

Clinicopathological Features of Breast Cancer Patients Who Have Type II Diabetes Mellitus

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Abstract

Background: The breast cancer is highly incident disease of women in Iraq. Type II diabetes mellitus is a common public health problem in Iraq related to high prevalence of obesity.

Objective: To clarify the association between type II diabetes and clinicopathological characteristics of women with breast cancer in Erbil city/Kurdistan region.

Patients and methods: A retrospective cross sectional study conducted in Oncology center of Rizgari Teaching hospital in Erbil city-Kurdistan region/Iraq through duration period of three years from first of January 2019 to 31st of December 2021 on sample of two hundred women with breast cancer was selected after eligibility to inclusion and exclusion criteria. The selected women were divided into two groups (100 breast cancer women with type II diabetes mellitus and 100 breast cancer women without type II diabetes mellitus).

Results: The means of age, body mass index and breast cancer duration for diabetic women with breast cancer were significantly higher than non-diabetic women with breast cancer ($p < 0.001$). A highly significant association was observed between tumor multi-focality diabetic women with breast cancer ($p = 0.04$). The distant metastasis of breast cancer was significantly associated with diabetic women with breast cancer ($p = 0.03$). Poor glycemic control of type II diabetic women with breast cancer are related to advanced lymph nodes invasion, advanced breast cancer grading and staging with positive perinural invasion.

Conclusions: The type II diabetic women with breast cancer are at high risk of multi-focal breast cancer with distant metastasis.

Keywords: Breast cancer, Type II diabetes mellitus, Glycemic control.

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1 | INTRODUCTION

Breast cancer is recently the most prevalent cancer globally with high incidence reaching to 2.3 million new cases and one of top five cancers responsible of higher mortalities all over the world (1). The breast cancer represented the highly incident cancer and the common cause of death for Iraqi women. The incidence of breast cancer increased in last two decades in Iraq with high age-related incidence rate exceeding incidence of the disease in neighboring countries (2). In Iraqi Kurdistan, the breast cancer is the first registered cancer for women in last ten years with higher incidence in younger age women (3,4). The main risk factors for breast cancer in women living in Kurdistan were unemployment, smoking, nulliparity, oral contraceptive pills and positive family history of breast cancer 4. Although this aggressiveness of breast cancer in Iraq, high proportion of women were diagnosed with locally advanced disease that enable preventive programs to limit the advancement of death rates (5).

The breast cancer staging is important for description of tumor extent and enabling the physicians in treatment plans and disease prognosis (6). Nowadays, the staging of breast cancer is commonly derived from the American Joint Committee on Cancer classification (7) that incorporated the biomarkers such as histological grading, estrogen receptors, progesterone receptors, human epidermal growth factor receptor 2 (HER2) expression and genes expression to the traditional anatomical TNM staging (8). The Iraqi women with breast cancer showed various clinical course in regard to different pathological and biological pictures of breast tumor that need different treatment plans. It was shown that these differences in clinicopathological characteristics of breast cancer women in Iraq are dependent on women's age and their clinical staging at diagnosis. For developing countries, the molecular subtype staging is favorable in classifying the breast cancer and helpful in prognosis and monitoring of management of cancer at late stages (9).

Diabetes mellitus (DM) type II is a metabolic public health problem with evolving incidence in all different areas of the world related to high prevalence of obesity, westernization of lifestyles and physical inactivity (10). The type II DM is regarded as an epidemic health burden affecting millions of peoples (11). The prevalence of type II DM in Iraq was (19.7%)

at 2012 and prevalence of poor glycemic control was (48.8%) (12). Predominance of female gender in type II DM in Kurdish population was observed and the common co-morbidities encountered for type II DM in Kurdistan were dyslipidemia, hypertension, cardiac disorders, renal diseases and neurological complications (13).

The relationship between breast cancer and non-communicable diseases risk factors is documented ecologically (14). The link between type II DM and risk of breast cancers and prognosis were recorded by many literatures. Many authors reported that type II DM is accompanied by 14-25% higher risk of breast cancers (15–17) and co-existence of both type II DM and breast cancer lead to increased mortality rate by 37-61% as compared to breast cancer women without type II DM (18–20). This effect of diabetes mellitus on prognosis of breast cancer might be attributed to abnormal metabolic changes in addition to effect of weak screening efforts and improper diagnosis (21). The type II DM is sharing the same risk factors of breast cancer like obesity and sedentary lifestyle which also affecting the prognosis of cancer (16). It was shown that diabetes mellitus increased the mortality rate by 30-60% higher than reported for women with breast cancer only (22). Uncontrolled DM associated with both hyperglycemia and hyperinsulinemia may results in accelerated reproduction and immigration of breast tumor cells which in turn lead to highly aggressive picture of breast cancer clinically and pathologically like increased size of tumor, lymphovascular invasion and distant metastasis (23,24). Unfortunately, the explanations clarifying the link between type II DM and risk of various breast cancer molecular subtypes are numerous but underestimated. Hyperinsulinemia and high levels of insulin like growth factor have oncogenic effects (25,26) that might be related to triple negative breast cancer disease (27). Despite these findings, this relationship between type II DM and aggressive clinical and pathological findings for breast cancers at diagnosis are reported by epidemiological literatures. One literature documented the association between type II diabetic women and breast cancer with advanced staging at diagnosis (28). The other literature found that type II DM increased risk of lymph node metastasis in women with breast cancer (29).

The present study aimed to clarify the association between type II diabetes and clinicopathological characteristics of women with breast cancer in Erbil city/Kurdistan region.

2 | PATIENTS AND METHODS

The design of present study was a retrospective cross sectional study conducted in Oncology center of Rizgari Teaching hospital in Erbil city-Kurdistan region/Iraq through duration period of three years from first of January 2019 to 31st of December 2021. Women with breast cancer admitted to Oncology center of Rizgari Teaching hospital were the study population. The inclusion criteria were Adult (age 30-60 years) women with all clinical and pathological stages of breast cancer (stage I-IV) and diabetes mellitus duration of ≥ 5 years for diabetic women. Exclusion criteria were younger age women, male gender patients, pregnancy, type II diabetes mellitus duration of less than five years and missing or incomplete women's data. The ethical considerations were implemented according Helsinki Declaration regarding ethical approval of Health authorities; an ethical approval was taken from Kurdistan Board Ethical Committee, agreement of hospital authorities and confidentiality of data. A convenient sample of two hundred women with breast cancer was selected after eligibility to inclusion and exclusion criteria. The selected women were divided into two groups (100 breast cancer women with type II diabetes mellitus and 100 breast cancer women without type II diabetes mellitus).

The data of enrolled patients were collected by from their saved records in Oncology center and fulfilled in a prepared questionnaire. The questionnaire was designed by the researchers. The questionnaire included the following information: general characteristics of breast cancer women (age, body mass index, residence, laterality of tumor, duration of cancer and types of surgery implemented), histopathology and TNM of breast cancer women (histopathological findings, tumor focality, TNM classifications, tumor size, number of invaded lymph nodes and distant metastasis), cancer grading and staging of women (tumor grades, stages, estrogen receptors, progesterone receptors, Ki-76 and molecular subtypes) and diabetes mellitus characteristics (HbA1c). The diagnosis of breast cancer was done by Oncologist in the hospital. The histopathological examination, TNM classifications,

cancer staging, grading and molecular subtypes were done either in the center or in private laboratories. Different surgical treatments were implemented by different surgeons for selected women according to their clinical status and tumor characteristics. The type II diabetes mellitus of breast cancer women was diagnosed by a Specialist physician and on treatment by oral hypoglycemic agents or by insulin or both of them. The HbA1c test was used to assess the glycemic control in women with breast cancer.

The data collected were analyzed statistically by Statistical Package of Social Sciences software version 22. The chi-square and Fishers exact tests were applied for analyzing categorical variables. Level of significance (p value) was regarded statistically significant if it was 0.05 or less.

3 | RESULTS

In present study, two hundred women with breast cancer were enrolled (100 women with type II diabetes mellitus and 100 women without diabetes mellitus). The mean age of diabetic women with breast cancer was significantly higher than non-diabetic women with breast cancer ($p < 0.001$). Similarly, the mean body mass index was significantly higher among diabetic women with breast cancer ($p < 0.001$). The residence, laterality of tumor and type of surgery characteristics were not significantly different between both study groups. The mean breast cancer duration was significantly longer in non-diabetic women with breast cancer as compared to diabetic women with breast cancer ($p < 0.001$). (Table 1)

The histopathology findings were not significantly different between breast cancer women with or without type II diabetes mellitus ($p = 0.5$). A highly significant association was observed between tumor multi-focality diabetic women with breast cancer ($p = 0.04$). Tumor size and number of invaded lymph nodes for breast cancer were not significantly different in both study groups. The distant metastasis of breast cancer was significantly associated with diabetic women with breast cancer ($p = 0.03$). (Table 2)

The breast cancer grading, lymphovascular invasion, perinural invasion, staging, estrogen receptor (ER), progesterone receptor (PR), Ki-67 marker and molecular subtypes were not significantly different between diabetic and non-diabetic women. (Table 3).

For one hundred diabetic breast cancer women, no significant differences were observed

between diabetic women with controlled glyceemic status and diabetic women with uncontrolled glyceemic status in regard to age, body mass index, residence, laterality of tumor, duration of cancer and type of surgery. (Table 4)

The breast cancer histopathology findings were not significantly different between diabetic breast cancer women with controlled or uncontrolled glyceemic status. No significant differences were observed between diabetic women with controlled glyceemic status and diabetic women with uncontrolled glyceemic status in regard to tumor focality, tumor size and distant metastasis. There was a significant association between advanced number of invaded lymph nodes and diabetic breast cancer women with uncontrolled glyceemic status ($p=0.02$). The mean number of invaded lymph nodes was significantly higher in diabetic breast cancer women with uncontrolled glyceemic status ($p=0.002$). (Table 5)

Advanced cancer grading and staging were significantly observed in diabetic breast cancer women with uncontrolled glyceemic status ($p=0.03$). There was a significant association between positive perinural invasion and diabetic breast cancer women with controlled glyceemic status ($p=0.03$). No significant differences were observed between diabetic women with controlled glyceemic status and diabetic women with uncontrolled glyceemic status in regard to lymphovascular invasion, estrogen receptor, progesterone receptor, Ki-76 marker and molecular subtypes. (Table 6)

Table 1. General characteristics of breast cancer women in both study groups.

Variable	Study groups				P
	Diabetics		Non-diabetics		
Age (mean) years	62.5±9.3		48.3±10.6		<0.001 ^S
BMI (mean) Kg/m ²	30.1±3.4		28.5±2.4		<0.001 ^S
Residence (%)					0.4 ^{NS}
Inside Hawler	87	87.0	83	83.0	
Outside Hawler	13	13.0	17	17.0	
Laterality (%)					0.4 ^{NS}
Right	40	40.0	46	46.0	
Left	59	59.0	54	54.0	
Bilateral	1	1.0	0	-	
Duration of cancer (mean) years	1.8±0.8		2.3±0.48		<0.001 ^S
Type of surgery (%)					0.07 ^{NS}
Mastectomy and axillary LN dissection	52	52.0	57	57.0	
Breast conserving surgery and axillary LN	2	2.0	7	7.0	
Only biopsy	17	17.0	7	7.0	
Partial Mastectomy and lymph nodes	0	-	1	1.0	
Mastectomy and sentinel LN biopsy	0	-	1	1.0	
Modified radical Mastectomy and LN	9	9.0	3	3.0	
Wide local excision and sentinel LN	4	4.0	4	4.0	
Wide local excision and LN dissection	16	16.0	18	18.0	
Quadrentectomy and LN dissection	0	-	2	2.0	

S=Significant, NS=Not significant.

Table 2. Histopathology and TNM of breast cancer women in both study groups.

Variable	Study groups				P
	Diabetics		Non-diabetics		
Histopathology (%)					0.5 ^{NS}
Invasive ductal ca.	88	88.0	86	86.0	
Papillary ca.	0	-	1	1.0	
Invasive lobular ca.	9	9.0	8	8.0	
Invasive mammary ca.	0	-	1	1.0	
Mucinous ca.	0	-	1	1.0	
Medullary ca.	1	1.0	1	1.0	
Invasive ductal and mucinous ca.	0	-	2	2.0	
Mammarian secretory	1	1.0	0	-	
Invasive ductal and lobular ca.	1	1.0	0	-	
Tumor focality (%)					0.04^S
Unifocal	68	78.2	83	89.2	
Multifocal	19	21.8	10	10.8	
T classifications (%)					0.15 ^{NS}
T1	13	15.7	22	23.7	
T2	60	72.3	56	60.2	
T3	7	8.4	14	15.1	
T4	3	3.6	1	1.1	
Tumor size (mean)					0.2 ^{NS}
cm		3.3±1.3		3.7±2.1	
N classifications (%)					0.89 ^{NS}
N0	27	32.5	33	35.5	
N1	25	30.1	29	31.2	
N2	12	14.5	14	15.1	
N3	19	22.9	17	18.3	
Number of invaded lymph nodes (mean)					0.5 ^{NS}
LN		3.9±5.3		3.5±4.8	
Distant metastasis (%)					0.03^S
Yes	17	17.0	7	7.0	
No	83	83.0	93	93.0	

S=Significant, NS=Not significant.

Table 3. Grading and staging of breast cancer women in both study groups.

Variable	Study groups				P
	Diabetics		Non-diabetics		
Grades (%)					0.4 ^{NS}
I	5	5.0	2	2.0	
II	64	64.0	70	70.0	
III	31	31.0	28	28.0	
Lymphovascular invasion (%)					1.0 ^{NS}
Positive	39	39.0	39	39.0	
Negative	61	61.0	61	61.0	
Perinural invasion (%)					0.3 ^{NS}
Positive	39	39.0	32	32.0	
Negative	61	61.0	68	68.0	
Stages (%)					0.27 ^{NS}
IA	9	9.0	13	13.0	
IB	1	1.0	1	1.0	
IIA	18	18.0	25	25.0	
IIB	21	21.0	18	18.0	
IIIA	13	13.0	19	19.0	
IIIB	4	4.0	3	3.0	
IIIC	17	17.0	15	15.0	
IV	17	17.0	6	6.0	
ER (%)					0.2 ^{NS}
Positive	83	83.0	89	89.0	
Negative	17	17.0	11	11.0	
PR (%)					0.1 ^{NS}
Positive	23	23.0	14	14.0	
Negative	77	77.0	86	86.0	
Ki-76 (mean)					0.5 ^{NS}
%	24.6±16.7		26.6±25.3		
Molecular subtype (%)					0.8 ^{NS}
Luminal A	26	26.0	29	29.0	
Luminal B	59	59.0	60	60.0	
Triple negative	7	7.0	5	5.0	
HER2 enriched	8	8.0	6	6.0	

NS=Not significant.

Table 4. General characteristics of diabetic breast cancer women according to glycemc status.

Variable	Glycemc status				P
	Controlled		Uncontrolled		
Age (mean)					0.67 ^{NS}
years	62.9±9.5		62.1±9		0.6 ^{NS}
BMI (mean)					
Kg/m ²	29.8±3.7		30.2±3.1		
Residence (%)					0.5 ^{NS}
Inside Hawler	46	85.2	41	89.1	
Outside Hawler	8	14.8	5	10.9	
Laterality (%)					0.63 ^{NS}
Right	22	40.7	18	39.1	
Left	31	57.4	28	60.9	
Bilateral	1	1.9	0	-	
Duration of cancer (mean)					0.8 ^{NS}
years	1.88±0.86		1.84±0.86		
Type of surgery (%)					0.21 ^{NS}
Mastectomy and axillary LN dissection	26	48.1	26	56.5	
Breast conserving surgery and LN dissection	2	3.7	0	-	
Only biopsy	7	13.0	10	21.7	
Modified radical Mastectomy and LN dissection	5	9.3	4	8.7	
Wide local excision and sentinel LN biopsy	4	7.4	0	-	
Wide local excision and LN dissection	10	18.5	6	13.0	

S=Significant, NS=Not significant.

Table 5. Histopathology and TNM of diabetic breast cancer women according to glyceimic status

Variable	Glyceimic status				P
	Controlled		Uncontrolled		
Histopathology (%)					0.45 ^{NS}
Invasive ductal ca.	49	90.7	39	84.8	
Invasive lobular ca.	4	7.4	5	10.9	
Medullary ca.	0	-	1	2.2	
Mammarian secretory	1	1.9	0	-	
Invasive ductal and lobular ca.	0	-	1	2.2	
Tumor focality (%)					0.37 ^{NS}
Unifocal	40	81.6	28	73.7	
Multifocal	9	18.4	10	26.3	
T classifications (%)					0.15 ^{NS}
T1	9	19.1	4	11.1	
T2	36	76.6	24	66.7	
T3	2	4.3	5	13.9	
T4	0	-	3	8.3	
Tumor size (mean)					0.07 ^{NS}
cm		3.1±1.3		3.6±1.3	
N classifications (%)					0.02 ^S
N0	20	42.6	7	19.4	
N1	16	34.0	9	25.0	
N2	4	8.5	8	22.2	
N3	7	14.9	12	33.3	
Number of invaded lymph nodes (mean)					0.002 ^S
LN		2.4±3.5		5.9±6.5	
Distant metastasis (%)					0.2 ^{NS}
Yes	7	13.0	10	21.7	
No	47	87.0	36	78.3	

S=Significant, NS=Not significant.

Table 6. Grading and staging of diabetic breast cancer women according to glycemic status.

Variable	Glycemic status				P
	Controlled		Uncontrolled		
Grades (%)					0.03^S
I	4	7.4	1	2.2	
II	39	72.2	25	54.3	
III	11	20.4	20	43.5	
Lymphovascular invasion (%)					0.09 ^{NS}
Positive	17	31.5	22	47.8	
Negative	37	68.5	24	52.2	
Perinural invasion (%)					0.03^S
Positive	16	29.6	23	50.0	
Negative	38	70.4	23	50.0	
Stages (%)					0.03^S
IA	7	13.0	2	4.3	
IB	1	1.9	0	-	
IIA	12	22.2	6	13.0	
IIB	15	27.8	6	13.0	
IIIA	6	11.1	7	15.2	
IIIB	0	-	4	8.7	
IIIC	6	11.1	11	23.9	
IV	7	13.0	10	21.7	
ER (%)					0.24 ^{NS}
Positive	47	87.0	36	78.3	
Negative	7	13.0	10	21.7	
PR (%)					0.21 ^{NS}
Positive	15	27.8	8	17.4	
Negative	39	72.2	38	82.6	
Ki-76 (mean)					0.08 ^{NS}
%		22±13.2		27.7±19.8	
Molecular subtype (%)					0.17 ^{NS}
Luminal A	15	27.8	11	23.9	
Luminal B	33	61.1	26	56.5	
Triple negative	1	1.9	6	13.0	
HER2 enriched	5	9.3	3	6.5	

S=Significant, NS=Not significant.

4 | DISCUSSION

Breast cancer incidence among Iraqi women is increasing gradually to reach which constituted 34.06% of all cancers and responsible of 23.02% of all cancer related deaths in Iraq (30). The type II diabetes mellitus is accompanied with high risk of cancers development and poor prognosis (31)

Present study showed that mean age of diabetic women with breast cancer was significantly higher than non-diabetic women with breast cancer ($p < 0.001$). Similarly, He et al (32) retrospective study in China found that breast cancer women with type II DM were older and in postmenopausal phase. However, Bronsveld et al (33) cross sectional study in Denmark revealed that premenopausal women with type II DM tend to have breast cancer with poor prognosis. It was found that mortality risk of breast cancer is increased among elderly aged women with pre-existing type II diabetes mellitus (34). Mean body mass index in our study was significantly higher among diabetic women with breast cancer ($p < 0.001$). This finding coincides with reports of Kang et al (35) study in USA which stated that obesity with type 2 DM increased the risk of development and aggressiveness of breast cancer. Buono et al (36) prospective study in Italy reported that elderly age, obesity and type II DM were the common risk factors for large breast cancer at diagnosis with worst prognosis. Our study showed that mean breast cancer duration was significantly longer in non-diabetic women with breast cancer as compared to diabetic women with breast cancer ($p < 0.001$). This finding is consistent with results of Karlin et al (37) study in USA which found that disease course and survival duration of breast cancer women with type II DM was shorted than breast cancer women without type II DM.

The current study showed that histopathology findings were not significantly different between breast cancer women with or without type II diabetes mellitus ($p = 0.5$). This finding is similar to results of Adel study (38) in Egypt which found no significant difference in pathology findings between breast cancer women with or without type II diabetes mellitus. However, another Egyptian study carried out by Ali et al (39) documented type II diabetic breast cancer women had more invasive pathologic subtypes. These differences might be related to discrepancies in many factors like DM duration, glycemic control, obesity prevalence, breast

cancer duration and other factors between different studies in addition to factors related to methodology and sample size of studies. Our study showed a highly significant association between tumor multi-focality diabetic women with breast cancer ($p=0.04$). Salgado et al (40) stated that multi-focality of breast cancer is accompanied with high risk of lymph nodes involvement with high tumor load. Our study revealed that TNM classifications were not significantly different in both study groups. Consistently, Adel study 38 in Egypt reported no significant difference in TNM classification between breast cancer women with or without type II DM. However, our study showed that distant metastasis of breast cancer was significantly associated with diabetic women with breast cancer ($p=0.03$). This finding is parallel to results of Schrauder et al (41) cohort study in Germany which diabetic women with breast cancer had two folds risk of distant metastasis than non-diabetic women. The breast cancer grading, lymphovascular invasion, perinural invasion, staging, estrogen receptor (ER), progesterone receptor (PR), Ki-67 marker and molecular subtypes were not significantly different between diabetic and non-diabetic women. These findings are in agreement to results of Lee et al (42) study in USA. Inconsistently, Zhang et al (43) systematic review and meta-analysis study in China showed higher risk of late-stage tumor, large size and invasive lymph nodes in breast cancer women with type II DM, while no significant associations were observed regarding tumor grading, estrogen/progesterone receptor and HER2. The current study is the first Iraqi study discussing the relationship between type 2 diabetes mellitus and clinicopathological characteristics of breast cancer. The relationship between type II DM and breast cancer clinicopathological features is controversial as some authors reported advanced breast cancer staging among diabetic women (44), while others failed to detect this association (45).

In present study, there was a significant association between advanced number of invaded lymph nodes and diabetic breast cancer women with uncontrolled glycemic status ($p=0.02$) and mean number of invaded lymph nodes was significantly higher in diabetic breast cancer women with uncontrolled glycemic status ($p=0.002$). These findings are similar to results of Hui et al (46) study in China which revealed that metformin treatment and improving the glycemic control had improved the prognosis of breast cancer. Our study also revealed that

advanced cancer grading and staging were significantly observed in diabetic breast cancer women with uncontrolled glycemic status ($p=0.03$). This finding is consistent with results of Erickson et al (47) study in USA which reported that chronic hyperglycemia is associated with advanced breast cancer staging and grading with reduced survival rate. In present study, there was a significant association between positive perinural invasion and diabetic breast cancer women with uncontrolled glycemic status ($p=0.03$). Consistently, Duan et al (48) study in China documented high risk of perinural invasion and locoregional recurrence of breast cancer in type II diabetic women with poor glycemic control.

5 CONCLUSIONS

This study concluded that type II diabetic women with breast cancer are at high risk of multifocal breast cancer with distant metastasis. Poor glycemic control of type II diabetic women with breast cancer are related to advanced lymph nodes invasion, advanced breast cancer grading and staging with positive perinural invasion. Elderly age and obesity are the common risk factors for development of breast cancer in women with type II DM. Emphasis on screening of type II diabetic women for breast cancer and prevention of modifiable risk factors for DM and breast cancer especially obesity, sedentary lifestyle and physical inactivity.

Ethical Issue:

All ethical issues were approved by the author, in accordance with Ethical Principles of Declaration of Helsinki of the world Medical Association, 2013, for research involving human subjects

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