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Lymph Nodes Metastasis is Associated with Higher Body Mass Index in Indonesian Breast Cancer Patients

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ABSTRACT

Background
Breast cancer is the most prevalent malignancy among women and is the second largest contributor to cancer-related deaths globally. Women with a high body mass index (BMI) are at a greater risk of developing breast cancer and an increased risk of lymph node metastasis. Therefore, this retrospective study aimed to determine the relationship between BMI and the clinical pathological profile of invasive breast carcinoma (IBC) patients.

Method
This study was conducted from January 2019 to November 2022, and data were collected through the archives of the Department of Anatomic Pathology FKUI/RSCM (Faculty of Medicine, University of Indonesia/Cipto Mangunkusumo Hospital). Clinical pathological data were collected, and the histological type, grade, lymphovascular invasion, and lymph node metastasis of the tumors were re-evaluated. The chi-square hypothesis test was used to determine the relationship between BMI and lymph node metastasis status, and the results were considered statistically significant with a $p < 0.05$.

Result
A total of 151 cases of IBC with lymph node dissection from January 2019 to November 2022 were included in this study, all of which were female, with the majority being >50 years old, accounting for 55%. The most common tumor size and histological type were T2 and invasive ductal carcinoma (NST), accounting for 39.7%and 74.8%, respectively, and 49% of cases were grade 3 tumors. Furthermore, most IBC cases had an obese BMI of 49%, while 63.1% with lymph node metastasis had an overweight-obese BMI. Statistical analysis was performed between BMI and lymph node metastasis status, and a value of $p=0.025$ was obtained. The relationship between tumor size and lymphovascular invasion with lymph node metastasis was also found to be statistically significant, as indicated by a p-value of 0.000.

Conclusion
Cases with lymph node metastasis had the highest rate of overweight-obesity, and a significant relationship was found between BMI and lymph node metastasis status. Furthermore, a significant relationship was also found between tumor size and lymphovascular invasion with lymph node metastasis.

Keywords: invasive breast carcinoma, body mass index, overweight, obesity, clinical pathological profile, lymph node metastasis

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INTRODUCTION

Breast cancer is the most prevalent malignancy in women and the second largest cause of cancer-related death worldwide.[1] According to GLOBOCAN 2020 data, breast cancer in women ranks first in the world with 2,261,419 cases. This number is the highest for new cancer cases worldwide, accounting for 11.7%, with 684,996 deaths at 6.9%.[2] In Asia, breast cancer ranks second with 1,026,171 new cases, accounting for 10.8%, and the fifth leading cause of death with 346,009 cases, at 6.0%.[3] It is the most common cancer in Indonesia and the second leading cause of death, with 65,858 and 22,430 cases, accounting for 16.6% and 9.6%, respectively.[3]

Breast cancer is a heterogeneous disease that involves genetic and environmental factors.[4] Its risk factors include gender, age, genetics, ethnicity, early menstruation or late menopause, alcohol consumption, oral contraceptive use, lack of physical activity, and excessive BMI/obesity. The risk increases with age, and it is mostly found in women over 50 years old. Postmenopausal obese women have a higher risk than those with normal weight.[5]

Obesity is an abnormal or excessive accumulation of fat that poses a health risk. It is estimated that overweight cases cause 20% of all cancers, and its prevalence is increasing worldwide. Almost one-third of the world's population is overweight or obese.[6–9] Obesity is also associated with an increased risk of recurrence and death by 35%-40%.[10] Previous studies found a relationship between high BMI and histological grades of breast cancer, including greater incidence of metastasis.[8,10]

The main cause of breast cancer's high death rate is metastasis, which contributes 90% to mortality. The 5-year survival rate of breast cancer patients without lymph node metastasis is 80%. However, the presence of the metastasis reduces the survival rate to 25%.[11] Patients with positive axillary lymph node status have a 6 times higher risk of distant metastasis. According to Wang et al.,[12] excessive BMI significantly increases the risk of lymph node metastasis.

An overweight/obese BMI is a risk factor for estrogen receptor-positive breast cancer, and estrogen has a proliferative effect that plays a role in tumorigenesis. Adipose tissue is the primary source of estrogen in the body after menopause. Estrogen plays an essential role under normal conditions in developing breast tissue epithelium by stimulating the proliferation and morphogenesis of ducts. When exposed to high estrogen levels, as in obesity, the pro-proliferative effects of this estrogen result in an accumulation of replication errors, causing mutations and the development of breast cancer. Estrogen also contributes to the migration and invasion of cancer cells.[13]

This retrospective study aims to investigate the relationship between BMI and the clinicopathological profile of invasive breast carcinoma patients in the Department of Anatomical Pathology, FKUI/RSCM, from 2019 to 2022. The results are expected to provide information for patients and clinicians about the importance of changing lifestyles and controlling the weight of obese breast cancer patients as part of a comprehensive therapy. In this study, breast carcinoma morphology was re-evaluated using the WHO classification of 2019, grade, lymphovascular invasion, and axillary lymph node metastasis.

METHOD

This analytical retrospective study was carried out using a cross-sectional design. Data were collected from the archives of the Department of Anatomic Pathology FKUI/RSCM from January 2019 to November 2022. The sample consisted of cases diagnosed at RSCM with invasive breast cancer that underwent surgery/mastectomy.

The inclusion criteria were cases of invasive breast carcinoma mastectomy and removal of axillary lymph nodes in the Department of Anatomic Pathology FKUI/RSCM from January 2019 to November 2022. The exclusion criteria were cases of breast carcinoma which are secondary tumors, cases of invasive breast carcinoma without data on the axillary lymph node metastasis, no H&E slides obtained, and lack of data on patients' weight, height, or BMI. This study used the total sampling technique that meets the inclusion and exclusion criteria.

Patient's clinical data were obtained from the histopathology and immunohistochemistry form, as well as the Hospital Information System (HIS). Clinical data recording was performed on all

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samples, including age, gender, and tumor size. The data for weight, height, and BMI were searched and recorded, and BMI was calculated using the formula weight (in kilograms) divided by the square of height (in meters). According to the Asia Pacific report, the body mass index is classified as follows (Table 1).[14]

Table 1. BMI Classification[14]

Classification	Body Mass Index (kg/m^2)
Underweight	<18.5
Normal	18.5-22.9
Overweight	23-24.9
Obesity	≥25

Reproduced from: Asia Pacific report (WHO, IASO, IOTF 2000)

Histopathological data were recorded on histological type, grade, lymphovascular invasion, and axillary lymph node metastasis status, as well as the Hematoxylin and Eosin (HE) slides of the cases were collected. The morphological appearance of the HE specimens was re-evaluated. The histopathological parameters evaluated included histological type, grade, lymphovascular invasion, and axillary lymph node metastasis.

The data obtained were then processed with statistical analysis using SPSS version 25.0. The chi-square hypothesis test was used to determine the relationship between excessive BMI and axillary lymph node metastasis status in patients with invasive breast carcinoma. When the chi-square test requirements were not met, an analysis with Fisher's exact test was performed. The results are considered statistically significant at a p-value less than 0.05.

RESULT

Based on the archive data of the Department of Anatomic Pathology FKUI/RSCM from January 2019 to November 2022, 209 cases of invasive breast carcinoma that have undergone mastectomy with axillary lymph node removal were found, with 38, 52, 73, and 46 cases in 2019, 2020, 2021, and 2022, respectively. A total of 58 cases did not have data on weight, height, or BMI, and their slides were not found in the archives, hence, were excluded from the study. The total number of cases that were evaluated in this retrospective study is 151. Furthermore, the distribution of clinicopathological data of invasive breast carcinoma cases is shown in Table 2.

Table 2. Distribution of clinicopathology data (N=151).

Variable	N (%)
Gender	
Female	151 (100)
Male	0
Age	
≤50 years old	68 (45)
>50 years old	83 (55)
Body mass index	
Underweight	8 (5.3)
Normal	40 (26.5)
Overweight	29 (19.2)
Obesity	74 (49)
Tumor size	
T1	27 (17.9)
T2	60 (39.7)
T3	33 (21.9)
T4	31 (20.5)
Histologic type	
NST	113 (74.8)
Special type	9 (6)
Mixed type	29 (19.2)
Grade	
Grade 1	8 (5.3)
Grade 2	69 (45.7)
Grade 3	74 (49)
Lymphovascular invasion	
Yes	67 (44.4)
No	84 (55.6)
Lymph node metastasis	
Yes	86 (57)
No	65 (43)

The demographic data of 151 IBC cases in this retrospective study are all female, with the majority aged over 50 years old, at 55%. Most of the IBC cases in this study were 74 obese (49%). The most common tumor size is >2-5 cm (T2), with 60 cases at 39.7%. In the overweight-obesity BMI, the majority are over 50 years old, and the most common tumor size is T2, accounting for 57.3% and 42.7%, respectively. Re-reading the histopathological slides of 151 IBC cases shows that the most common type is invasive No Special Type (NST) carcinoma with 113 cases (74.8%), respectively, as shown in Table 2. The most common histological type in overweight-obesity BMI is NST (74.8%), as shown in Table 3.

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Table 3. IBC clinicopathological characteristics with overweight-obese and underweight-normal BMI.

Variable	Overweight-obesity N (%)	Underweight-normal N (%)	*p-value*
Age			
≤50 years old	44 (42.7)	24 (50)	0.402
>50 years old	59 (57.3)	24 (50)	
Tumor Size			
T1	15 (14.6)	12 (25)	
T2	44 (42.7)	16 (33.3)	0.117
T3	26 (25.2)	7 (14.6)	
T4	18 (17.5)	13 (27.1)	
Histologic type			
NST	77 (74.8)	36 (75)	0.788
Special type	7 (6.8)	2 (4.2)	
Mixed type	19 (18.4)	10 (20.8)	
Grade			
Grade 1	5 (4.9)	3 (6.3)	0.933
Grade 2	47 (45.6)	22 (45.8)	
Grade 3	51 (49.5)	23 (47.9)	
Lymphovascular invasion			
Yes	47 (45.6)	20 (41.7)	0.648
No	56 (54.4)	28 (58.3)	
Lymph node metastasis			
Yes	65 (63.1)	21 (43.8)	0.025*
No	38 (36.9)	27 (56.3)	

**Chi-Square Test*

Table 4. IBC clinicopathologic characteristics with lymph node metastasis.

Variable	Lymph node metastasis		*p-value*
	Yes	No	
Age			
≤50 years old	40 (58.8%)	28 (41.2%)	0.674
>50 years old	46 (55.4%)	37 (44.6%)	
Tumor Size			
T1	4 (14.8%)	23 (85.2%)	
T2	39 (65%)	21 (35%)	0.000*
T3	25 (75.8%)	8 (24.2%)	
T4	18 (58.1%)	13 (41.9%)	
Histologic type			
NST	62 (54.9%)	51 (45.1%)	
Special type	3 (33.3%)	6 (66.7%)	0.079
Mixed type	21 (72.4%)	8 (27.6%)	
Grade			
Grade 1	2 (25%)	6 (75%)	
Grade 2	41 (59.4%)	28 (40.6%)	0.170
Grade 3	43 (58.1%)	31 (41.9%)	
Lymphovascular invasion			
Yes	53 (79.1%)	14 (20.9%)	0.000*
No	33 (39.3%)	51 (60.7%)	

**Chi-Square Test*

The invasive NST carcinoma in one of the histopathological specimens appears as a solid, trabecular, and infiltrative mass of tumor. The tumor cells have moderate-hard pleomorphic nuclei and there is lymphovascular invasion. In the lymph nodes, similar metastatic tumors are found, as shown in Figure 2.

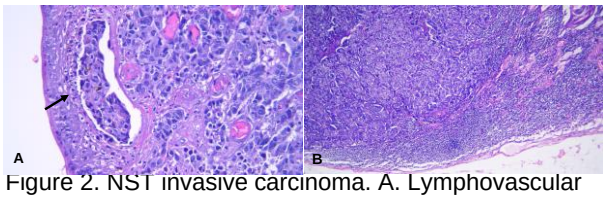

Figure 2. NST invasive carcinoma. A. Lymphovascular invasion (arrow), HE 400 times. B. Lymph nodes positive for tumor, HE 100 times.

Most breast carcinomas are grade 3 at 49%. Lymphovascular invasion is found in 67 cases (44.4%) and lymph node metastasis in 57% of cases as shown in Table 2. The most common histological grade in overweight-obesity BMI is grade 3 at 49.5%. The lymphovascular invasion is 45.6% in overweight-obesity, as shown in Table 3.

The most common IBC cases with lymph node metastasis have 65 overweight-obesity BMI, accounting for 63.1%. A significant relationship exists between BMI and lymph node metastasis, as indicated by a p-value of 0.025 (Table 3).

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Lymphovascular invasion is found in 44.4% of cases. A total of 45.6% of cases are found in overweight and obese (Table 3). Furthermore, 79.1% of cases with positive lymphovascular invasion show evidence of lymph node metastasis, and 60.7% with negative show no evidence. A significant relationship exists between lymphovascular invasion and lymph node metastasis status, as indicated by a p-value of 0.000 (Table 4).

DISCUSSION

The total of 151 IBC cases in this study are female, and the majority of breast cancer occurs in women, with the number of cases a hundred times higher than in men.[15] Breast cancer in men is found in less than 1% of total cases. Female gender is one of the unmodifiable risk factors for breast cancer, associated with increased hormonal stimulation. Unlike the male, whose estrogen levels are insignificant, the female has breast cells that are very sensitive to both estrogen and progesterone and hormonal imbalances. According to Lukasiewicz *et al.,*[16] estrogen circulation is positively related to an increased risk of breast cancer.

Breast cancer is a disease with complex and multiple risk factors, and lifestyle, such as obesity, is known to increase the risk.[17] The prevalence of obesity has increased worldwide and has become a cause of the development of some cancers, including breast. In Indonesia, its prevalence in 2018 was 23.1%, and 28% experienced central obesity.[18] In this study, the majority of IBC patients have a BMI ≥25 kg/m^2 (obesity), with 74 cases (49%). In line with Alshamsan *et al*.[19], most IBC patients have obesity, followed by overweight and normal weight, accounting for 53.4%, 30.9%, and 15.6%, respectively.

About 80% of breast cancer patients are over 50 years old because the risk increases with age. It increases by 1.5% at age 40, 3% at 50, and more than 4% at 70.[16] According to Wu *et al*.,[19] the incidence of breast cancer is in the range of 50-59 years and over 85 years. Meanwhile, obesity is associated with an increased risk of breast cancer, specifically in postmenopausal women.[20] Wang *et al*.[21] found that patients with obesity have the highest age >50 years (59.5%). This is consistent with this study's results, where 55% of breast cancer cases are >50 years old, and 57.3% have overweight-obesity BMI.

The most common tumor size in this study was T2 at 39.7% or >2-5 cm. IBC cases with overweight-obesity BMI, the most common tumor size was T2 (42.7%). According to Alshamsan *et al*.,[19] the largest tumor size is at T2 (42.3%). The statistical test showed no significant relationship between tumor size and BMI, as indicated by a p-value of 0.117 (Table 3). This contradicts the results of Alshamsan *et al*.,[19] that a significant relationship is found between tumor size and BMI, p=0.04. Furthermore, the statistical test showed a significant relationship between tumor size and lymph node metastasis, p=0.000, as shown in Table 4.

Based on the histopathological description, breast cancer is classified into invasive-special types and invasive NST carcinoma. Some IBC contain a mixture of special types and NST when the special subtype ranges from 10-90% of the tumor.[22] Invasive special types show special morphology in more than 90% of the tumor. On the other hand, the invasive NST is a breast carcinoma that cannot be classified as a specific special type morphologically and is the most common among IBCs, accounting for about 60-75% of all breast cancer cases.[22,23]

The most common histological type and grade in this study is NST carcinoma and grade 3, respectively, accounting for 74.8% and 49%. In line with Alshamsan *et al*.,[19] the most common histological type is invasive ductal/NST, accounting for 89.7%. According to Turkoz *et al*.,[24] obesity is most commonly found in grade 3, with a percentage of 57.1%.

Positive lymphovascular invasion (LVI) is commonly found in cases with positive lymph node metastasis, with a percentage of 79.1%. In overweight-obesity BMI, the most common is no-LVI, with a percentage of 54.4%, while in underweight-normal BMI, there were 58.3% with no-LVI. In contrast, Turkoz *et al*.[24] stated that there is a significant relationship between increasing BMI and LVI. The lack of LVI in specimens with lymph node metastasis is due to the limitations of the peritumoral sampling area, specifically in large mass tumors.

In this retrospective study, patients with overweight obesity were found to be more likely to have IBC with lymph node metastasis, with a percentage of 63.1% compared to those without distant lymph node metastasis at 36.9%. Meanwhile, underweight-normal BMI was more

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commonly found in IBC cases without lymph node metastasis at 56.3%, while IBC with lymph node metastasis was found in 43.8% of cases. The chi-square analysis test showed a significant relationship between BMI and lymph node metastasis, as indicated by a p-value of 0.025.

This result is consistent with Wang *et al*.,[12] which found a significant relationship between excessive BMI and the risk of lymph node metastasis. Each 1 kg/m^2 rise in BMI increased the chance of lymph node metastasis by 0.89%. In obese postmenopausal women, there is a high concentration of estrogen. Furthermore, an increase in estradiol is important in developing cancer and lymph node metastasis.

The hypertrophy and hyperplasia of adipose tissue in individuals with obesity lead to the release of more than 20 hormones and molecular signals called adipokines or adipocytokines. Some adipokines include leptin, resistin, and visfatin, which play a role in breast cancer initiation, progression, recurrence, and metastasis. Leptin binds to the leptin receptor and initiates JAK2 phosphorylation. The Ras/Raf signal is activated and induces mitogen-activated protein kinase (MAPK) activity, resulting in cell cycle induction and inactivation of tumor suppressor protein p53. Furthermore, the activation of phosphoinositide 3-kinase (PI3K) stimulates AKT/mTOR, which promotes cell growth and survival in cancer cells.[6] Leptin also plays a significant role in the progression of breast cancer, in conjunction with the epithelial-mesenchymal transition (EMT) process, which contributes to lymph node metastasis.[25]

In obese individuals, a rise in adipose tissue causes an increase in the release of resistin dan visfatin, which causes tumor development and cancer cell migration or metastasis.[6] Additionally, excessive adipose tissue can change the microenvironment through extracellular matrix remodeling and provide energy for cancer cell proliferation, metastasis, and evasion of chemotherapy.[5–7]

Obesity is a complex condition with physiological and molecular changes that play a role in cancer initiation, progression, and metastasis. It has negative effects on cancer therapy given to patients, such as increasing surgical complications and the side effects of radiation, chemotherapy, and immunotherapy. It also decreases the efficacy of chemotherapy and endocrine therapy. Therefore, managing overweight and obesity is crucial as part of comprehensive therapy for patients.[7]

CONCLUSION

From January 2019 to November 2022, 151 cases of IBC with axillary lymph node removal were female, and the majority were over 50 years old. The most common tumor size and histologic type were T2 and grade 3 invasive ductal carcinoma, respectively. Furthermore, the majority of cases had an obese BMI, and IBC with lymph node metastasis had the highest rate of overweight-obesity BMI. A significant relationship was found between BMI and lymph node metastasis status, as well as between tumor size and LVI with lymph node metastasis. Based on the explanation above, recording complete clinical data, including weight, height, and BMI, for IBC patients is necessary.

REFERENCES

1. Garcia EL, Moreno BG. Updating the role of obesity and cholesterol in breast cancer. Breast CA Res. 2019;21:35.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71:209–49.
3. The Global Cancer Observatory. Breast Cancer, Globocan 2020. WHO. 2021:1-2.
4. Barzaman K, Karami J, Zarei Z, Hosseinzadeh A, Kazemi MH, Moradi-Kalbolandi S, et al. Breast cancer: Biology, biomarkers, and treatments. Elsevier B.V. 2020;84:1-10.
5. Youn HJ, Han W. A review of the epidemiology of breast cancer in Asia: Focus on risk factors. Asian Pac J of CA Prev. 2020; 21:867–80.
6. Booth A, Magnuson A, Fouts J, Foster M. Adipose tissue, obesity and adipokines: Role in cancer promotion. Horm Mol Biol Clin Investig. 2015;21:57–74.
7. Zhao C, Hu W, Xu Y, Wang D, Wang Y, Lv W, et al. Current landscape: The mechanism and therapeutic impact of obesity for breast cancer. Frontiers Media S.A. 2021;11:1-20.
8. Mardiah H, Ginting RNA, Rahmadhany H, Sitorus ERD. Correlation between age and body mass index (BMI) with histopathological features of breast cancer

patients in RSUP Haji Adam Malik Medan. Indonesian J of CA. 2021;15:46.
9. Chooi YC, Ding C, Magkos F. The epidemiology of obesity. Metabolism. J Metabol. 2019;92:6–10.
10. Jiralerspong S, Goodwin PJ. Obesity and breast cancer prognosis: Evidence, challenges, and opportunities. J of Clin Oncol. 2016;34:4203–16.
11. Liang Y, Zhang H, Song X, Yang Q. Metastatic heterogeneity of breast cancer: Molecular mechanism and potential therapeutic targets. Academic Press. 2020;60:14–27.
12. Wang J, Cai Y, Yu F, Ping Z, Liu L. Body mass index increases the lymph node metastasis risk of breast cancer: A dose-response meta-analysis with 52904 subjects from 20 cohort studies. BMC Cancer. 2020;29:20.
13. Bhardwaj P, Au CMC, Benito-Martin A, Ladumor H, Oshchepkova S, Moges R, et al. Estrogens and breast cancer: Mechanisms involved in obesity-related development, growth and progression. J of Steroid Biol and Mol. 2019;189:161–70.
14. Jidi C, Clive C, Hwang K. The Asia-Pacific Perspective: Redefining obesity and its treatment. WHO, International Association For The Study of Obesity (IASO). 2000:19–20.
15. Sun YS, Zhao Z, Yang ZN, Xu F, Lu HJ, Zhu ZY, et al. Risk factors and preventions of breast cancer. Int J of Biol Sc. 2017;13:1387–97.
16. Łukasiewicz S, Czeczelewski M, Forma A, Baj J, Sitarz R, Stanisławek A. Breast cancer: epidemiology, risk factors, classification, prognostic markers, and current treatment strategies, an updated review. Cancers MDPI. 2021;13:1-18.
17. Chauhan R, Trivedi V, Rani R, Singh U. A comparative analysis of body mass index with estrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 status in pre- And postmenopausal breast cancer patients. J Midlife Health. 2020;11:210–6.
18. Harbuwono DS, Pramono LA, Yunir E, Subekti I. Obesity and central obesity in indonesia: Evidence from a national health survey. Med J of Ind. 2018;27:53–9.
19. Alshamsan B, Suleman K, Agha N, Abdelgawad MI, Alzahrani MJ, Elhassan T, et al. Association between obesity and clinicopathological profile of patients with newly diagnosed non-metastatic breast cancer in Saudi Arabia. Int J Womens Health. 2022;14:373–84.
20. Patel V, James M, Frampton C, Robinson B, Davey V, Timmings L. Body mass index and outcomes in breast cancer treated with breast conservation. Int J Radiat Oncol Biol Phys. 2020;106:369–76.
21. Wang X, Hui TL, Wang MQ, Liu H, Li RY, Song ZC. Body mass index at diagnosis as a prognostic factor for early stage invasive breast cancer after surgical resection. Oncol Res Treat. 2019;42:190–6.
22. Rakha EA, Allison KH, Ellis IO, Horii R, Masuda S PLF. Invasive breast carcinoma. In: Allison KH, Brogi E, Ellis IO, FOX SB, Lakhani SR LS, editor. WHO Classification of tumours of breast tumours. 5th ed. Switzerland: WHO. 2019:82–112.
23. Eliyatkin N, Yalcin E, Zengel B, Aktaş S, Vardar E. Molecular classification of breast carcinoma: from traditional, old-fashioned way to a new age, and a new way. J of Breast Health. 2015;11:59–66.
24. Turkoz FP, Solak M, Petekkaya I, Keskin O, Kertmen N, Sarici F, et al. The prognostic impact of obesity on molecular subtypes of breast cancer in premenopausal women. JBUON. 2013;18:335–41.
25. Olea FM, Cruz JC, Mendoza MA, Benavides T, Tito N. Signaling pathways induced by leptin during Epithelial Mesenchymal transition in breast cancer. Int J of Mol Sc. 2018;19:1-11.