IMPACT OF BLOOD GLUCOSE TRAJECTORIES ON PATHOLOGICAL RESPONSES, SEVERITY AND QUALITY OF LIFE ASSOCIATED WITH CIPN IN BREAST CANCER WOMEN AFTER RECIVING NEO ADJUVANT CHEMOTHERAPY: A SINGLE CENTER STUDY IN PAKISTAN

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LIST OF ABBREVIATIONS

ACS	American Cancer Society
AJCC	American Joint Committee on Cancer
BC	Breast Cancer
BCS	Breast conservation surgery
BMI	Body mass index
BMI	Body mass index
CIPN	Chemotherapy-induced peripheral neuropathy
Diabetes	type 2 diabetes
ER	Estrogen receptor
ESMO	European Society for Medical Oncology
EWB	Emotional well-being
FACT/GOG Ntx	Functional Assessment of Cancer Therapy/Gynecological Oncology Group Neurotoxicity
FBG	Fasting blood glucose
FDA	Food and Drug Administration
FWB	Functional well-being
Hb	Hemoglobin
HER2	Human epidermal growth factor receptor 2
HOMA-IR	Homeostatic model assessment
HRQOL	Health-related quality of life
MP	Miller-Payne system
NACT	Neo-adjuvant chemotherapy
NCCN	National Comprehensive Cancer Network

NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Event
NLR	Neutrophil lymphocyte ratio
PCR	Pathological complete response
PNR	Pathological no response
PPR	Pathological partial response
PR	Progesterone receptor
PRO	Patient-reported outcome
PWB	Physical well-being
SWB	Social well-being
T2DM	Type 2 diabetes mellitus
TNBC	Triple-negative breast cancer
TNM	Tumor node metastases
TOI	Trial outcome index
WBC	White blood cell
WHO	World Health Organization

LIST OF APPENDICES

KESAN TRAJEKTORI GLUKOSA DARAH TERHADAP TINDAK BALAS PATOLOGI, KETERUKAN DAN KUALITI HIDUP YANG BERKAITAN DENGAN CIPN PADA WANITA KANSER PAYUDARA SELEPAS MENERIMA KEMOTERAPI NEOADJUVAN: KAJIAN BERPUSAT TUNGGAL DI PAKISTAN

ABSTRAK

Kanser payudara adalah kebimbangan kesihatan yang penting di negara maju dan kurang membangun. Kajian dwi-fasa (Retrospektif dan Prospektif) telah dilakukan di Institut Perubatan Nuklear dan Radioterapi Gujranwala (GINUM), Gujranwala, Pakistan. Fasa retrospektif, yang melibatkan pengekstrakan data daripada rekod perubatan 1,372 wanita dengan kanser payudara antara Januari 2016 dan Januari 2021, berjaya mencapai objektif pertama projek. Fasa kajian ini mendedahkan perbezaan ketara dalam tindak balas patologi terhadap rawatan antara pesakit kanser payudara diabetes dan bukan diabetes ($p<0.001$). Pesakit diabetes menunjukkan kadar tindak balas lengkap patologi yang lebih rendah (15.7%) berbanding (19.9%) pesakit bukan diabetes. Tindak balas patologi separa (pPR) juga kurang biasa pada pesakit diabetes (43.8%) berbanding pesakit bukan diabetes (50.7%). Sebagai perbandingan, peratusan pesakit diabetes yang lebih tinggi (40.6%) menunjukkan tiada tindak balas patologi (pNR) berbanding pesakit bukan diabetes (29.4%). Fasa prospektif termasuk 560 wanita kanser payudara dengan dan tanpa diabetes bersamaan, 280 diabetes sedia ada dan 280 tanpa diabetes bersamaan antara September 2023 dan Mei 2024. Kajian kohort prospektif ini memberi tumpuan kepada perubahan dinamik dalam glukosa darah berpuasa semasa kemoterapi neo-adjuvant pada tindak balas patologi dalam kanser payudara perempuan. Dalam fasa prospektif, majoriti pesakit mencapai pPR

290 (51.8%); umur, BMI, kumpulan trajektori, dan anti-antidiabetik dikaitkan dengan ketara ($p<0.05$) dengan tindak balas patologi yang berbeza. Untuk menyemak perubahan dinamik dalam wanita kanser payudara, pesakit diklasifikasikan ke dalam trajektori glisemik berdasarkan nilai ujian FBG mereka. Menariknya, dalam fasa prospektif, diabetes tidak menunjukkan hubungan yang signifikan dengan tindak balas patologi. Tahap HbA1c dinilai pada tiga titik masa yang berbeza, dan di kalangan pesakit bukan diabetes yang menerima NACT, 213 (76.1%) didapati pra-diabetes. Walau bagaimanapun, selepas 3 bulan susulan, hanya 102 (36.4%) kekal dalam julat pra-diabetes. Objektif 3 dan 4 mentakrifkan kesan perubahan dinamik dalam glukosa darah pada kejadian dan QoL yang dikaitkan dengan CIPN dalam wanita kanser payudara tanpa diabetes bersamaan. Untuk objektif ini, hanya wanita kanser payudara tanpa diabetes bersamaan dimasukkan, kerana jika kita memasukkan pesakit diabetes adalah sangat sukar untuk membezakan bahawa CIPN disebabkan oleh diabetes atau kemoterapi, jadi semak QOL yang dikaitkan dengan CIPN pada wanita kanser payudara tanpa diabetes. Soal selidik yang dilaporkan oleh pesakit NCI-CTCAE dan FACT/GOG-Ntx yang dinilai oleh doktor telah digunakan. Mengikut keputusan kumpulan trajektori dalam hiperglikemia secara konsisten, 53 (65.4%) pesakit mempunyai CIPN yang lebih sederhana dan 6 (4.7%) teruk selepas NACT berbanding kumpulan trajektori lain. Kualiti hidup pesakit CIPN dipengaruhi oleh perubahan dalam tahap glukosa darah semasa dan selepas NACT. Kesimpulannya, fasa retrospektif menunjukkan bahawa diabetes memberi kesan negatif kepada kedua-dua tindak balas lengkap patologi (pCR) dan tindak balas separa patologi (pPR). Walau bagaimanapun, analisis prospektif mendapati tiada perkaitan yang signifikan antara perubahan glukosa darah dinamik semasa rawatan dan tindak balas patologi.

IMPACT OF BLOOD GLUCOSE TRAJECTORIES ON PATHOLOGICAL RESPONSES, SEVERITY AND QUALITY OF LIFE ASSOCIATED WITH CIPN IN BREAST CANCER WOMEN AFTER RECEIVING NEO-ADJUVANT CHEMOTHERAPY: A SINGLE CENTER STUDY IN PAKISTAN

ABSTRACT

Breast cancer is a significant health concern in developed and underdeveloped countries. A dual-phase study (Retrospective and Prospective) was performed at the Gujranwala Institute of Nuclear Medicine and Radiotherapy (GINUM), Gujranwala, Pakistan. The retrospective phase, which involved the extraction of data from the medical records of 1,372 women with breast cancer between January 2016 and January 2021, successfully accomplished the first objective of the project. This study phase revealed significant differences in pathological responses to treatment between diabetic and non-diabetic breast cancer patients ($p<0.001$). Diabetic patients exhibited a lower rate of pathological complete response (15.7%) compared to (19.9%) non-diabetic patients. Partial pathological response (pPR) was also less common in diabetic patients (43.8%) than in non-diabetic patients (50.7%). In comparison, a higher percentage of diabetic patients (40.6%) showed no pathological response (pNR) compared to non-diabetic patients (29.4%). The prospective phase included 560 breast cancer women with and without concomitant diabetes, 280 pre-existing diabetes, and 280 without concomitant diabetes between September 2023 and May 2024. This prospective cohort study focuses on the dynamic changes in fasting blood glucose during neo-adjuvant chemotherapy on the pathological responses in breast cancer

women. In the prospective phase, the majority of the patients achieved the pPR 290 (51.8%); the age, BMI, trajectories groups, and anti-antidiabetic were significantly associated ($p<0.05$) with different pathological responses. To check the dynamic changes in breast cancer women, patients were classified into glycemic trajectories based on the values of their FBG tests. Interestingly, in the prospective phase, diabetes did not show a significant association with pathological responses. HbA1c levels were assessed at three different time points, and among nondiabetic patients who received NACT, 213 (76.1%) were found to be pre-diabetic. However, after a 3-month follow-up, only 102 (36.4%) remained in the pre-diabetic range. Objectives 3 and 4 defined the effect of dynamic changes in blood glucose on the occurrence and QoL associated with CIPN in breast cancer women without concomitant diabetes. For these objectives, only breast cancer women without concomitant diabetes were included, because if we include diabetes patients it is very difficult to differentiate that the CIPN is caused by diabetes or chemotherapy, so only check the QOL associated with CIPN in breast cancer women without diabetes. The clinician-rated scale NCI-CTCAE and FACT/GOG-Ntx patient-reported questionnaire were used. According to the results of trajectory groups in consistently hyperglycemia, 53(65.4%) patients had more moderate CIPN and 6(4.7%) severe after NACT compared to other trajectory groups. The quality of life for CIPN patients was affected by changes in blood glucose levels during and after NACT. In conclusion, the retrospective phase shows that diabetes negatively affects both pathological complete response (pCR) and pathological partial response (pPR). However, the prospective analysis found no significant association between dynamic blood glucose changes during treatment and pathological responses.

CHAPTER 1

INTRODUCTION

1.1 Background and Context

1.1.1 Epidemiology of Breast Cancer

Cancer is a disease that is characterized by uncontrolled growth of affected body cells and leads to disruption of the proper functioning of normal cells within the body. According to the World Health Organization (WHO) fact sheet from 2018, cancer is one of the major causes of death around the world, with 9.6 million deaths in 2018 (Shimbre et al., 2019) to a 22 million increase in cancer incidence in 2032 (Wang et al., 2020).

Breast cancer is a significant health concern in developed and underdeveloped countries. According to the 2022 cancer statistics, there are 287,850 new cases of breast cancer in females, with more than 43,250 estimated mortalities in developing countries (Giaquinto et al., 2022). According to the Global Cancer Observatory (GLOBOCAN 2020), breast cancer is the 5th leading cause of mortality, and 2.3 million new cases have been reported worldwide (Łukasiewicz et al., 2021). In the USA and Asia, the global prevalence of breast cancer ranges from 15.8% to 29.6% (DeSantis et al., 2016). 45.4% of the 2.3 million breast cancer (BC) cases diagnosed in 2020 were from Asia(Lim et al., 2022). The mortality rate of breast cancer patients is 16.3% in Europe, whereas 14.6% in Asia. The mortality rate is increasing gradually, and approximately one million women are expected to die due to breast cancer by 2040 (Sung et al., 2021).

1.1.2 Epidemiology of Breast Cancer in Pakistan

In Asia, there are 8.2 million newly diagnosed cancer cases annually, with about 404,000 cases related to breast cancer (Youlden et al., 2014). In Pakistan, a total of 178,388 individuals were diagnosed with various forms of cancer in 2020, with 25,928 newly diagnosed breast cancer cases, which represents the highest ratio in Asia (Javed et al., 2022). The incidence of cancer is on the rise globally, with particularly high rates in countries such as India, Sri Lanka, Bangladesh, and Pakistan. Various reports indicate an alarming situation regarding cancer in the population of Pakistan. Breast cancer is the most prevalent cancer in the population of Punjab, Pakistan, and it is especially common among females. The prevalence rate consistently increased throughout the period, with a higher number of new cases emerging each year (Hafeez et al., 2020). In Pakistan, every 1 out of 9 women is at risk of breast cancer, an expected 90,000 women are diagnosed, and 40,000 women die every year in Pakistan with breast cancer (Abid et al., 2022). Lung cancers are the highest cause of mortality worldwide. Nevertheless, breast cancer had the highest mortality rate in Pakistan (Saeed et al., 2019).

The significant increase in annual breast cancer cases may be attributed to lifestyle changes, obesity, reduced breastfeeding, and the use of oral contraceptives. (Asif et al., 2014).According to the 2018-2019 Pakistan Atomic Energy Cancer Registry Report (PAEC), there were 5,249 cases of breast cancer in Punjab. The available data from these countries is mainly hospital-based. Hospital and institutional records are essential sources of information in these regions. Hospital records provide convenient data for understanding disease patterns and highlight critical research issues (Khokher et al., 2012).

Some specialized cancer hospitals in Pakistan, such as the Gujranwala Institute of Nuclear Medicine and Radiotherapy (GINUM) in Gujranwala, Punjab, play a crucial role in cancer care. GINUM, a tertiary care nuclear medical center and dedicated cancer hospital, has been offering cancer treatment and services as a public-sector institution since 2010. Our study on breast cancer was conducted for the first time in Gujranwala, Punjab, Pakistan, which is a major industrial city (Shaukat et al., 2013). According to the medical record of the GINUM hospital, a total of 3982 cancer cases were enrolled in the last 5 years (Jan 2016-Jan 2021), including breast cancer, gallbladder, prostate, colon, liver, and uterus. The total number of breast cancer cases within 5 years was 2332(58.6%) as compared to other cancers, 1650 (41.4%) (gallbladder, prostate, colon, liver, uterus).

1.1.3 Breast Cancer and Diabetes

Type 2 diabetes mellitus (hereafter referred to as diabetes) is a heterogeneous disease, and its prevalence is increasing globally. According to the report of recent international diabetic federation statistics (Atlas, 2015), an estimated 424 million people are affected by diabetes, an expected rise to 552 million by 2030 (Saeedi et al., 2019). Diabetes and breast cancer are both the most prevalent diseases among women. Approximately 15-20% of breast cancer patients are affected by diabetes (Bronsveld et al., 2017). The presence of diabetes along with breast cancer could alter treatment response, chemotherapy complications, or affect prognosis (Zhao et al., 2016). Previous studies have shown that diabetes reduces the sensitivity of tumors and decreases the effectiveness of chemotherapy in breast cancer patients. Consequently, a lower response rate to chemotherapy is observed in diabetic breast cancer patients (Arici et al., 2020a; Jiralerspong et al., 2009b).

The several mechanism including on how diabetes reduces sensitivity of tumor like hyperinsulinemia, hyperglycemia (insulin resistance) or chronic inflammation (Giovannucci et al., 2010). Diabetes, particularly type 2 can lead to change in the tumor microenvironment that make cancer cells less sensitive to treatment and potentially more aggressive. High blood glucose provide abundant energy source for tumor cells,enhancing their proliferaton and survival through warburg effect.T2DM often involve insuline resistance leading to compensatory hyperinsulinemia. Insulin is a growth factor that activates P13/AKT/mTOR signaling pathway, promoting cell survival, proliferation ,Angiogensis. Diabetes induce a low grade chronic inflammatory state:(TNF-Alpha,IL-6)enhance DNA damage repair and inhibit apoptosis. This make tumor cell more resilient to cytotoxic agent(Xu et al., 2014).

Cancer patients with and without diabetes who undergo chemotherapy may have an increased risk of chemotherapy-induced peripheral neuropathy (CIPN) due to high blood glucose levels during treatment (Sempere-Bigorra et al., 2021).

A well-designed meta-analysis by De Brujin KM et al. reported breast cancer with concomitant diabetes increases breast cancer mortality with a hazard ratio of 1.26 (95%CI: 1.14 -1.40) as compared to the peers without diabetes (De Bruijn et al., 2013). Another published meta-analysis demonstrated that preexisting diabetes is associated with a 37% greater risk of all-cause mortality in breast cancer women (Y. Zhou et al., 2015). Another systematic review and meta-analysis were performed focusing on the impact of diabetes in terms of disease-free survival and relapse-free period in women with breast cancer, demonstrating breast cancer women with diabetes have poor overall survival and disease-free survival by 51% and 28%, respectively, compared to those without diabetes. However, the relapse-free period did not differ significantly between the two populations (Zhao et al., 2016).

1.2 Breast Cancer Molecular Subtypes

Breast cancer can be classified into four major molecular subtypes based on their estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) status, and ki67 status (Ross et al., 2005).

Figure 1.1 illustrates the classification of major molecular subtypes of breast cancer.

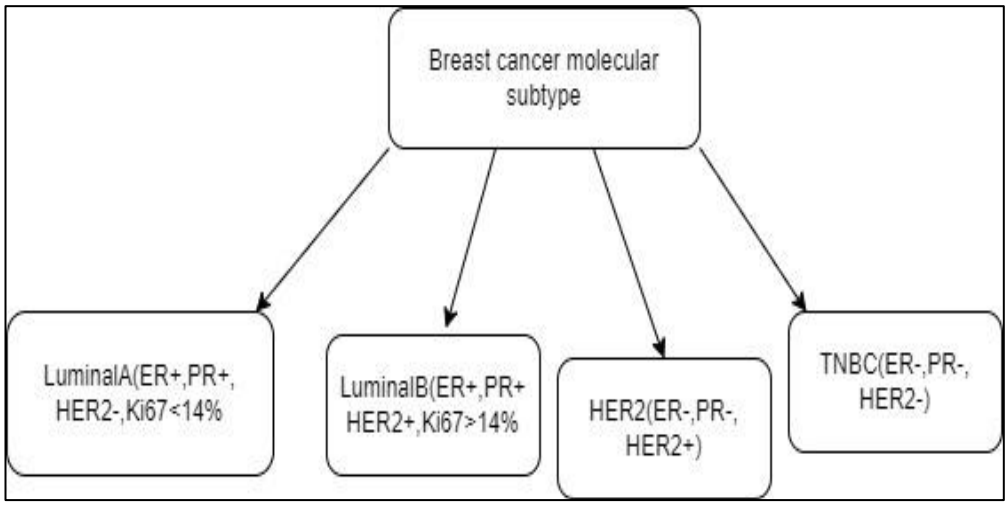

Figure 1.1 Breast cancer molecular subtypes (Burguin et al., 2021)

Luminal A breast cancer is characterized by positive ER and PR status (often higher levels of ER and PR receptor compared to other subtypes), negative HER2 status, and low levels of Ki-67, a marker for cell proliferation (ER+, PR+, and HER2-). This type of breast cancer accounts for 60% of breast cancer cases and is associated with a favorable prognosis, indicated by a Ki-67 proliferation marker level of less than 14% (Inic et al., 2014).The 30% of breast cancer cases are associated with Luminal B breast cancer, characterized by being ER+, PR+, and HER2+, and a proliferation marker ki-67 (>14%), leading to a poor prognosis (Tran et al., 2011).

HER2-positive breast cancer, which is estrogen receptor-negative, progesterone receptor-negative, and HER2-positive, accounts for 10% of breast cancer cases and is associated with a poor prognosis. Triple-negative breast cancer, which is estrogen receptor-negative, progesterone receptor-negative, and HER2-negative, represents 15-20% of breast cancer cases and is associated with a worse prognosis compared to other molecular subtypes (Burguin et al., 2021). The common treatment in all breast cancer subtypes involves chemotherapy, surgery, and radiotherapy (Pisani et al., 2002).

1.3 Breast Cancer Stages

Breast cancer stages can be defined as the combination of tumor (T), nodes (N), and distant metastases (M) category designations. It is the most clinically useful staging system developed by the AJCC; based on T, N, and M classification, the stages can be categorized into 4 stages as described in Table 1.1. Stage 0 is defined as carcinoma in situ (Tis) (Koh et al., 2019).

Table 1.1 Breast cancer staging

Stages	**T stage**	**N stage**	**M stage**
Stage 0	Tis	N0	M0
Stage1			
IA	T1	N0	M0
IB	T0-T1	N1	M0
Stage 2			
IIA	T0-T1	N0-N1	M0
IIB	T2-T3	NO-N1	M0

Table 1.1 (Continued)

Stages	T stage	N stage	M stage
Stage 3			
IIIA	T0-T3	N2	M0
IIIB	T4	N0-N2	M0
IIIC	Any T	N3	M0

Abbreviation: Tis=Carcinoma in situ, T0=No evidence of primary tumor, T1-T4=a higher category means increasing in tumor size, N0=No regional lymph node, N1-N3=increasing the regional nodal group, M0=no evidence of metastasis

1.4 Breast Cancer Grades

Breast cancer grades are defined as the qualitative assessment of the degree of differentiation of the tumor. It may show the extent to which a tumor resembles normal tissue. Breast cancer grades are classified into 3 grades: Grade 1, a low, and a well-differentiated grade. Grade 1 cancer cells are slightly different from normal cells. Grade 2 cancers are moderately differentiated; they are different from normal cells and grow faster than normal. Grade 3 is poorly differentiated, is different from normal cells and disorganized, irregular patterns, and many cells divide and make a new cell (Van Dooijeweert et al., 2022).

The Tumor Node Metastasis (TNM) system is used to determine the stage of cancer based on tumor size, involvement of lymph nodes, and metastasis. The grade of cancer indicates how different the cancer cells look compared to normal cells (Amin et al., 2017).

1.5 Breast Cancer Treatment

The treatment options for breast cancer patients are determined by the cancer stage, grade, and molecular subtypes to ensure safe and effective treatment. In Pakistan, the National Comprehensive Cancer Network (NCCN) or European Society

for Medical Oncology (ESMO) guidelines are used to guide the treatment of breast cancer (Gradishar et al., 2021). In Pakistan, the standard treatment for locally advanced breast cancer patients is taxane and anthracycline-based neo-adjuvant chemotherapy (NACT). After the course of chemotherapy, patients undergo surgery and radiation (Zahid et al., 2010). The standard neo-adjuvant chemotherapy (NACT) protocol for breast cancer includes Adriamycin and cyclophosphamide for 4 cycles, followed by docetaxel for 4 cycles. For HER2-positive patients, trastuzumab is administered along with docetaxel. After 4 weeks of NACT, the surgical procedures of modified radical mastectomy and breast conservation surgery were performed (Farrukh et al., 2022). Figure 1.2 explain the breast cancer treatment according to the breast cancer stages.

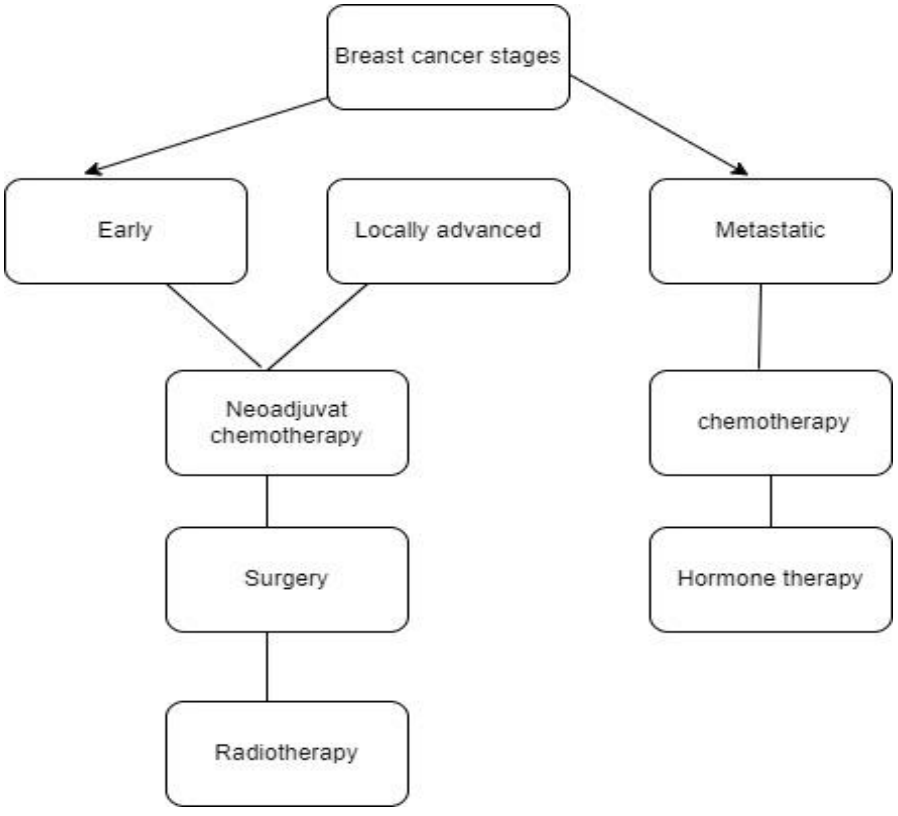

Figure 1.2 Breast cancer treatment according to the stages

1.5.1 Chemotherapy

Breast cancer chemotherapy includes different families of cytotoxic drugs, containing alkylating agents, antimetabolites, and tubulin inhibitors (Nabholtz et al., 2005). The selection of preoperative chemotherapy is according to the characteristics of the breast tumor (Łukasiewicz et al., 2021). The anthracyclines mechanism includes DNA intercalation or inhibiting macromolecular biosynthesis (Gewirtz, 1999). Taxane, containing paclitaxel and docetaxel, binds to microtubules, leading to cell cycle arrest and apoptosis (Moos et al., 1998). Chemotherapy can be categorized into neo-adjuvant or adjuvant chemotherapy.

1.5.2 Neo-Adjuvant Chemotherapy

Neo-adjuvant chemotherapy (NACT) is used for locally advanced breast cancer before the surgical procedure to make inoperable tumors into operable tumors. (Montemurro et al., 2020).NACT is also a treatment for stage II/III breast cancer patients (Y. Yang et al., 2016b).

Chemotherapy administered before surgery (NACT) or after surgery(Adjuvant chemotherapy) (Broët et al., 1999; G von Minckwitz et al., 2001). NACT is used to maximize the pathological response in breast cancer molecular subtypes (HER2, TNBC). NACT may minimize the tumor or simplify the surgical procedure. Additionally, it determines which drugs will produce the best response or evaluates how susceptible they are to the tumor (Chou et al., 2019b).

However, many breast cancer patients who undergo NACT may not achieve a pathological complete response (pCR). Therefore, clinical intervention is necessary to improve their outcomes. One potential approach to overcome treatment resistance

involves additional adjuvant therapy for patients who do not achieve pCR after NACT (Caparica et al., 2019). The main disadvantages of NACT during the early stage (0-6 months after the treatment) include hair loss, low blood cell count, muscle pain, and chemotherapy-induced peripheral neuropathy (CIPN) (Tao et al., 2015).

1.5.3 Adjuvant Chemotherapy

Adjuvant chemotherapy is administered after primary surgery to inhibit micro-metastases or to extend the survival of breast cancer patients. It is given to patients at high risk of recurrence or with lymph node metastases (Chew, 2001).

The adjuvant chemotherapy consists of anthracyclines and taxane. HR-negative breast cancer patients benefit more from adjuvant chemotherapy in terms of mortality and recurrence than HR-positive patients (Berry et al., 2006). Adjuvant chemotherapy can be administered along with targeted therapy (trastuzumab for HER2 patients) in breast cancer molecular subtypes. Patients with hormone receptor-positive (estrogen and progesterone receptor-positive) breast cancer after chemotherapy should receive endocrine therapy, and HER2-positive breast cancer patients should receive trastuzumab (Berry et al., 2006).

1.5.4 Surgery

Surgery is the most suitable option for patients whose breast cancer has not spread to other areas of the body (Akram et al., 2017). Surgery is helpful in decreasing the spread of cancerous cells. The two primary surgical approaches for treating breast cancer are mastectomy, which involves the total removal of the breast, and lumpectomy, which entails removing the tumor along with a margin of surrounding

healthy tissue (Schnitt et al., 2020). The surgical procedure is performed 3-4 weeks after NACT (Farrukh et al., 2022).

1.5.5 Radiotherapy

Radiotherapy is started after 1 month of surgery and chemotherapy in breast cancer treatment (Łukasiewicz et al., 2021). The purpose of radiotherapy is to destroy all cancerous cells or reduce the risk of breast cancer recurrence. The selection of radiotherapy type depends on the type of surgery or other clinical situation (Łukasiewicz et al., 2021).

After a mastectomy, high-energy radiation is used to treat the entire breast or the affected area of the breast (Boyages, 2017). This treatment is recommended for patients at high risk of recurrence, those with a high tumor burden, positive lymph nodes, and grade 3 breast cancer (Bartelink et al., 2015). For patients with positive lymph nodes, radiation therapy reduces the chance of recurrence and breast cancer mortality compared to patients with negative lymph node status (McGale et al., 2014).

1.6 Pathological Responses Measured after NACT

The main aims of NACT are to reduce the size of the tumor, make breast-conserving surgery easier, and evaluate the tumor's response to chemotherapy. Following 2-4 weeks of NACT, patients with locally advanced breast cancer undergo surgery (Chou et al., 2019a).

NACT has the benefit of downsizing the tumor and enabling monitoring of the treatment effectiveness, including the treatment of micrometastasis (Makris et al., 1998; Mauriac et al., 1999). It assesses the tumor's sensitivity to certain drugs and

identifies which drugs yield the most favorable response. This process aids in gauging the effectiveness of various drugs against the tumor (Gralow et al., 2008; King et al., 2015).

Evaluating tumor response to specific drugs during NACT involves several key aspects. In addition to tumor reduction, pathological assessment is one of the evaluation parameters. Following surgical removal of the tumor after NACT, a pathological examination of the tumor tissue is conducted. This assessment provides valuable information about the extent of tumor cell death (necrosis) and the degree of tumor regression. Pathologists evaluate factors like the percentage of viable tumor cells, fibrosis, and inflammation, which help gauge the tumor response to chemotherapy (Carey et al., 2007).The pathological responses are categorized as pathological complete response (pCR), pathological partial response (pPR), and pathological no response (pNR), serving as a validated surrogate endpoint for survival after NACT. The main goal of this chemotherapy efficacy evaluation is achieving a complete pathological response (pCR) and removing the invasive tumor in the surgical specimen after the NACT (Carey et al., 2007).

pCR is dependent on the molecular subtypes of breast cancer, with estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor (HER2) (Hassinger et al., 2020). Some molecular subtypes have a favorable response to NACT i.e., tumors that are positive for HER2 and triple-negative breast cancer (TNBC). Tumors that are negative for HER2 and positive for hormone receptor (HR) have a poor pathological response, so in this type of patient, surgery may be preferable to NACT (Coates et al., 2012; Schott et al., 2012). HER2-positive patients are associated with a high pCR rate when NACT contains HER2-directed therapy e.g. trastuzumab (Rouzier et al., 2005).

Those with a partial pathological response or no response are commonly categorized as one term called ‘residual disease’. This group may require additional personalized treatments such as post-neoadjuvant chemotherapy (Caparica et al., 2019). An accurate assessment of the response to NACT gives important information regarding the impact of systemic treatment on breast cancer prognosis and additional therapy (H. Wang et al., 2020).

1.7 Pathological Responses Assessment

The pathological responses are assessed separately following the surgical removal of the remaining tumor and subsequently are reviewed by an independent pathologist using the multiple techniques available to asses pathological responses, including the Miller-Payne (MP), Chevallier, Sataloff, and American Joint Committee on Cancer (AJCC) response criteria (Shintia et al., 2016).

In the MP method, responses are assessed by measuring the decrease in tumor cellularity between biopsy and mastectomy tissues. This MP method contains the following categories. Grade 1 (no response), Grade 2 (a minor loss of tumor cell), Grade 3 (30% and 90% reduction in tumor cells), Grade 4 (more than 90% loss of tumor cell) and Grade 5(pCR) (Shintia et al., 2016).

In the Sataloff and Chevallier system, similar to the MP system, the cellularity and histological grade of pre-NACT tumors and those of post-NACT tumors are compared. This comparison depends on the initial carcinoma and lymph node status (Earl et al., 2015; Sahoo et al., 2009).

Residual Cancer Burden (RCB) is a different method that measures the remaining disease after NACT without focusing on the actual response. The score is

calculated based on the dimensions of the remaining invasive cancer, including the size of the tumor and the proportion of in-situ disease. This is determined by examining up to five slides representing the largest tumor size, the number of affected nodes, and the size of the metastasis. RCB scores and class can be obtained by an online calculator that quantifies residual disease. It is user-friendly, reproducible, and has been clinically verified using long-term follow-up data (Provenzano et al., 2015).

The AJCC has postoperative pathologic stage classification criteria based on the findings in the breast and regional lymph node after surgery (H. Wang et al., 2020). Recently, the AJCC established new response criteria for NACT in breast cancer, it is clinically useful for evaluating the response of NACT (Keam et al., 2013). The AJCC response criteria are simple and mostly used in high-risk patients requiring additional adjuvant treatment (Y. Yang et al., 2016a).

1.8 Blood Glucose Trajectories

A single blood glucose value is insufficient to explain the patterns of morbidity and mortality associated with dysglycemia in diabetes. Dysglycemia, which encompasses both hyperglycemia and hypoglycemia and the degree of glucose fluctuation, is collectively referred to as glycemic variability (Jin et al., 2016). Glucose variability refers to the degree of fluctuation in blood glucose levels within a given timeframe, including rapid swings between hyperglycemia (high blood glucose) and hypoglycemia (low blood glucose) and the stability of glucose levels. High glucose variability is often associated with an increased risk of diabetes-related complications, including cardiovascular events, and can complicate diabetes management (DeVries, 2013).

Glycemic variability can be measured using several methods, including fluctuations in blood glucose levels within a single day, hypoglycemic episodes, and variations in glucose levels from visit to visit (Yang et al., 2015). The rising trend of both high and low blood glucose levels can lead to diabetes-related complications such as neuropathy, nephropathy, and cardiovascular diseases (Huang et al., 2023). Furthermore, glycemic variability is associated with oxidative stress, endothelial dysfunction, and inflammation—variables commonly linked to vascular damage that might be missed with a single measurement (Prázný et al., 2017) Glycemic variability exacerbate oxidative stress and mitochondrial damage in peripheral nerves. GV may potentiate this damage and worsen nerve degeneration. Reactive oxygen species (ROS) to induce apoptosis in cancer cells. However, ROS generated during chemotherapy may interfere with the normal cells and tissues and may be associated with the various toxic events like cardio toxicity, nephrotoxicity, neurotoxicity, etc (Areti et al., 2014).

It is important to assess glycemic variability at each time points with FBG or HbA1c (Lee et al., 2018) and through group trajectories during treatment (Penckofer et al., 2012). Despite its significance, glycemic variability has often been overlooked. It is recognized as an independent factor in developing microvascular and macrovascular complications in diabetes patients, exerting negative effects beyond hyperglycemia and hypoglycemia alone (DeVries, 2013).

Glucose trajectories refer to the patterns and trends of blood glucose levels over time. Repeated measurements can track these trajectories, illustrating how glucose levels rise and fall in response to various factors such as medication, diet, exercise, stress, and disease progression (Swislocki, 2022). Glucose trajectories provide a comprehensive view of a patient's glucose control, capturing both short-term

fluctuations and long-term trends. The interdependence of glucose trajectories and glucose variability is crucial. A trajectory showing significant fluctuations indicates high glucose variability, while a more stable trajectory suggests low variability (Ceriello et al., 2010). Analyzing both aspects provides a clearer picture of a patient's glycemic control. Understanding glucose trajectories and variability together can improve risk assessment for diabetes-related complications. For instance, a trajectory with frequent and large fluctuations (high variability) may indicate a higher risk of complications than a more stable trajectory, even if average glucose levels are similar (Penckofer et al., 2012).

Monitoring glucose trajectories helps identify periods of high variability, which can inform adjustments in treatment plans. For example, recognizing that a patient experiences frequent postprandial hyperglycemia (a peak in the glucose trajectory) can lead to changes in medication timing or dietary advice to reduce variability (Nagin et al., 2010). Detailed glucose trajectories and variability analysis can provide insights into how different behavior or external factors affect blood glucose control. This can be useful for personalized diabetes management, allowing patients and healthcare providers to identify and mitigate specific causes of high variability.

Studies have shown that sustained hyperglycemia and high glucose variability are linked to poor clinical outcomes. Therefore, addressing both the overall glucose trajectory (long-term control) and variability (short-term stability) is crucial for optimizing diabetes management and reducing the risk of complications (Martinez et al., 2021).

Group-based trajectories are crucial for capturing dynamic changes during treatment and are invaluable for clinicians in observing the progression of various chronic diseases and treatment responses (Nagin & Odgers, 2010). Individuals who regularly experience hypoglycemia and glycemic variability are more likely to suffer from mood swings, depression, and a lower quality of life (Krishna et al., 2013).

To better understand the relationship between diabetes and breast cancer, future research should investigate the link between glycemic fluctuation episodes in individuals with and without diabetes, as well as in breast cancer patients (Monnier et al., 2011). Previous retrospective studies have shown a higher incidence of diabetes and hyperglycemic episodes in breast cancer patients (Arici et al., 2020a). Further prospective studies are necessary to determine the impact of fluctuating blood glucose levels on the pathological responses in women with breast cancer, both with and without diabetes (Hirakawa et al., 2014).

1.9 CIPN Occurrence and QoL Associated with CIPN

QoL is recognized as a subjective multidimensional concept. The term health-related quality of life is often used to indicate the QoL as it links to disease or treatment (Boling et al., 2003). Breast cancer has a predominant malignant tumor. Taxanes are one of the most important NACT for breast cancer. Chemotherapy-induced peripheral neuropathy (CIPN) is a well-known side effect of taxanes, which has a negative effect on patient QoL (Mo et al., 2022).

CIPN is a group of neuromuscular symptoms that occur due to nerve damage caused by different chemotherapy treatments for cancer. CIPN is the most common side effect of chemotherapy (Visovsky, 2003). Furthermore, CIPN has the potential to

disrupt the QoL of breast cancer women, such as physical, social, functional, and emotional well-being (Tanay et al., 2017).

A 30%-40% prevalence of CIPN was reported after the use of chemotherapy. CIPN depends on the type, duration, and dosage of chemotherapy used during treatment. The symptoms of CIPN are reversed, but most patients experience symptoms after the chemotherapy (Vissers et al., 2015).

1.9.1 Risk Factors and Symptoms of CIPN

CIPN can be categorized as either sensory or motor symptoms. Motor symptoms include myalgias, arthralgias, muscle weakness, and loss of balance. Sensory symptoms affect sensation and may include pain, tingling, numbness and sensitivity to cold or heat (Sweeney, 2002).CIPN starts with numbness and paresthesia and results in patient functional impairment. These symptoms are responsible for impaired individual QoL and can be assessed through communication with the patient rather than clinical tests. While in some patients symptoms improve through effective glycemic control (Sempere-Bigorra et al., 2021).

CIPN strongly affects patients' daily activities like buttoning up a blouse, holding a pen, and opening a bottle. Also, aching or burning in the hand and fingers and similar effects might be experienced in the feet and toes when walking or driving. These symptoms can cause interruptions in social well-being, usual activities, and household work (Mols et al., 2014).The symptoms can occur at any point at the start of the treatment, including weeks to months or after the end of chemotherapy. The main risk factors include neurotoxic agent, diabetes ,older age, and obesity (Brewer et al., 2016).

1.9.2 Measurement of CIPN

There is a lack of assessment of psychometric evidence to support the use of patient-reported instruments in cancer populations. The existing literature mainly uses two methods: clinician evaluation and patient-reported outcome measures (Dunlap et al., 2006).

1.9.3 Clinical Evaluation of CIPN

The evaluation of the symptoms during and after chemotherapy is essential for the oncologist and patients to completely understand the occurrence of CIPN and treat it at an early stage. Evaluation of subjective symptoms using the National Cancer Institute Common Toxicity Criteria (NCI-CTCAE) version 4.0, mostly used by physicians to grade neuropathy (Shimozuma et al., 2012). The NCI-CTCAE criteria are widely used in oncology settings to assess the severity of CIPN during cancer therapy. The severity of peripheral sensory or motor neuropathy is assessed in 5 grades, as shown in Table 1.2 (Hung et al., 2021).

Table 1.2 National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE)

CTCAE term	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Peripheral motor neuropathy	Normal	Asymptomatic, clinical, or diagnostic observational only (including tingling) Paresthesia	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting instrumental ADL	Life-threatening consequences: urgent intervention indicated	Death
Peripheral sensory neuropathy	Normal	Asymptomatic	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting instrumental ADL	Life-threatening consequences: urgent intervention indicated	-

Abbreviation: ADL=Activity of daily living

The grade 0=normal, grade1=mild symptoms, grade2=moderate, grade 3=severe, grade=4 life-threatening symptoms, and grade 5=death (Cavaletti et al., 2010; Tan et al., 2019).According to the previous study, it was determined that 73% of the patients developed CIPN after completing chemotherapy. Among these patients, 36% had grade 2, 4% had grade 3 neuropathy, whereas less than 1% had grade 4 neuropathy (Srivastava et al., 2022).

1.9.4 Patient-Reported Outcome of CIPN

QoL questionnaires are commonly used to assess the progress of patients and their response to ongoing therapies, validate the laboratory test results, and evaluate the effect of clinical interventions (Meguro et al., 2007).

The most important patient-reported outcome (PRO) questionnaire for CIPN is the Functional Assessment of Cancer Therapy/Gynecological Oncology Group-Neurotoxicity scale (FACT/GOG-Ntx). This scale has shown good reliability, internal consistency, and validity (Park et al., 2019). In our cohort study, both physicians rated CIPN, and patients reported CIPN is used for accurate evaluation of CIPN. FACT/GOG-Ntx is mostly used in cancer patients to assess the QoL associated with CIPN. It has been translated into 27 languages, including French, German, Spanish, Thai, and Japanese. This questionnaire is used in breast, nasopharynx, lung, and liver cancers. It consists of four general subscales or symptoms-specific domains (Boling et al., 2003).Different factors are involved in selecting the most appropriate CIPN scale when considering neuropathy. First, the impact on the patient's well-being. Second, factors such as the patient's literacy rate. The FACT/GOG-Ntx subscale is comprehensive and correlated with the objective measure of neuropathy over time. The FACT/GOG-Ntx is a disease-specific measure because each measure describes

the responsive dimension of life, valid and reliable for assessing the impact of QoL associated with CIPN (Calhoun et al., 2003).

1.10 Problem Statements

The impact of diabetes on the pathological responses in women with breast cancer during NACT treatment has been highlighted in previous literature. However, no major study has been conducted on the Pakistani population. Assessing the NACT response plays a crucial role in clinical research and guides further therapy for breast cancer patients. Previous literature has provided predictors of pCR, but the risk factors for achieving a pathological partial response (pPR) and pathological no response (pNR) have not been fully reported. Those with a pPR or pNR are commonly categorized as one term called 'residual disease'. This group may require additional personalized treatments, such as post-neo adjuvant chemotherapy (Caparica et al., 2019).

Multiple techniques are available to asses pathological responses, including the Miller-Payne (MP), Chevallier, Sataloff, and American joint committee on Cancer (AJCC) response criteria (Shintia et al., 2016). The AJCC response criteria provide a straightforward and easily applicable approach to appraising treatment responses among breast cancer patients undergoing NACT, as compared to other methods such as Residual Cancer Burden and the MP grading system. The American Joint Committee on Cancer (AJCC) response criteria are widely accepted and employed globally for tumor classification and staging. Their validity is well-supported by numerous studies demonstrating a consistent association between AJCC-based response assessments and long-term clinical outcomes, including overall survival and disease-free survival, particularly across various solid tumors. In terms of reliability,

several investigations have reported acceptable interobserver agreement when the criteria are applied by trained healthcare professionals, especially in centers where standardized training and staging protocols are in place (Ogston et al., 2003; Symmans et al., 2007). The AJCC response criteria provide a structured and widely endorsed framework for assessing tumor response. These criteria have been validated across multiple cancer types, with demonstrated prognostic value for survival and recurrence outcomes(Gan et al., 2025). Furthermore, studies have shown that the criteria can be reliably applied by trained clinicians, though inter observer variation may occur in borderline cases (Elmore et al., 2018; Jang et al., 2019)

Furthermore, the AJCC response criteria possess the potential to address the limitations of pathological responses as they may be effectively applied across diverse breast cancer subtypes and demonstrate greater utility in high-risk patients who subsequently receive adjuvant chemotherapy (Y. Yang et al., 2016b).

Previous studies have demonstrated a significant impact of diabetes status on pathological response in breast cancer patients; however, many of these studies have relied on categorical data of blood glucose levels or cross-sectional information on diabetes status to investigate causality. Categorical data simplify individuals into distinct groups, potentially overlooking variability within each group and obscuring nuances in the relationship between diabetes status and pathological responses, such as differences in glycemic control, duration of diabetes or treatment regimens among diabetic individuals.

Determining the impact of trajectories of blood glucose over the treatment period of breast cancer on pathological responses provides a granular understanding. Trajectories of blood glucose offer a detailed insight into glycemic control dynamics,

enabling the detection of subtle changes over time. This granularity is crucial for capturing fluctuations in blood glucose levels that potentially influence cancer progression and treatment outcomes.

Examining blood glucose trajectories also facilitates exploring temporal relationships between glycemic control and pathological responses in breast cancer. Longitudinal tracking of blood glucose levels allows us to assess how changes in glycemic control correlate with changes in cancer pathology, thereby offering insights into potential causal relationships. The variabilities in glucose metabolism, treatment adherence, and lifestyle factors affect individualized individualised responses to glycemic control measures (Hershey, 2014). This personalized approach aids in identifying patients who may benefit most from targeted interventions to optimize glycemic control and improve cancer outcomes. Moreover, in patients with breast cancer, many factors can contribute to hyperglycemia, including nutritional imbalances, physical inactivity, older age, high body mass index, and high-stress levels (Hershey, 2014).

However, to date, few studies have examined these dynamic patterns longitudinally in the context of breast cancer treatment, particularly regarding its impact on pathological responses in women with breast cancer undergoing neo-adjuvant chemotherapy.

Chemotherapy-induced peripheral neuropathy (CIPN) can present a significant challenge for the oncology team in a clinical setting. When treating CIPN, the major focus is on reducing pain, and maintaining daily activities is of primary importance (C. S. Tofthagen et al., 2020). Generic instruments may not sufficiently address specific issues related to cancer. Cancer-specific QoL instruments have been used for

cancer patients in oncology studies. FACT-G is the generic questionnaire along with the disease-specific, symptoms-specific domains. For CIPN, the FACT-G is used along with Ntx (FACT/GOG-Ntx) symptoms-specific domains (Boling et al., 2003).

Currently, in Asian countries like Pakistan, there is a lack of a tool to assess CIPN symptoms and to assess the QoL associated with CIPN in breast cancer women without concomitant diabetes. To assess the severity of the CIPN, the use of FACT/GOG-Ntx along with the FACT-G was not validated or used in the Pakistani population, especially for CIPN breast cancer women. Thus, in this study, we evaluated the psychometric properties of the FACT/GOG-Ntx subscale in breast cancer women without concomitant diabetes.

Early detection of CIPN may prevent long-term damage to peripheral nerves. The assessment of CIPN should depend on effective and reliable clinical approaches (Tanay et al., 2017). Typically, physicians evaluate neuropathic signs through clinical examination (sensory and motor abnormalities). Oncology practitioners use the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) as the most commonly used criteria for neuropathy in clinical practice (Tan et al., 2019).

There has been a need to understand the patient's perception of CIPN because patient-reported outcomes are important to capture the symptoms' severity and impact on the patient's activities of daily living. Patient-reported information is also important for the clinician, as treatment modification often occurs due to the CIPN (T. Li et al., 2022). For this purpose, various questionnaires have been created to overcome the limitation of patient interviews during the medical examination (Cavaletti et al., 2010). Currently, there is a lack of a QoL of CIPN instrument specifically designed in the