women who have a confirmed breast cancer diagnosis and receive treatment for breast cancer.
- Women above 18 years of age.
- Women who agreed to participate in the study.

2.6 Exclusion criteria

- Women under 18 years of age.
- Pregnant women.
- Women with psychiatric illness.

2.7 Data collection tools

M.D. Anderson symptom inventory questionnaire (MDASI), European quality of life 5 Dimension 5 Level (EQ-5D-5 L) questionnaire were used as shown in appendix A.

All the questionnaires were valid and reliable, in which cronbach's alpha was 0.919 and 0.992 for the symptom interference scale and symptom interference scale, respectively, and 0.827 for the EQ-5D-5 L scale.

2.8 Data collection

The data collection form comprised four distinct sections as shown in (Appendix A):

1. The initial section aimed to gather sociodemographic information, encompassing age, place of residence, height, weight for Body Mass Index (BMI) computation, marital status, employment status, educational level, and family monthly income.
2. The second section focused on patient clinical data, including the stage and type of breast cancer, disease duration, the types of treatment regimens administered, and the patient's medical history.
3. The third section incorporated the M. D. Anderson Symptom Inventory, a concise questionnaire featuring two subscales: the symptom severity scale and the symptom interference scale. The symptom severity scale comprised 13 core symptoms acknowledged as the most severe experienced by cancer patients. This scale utilized a range from 0 (absent) to 10 (as severe as imaginable), facilitating ease of comprehension and completion for the patients.

4. The Symptom Interference Scale comprises six items designed to assess an individual's perceived level of interference resulting from symptoms across various facets of daily life. These facets include general activity, mood, work (e.g., household tasks), interpersonal relations, mobility, and overall life enjoyment. Responses on this scale range from 0 (indicating no interference) to 10 (indicating complete interference).

The fourth section of this study will utilize the 5-level EQ-5D version (EQ-5D-5 L), developed by the EuroQol Group [94], to evaluate Quality of Life (QOL) [95, 96]. This instrument comprises two components: the descriptive system and the EQ visual analog scale (EQ-VAS). The descriptive system encompasses five dimensions, namely mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension comprises five levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. Participants are instructed to denote their health state by selecting the most appropriate statement within each of the five dimensions. The EQ-VAS gauges the patient's self-rated health using a vertical visual analog scale. The scale's endpoints are labeled 'The best health you can imagine' and 'The worst health you can imagine.' This visual analog scale serves as a quantitative measure of health outcomes, reflecting the patient's subjective judgment. The Arabic version of EQ-5D was approved for use via the online system of the EuroQol Research Foundation (ID: 60511) and has been comprehensively documented in earlier investigations led by the primary researcher in Palestine [97-105]. The computation of EQ-5D index scores followed established procedures outlined elsewhere [106-110], employing the EQ-5D-5L Crosswalk Index Value Calculator [111], which is based on the scoring algorithm derived from the general population of the United Kingdom.

2.9 Statistical analysis

The data underwent entry and analysis utilizing the Statistical Package for Social Sciences program (IBM-SPSS) version 21. Continuous variables are presented as means ± standard deviations, while categorical variables are expressed as frequencies and percentages. Non-normally distributed variables are conveyed as medians with lower and upper quartiles indicated. The normality of variables was assessed through the Kolmogorov–Smirnov test. To examine differences in means across categories, the Kruskal–Wallis test or Mann–Whitney test was employed. The relationship between

variables was assessed using Pearson and Spearman correlation coefficients. Statistical significance was established at a p-value below 0.05.

2.10 Ethical approval

All facets of the research protocol, encompassing the retrieval and utilization of clinical information pertaining to patients, received approval from both the Institutional Review Boards (IRB) and local health authorities.

2.11 Confidentiality

We confirm that the collected data and information in this study will be used for clinical research only. Information will be confidential and will not be used for any purpose other than that of this study.

Chapter Three

Results

3.1 Sociodemographic and clinical characteristics

A total of 229 Palestinian women with breast cancer were interviewed. The majority of patients 78 (34.1%) aged between 50-59 years old, 124(54.1%) patients lived in villages and 96(41.9%) and 9(3.9%) lived in city and refugees campaign, respectively, majority of patients 178 (77.7%) were married, 27(11.8%), 21(9.2%) and 3(1.3%) were single, widowed and divorced, respectively, according to level of education most of the participants 99 (43.2%) completed the secondary level of education, 48(21%), 44(19.2%), 25(10.9) and 12(5.2%), completed the elementary, bachelor's degree, and diploma, respectively, 12(5.2%) were uneducated and 1(0.4%) was post graduate, majority of patients 203(88.6%) were housewives, 15(6.6%) were private employee and only 11(4.8%) were governmental employee, the majority of patients 118 (51.5%) lived in families with moderate outcome, 88(38.4%) and 23(10%) lived in families with low and high outcome, respectively, more than half of participants were not smoker 196(85.6%), and 33(14.4%) were smoker, majority of participants were 96(41.9%) were overweight, 81(35.4%), 51(22.3%) and 1(0.4%) were obese, normal weight and underweight, respectively. Patient demographic characteristics are listed in Table 1.

According to the clinical characteristics of the study participants, more than half of the participants (124, 54.1%) had no diseases. Hypertension was the most common chronic disease seen among the participants (29, 12.7%), followed by diabetes mellitus (20, 8.7%). The most common two or more chronic diseases were diabetes mellitus and hypertension (19, 8.3%), followed by diabetes mellitus, dyslipidemia and hypertension (14, 6.1%). Chronic diseases among participants of the study are shown in Figure F1 in appendix F.

Data about the type of breast cancer were missing for 103 (45%) of the participants, and the majority of participants with available data had invasive ductal carcinoma (IDC) (105, 45.9%). Additionally, the study missed more than 50% of the data regarding the stage of breast cancer among the participants. According to the available data, the majority of participants had stage 4 disease (metastatic breast cancer). Types and stages of breast cancer among participants are shown in Table E1 in appendix E.

Table 1

Patient Demographic Characteristics

Characteristic	N (229) Frequency (%)
Age category	
<40	23 (10)
40-49	61 (26.6)
50-59	78 (34.1)
=>60	67 (29.3)
Residence	
city	96 (41.9)
village	124 (54.1)
refugee's campaign	9 (3.9)
Marital status	
Single	27 (11.8)
Married	178 (77.7)
Divorced	3 (1.3)
Widowed	21 (9.2)
Education level	
Uneducated	12 (5.2)
Elementary	48 (21)
Secondary	99 (43.2)
Diploma	25 (10.9)
Bachelor's degree	44 (19.2)
Post graduate	1 (0.4)
Employment status	
Private employee	15 (6.6)
Government employee	11 (4.8)
Housewife	203 (88.6)
Monthly income	
Low (less than 500 JD)	88 (38.4)
Moderate (500 JD–1000 JD)	118 (51.5)
High (more than 1000 JD)	23 (10)
Smoking	
non smoker	196 (85.6)
smoker	33 (14.4)
*BMI	
Underweight (< 18.5)	1 (0.4)
Normal weight (18.5–24.9)	51 (22.3)
Overweight (25–29.9)	96 (41.9)
Obese (> 30)	81 (35.4)

*****BMI - Body mass index

Regarding breast cancer treatment type, 81 (35.4%) were treated with one or more chemotherapy agents, 110 (48%) were treated with hormonal therapy, 22 (9.6%) were treated with targeted therapy, the rest of the participants were treated with combination agents, 9 (3.9%) were treated with hormonal therapy plus targeted therapy, and 7 (3.1%) were treated with chemotherapy plus targeted therapy, as shown in Figure 1.

Cyclophosphamide plus doxorubicin (AC) 51 (62.9%) and AC followed by Taxol, either paclitaxel 20 (24.7%) or docetaxel 2 (2.5%), were the most commonly used chemotherapies; 2 (2.5%) used carboplatin plus gemcitabine, and 6 (7.4%) used gemcitabine only, as shown in Figure 2.

Letrozole was the most commonly used hormonal therapy among patients (55, 50%), followed by selective estrogen receptor modulator (SERM) tamoxifen (24, 21.8%), anastrozole (14, 12.7%), and exemestane (17, 15.5%), as shown in Figure 3.

Trastuzumab 20 (90.9%) was the most common targeted therapy used, and 2 (9.1%) patients used a combination of trastuzumab and dertuzumab, as shown in figure 4. Trastuzumab and dertuzumab are a new and expensive drugs, according to that it is preserved for a certain cases that seriously need their addition.

Regarding targeted therapy plus hormonal therapy, 7 (3.1%) used trastuzumab plus tamoxifen, and 2 (0.9%) used trastuzumab plus AIs. Regarding targeted therapy plus chemotherapy, trastuzumab in combination with paclitaxel was used in 7 (3.1%) patients, as shown in Figure 5.

Figure 1

Treatment methods

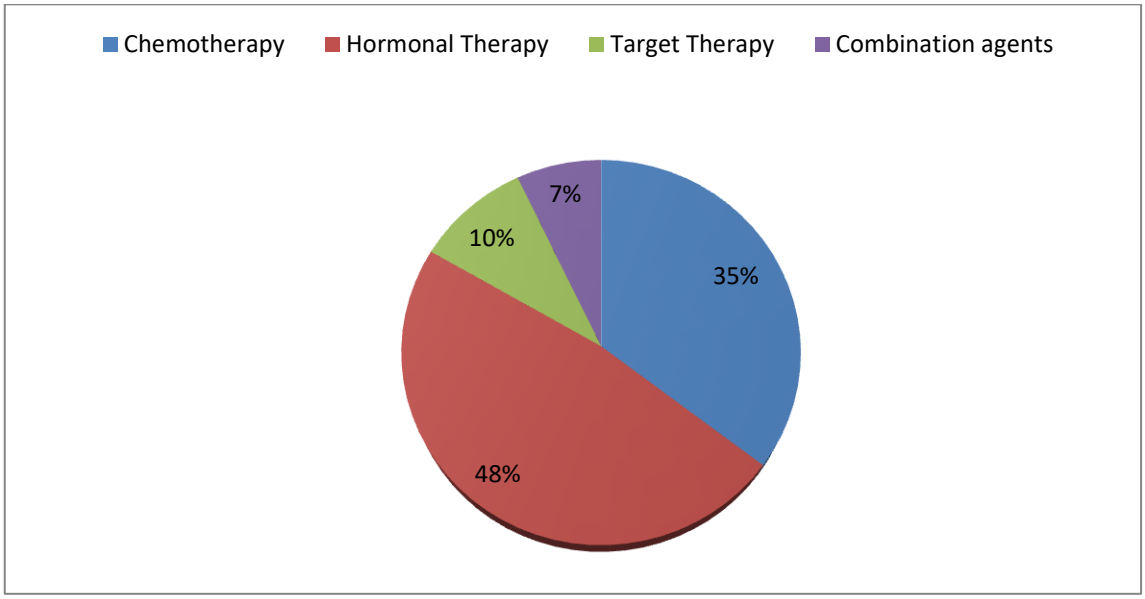


Figure 2

Types of chemotherapy among participants

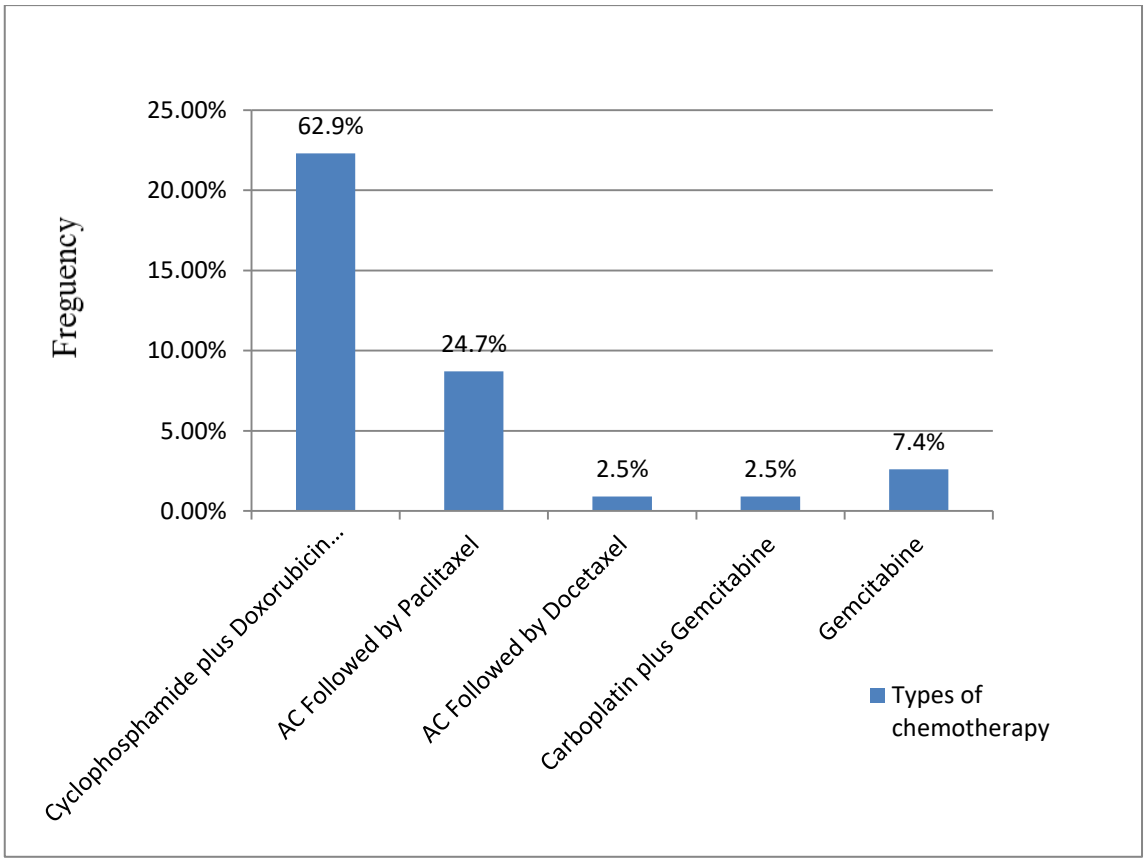


Figure 3

Types of hormonal therapy among participants

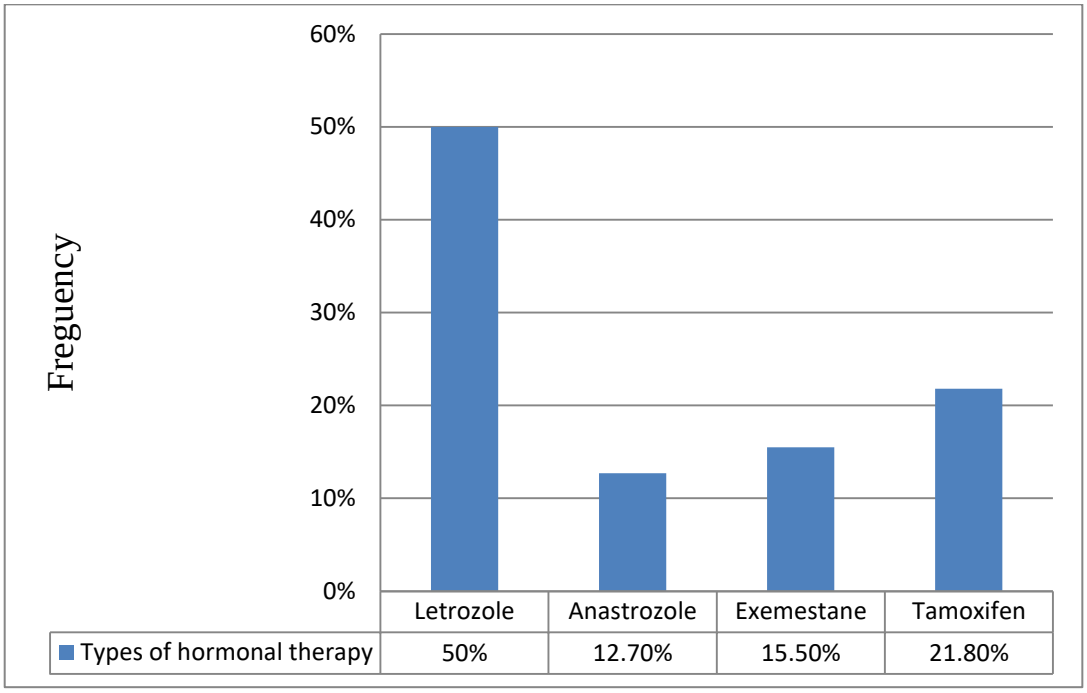


Figure 4

Types of targeted therapy among participants

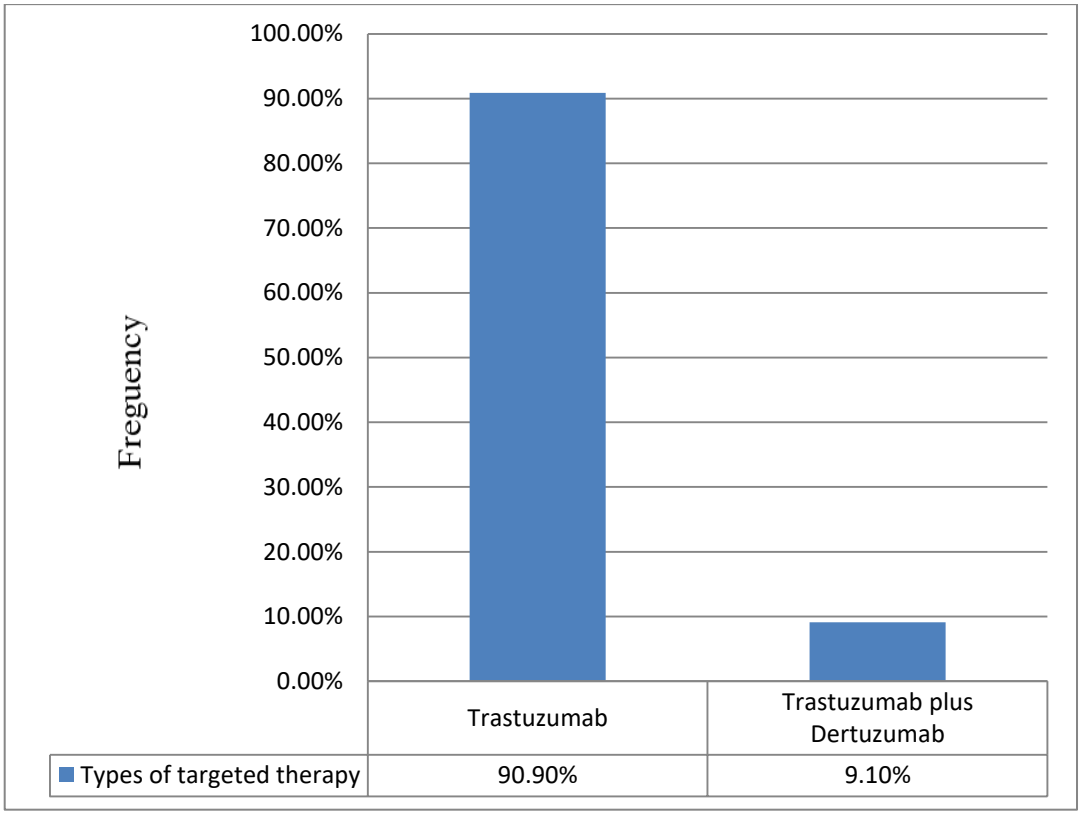
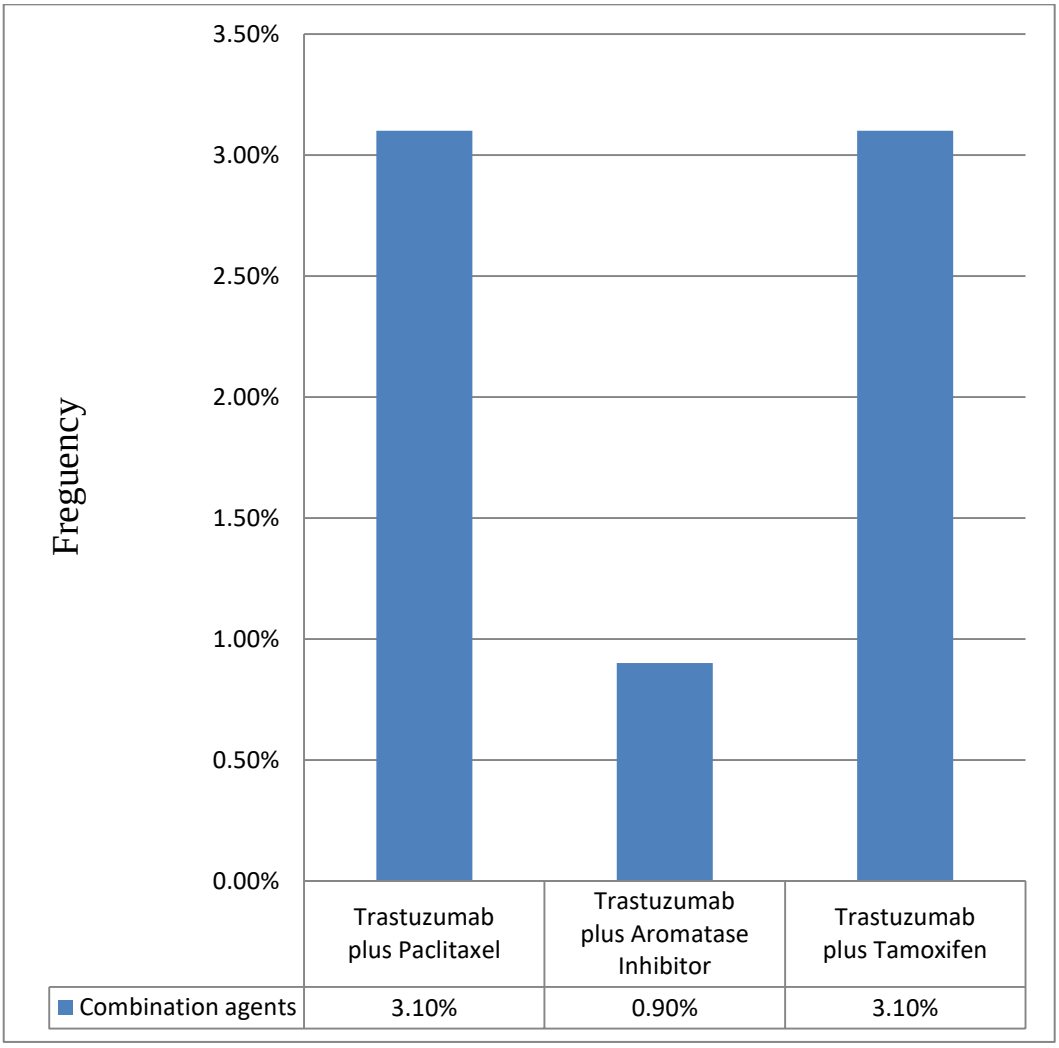


Figure 5

Combination agents among participants



3.2 Symptom severity and symptom interference among Palestinian women

The reliability of the symptom severity and symptom interference scales was assessed, in which Cronbach's alpha was 0.919 and 0.992 for the symptom severity scale and for the symptom interference scale, respectively.

The most frequent symptoms were fatigue ($\bar{x}$ =7.275), dry mouth ($\bar{x}$ =6.6) and sleep disturbances ($\bar{x}$ =5.45), followed by distress ($\bar{x}$ =4.85) and sadness ($\bar{x}$ =4.7125) in women receiving chemotherapy. According to the MDASI interference scale, the highest mean scores of symptom interference items were mood ($\bar{x}$ =6.1875) and work ($\bar{x}$ =5.6125). (Table 2)

Table 2

Reported symptom severity and symptom interference scores for Palestinian women receiving chemotherapy

	Symptom score	
*MDASI Severity Scale	Mean($\bar{x}$)	S.D
Fatigue	7.275	3.15416
Dry mouth	6.6	3.83719
Sleep disturbance	5.45	3.69707
Distress	4.85	3.82232
Sadness	4.7125	3.74569
Pain	4.5375	4.23351
Nausea	4.55	4.05313
Loss of appetite	4.5	3.98415
Drowsiness	3.8375	3.54159
Numbness	3.075	3.45962
Difficulty remembering	2.6125	3.54891
Vomiting	1.7625	3.2423
Shortness of breath	1.2625	2.62772
*MDASI Interference Scale		
Mood	6.1875	3.65989
Work (including housework)	5.6125	3.92168
General activity	5.4875	3.66990
Walking	4.15	3.95257
Enjoyment of life	3.0375	3.15604
Relations with others	2.5125	3.34132

*MDASI – M.D. Anderson Symptom Inventory.
Note. Higher mean scores indicate greater symptom severity and interference.

For women who were receiving hormonal therapy and targeted therapy, fatigue, pain and dry mouth were the most frequent symptoms, followed by sleep disturbances and numbness, and the highest mean scores of the symptom interference items were general activity ($\bar{x}$ =1.3364) and mood ($\bar{x}$ =1.2818) for hormonal therapy and general activity ($\bar{x}$ =2.619) and walking ($\bar{x}$ =2.4762) for targeted therapy (Table 3 and Table 4).

Table 3

Reported symptom severity and symptom interference scores for Palestinian women receiving hormonal therapy

	Symptom score	
MDASI Severity Scale	Mean($\bar{x}$)	S.D
Fatigue	2.1636	3.3167
Pain	1.9636	2.95199
Dry mouth	1.2909	2.80021
Sleep disturbance	1.2636	2.87564
Numbness	1.0000	2.38112
Sadness	0.9636	2.46416
Distress	0.9273	2.34505
Difficulty remembering	0.8909	2.38245
Drowsiness	0.88182	2.2857
Loss of appetite	0.7636	2.27442
Nausea	0.6636	2.06445
Shortness of breath	0.5091	1.57821
Vomiting	0.3091	1.64649
MDASI Interference Scale		
General activity	1.3364	2.72022
Mood	1.2818	2.80606
Work (including housework)	1.2273	2.62891
Walking	1.0091	2.50685
Enjoyment of life	0.5364	1.54253
Relations with others	0.4818	1.62397

*MDASI – M.D. Anderson Symptom Inventory
Note. Higher mean scores indicate greater symptom severity and interference.

The most frequent symptom severities associated with hormonal plus targeted therapy were sleep disturbances ($\bar{x}$ =5.7), fatigue($\bar{x}$ =5. 5) and pain($\bar{x}$ =5.0), as shown in Table 5, whereas the most frequent symptoms with chemotherapy plus targeted therapy were fatigue ($\bar{x}$ =6.375), dry mouth ($\bar{x}$ =6.625) and sleep disturbances ($\bar{x}$ =5.625), as shown in Table 7. The highest mean scores of symptom interference items for hormonal plus targeted therapy were mood ($\bar{x}$ =5.4) and walking ($\bar{x}$ =4.2) (Table 5), whereas the highest mean scores of symptom interference items for chemotherapy plus targeted therapy were general activity ($\bar{x}$ =6.375) and mood ($\bar{x}$ =5.75) (Table 6).

Table 4

Reported symptom severity and symptom interference scores for Palestinian women receiving targeted therapy

	Symptom score	
*MDASI Severity Scale	Mean($\bar{x}$)	S.D
Fatigue	3.1429	3.87667
Pain	2.8571	3.87667
Dry mouth	2.8095	4.26168
Sleep disturbance	2.4762	3.7097
Numbness	1.9048	3.03158
Distress	1.8571	3.51121
Nausea	1.7619	3.34522
Sadness	1.7143	3.30368
Difficulty remembering	1.5714	2.74903
Drowsiness	1.5714	2.99285
Shortness of breath	1.3333	2.81662
Loss of appetite	0.6667	2.19848
Vomiting	0.4762	1.40068
*MDASI Interference Scale		
General activity	2.619	3.52812
Walking	2.4762	3.85511
Work (including housework)	2.4286	3.51527
Mood	2.3333	3.71932
Enjoyment of life	1.5238	3.09223
Relations with others	1.381	2.81915

*MDASI – M.D. Anderson Symptom Inventory
Note. Higher mean scores indicate greater symptom severity and interference.

Table 5

Reported symptom severity and symptom interference scores for Palestinian women receiving hormonal therapy plus targeted therapy

	Symptom score	
*MDASI Severity Scale	Mean($\bar{x}$)	S.D
Sleep disturbance	5.7	3.83116
Fatigue	5.5	3.97911
Pain	5.0	3.23179
Distress	4.1	4.53260
Numbness	4	3.49603
Difficulty remembering	3.4	4.11501
Sadness	3.2	4.02216
Dry mouth	3.0	3.52767
Nausea	2.5	4.14327
Loss of appetite	2.0	3.29983
Shortness of breath	1.7	2.75076
Vomiting	1.7	3.653
Drowsiness	1.0	1.49071
*MDASI Interference Scale		
Mood	5.4	4.32563
Walking	4.2	3.58391
Work (including housework)	4.1	3.755
General activity	4	3.49603
Enjoyment of life	3.1	3.69534
Relations with others	2.7	3.653

*MDASI – M.D. Anderson Symptom Inventory
Note. Higher mean scores indicate greater symptom severity and interference.

The relation between the severity scale and interference scale was strong and significant for chemotherapy ($r = 0.685$, $p < 0.05$), hormonal therapy ($r = 0.827$, $P < 0.05$), targeted therapy ($r = 0.922$, $P < 0.05$) and hormonal plus targeted therapy ($r = 0.699$, $P < 0.05$).

Among the 13 symptom severity items, sadness and distress ($r = 0.752$, $P < 0.05$) followed by pain and fatigue ($r = 0.605$,$P < 0.05$) were the strongest bivariate relationships among individual symptoms receiving chemotherapy. Bivariate correlations between symptom severity and total symptom interference score for Palestinian women receiving chemotherapy are shown in Table 7.

Table 6

Reported symptom severity scores for Palestinian women receiving chemotherapy plus targeted therapy

	Symptom score	
*MDASI Severity Scale	Mean($\bar{x}$)	S.D
Fatigue	6.375	3.06769
Dry mouth	6.625	4.20671
Sleep disturbance	5.625	3.88909
Sadness	4.875	2.79987
Distress	4.875	2.90012
Pain	4.625	3.5431
Drowsiness	3.875	3.4821
Loss of appetite	3.375	3.15945
Shortness of breath	3.125	3.4821
Difficulty remembering	2.75	3.24037
Numbness	1.625	2.72226
Nausea	1.375	2.66927
Vomiting	0.5	1.41421
*MDASI Interference Scale		
General activity	6.375	2.50357
Mood	5.75	3.28416
Work (including housework)	5.375	3.37797
Relations with others	4.375	3.5431
Walking	4.125	2.47487
Enjoyment of life	3.375	2.66927

*MDASI – M.D. Anderson Symptom Inventory
Note. Higher mean scores indicate greater symptom severity and interference.

Table 7

Bivariate correlations between symptom severity and total symptom interference score for Palestinian women receiving chemotherapy

Variable	Pearson (r)	P value
Sadness	0.675	0.000
Distress	0.584	0.000
Fatigue	0.524	0.000
Dry mouth	0.446	0.000
Sleep disturbance	0.443	0.000
Pain	0.386	0.000
Difficulty remembering	0.349	0.002
Nausea	0.333	0.003
Drowsiness	0.322	0.004
Shortness of breath	0.275	0.014
Numbness	0.246	0.028
Loss of appetite	0.239	0.033
Vomiting	0.045	0.691

P value < 0.05; the correlation is significant, Pearson correlation coefficient (r); between 0 and 1 indicate positive correlation, 0 indicate no correlation, between 0 and -1 indicate negative correlation.

In the context of individuals undergoing hormonal therapy, modest bivariate correlation were observed between pain and fatigue ($r = 0.863$, $p < 0.05$), as well as difficult remembering and drowsing ($r = 0.8000$, $p < 0.05$). These findings signify the pronounced associations between these specific symptoms. The comprehensive details of bivariate correlations, specifically examining the relationships between symptom severity and the overall symptom interference score, are presented in Table 8 for Palestinian women undergoing hormonal therapy.

Similarly, within the cohort receiving targeted therapy, noteworthy bivariate correlation were identified, with pain and fatigue ($r = 0.963$, $p < 0.05$) and pain and sleep disturbances ($r = 0.871$, $p < 0.05$) emerging as the most prominent associations among individual symptoms. The corresponding bivariate correlations between symptom severity and the total symptom interference score for Palestinian women undergoing targeted treatment are provided in Table 9 for further elucidation.

Table 8

Bivariate correlations between symptom severity and total symptom interference score for Palestinian women receiving hormonal therapy

Variable	Pearson (r)	P value
Sadness	0.802	0.000
Fatigue	0.736	0.000
Distress	0.675	0.000
Difficulty remembering	0.625	0.000
Sleep disturbance	0.622	0.000
Dry mouth	0.614	0.000
Pain	0.612	0.000
Loss of appetite	0.604	0.000
Shortness of breath	0.594	0.000
Drowsiness	0.593	0.000
Nausea	0.479	0.000
Numbness	0.470	0.000
Vomiting	0.400	0.000

P value < 0.05; the correlation is significant, Pearson correlation coefficient (r); between 0 and 1 indicate positive correlation, 0 indicate no correlation, between 0 and -1 indicate negative correlation.

Table 9

Bivariate correlations between symptom severity and total symptom interference score for Palestinian women receiving targeted therapy

Variable	Pearson (r)	P value
Pain	0.926	0.000
Nausea	0.897	0.000
Fatigue	0.892	0.000
Shortness of breath	0.866	0.000
Drowsiness	0.826	0.000
Distress	0.803	0.000
Sleep disturbance	0.796	0.000
Numbness	0.772	0.000
Dry mouth	0.749	0.000
Sadness	0.725	0.000
Vomiting	0.685	0.001
Difficulty remembering	0.612	0.003
Loss of appetite	0.548	0.01

P value < 0.05; the correlation is significant, Pearson correlation coefficient (r); between 0 and 1 indicate positive correlation, 0 indicate no correlation, between 0 and -1 indicate negative correlation.

Numbness and distress ($r = 0.926$, $p < 0.05$) followed by pain and fatigue ($r = 0.838$, $p < 0.05$) were the strongest bivariate relationships among individual symptoms receiving hormonal plus targeted therapy. Bivariate correlations between symptom severity and total symptom interference score for Palestinian women receiving hormonal plus targeted therapy are shown in Table 10.

Table 10

Bivariate correlations between symptom severity and total symptom interference score for Palestinian women receiving targeted therapy plus hormonal therapy

Variable	Pearson (r)	P value
Fatigue	0.755	0.012
Shortness of breath	0.730	0.017
Pain	0.683	0.029
Sadness	0.630	0.051
Sleep disturbance	0.612	0.06
Distress	0.592	0.071
Numbness	0.539	0.108
Nausea	0.538	0.109
Vomiting	0.464	0.177
Loss of appetite	0.213	0.554
Difficulty remembering	0.202	0.576
Dry mouth	0.107	0.768
Drowsiness	-0.250	0.487

P value < 0.05; the correlation is significant, Pearson correlation coefficient (r); between 0 and 1 indicate positive correlation, 0 indicate no correlation, between 0 and -1 indicate negative correlation.

A strong negative bivariate correlation ($r = -0.923$, $p < 0.05$) was observed between dry mouth and shortness of breath, and a strong positive ($r = 0.874$, $p < 0.05$) correlation was observed between dry mouth and distress among individual symptoms receiving chemotherapy plus targeted therapy.

The strongest relationships were seen between the total mean score of the interference scale and sadness ($r = 0.675$, $p < 0.05$), distress ($r = 0.584$, $p < 0.05$) and fatigue ($r = 0.524$, $p < 0.05$) for chemotherapy (Table 7); sadness ($r = 0.802$, $p < 0.05$), fatigue ($r = 0.736$, $p < 0.05$) and distress ($r = 0.675$, $p < 0.05$) for hormonal therapy (Table 8); pain ($r = 0.926$, $p < 0.05$), nausea ($r = 0.897$, $p < 0.05$) and fatigue ($r = 0.892$, $p < 0.05$) for targeted therapy (Table 9); and fatigue ($r = 0.755$, $p < 0.05$), shortness of breath ($r = 0.730$, $p < 0.05$), and pain ($r = 0.683$, $p < 0.05$) for targeted plus hormonal therapy (Table 10).

No significant relation was found between the total mean score of the symptom severity scale and the total mean score of the symptom interference scale for chemotherapy plus targeted therapy ($r=0.398$, $p=0.329$).

In general, a strong bivariate correlation was observed between the total mean score of symptom interference and sadness (r=0.792, P< 0. 05), followed by fatigue (r=0.774, P< 0. 05), and distress (r=0.743< P< 0. 05). Sadness had a strong bivariate correlation with mood (r=0.812) and enjoyment of life (r=0.690, P< 0. 05), and fatigue had a strong bivariate correlation with general activity (r=0.791, P< 0.05) and work (r=0.761, P< 0. 05), and distress had a strong bivariate correlation with mood(r=0.805, P< 0.05) and general activity (r=0.653, P< 0.05).

The strongest relation was seen between the total mean score of symptom interference and sadness, fatigue and distress among symptom severity items. These items had the highest bivariate correlation coefficient among women receiving chemotherapy and hormonal therapy, in which more than half of women (191, 83.4%)were treated with either chemotherapy (81, 35.4%) or hormonal therapy (110, 48%) in the study.

3.3 Symptom severity relation to sociodemographic and clinical characteristics

As shown in Table E2 in appendix E, there were significant differences between study participants in relation to patient age, smoking status and treatment methods (p value<0.05).

Women aged 60 and older, nonsmoker women, had a lower symptom severity score. Related to the treatment methods, a higher score on the MDASI scale indicated higher symptom severity. Patients who received chemotherapy, chemotherapy plus targeted therapy, and hormonal plus targeted therapy had the highest symptom severity scores compared with those who received targeted therapy or hormonal therapy. (Table E2)

The number of women who received chemotherapy plus targeted therapy (n = 7) and hormonal therapy plus targeted therapy (n = 9) was small, so the results need to be treated with caution.

Other sociodemographic and clinical characteristics, such as BMI, education level, residency, marital status, employment status, monthly income, and presence of comorbid disease, were not significantly associated with the total mean score of symptom severity (P < 0.05).

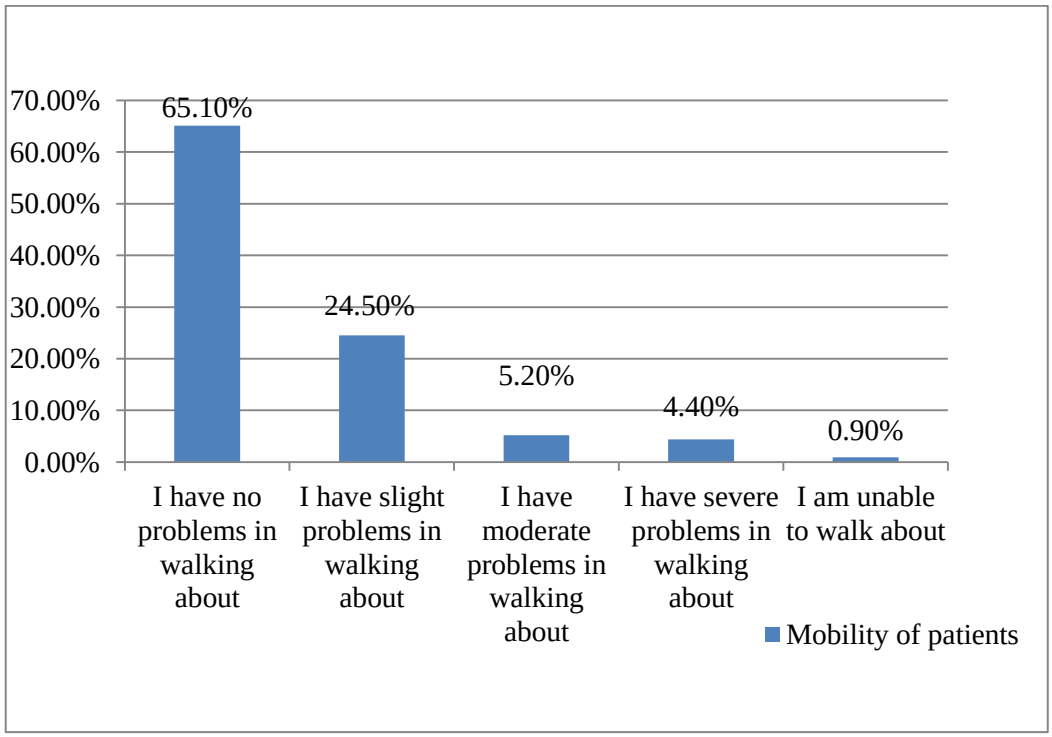
3.4 Quality of life, EQ-5D-5 L index score and EQ-VAS score

Quality of life was evaluated using the EQ-5D-5L scale, and internal consistency was satisfactory, with a Cronbach's alpha of 0.827 for the EQ-5D-5L scale.

According to the mobility dimension question in the EQ-5D-5L questionnaire, more than half of the patients (149, 65.1%) had no problems walking, while the remaining 56 (24.5%), 12 (5.2%) and 10 (4.4%) had slight, moderate and severe problems walking, respectively. Only two patients were unable to walk (Figure 6).

Figure 6

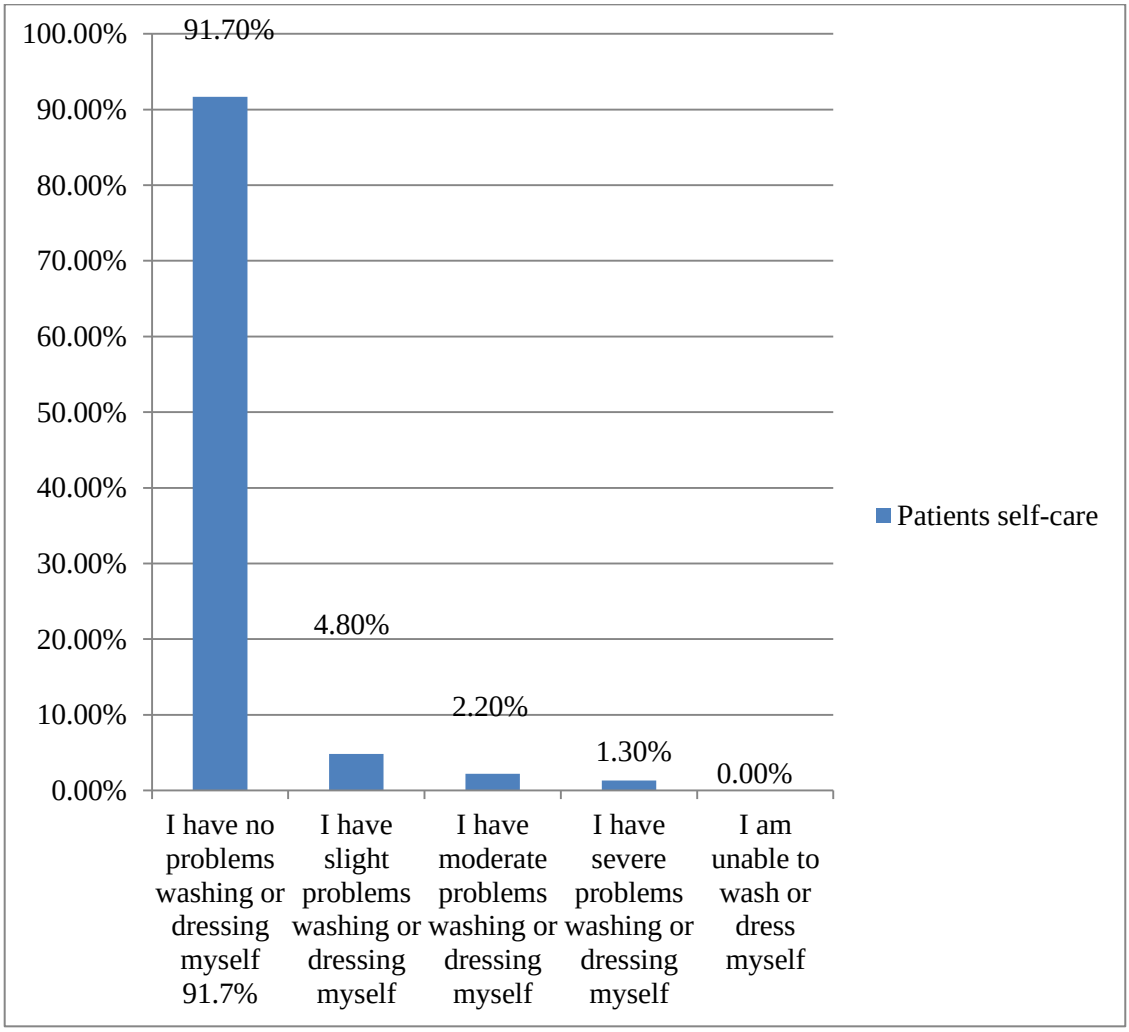
Patient mobility



According to the self-care dimension question in the EQ-5D-5L questionnaire, 210 (91.7%) had no problems washing or dressing themselves, the remaining 11 (4.8%), 5 (2.2%) and 3 (1.3%) had mild, moderate, and severe problems in washing or dressing, respectively, and none of the participants had problems in washing or dressing themselves (Figure 7).

Figure 7

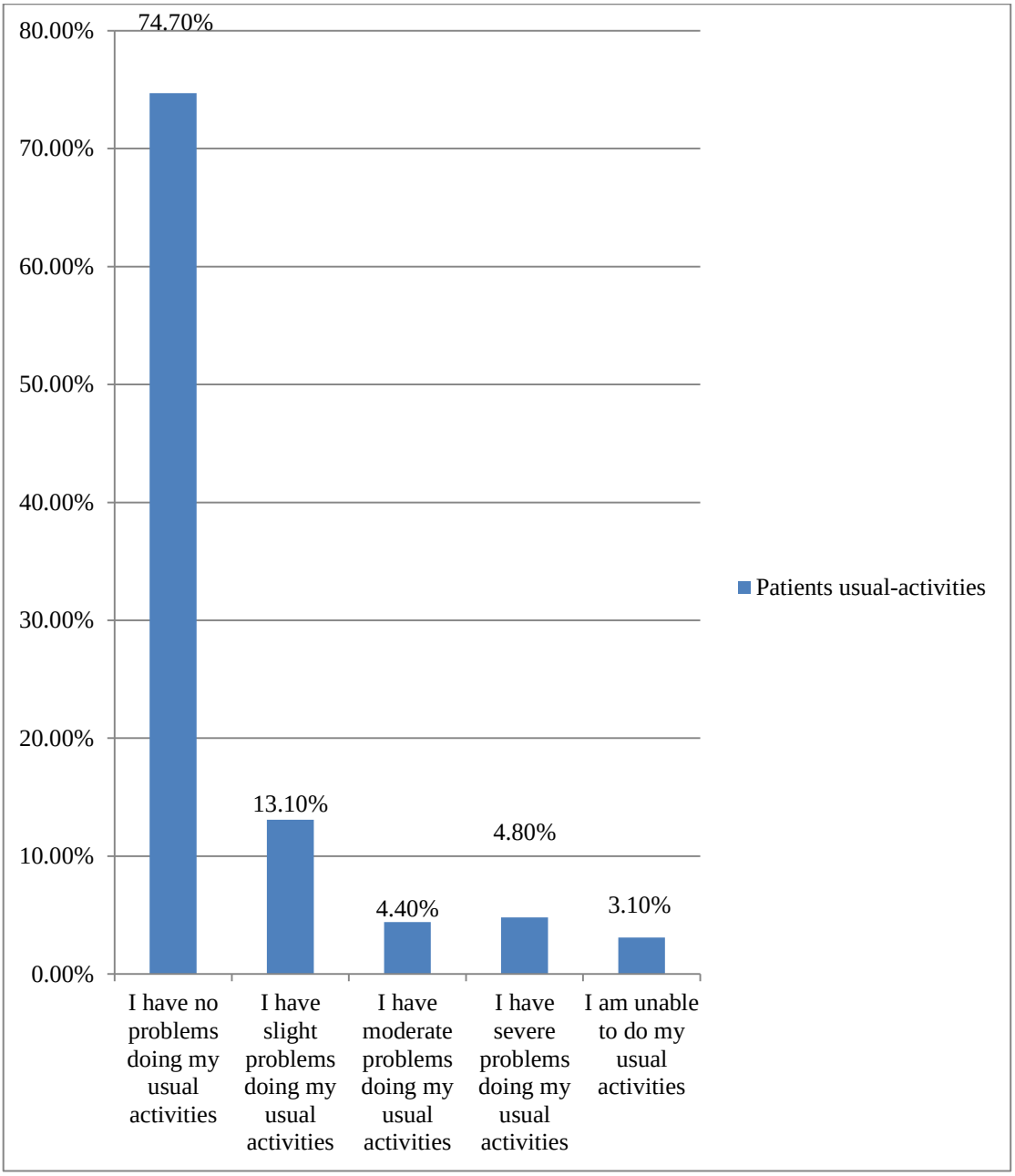
Patient self-care



According to the usual activities dimension question in the EQ-5D-5L questionnaire, more than half of the patients (171, 74.7%) had no problems doing their usual activities, 30 (13.1%) patients had mild problems doing their usual activities, 10 (4.4%) and 11 (4.8%) patients had moderate and severe problems, respectively, in performing their usual activities, and only 7 (3.1%) were unable to perform their usual activities (Figure 8).

Figure 8

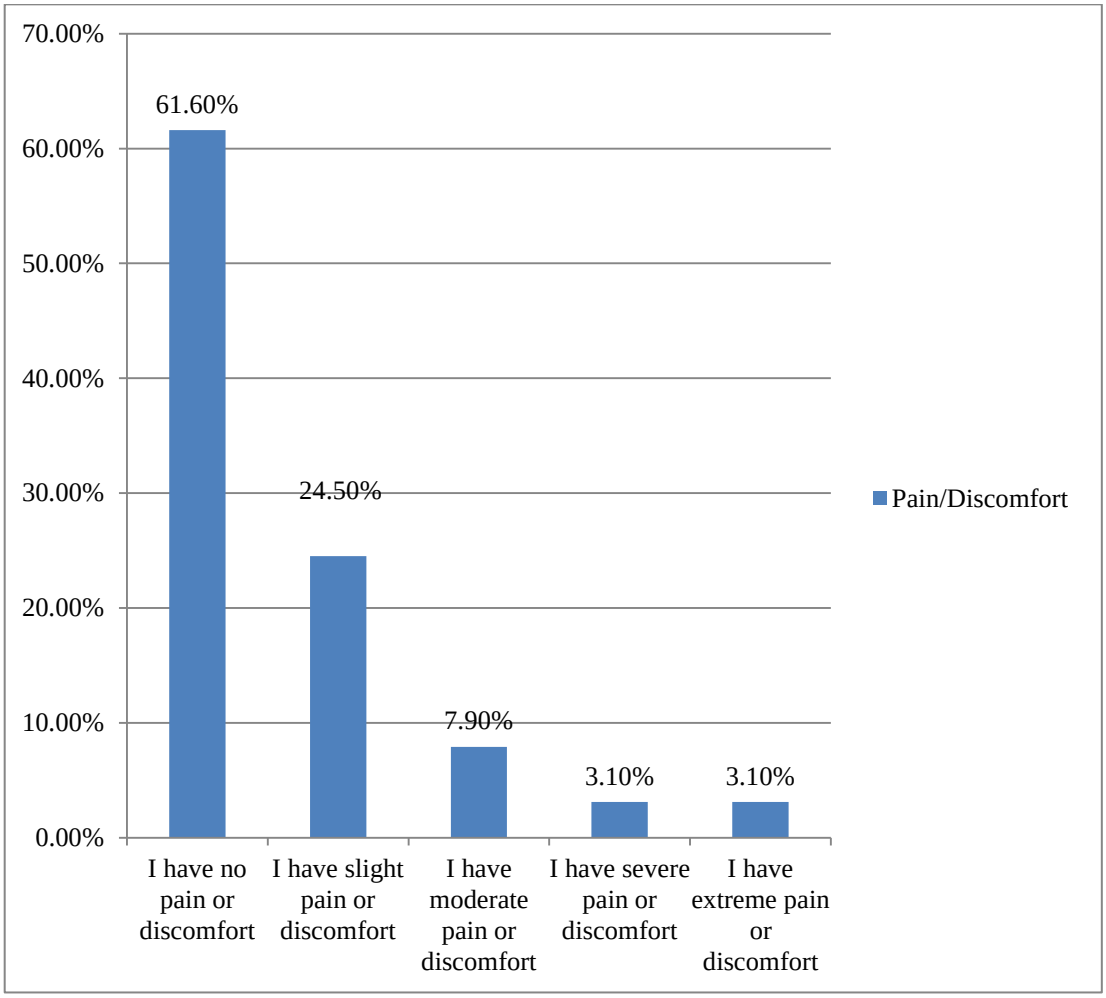
Usual patient activities



According to the pain/discomfort dimension question in the EQ-5D-5L questionnaire, most patients (141, 61.6%) had no pain or discomfort, 56 (24.5%) patients had mild pain or discomfort, 18 (7.9%) and 7 (3.1%) patients had moderate and severe pain or discomfort, respectively, and 7 (3.1%) patients had extreme pain or discomfort (Figure 9).

Figure 9

Pain/Discomfort

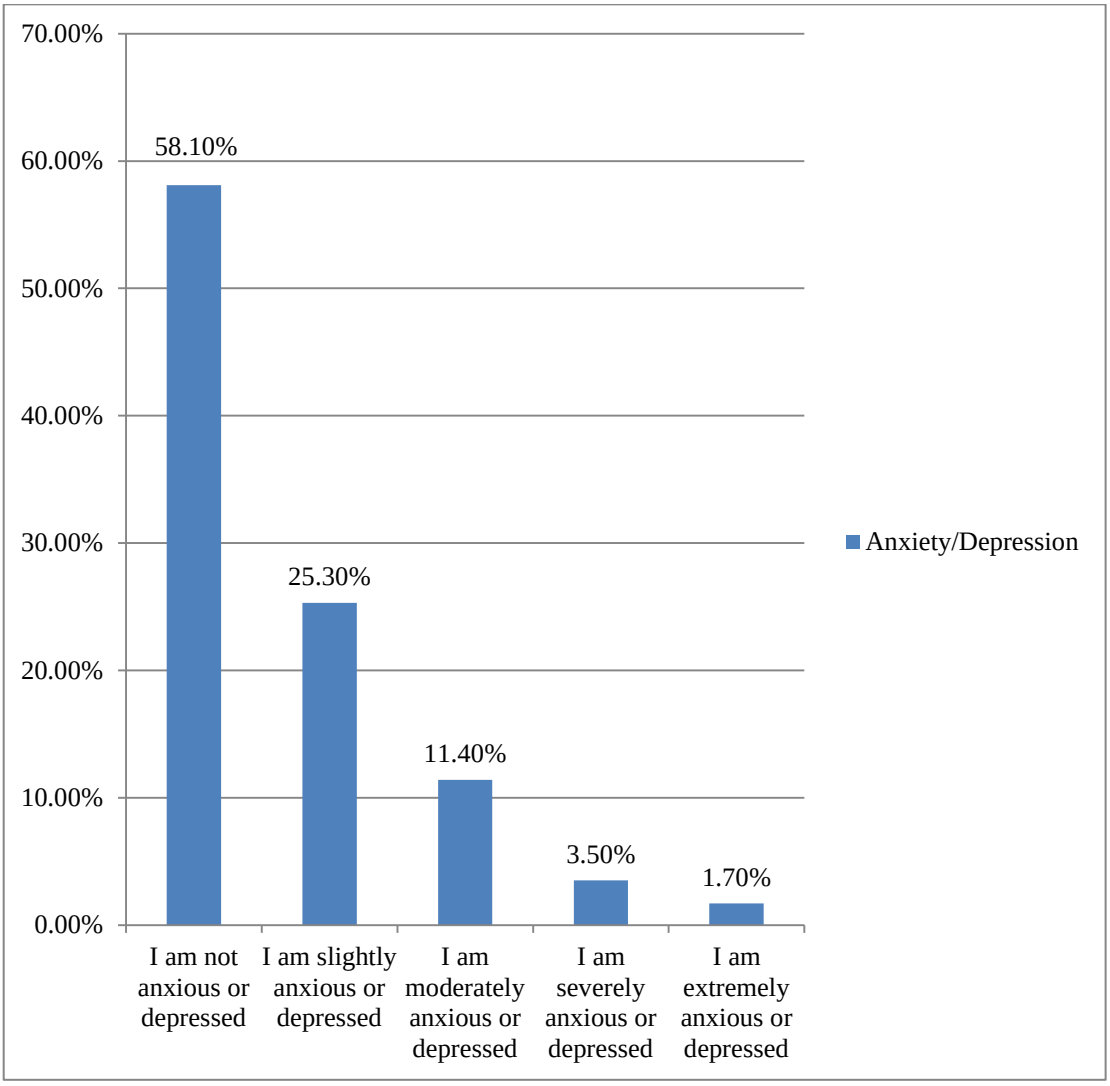


According to the anxiety/depression dimension question in the EQ-5D-5 L scale, the majority of patients (133, 58.1%) were not anxious or depressed, while 58 (25.3%), 26 (11.4%) and 8 (3.5%) of the patients were slightly, moderately and severely anxious or depressed, respectively, and only 4 (1.7%) patients were extremely anxious or depressed. (Figure 10)

The median EQ-5D-5L index score was 0.8760 (IQR: 0.7900 – 1.000), and the median EQ-VAS score was 70 (IQR: 60.00 – 85.00). The study showed that the EQ-5D-5L index score had a strong significant correlation with the EQ-VAS score ($r = 0.568$, P value < 0.05), and the EQ-5D-5L index score had a significant negative correlation with the total mean score of symptom severity ($r = -0.664$, P value < 0.05). Additionally, the study showed that the EQ-5D-5L index score had a significant negative correlation with the symptom interference total mean score ($r = -0.651$, P value < 0.05).

Figure 10

Anxiety/Depression



The study found that there were no significant differences between sociodemographic or clinical characteristics regarding the EQ-5D-5L index score except for treatment methods and emolument status (P<0.05), in which private employee and hormonal treatment were both associated with the highest EQ-5D-5L index score. Additionally, there were no significant differences between sociodemographic or clinical characteristics regarding the EQ-VAS score except for smoking, comorbid disease and treatment method (P> 0.05), in which women who were nonsmokers, without comorbid disease, and who received hormonal or biological therapy had higher EQ-VAS scores. (Table E3 and Table E4) in appendix E.

The EQ-5D-5L index score showed a significant negative bivariate correlation with the symptom severity score for hormonal therapy ($r = -0.375$, P value < 0.05) and targeted therapy ($r = -0.774$, P value < 0.05). The correlation was not significant for chemotherapy ($r = -0.103$, P value $=0.365$), hormonal therapy plus targeted therapy ($r = 0.103$, P value $=0.792$), or chemotherapy plus targeted therapy ($r = 0.335$, P value $= 0.462$).

Chapter Four

Discussion

4.1 Discussion

The study was conducted among Palestinian women with a confirmed diagnosis of breast cancer at Palestine, West Bank, Nablus, to evaluate the relationship between the severity of symptoms, symptoms interference, quality of life and type of treatment.

The MDASI questionnaire was used, and the questionnaire showed advantages for clinical use and was assessed and used by many studies [112]. The MDASI consists of two subscales, a symptom severity scale and a symptom interference scale, to evaluate the severity and interference of symptoms among women with breast cancer.

The study results show that fatigue was the most frequent and severe symptom for all regimens of breast cancer therapy except for hormonal therapy plus targeted therapy, in which sleep disturbances were the most prevalent symptom followed by fatigue. This result corresponds with other studies assessing symptom severity and symptom interference among women with breast cancer [66, 68, 74, 113].

Sleep disturbances were reported by Berger et al. as the most common symptom among breast cancer survivors who completed treatments [72]. Berger et al.*'s* study corresponded with a study performed in Taiwan in which sleep disturbances had a significantly higher level of severity than other symptoms, in which the Taiwan study showed that there were no differences between healthy individuals and breast cancer survivors in symptom severity and symptom interference except for sleep disturbances; breast cancer survivors had a higher rate of adaptation and tolerance than breast cancer patients who were still receiving breast cancer treatments [73].

Baron et al. found that fatigue persists after completion of treatment and interferes with patients' life domains [114]. Additionally, Bower et al. found that fatigue was also significantly associated with higher levels of other symptoms, such as sleep disturbances, pain and depression [115].

A significant relationship between symptom severity and their interference with patients' daily life activities was assessed and identified, particularly for chemotherapy

regimens. This study found that the strongest relationship was seen between the total mean score of the symptom inference scale and sadness (r=0.792, P < 0.05), fatigue (r=0.774, P < 0.05) and distress (r=0.743, P < 0.05) among breast cancer women who received chemotherapy regimen. This finding is corresponded with another study using the same data collection instrument, the MDASI scale, published in 2010 and performed on women with breast cancer treated only with chemotherapy [66], in which the strongest relationships were observed between symptom interference and fatigue (r = 0.76, p < 0.05), followed by distress (r = 0.59, p < 0.05) and sadness (r = 0.54, p < 0.05), that is agreed with this study results, because distress and sadness were the symptoms with the strongest bivariate correlation (r=0.752, P< 0.05) among individuals who received chemotherapy regimen only.

Chemotherapy was evaluated in several studies in terms of symptom severity and the extent of their interference with the patient's life activities among cancer patients. Limited data are available about women who are receiving or had received hormonal, immunotherapy, targeted therapy, or combination treatments compared with studies performed on chemotherapy alone using MDASI scales because the MDASI scale is a specific symptom measurement tool for chemotherapy and is not specific for other therapies [77].

The available data show that women on hormonal therapy experience a low mean score of symptom severity and symptom interference, which corresponds with our results. Women with previous hormonal therapy also show a lower score of symptom severity than women who never received hormonal therapy [78]. Additionally, hormone-positive breast cancer is more prevalent than hormone-negative breast cancer and is associated with better prognosis and survival [79].

According to the MDASI scale, trastuzumab symptom severity overall mean scores were mild, in which fatigue, sleep disturbances, and numbness were the most severe symptoms reported, with a mild overall mean score for the symptom interference scale [81].

Targeted therapy and hormonal therapy are tolerated therapies and show a lower side effect profile and better quality of life than chemotherapy, which is associated with aggressive side effects and a higher rate of side effects [82, 83].

In this study, age and smoking status were sociodemographic factors that were significantly associated with the symptom severity score. According to clinical characteristics, treatment method was significantly associated with symptom severity score, in which chemotherapy was the most common treatment method associated with the symptom severity score.

Ina study conducted among women with breast cancer who were receiving hormonal therapy, age was not significantly associated with the overall mean score of the symptom severity scale, education was significantly associated with the overall mean score of symptom severity, and more highly educated women complained of less severe symptoms [69]. In another study conducted among women with breast cancer receiving chemotherapy, age was not significantly associated with the MDASI severity scale total mean score [66].

Many studies have been conducted to assess the implications of breast cancer and treatments between younger and older women. A negative impact was seen on younger women compared with older women because younger women experience more interference with daily life activities and fear of death, with little life experience adapting to new situations [116, 117]. Additionally, Nyrop et al. found that both older and younger women perceived symptom interference with activities of daily living to be less concerning than symptom severity [75].

The study also used the EQ-5D-5 L measurement scale to evaluate the quality of life of women with breast cancer, which consists of two parts: the EQ-5D-5 L descriptive system and the EQ visual analog scale (EQ-VAS).

The EQ-5D-5 L measurement scale has been used in different studies to evaluate breast cancer patients' quality of life in different countries [84, 86, 89, 118]. The EQ-5D-5 L measurement scale is an important and promising tool for evaluating quality of life among cancer patients [85].

The results of the current study show that among sociodemographic and clinical characteristics, employment status and treatment method were significantly associated with the EQ-5D-5 L index score. Employment status was significantly associated in other studies ($P < 0.05$) [119, 120], and among the clinical characteristics, comorbid

disease significantly adversely affected the EQ-5D-5 L index score (r = -0.145, P value < 0. 05) [89, 121].

Marital status was not significantly associated with quality of life domains. This finding is the same as that of a study conducted among Lebanese patients [122]. Also same result among participants of a study performed at University Kebangsaan Malaysia Medical Centre (UKMMC) [89], and corresponded with a study performed among the Vietnamese general population [123]. This findings was same because it was impressed to see single, divorced and widowed women obtain support, help and encouragement from their close family members or friends.

In this study, the median EQ-5D-5 L index score among women with breast cancer was 0.8320 (IQR: 0.7770-1.000). Compared to the study in India using the same instrument, the median was 0.8703 at the time of baseline, 0.8745 after completion of the treatment, and 0.8902 at the time of follow-up [86]. In our results, the median EQ-5D-5 L index score seemed to be lower because the patient was still receiving treatment.

The median EQ-5D-5 L index score in the Malaysian study was 0.78(IQR: 0.65-1.000), and the median EQ-VAS score was 80 (IQR: 70-90). The median was lower than that in our study because the Malaysian study also included women who had received radiotherapy and underwent surgery [89].

According to our study, the anxiety/depression domain was the most affected domain, followed by the pain/discomfort domain, which is the same finding as an Indian study, in which anxiety/depression followed by pain/discomfort was the most affected domain [86], compared with a study conducted in Malaysia, in which the pain/discomfort domain was the most affected domain among Malaysian participants [89], and the results of a Canadian study showing that pain/discomfort followed by anxiety/depression was the most affected domain [87].

Pain/discomfort was reported by women with advanced-stage breast cancer, in which pain adversely affected the patients' anxiety/discomfort domain as expected, and younger women were more anxious regarding disease status and treatment methods.

4.2 Clinical Future Implications of the Study

The performed study examining the correlation between symptom severity, symptom interference, quality of life, and treatment modality among Palestinian women diagnosed with breast cancer has significant future therapeutic implications. Significant insights are provided by the study's findings regarding the experiences of individuals diagnosed with breast cancer and the impacts of various treatment approaches on their symptoms and overall quality of life. The aforementioned implications have the potential to have a substantial impact on numerous facets of the medical field, including clinical practice, patient care, and future breast cancer research endeavors.

1. The study shows a significant variation in the severity of symptoms among patients and different impacts of various treatment methods on patients' daily life activities. Healthcare care professionals can utilize those findings to prepare treatment methods based on patients' personal preferences and achieve a higher efficacy with fewer side effects.In this way, the patients will be part of treatment method decision making, resulting in more adherences and more satisfaction with the treatment results, ultimately producing a better overall outcome.
2. Patients' participation in treatment methods decision-making was emphasized by the study, in which study results can be utilized by healthcare providers to discuss with patients and explain potential side effects, and how to manage bothersome symptoms, finally how those symptoms could affect their daily life activities. Patients with higher knowledge regarding their medical condition and treatment protocols showed greater levels of satisfaction regarding treatment methods and their outcomes.
3. Examination of the relationship between symptom severity and symptom interference is very important to ward patients in cantered care, in which health care providers must be in close contact with patients and do not underestimate their concerns and complaints. As a result, any side effects or complaints requiring supportive care should be addressed. Health care providers take responsibility for the ward enhancement of patient quality of care by placing a high priority on patient welfare and employing a holistic approach to managing their symptoms.
4. Patients’ expectations regarding symptom severity and symptom interference related to treatment methods can be clearly clarified by health care providers, in which different treatment methods are associated with varying levels of symptom severity

and symptom interference, which must be discussed and clarified before starting treatment, thus allowing health care providers to manage patients' expectations and provide accurate information regarding possible adverse effects, resulting in better adherence and satisfaction regarding treatment and treatment outcomes.

5. After discussing with the patient about the side effects that may occur, the study emphasizes the importance of following up and monitoring the side effects and the effectiveness of the treatment method. Regular follow-up meetings and continuous communication with patients can aid healthcare professionals in identifying and managing new symptoms, as appropriate adjustments to the treatment can be made through continuous follow-up.
6. The need for additional research was strongly emphasized by the study to reject or accept the results of recent studies. A variety of treatment methods still need further research to analyze the effectiveness and side effects that may affect individual life, and treatments that are designed to reduce patient side effects and complaints need further investigation. This research has the potential to enhance our understanding of the patient's perspective and provide valuable insights for the development of novel therapeutics.
7. The current study mainly focused on the impact of breast cancer on Palestinian women, even though its repercussions affect breast cancer patients worldwide. In terms of the severity of symptoms, their impact on daily functioning, and the overall quality of life, the study's findings highlight the difficulties commonly encountered by breast cancer patients. Consequently, healthcare practitioners and researchers in a variety of geographic regions can use the findings of this study to enhance patient care and advance their own research endeavors.

4.3 Strengths and limitations

4.3.1 Strengths

Based on our information, this study was the first to explore the relationship between symptom severity and symptom interference among women receiving different types of treatment (chemotherapy, hormonal therapy, and targeted) using MDASI scales and one of the first studies using EQ-5D-5 L and EQ-VAS scales to assess quality of life among breast cancer patients.

4.3.2 Limitations

1. The study is a cross-sectional study that did not identify changes in symptom severity over time.

2. Another limitation of this study pertains to its location in Nablus city, which is just one part of the broader Palestinian West Bank. Consequently, it is not possible to extrapolate the findings to the entirety of Palestine.

3. The sampling method employed was convenience sampling, which implies that it may be challenging to make broad generalizations based on the obtained results. Limited data are available about the quality of life of patients receiving hormonal therapy using the EQ-5D-5 L quality of life questionnaire.

4. Limited data are available among breast cancer patients who are receiving targeted therapy or combination therapy regarding symptom severity, symptom interference and quality of life.

4.4 Conclusions and Recommendations

4.4.1 Conclusions

Symptoms that appear during the administration of breast cancer treatments differ in severity and influence on patients' daily life activities. The most common type of treatment associated with severe symptoms and affecting patients' daily life activities is chemotherapy, which has no significant influence on patients' quality of life. Hormonal therapy and targeted therapy are associated with fewer side effects and have the least influence on patients' daily life activities. Hormonal therapy and targeted therapy have been shown to enhance patients' quality of life.

Fatigue was the most severe symptom associated with the breast cancer treatment method, followed by sleep disturbances.

Quality of life was not affected during chemotherapy treatment, and it was enhanced during hormonal therapy and targeted therapy.

4.4.2 Recommendations

According to the study results

1. We advise health care providers to not underestimate concerns and complaints from patients regarding treatment methods. Different treatment methods result in different side effect profiles that adversely affect patients' daily life activities, and as a consequence, patients are less satisfied with the treatment and disease outcome.
2. We advise health care providers to be in close contact with patients and to incorporate patients in decision making about their treatment method and schedule, thus resulting in better satisfaction and compliance from patients with their treatment method.
3. We advise health care providers to evaluate the efficacy and side effects of received treatment individually.
4. More research is needed to support our findings regarding symptom severity, symptom interference, and quality of life among women with breast cancer receiving different types of treatment.

List of Abbreviations

Abbreviation	Meaning
AJCC	American Joint Committee on Cancer
ADCs	Antibody–drug conjugates
AIs	Aromatase inhibitors
BPA	Bisphenol A
BMD	Bone mineral density
BRCA1	Breast Cancer gene 1
BRCA2	Breast Cancer gene 2
BCPT	Breast Cancer Prevention Trail
CDKs	Cyclin-dependent kinases
AC	Cyclophosphamide plus Doxorubicin
DMMR	DNA mismatch repair pathway
DEXA	Dual-energy X-ray absorptiometry
ER	Estrogen receptor
EORTC-QLQ-	European Organization for the Research and Treatment of Cancer
C30	Quality of Life Questionnaire
EQ-5D-5L	European quality of life 5 Dimension 5 Level Questionnaire
FGFs	Fibroblast growth factors
FACT-ES	Functional Assessment of Cancer Therapy - Endocrine Symptoms
HER2	Human epidermal growth factor receptor 2
LHRH	Luteinizing hormone-releasing hormone
mTOR	Mammalian target of Rapamycin
MDASI	MD Anderson Symptom Inventory
MSI	Microsatellite Instability
MSVS	Moderate sever to very severe
OCPs	Organochlorine pesticides
PROs	Patient-reported outcomes
PI3K-AKT	Phoshoinositide3-kinases- protein kinase B
PTEN	Phosphatase and tensin homolog
PI3K	Phosphatidylinositol 3-kinase
PDGF	Platelet-derived growth factor
PARP	Poly (ADP-ribose) polymerase

PBDEs	Polybrominateddiphenyl ethers
PCBs	Polychlorinated biphenyls
PR	Progesterone receptor
PDL-1	Programmed cell death ligand-1
PD-1	Programmed death receptor 1
RTKs	Receptor tyrosine kinases
SERD	Selective estrogen receptor degrader
SERMs	Selective estrogen receptor modulators
SPSS	Statistical Package for Social Sciences
SRC	Steroid receptors coactivators
TGFα	Transforming growth factor alpha
Trop-2	Trophoblast cell-surface antigen 2
TIL	Tumor infiltrating lymphocyte
TP53	Tumor protein 53
VAS	Visual Analog Scale
WHO	World Health Organization

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Appendices

Appendix A

Data collection form

*Clinical and Demographics Form

Patient medical record

Age (year)	○ Less than 40 ○ 40-49 ○ 50-59 ○ > 60
Place of residence	○ City ○ Village ○ Palestinian refugee's campaign
Weight	
Height	
Body mass index (BMI)	○ Underweight (< 18.5) ○ Normal weight (18.5–24.9) ○ Overweight (25–29.9) ○ Obese (> 30)
Marital status	○ Single ○ Married ○ Divorced ○ Widowed
Educational level	○ Elementary ○ Preparatory ○ Secondary ○ Diploma ○ Bachelor's degree ○ Uneducated
Employment status	○ Private employee ○ Government employee ○ Housewife
Family monthly income	○ Low (less than 500 JD) ○ Moderate (500 JD–1000 JD) ○ High (more than 1000 JD)
Smoking	○ Non-Smoker ○ Smoker
Stage of breast cancer	○ Stage 0 ○ Stage 1 ○ Stage 2 ○ Stage 3 ○ Stage 4

Type of breast cancer	○ Invasive ductal carcinoma ○ Invasive lobular carcinoma ○ Ductal carcinoma in situ
diagnosis date	
Treatment method	○ Chemotherapy ○ Hormonal therapy ○ Anti HER2 (biological) therapy
Types of chemotherapy regimen	○ AC (Doxorubicin, Cyclophosphamide) ○ TC (Docetaxel, Cyclophosphamide) ○ FAC(Fluorouracil, Doxorubicin and Cyclophosphamide) ○ TAC(Docetaxel, Doxorubicin, and Cyclophosphamide) ○ AC followed by Paclitaxel ○ Paclitaxel followed by FAC ○ CMF(Cyclophosphamide, Methotrexate, Fluorouracil) ○ Dose-Dense AC followed by Paclitaxel ○ FEC(Fluorouracil, Epirubicin and Cyclophosphamide) ○ CEF(Cyclophosphamide, Epirubicin and Fluorouracil)
Number of cycles completed	
Type of Hormonal therapy	
Type of Targeted therapy	
Comorbid disease	○ Diabetes ○ Hypertension ○ Dyslipidemia ○ Cardiovascular disease ○ Stroke ○ Asthma ○ COPD ○ Goat ○ Osteoporosis ○ Rheumatoid arthritis ○ Liver disease ○ Kidney disease ○ Ulcer and other GI disease ○ Secondary cancer
Medications	

(MDASI Arabic sample questionnaire)

التاريخ: _____ المؤسسة: _____

الحروف الأولى من اسمالمشارك: _____ رقم ملف المريض بالمستشفى: _____

رقم المشارك: _____

البنود الرئيسية لقائمة أعراض مركز إم دي أندرسون (MDASI)

الجزء الأول – ما مدى **شدة** أعراضك؟

كثيراً ما تحدث لدى المصابين بالسرطان أعراضٌ سببُها المرض أو العلاج. نودُّ منك أن تُقَدِّرَ شدَّةَ الأعراض التالية ***خلال الأربع والعشرين ساعة الماضية***. من فضلك، اختر رقم من صفر (يشير إلى عدم وجود العرض المذكور) إلى 10 (يشير إلى وجود العرض في أسوأ ما يمكن أن تتصور من الشدَّة) لكلِّ عَرَض من الأعراض المذكورة.

	غير موجود 0	1	2	3	4	5	6	7	8	9	أسوأ ما تتصور 10
1. **الألم** في أسوأ حالاته؟	○	○	○	○	○	○	○	○	○	○	○
2. **الإرهاق (التعب)** في أسوأ حالاته؟	○	○	○	○	○	○	○	○	○	○	○
3. **الغثيان** في أسوأ حالاته؟	○	○	○	○	○	○	○	○	○	○	○
4. **اضطراب النوم** في أسوأ حالاته؟	○	○	○	○	○	○	○	○	○	○	○
5. إحساسُك **بأنك مُستاء (منزعج)** في أسوأ الحالات؟	○	○	○	○	○	○	○	○	○	○	○
6. **ضيق التنفس** في أسوأ حالاته؟	○	○	○	○	○	○	○	○	○	○	○
7. صعوبة **تذكر الأشياء** في أسوأ حالاتها؟	○	○	○	○	○	○	○	○	○	○	○
8. **فقدان الشهية** في أسوأ حالاتها؟	○	○	○	○	○	○	○	○	○	○	○
9. شعورك **بالدوخة (النعاس)** في أسوأ حالاتها؟	○	○	○	○	○	○	○	○	○	○	○
10. **جفاف الفم** في أسوأ حالاته؟	○	○	○	○	○	○	○	○	○	○	○

التاريخ: _____ المؤسسة: _____

الحروف الأولى من اسمالمشارك: _____ رقم ملف المريض بالمستشفى: _____

رقم المشارك: _____

	غير موجود 0	1	2	3	4	5	6	7	8	9	أسوأ ما تتصور 10
11. الشعور **بالحزن** في أسوأ حالاته؟	○	○	○	○	○	○	○	○	○	○	○
12. **القيء** في أسوأ حالاته؟	○	○	○	○	○	○	○	○	○	○	○
13. **التنميل أو النخز (الوخز)** في أسوأ حالاته؟	○	○	○	○	○	○	○	○	○	○	○

الجزء الثاني: كيف **تداخلت** أعراضُك مع مُجريات حياتك؟

كثيراً ما تؤثّرُ الأعراض على مشاعرنا وأداءنا لنشاطاتنا. إلى أيّ مدى تداخلت أعراضك مع الأشياء التالية ***خلال الأربع والعشرين ساعة الماضية؟*** اختر رقم من صفر (يشير إلى عدم وجود العرض المذكور) إلى 10 (يشير إلى وجود العرض في أسوأ ما يمكن أن تتصور من الشدّة) لكلّ عَرَض من الأعراض المذكورة.

	لا تداخل 0	1	2	3	4	5	6	7	8	9	تداخل كامل 10
14. النشاط العامة؟	○	○	○	○	○	○	○	○	○	○	○
15. المزاج؟	○	○	○	○	○	○	○	○	○	○	○
16. العمل (بما في ذلك الأعمال المنزلية)؟	○	○	○	○	○	○	○	○	○	○	○
17. العلاقة مع الأشخاص الآخرين؟	○	○	○	○	○	○	○	○	○	○	○
18. المشي؟	○	○	○	○	○	○	○	○	○	○	○
19. التمتع بالحياة	○	○	○	○	○	○	○	○	○	○	○

(MDASI English sample questionnaire)

Date: _____ **Institution:** _____

Participant Initials: _____ **Hospital Chart #:** _____

Participant Number: _____

M. D. Anderson Symptom Inventory - Breast (MDASI-Breast)

Part I. How **severe** are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been ***in the last 24 hours.*** Please select a number from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present 0	1	2	3	4	5	6	7	8	9	**As Bad As You Can Imagine** 10
1. Your **pain** at its WORST?	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯
2. Your **fatigue (tiredness)** at its WORST?	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯
3. Your **nausea** at its WORST?	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯
4. Your **disturbed sleep** at its WORST?	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯
5. Your feelings of being **distressed (upset)** at its WORST?	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯
6. Your **shortness of breath** at its WORST?	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯
7. Your problem with **remembering things** at its WORST?	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯
8. Your problem with **lack of appetite** at its WORST?	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯
9. Your feeling **drowsy (sleepy)** at its WORST?	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯
10. Your having a **dry mouth** at its WORST?	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯
11. Your feeling **sad** at its WORST?	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯
12. Your **vomiting** at its WORST?	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯
13. Your **numbness or tingling** at its WORST?	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯
14. Your **hot flashes** at its WORST?	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯	◯

Date: _____ Institution: _____

Participant Initials: _____ Hospital Chart #: _____

Participant Number: _____

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
15. Your **breast changes** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
16. Your **constipation** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
17. Your **arm swelling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
18. Your **fingernail or toenail changes** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
19. Your **skin changes** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
20. Your **decrease in sexual interest or activity** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
21. Your **vaginal dryness** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Part II. How have your symptoms **interfered** with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items ***in the last 24 hours***? Please select a number from 0 (symptoms have not interfered) to 10 (symptoms interfered completely) for each item.

	Did Not Interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
22. **General activity**?	○	○	○	○	○	○	○	○	○	○	○
23. **Mood**?	○	○	○	○	○	○	○	○	○	○	○
24. **Work** (including work around the house)?	○	○	○	○	○	○	○	○	○	○	○
25. **Relations** with other people?	○	○	○	○	○	○	○	○	○	○	○
26. **Walking**?	○	○	○	○	○	○	○	○	○	○	○
27. **Enjoyment** of life?	○	○	○	○	○	○	○	○	○	○	○

Signature: _____

*EQ-5D-5 L questionnaire (Arabic version)

تحت كل عنوان، ضع من فضلك علامة على مربع **واحد** لأفضل عبارة لوصف صحتك **اليوم**.

القدرة على التنقل

- ❑ لا مشاكل عندي في المشي
- ❑ عندي مشاكل طفيفة في المشي
- ❑ عندي مشاكل متوسطة في المشي
- ❑ عندي مشاكل حادة في المشي
- ❑ ليست لدي القدرة على المشي

قدرتي على الاهتمام بنفسي

- ❑ لا مشاكل عندي في الاستحمام أو في ارتداء الملابس بمفردي
- ❑ عندي مشاكل طفيفة في الاستحمام أو في ارتداء الملابس بمفردي
- ❑ عندي مشاكل متوسطة في الاستحمام أو في ارتداء الملابس بمفردي
- ❑ عندي مشاكل حادة في الاستحمام أو في ارتداء الملابس بمفردي
- ❑ ليست لدي القدرة على الاستحمام أو ارتداء الملابس بمفردي

الأنشطة المعتادة *(مثل العمل، الدراسة، الأعمال المنزلية،النشاطات الأسرية أو الترفيهية)*

- ❑ لا مشاكل عندي في ممارسة نشاطاتي المعتادة
- ❑ عندي مشاكل طفيفة في ممارسة أعمالي المعتادة
- ❑ عندي مشاكل متوسطة في ممارسة نشاطاتي المعتادة
- ❑ عندي مشاكل حادة في ممارسة نشاطاتي المعتادة
- ❑ ليست لديّ القدرة على ممارسة نشاطاتي المعتادة

الإحساس بعدم الراحة/الألم

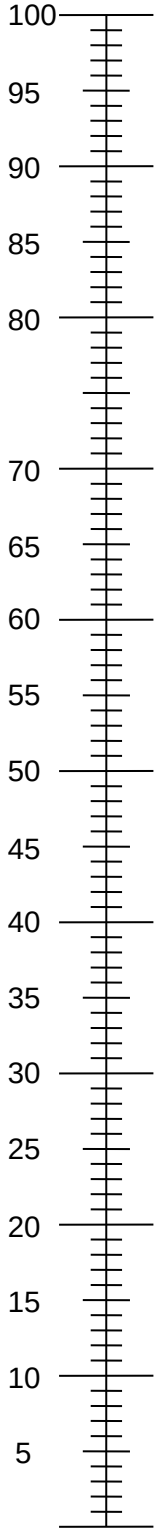
- ❑ لا ألم عندي أو انزعاج
- ❑ عندي ألم أو انزعاج طفيف
- ❑ عندي ألم أو انزعاج متوسط
- ❑ عندي ألم أو انزعاج حاد
- ❑ عندي ألم شديد جداً أو انزعاج شديد جداً

قلق/اكتئاب

- ❑ لست قلقاً أو مكتئباً
- ❑ أنا قلق أو مكتئب قليلاً
- ❑ أنا قلق أو مكتئب بشكل متوسط
- ❑ أنا قلق بشكل حاد أو مكتئب بشكل حاد
- ❑ أنا شديد القلق أو شديد الاكتئاب

أفضل حالة

صحّية يُمكنك



أسوأ حالة صحّية

يُمكنك تصورها

- نود أن نعرف مدى جودة أو سوء صحتك **اليوم**.
- هذا المقياس مدرج من الرقم 0 حتى 100.
- الرقم 100 يعني أفضل حالة صحية يمكنك تصوّرها.

  0 يعني أسوأ حالة صحية يمكنك تصوّرها.
- ضع X على المقياس للإشارة إلى صحتك **اليوم**.
- والآن اكتب من فضلك الرقم الذي حددته على المقياس في المربع أدناه.

=حالتك الصحية اليوم

The English version for the UK

Please select the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g., work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN/DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY/DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

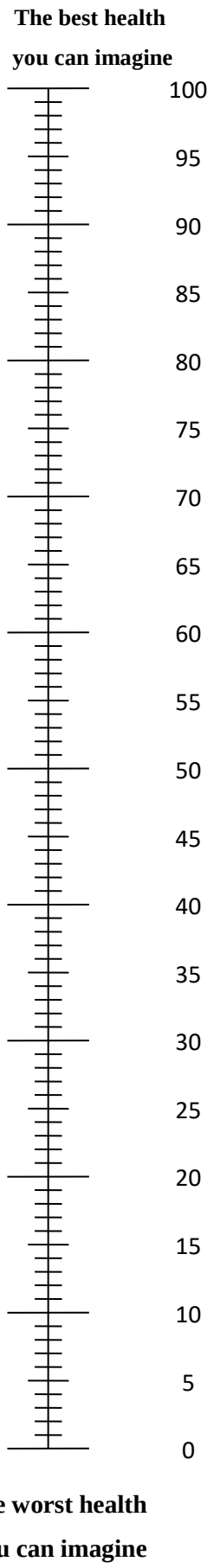
-We would like to know how good or bad your health is TODAY.

-You will see a scale numbered from 0 to 100.

-100 means the best health you can imagine.
0 means the worst health you can imagine.

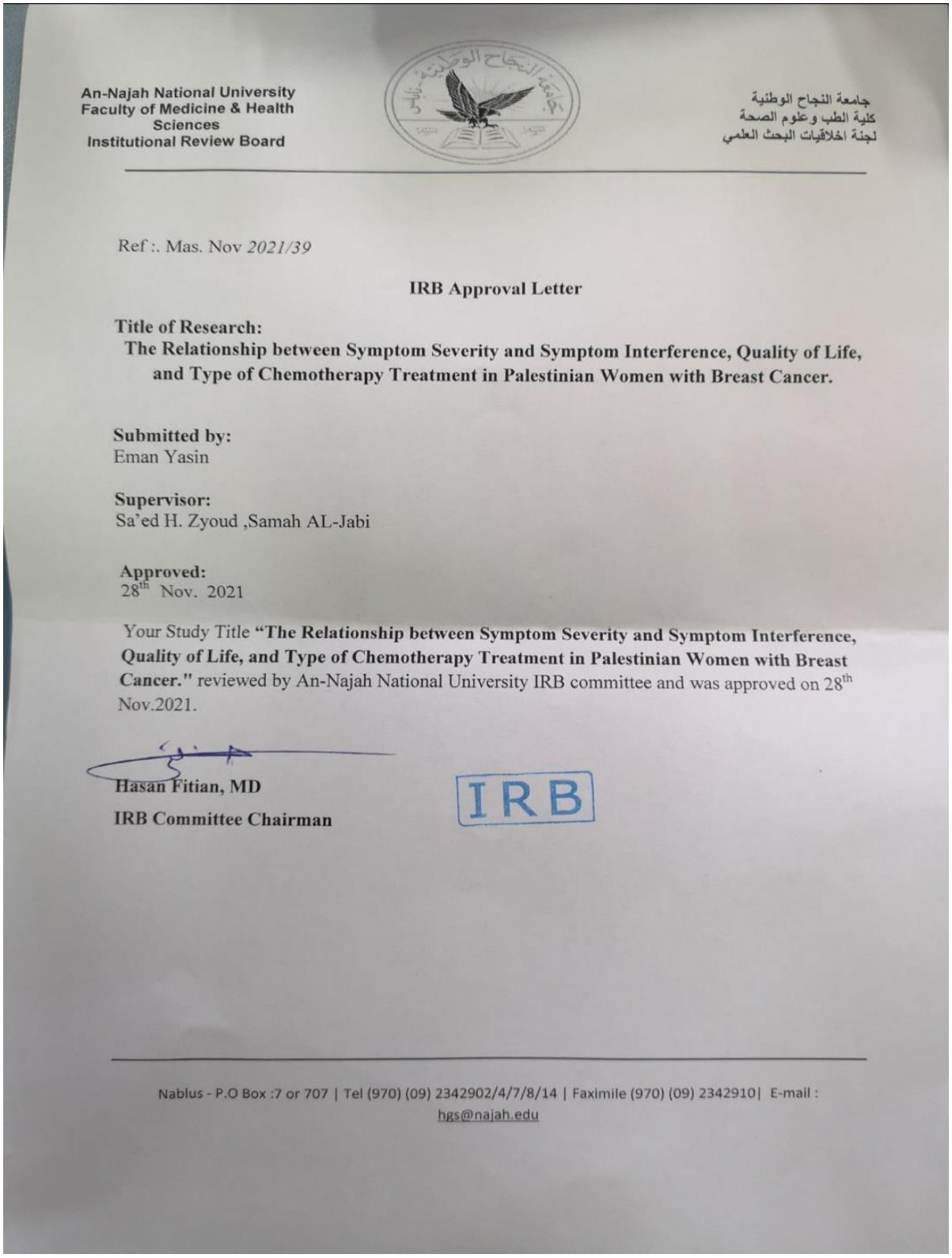
- Please mark an X on the scale to indicate how your health is TODAY.

YOUR HEALTH TODAY =



Appendix B

An-Najah National University Institutional Review Board (IRB) approval



An-Najah National University
Faculty of Medicine & Health Sciences
Institutional Review Board

جامعة النجاح الوطنية
كلية الطب وعلوم الصحة
لجنة اخلاقيات البحث العلمي

Ref :. Mas. Nov *2021/39*

IRB Approval Letter

Title of Research:
The Relationship between Symptom Severity and Symptom Interference, Quality of Life, and Type of Chemotherapy Treatment in Palestinian Women with Breast Cancer.

Submitted by:
Eman Yasin

Supervisor:
Sa'ed H. Zyoud ,Samah AL-Jabi

Approved:
28th Nov. 2021

Your Study Title **"The Relationship between Symptom Severity and Symptom Interference, Quality of Life, and Type of Chemotherapy Treatment in Palestinian Women with Breast Cancer."** reviewed by An-Najah National University IRB committee and was approved on 28th Nov.2021.

Hasan Fitian, MD
IRB Committee Chairman

IRB

Nablus - P.O Box :7 or 707 | Tel (970) (09) 2342902/4/7/8/14 | Faximile (970) (09) 2342910| E-mail : hgs@najah.edu

Appendix C

Palestinian Ministry of Health approval

State of Palestine
Ministry of Health
Education in Health and Scientific Research Unit

دولة فلسطين
وزارة الصحة
وحدة التعليم الصحي والبحث العلمي

Ref.: ………………
Date:………………

الرقـــم: ١٦٤/٢٦٦/٢٠٢٢
التــاريخ: ٢١/٤/٢٠٢٢

الأخ مدير عام الادارة العامة للمستشفيات المحترم،،،

تحية واحترام،،،

<u>الموضوع: تسهيل مهمة</u>

يرجى التكرم بتسهيل مهمة الطالبة: **ايمان لطفي فوزي ياسين– ماجستير علم أدوية–**

جامعة النجاح، لعمل بحث بعنوان:

"The Relationship between Symptom Severity and Symptom Interference, Quality of Life, and Type of Chemotherapy Treatment in Palestinian Women with Breast Cancer"

حيث ستقوم الطالبة بجمع معلومات عن طريق تعبئة استبانة من قبل المريضات (بعد أخذ موافقتهن) ، مع العلم أن مشرفي الدراسة: د. سائد زيود و د. سماح الجابي.

وذلك في : **مستشفى الوطني**

على ان يتم الالتزام بالمحافظة على اخلاقيات البحث العلمي وسرية المعلومات.
على ان يتم الالتزام بجميع تعليمات واجراءات الوقاية والسلامة الصادرة عن وزارة الصحة بخصوص جائحة كورونا، وتحت طائلة المسؤولية. وابراز شهادة التطعيم قبل دخول مرافق وزارة الصحة.
على ان يتم تزويد الوزارة بنسخة PDF من نتائج البحث، التعهد بعدم النشر لحين الحصول على موافقة وزارة الصحة.

مع الاحترام،،،

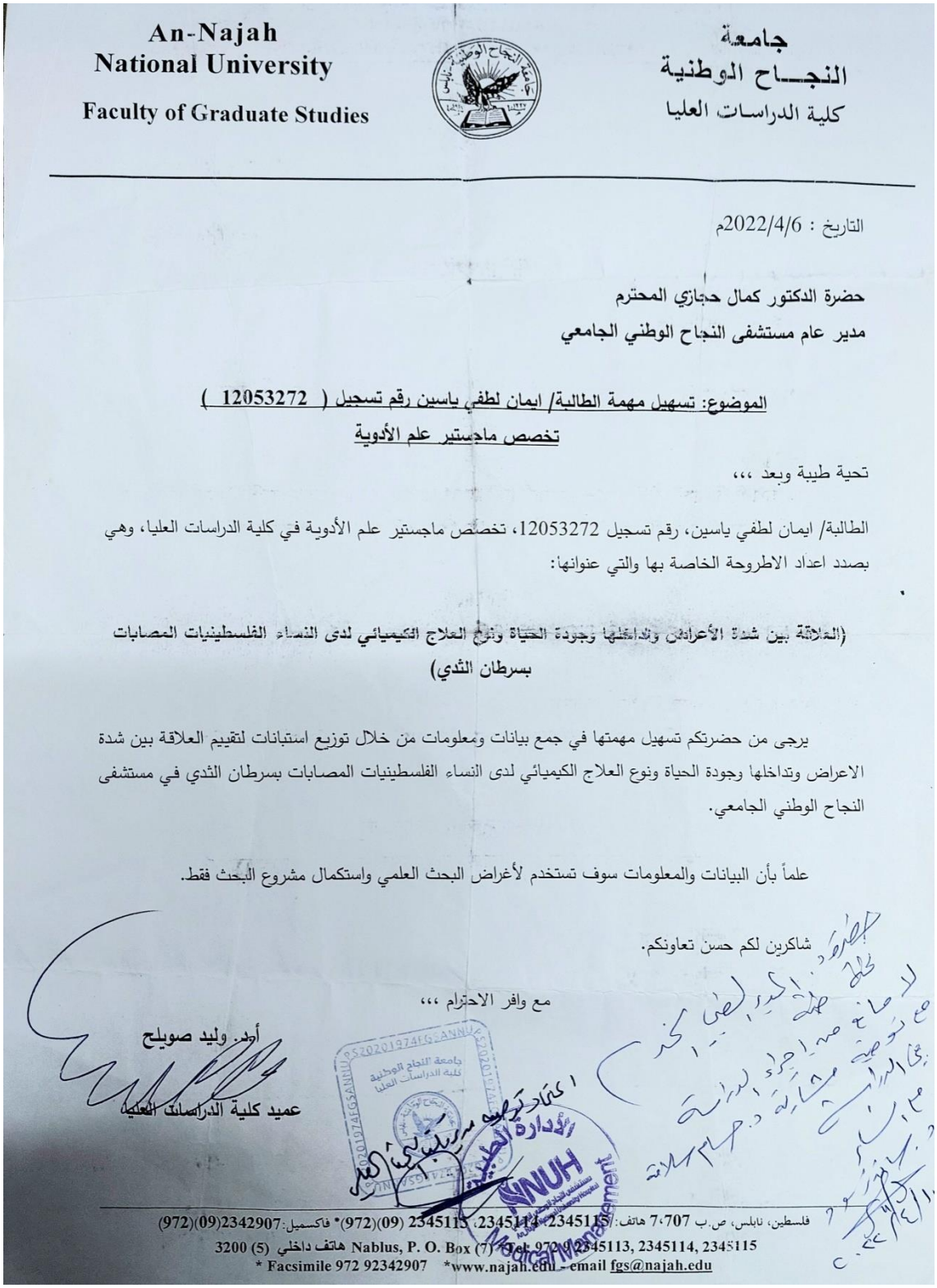
د. عبد الله القواسمي
رئيس وحدة التعليم الصحي والبحث العلمي

نسخة : مشرفي الدراسة المحترمين/ جامعة النجاح

Telfax.:09-2333901 scientificresearch.dep@gmail.com 09-2333901 :تلفاكس

Appendix D

An-Najah National University Hospital approval



An-Najah
National University
Faculty of Graduate Studies

جامعة
النجـــاح الوطنية
كلية الدراسات العليا

التاريخ : 2022/4/6م

حضرة الدكتور كمال حجازي المحترم
مدير عام مستشفى النجاح الوطني الجامعي

الموضوع: تسهيل مهمة الطالبة/ ايمان لطفي ياسين رقم تسجيل (12053272)
تخصص ماجستير علم الأدوية

تحية طيبة وبعد ،،،

الطالبة/ ايمان لطفي ياسين، رقم تسجيل 12053272، تخصص ماجستير علم الأدوية في كلية الدراسات العليا، وهي بصدد اعداد الاطروحة الخاصة بها والتي عنوانها:

(العلاقة بين شدة الأعراض وتداخلها وجودة الحياة ونوع العلاج الكيميائي لدى النساء الفلسطينيات المصابات بسرطان الثدي)

يرجى من حضرتكم تسهيل مهمتها في جمع بيانات ومعلومات من خلال توزيع استبانات لتقييم العلاقة بين شدة الاعراض وتداخلها وجودة الحياة ونوع العلاج الكيميائي لدى النساء الفلسطينيات المصابات بسرطان الثدي في مستشفى النجاح الوطني الجامعي.

علماً بأن البيانات والمعلومات سوف تستخدم لأغراض البحث العلمي واستكمال مشروع البحث فقط.

شاكرين لكم حسن تعاونكم.

مع وافر الاحترام ،،،

أ.د. وليد صويلح
عميد كلية الدراسات العليا

جامعة النجاح الوطنية
كلية الدراسات العليا

الإدارة الطبية
NUH
Medical Management

فلسطين، نابلس، ص.ب 7،707 هاتف: 2345115 ،2345114 ،2345115 (09)(972)* فاكسميل: 2342907(09)(972)
Nablus, P. O. Box (7) 707 Tel: 972 2345113, 2345114, 2345115 هاتف داخلي (5) 3200
* Facsimile 972 92342907 *www.najah.edu - email fgs@najah.edu

Appendix E

Tables of Study

Table E1

Type and Stage of breast cancer

Type of cancer	N(229) frequency(%)
DCIS	7 (3.1)
IDC	105 (45.9)
ILC	14 (6.1)
Missing data	103 (45)
Stage of cancer	n(299) frequency(%)
Stage 1	10 (4.4)
Stage 2	21 (9.2)
Stage 3	23 (10)
Stage 4	47 (20.5)
Missing data	128 (55.9)

Table E2

Scio-demographic and clinical characteristics relation to symptoms severity

Scio-demographic characteristics	Median symptom severity score (1st percentile-3rd percentile)	p value
Age category		0.029 [b]
<40	2.0000[0.3846 – 4.5385]	
40-49	2.6923[0.4231 – 4.6538]	
50-59	1.7692[0.0000 – 5.2692]	
=>60	0.7692[0.0000 – 2.6154]	
Residence		0.718 [b]
City	1.3846 [0.0000 – 4.5385]	
village	1.5769 [0.0000 – 4.7500]	
refugee's campaign	2.6154 [0.5000 – 5.9615]	
Marital status		0.215 [b]
Single	1.0769 [0.0000 – 4.8462]	
Married	2.0000 [0.0769 – 4.7692]	
Divorced	0.0000 [0.0000 – 3.2692]	
Widowed	0.8462 [0.3846 – 1.0769]	
Education level		0.126 [b]
Uneducated	0.6154 [0.0000 – 1.4808]	
Elementary	1.6538 [0.0000 – 4.8077]	
Secondary	2.8462 [0.0769 – 5.0000]	
Diploma	0.3846 [0.0000 – 3.7692]	
Bachelor's degree	1.6154 [0.4423 – 4.2692]	
Employment status		0.176 [b]
Private employee	0.3077 [0.0000 – 2.6923]	

Government employee	2.0000 [0.0000 – 5.8462]	
Housewife	1.5385 [0.0000 – 4.6923]	
monthly income		0.825 [b]
Low (less than 500 JD)	1.1538 [0.0000 – 4.8846]	
Moderate (500 JD–1000 JD)	1.6923 [0.0000 – 4.5385]	
High (more than 1000 JD)	3.2308 [0.0000 – 5.3846]	
Smoking		0.016 [a]
non smoker	1.2692 [0.0000 – 4.4615]	
smoker	2.9231 [0.8077 – 5.6154]	
BMI		0.292 [b]
Underweight (< 18.5)	–	
Normal weight (18.5–24.9)	0.0000 [0.0000 – 7.000]	
Overweight (25–29.9)	1.5000 [0.0000 – 5.750]	
Obese (> 30)	1.0000 [0.0000 – 7.000]	
Stage of breast cancer		0.255 [b]
Stage 1	0.1500 [0.000 – 4.2308]	
Stage 2	0.4615 [0.000 – 2.3080]	
Stage 3	1.3846 [0.000 – 4.3077]	
Stage 4	1.3846 [0.000 – 4.9231]	
Types of breast cancer		0.589 [b]
DCIS	0.0000 [0.000 – 2.6923]	
IDC	1.0000 [0.000 – 3.7308]	
ILC	1.0000 [0.000 – 3.5769]	
Comorbid diseases		0.47 [a]
Yes	1.0769 [0.000 – 5.3077]	
No	2.0000 [0.250 – 4.4423]	
Treatment method		0.000 [b]
Chemotherapy	4.5385 [2.9231 – 5.6154]	
Hormonal therapy	0.3462 [0.0000 – 1.2500]	
Targeted therapy	0.0769 [0.0000 – 4.0385]	
Hormonal plus targeted therapy	2.6923 [1.3077 – 6.3077]	
Chemotherapy plus targeted therapy	4.0385 [3.5000 – 4.9615]	

[a]Calculated by using the Mann–Whitney U test

[b] Calculated by using the Kruskal–Wallis test

Table E3

Scio-demographic characteristics and quality of life scores

Scio-demographic characteristics	EQ-5D index Score Median (IQR)	P valve	EQ-VAS Median (IQR)	P value
Age category		0.616 [b]		0.350 [b]
<40	1.0000[0.8260 – 1.0000]		80(60-90)	
40-49	0.8760[0.7865 – 1.0000]		70(57-80)	
50-59	0.8760[0.7785 – 1.0000]		70(58-85)	
=>60	0.8800[0.7560 – 1.0000]		70(50-80)	
Residence		0.320 [b]		0.474 [b]
City	0.8760 [0.7733 – 1.0000]		70(50-80)	
village	0.8800 [0.8075 – 1.0000]		70(60-80)	
refugee's campaign	0.8610 [0.5395 – 1.0000]		65(52-80)	
Marital status		0.796 [b]		0.986 [b]
Single	0.8800 [0.7960 – 1.0000]		70(60-90)	
Married	0.8765 [0.7900 – 1.0000]		70(60-85)	
Divorced	1.0000 [0.1040 – 1.0000]		60(55-75)	
Widowed	0.8800 [0.8100 – 1.0000]		75(60-80)	
Education level		0.191 [b]		0.193 [b]
Uneducated	0.8780 [0.7950 – 1.0000]		70(50-84)	
Elementary	0.8440 [0.7440 – 1.0000]		70(50-80)	
Secondary	1.0000 [0.8115 – 1.0000]		80(65-87)	
Diploma	0.8780 [0.8225 – 1.0000]		72(60-85)	
Bachelor's degree	0.8540 [0.8225 – 1.0000]		70(60-80)	
Employment status		0.009 [b]		0.322 [b]
Private employee	1.0000 [0.8760 – 1.0000]		80(70-85)	
Government	0.8200 [0.7560 – 1.0000]		70(50-90)	
employee	0.8760 [0.7860 – 1.0000]		70(60-80)	
Housewife				
monthly income		0.709 [b]		0.557 [b]
Low (less than 500	0.8780 [0.7915 – 1.0000]		70(50-85)	
JD)	0.8760 [0.7900 – 1.0000]		70(60-80)	
Moderate (500			80(60-85)	
JD–1000 JD)	0.8610 [0.8090 – 1.0000]			
High (more than 1000 JD)				
Smoking		0.106 [a]		0.015 [a]
non smoker	0.8760 [0.8030 – 1.0000]		70(60-85)	
smoker	0.8440 [0.7315 – 1.0000]		70(55-75)	
BMI		0.279 [b]		0.477 [b]
Underweight (<	–		–	
18.5)	0.8800 [0.8090 – 1.000]		75(60-85)	
Normal weight			70(60-80)	
(18.5–24.9)	0.8800 [0.8090 – 1.000]		70(50-85)	
Overweight (25–	0.8440 [0.7560 – 1.000]			
29.9)				
Obese (> 30)				

[a] Calculated by using the Mann–Whitney U test

[b] Calculated by using the Kruskal–Wallis test

Table E4

clinical characteristics and quality of life

Scio-demographic characteristics	EQ-5D index Score Median (IQR)	P value	EQ-VAS Median (IQR)	P value
Stage of breast cancer		0.328 [b]		0.219 [b]
Stage 1	0.9400 [0.8480 – 1.0000]		77(60-86)	
Stage 2	0.8800 [0.8685 – 1.0000]		80(70-82)	
Stage 3	0.8610 [0.8200 – 1.0000]		70(60-80)	
Stage 4	0.8560 [0.7560 – 1.0000]		70(50-85)	
Types of breast cancer		0.487 [b]		0.440 [b]
DCIS	1.0000 [0.8530 – 1.0000]		85(40-90)	
IDC	0.8800 [0.8200 – 1.0000]		70(60-85)	
ILC	0.8760 [0.7788 – 1.0000]		70(56-75)	
Comorbid diseases		0.188 [a]		0.038 [a]
Yes	0.8540 [0.8560 – 1.0000]		70(55-80)	
No	0.8760 [0.8090 – 1.0000]		75(60-85)	
Treatment method		0.000 [b]		0.006 [b]
Chemotherapy	0.8200 [0.7425 – 0.8760]		70(50-80)	
Hormonal therapy	1.0000 [0.8400 – 1.0000]		77(60-85)	
Targeted therapy	0.9400 [0.7428 – 1.0000]		77(60-90)	
Hormonal plus targeted therapy	0.8610 [0.7560 – 0.8800]		55(45-75)	
Chemotherapy plus targeted therapy	0.8030 [0.7560 – 1.0000]		60(50-80)	

[a] Calculated by using the Mann–Whitney U test

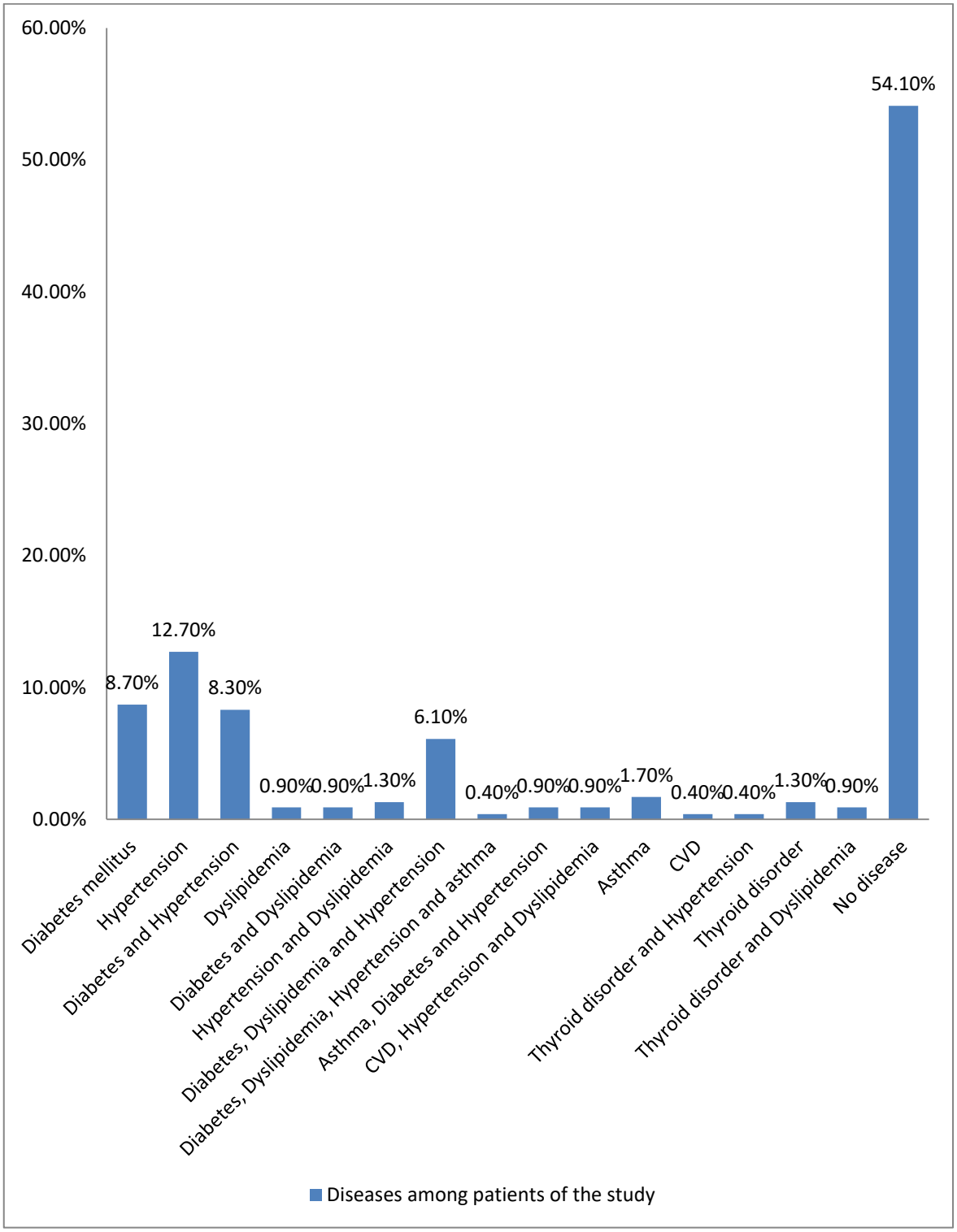
[b] Calculated by using the Kruskal–Wallis test

Appendix F

Figures of Study

Figure F1

Chronic diseases among participants of the study



جـامعـــة النجاح الوطنية

كليـــة الدراســـات العليـــا

العلاقة بين شدة الأعراض وتداخلها وجودة الحياة ونوع العلاج لدى النساء الفلسطينيات المصابات بسرطان الثدي

إعداد

إيمان لطفي فوزي ياسين

إشراف

د. سائد زيود

د. سماح الجابي

قدمت هذه الرسالة استكمالا لمتطلبات الحصول على درجة الماجستير في علم الأدوية، من كلية الدراسات العليا، في جامعة النجاح الوطنية، نابلس– فلسطين.

2024

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الملخص

الخلفية: يعد سرطان الثدي من أكثر أنواع السرطان شيوعاً ويصيب النساء أكثر من الرجال ويعتبر سبباً رئيسياً للوفاة بالسرطان بين النساء. تعاني النساء المصابات بسرطان الثدي من أعراض مزعجة تتعلق إما بالمرض نفسه أو بعلاجات سرطان الثدي التي تتعارض مع أنشطة حياة المرضى وتؤثر على نوعية حياتهم.

الأهداف: تقديم شرح شامل للعلاقة بين شدة الأعراض وتداخل الأعراض، ونوعية الحياة ونوع العلاج.

المنهجية: هذه دراسة مقطعية أجريت من خلال استبيان MDASI لتقييم شدة الأعراض وتداخل الأعراض واستبيان EQ-5D-5 L لتقييم جودة الحياة بين النساء اللواتي تأكد تشخيصهن بسرطان الثدي في مستشفى جامعة النجاح الوطنية والمستشفى الوطني. تم استكمال الاستبيان من خلال المقابلات وجهاً لوجه ومراجعة السجلات الطبية للمرضى.

النتائج: تم تضمين 229 مشاركا في الدراسة. غالبية المرضى (34.1٪، ن = 78) تتراوح أعمارهم بين 50–59 سنة. وشملت طرائق العلاج, العلاج الكيميائي وحده (35.4٪، ن = 81)، والعلاج الهرموني (48٪، ن = 110)، والعلاج الموجه (9.6٪، ن = 22)، وأنظمة اخرى من العلاجات المركبة. على وجه

التحديد، تلقى (3.9٪، ن = 9) علاجًا هرمونيًا جنبًا إلى جنب مع العلاج الموجه، وخضع (3.1٪، ن = 7) للعلاج الكيميائي والعلاج الموجه كان التعب هو العرض الأكثر انتشارا و شدة، باستثناء النساء اللواتي يتلقين العلاج الكيميائي بالإضافة إلى العلاج الموجه بحيث كانت اضطرابات النوم هي العرض الاكثر تكرارا وشدة. كانت الارتباطات بين إجمالي متوسط شدة أعراض MDASI وإجمالي متوسط درجة تداخل أعراض MDASI إيجابية بشكل عام، مع وجود استثناءات ملحوظة لمجموعة العلاج الكيميائي بالإضافة إلى العلاج المستهدف. العلاقة الأقوى وجدت بين مشاعر الحزن والتعب والضيق. لم يلاحظ أي ارتباطات بين العوامل الاجتماعية والديموغرافية والنتيجة المتوسطة الإجمالية لمقياس شدة الأعراض. فيما يتعلق بأبعاد EQ-5D-5 L، لم يبلغ غالبية المرضى عن أي مشاكل. أظهرت درجة مؤشر EQ-5D-5 Lارتباطًا إيجابيًا قويًا وهامًا مع درجة EQ-VAS على العكس من ذلك، فقد أظهرت ارتباطات سلبية كبيرة مع كل من متوسط النتيجة الإجمالية لشدة الأعراض ومتوسط النتيجة لنتيجة الإجمالية لتداخل الأعراض.

الاستنتاجات: العلاج الأكثر شيوعاً والمرتبط بالأعراض الشديدة والمؤثرة على أنشطة الحياة اليومية للمرضى هو العلاج الكيميائي، والذي ليس له تأثير كبير على نوعية حياة المرضى. كان الإرهاق من أشد الأعراض المرتبطة بطريقة علاج سرطان الثدي.

الكلمات المفتاحية: شدة الأعراض، تداخل الأعراض، نوعية الحياة، ونوع العلاج.