https://doi.org/10.15218/zjms.2025.050

Molecular subtypes of breast cancer: distribution and prognostic implications

Received: 24/06/2024 Accepted: 30/09/2024

Shwan Salam Marouf [1*]

Abstract

Background and objectives: Breast cancer is a heterogeneous disease complex with various molecular subtypes, each having unique features that significantly affect the disease's course, behavior, treatment response, and prognosis. This study aimed to investigate the incidence of different breast cancer molecular subtypes and to explore the associations between these subtypes and important prognostic characteristics, such as tumor grade and disease stage.

Methods: This study was a retrospective observational analysis of paper-based medical records of 187 female patients diagnosed with breast cancer and registered at the Oncology Center of Rizgary Teaching Hospital in Erbil City in 2021.

Results: Analyzing the records of the 187 confirmed breast cancer patients revealed that luminal-B was the most frequent breast cancer molecular subtype, followed by luminal-A, TNBC and HER2-enriched subtypes in order of decreasing frequency. Additionally, the study found a statistically significant association between breast cancer molecular subtypes and prognostic characteristics such as tumor grade (P <0.001), primary tumor size (P = 0.017) and axillary lymph node status (P = 0.002).

Conclusion: The findings revealed a significant association between different breast cancer molecular subtypes and key tumor characteristics such as tumor grade and TNM disease stage, potentially influencing therapeutic and prognostic outcomes.

Keywords: Breast cancer; Molecular subtypes; Prognostic tumor characteristics.

Introduction

Breast cancer is a genetically diverse and complex disease consisting of numerous histological subtypes with unique biological characteristics. These differences have led to significant variations in disease behavior, aggressiveness, treatment response and prognosis. This heterogeneity is considered one of the major challenges in managing breast cancer patients globally. In addition, research has shown that breast cancer has different molecular subtypes; each exhibits diverse phenotypes and responds differently to treatment.[1-4]

A gross pathological appearance of invasive ductal carcinoma of the breast, which is the most common histological subtype of breast cancer, is shown in Figure 1. Furthermore, Figure 2 reveals macroscopic appearance of invasive lobular carcinoma, which is the second most common histological subtype of breast cancer.

Traditional breast cancer classification systems, which focus on tumor characteristics like size, lymph node status, histological grade, and histological subtype, may not adequately capture the complex genetic changes and biological processes involved in cancer development and progression. Consequently, tumors that appear similar clinically and pathologically may exhibit different behaviors.[5,6]

Recently, newer classification methods based on immunohistochemical, genetic,

[1] Rizgary Teaching Hospital, Erbil, Iraq.
Correspondence: shwan.marouf@gmail.com

https://doi.org/10.15218/zjms.2025.050

and molecular findings in breast cancer have been developed. The identification of hormone (estrogen and progesterone) receptor status, HER-2 receptor status, and the Ki-67 index initiated these new molecular classifications. According to this system, breast cancer is divided into four major molecular subtypes: luminal-like, basal-like, normal-like, and HER-2 positive. The luminal class is further subdivided into luminal-A and luminal-B subtypes.[7-10] The microscopic appearances of some of the breast cancer subtypes based on tumor grade and immunohistochemistry, such as estrogen receptor, progesterone receptor and HER2 receptor status, are demonstrated in Figures 3 and 4.

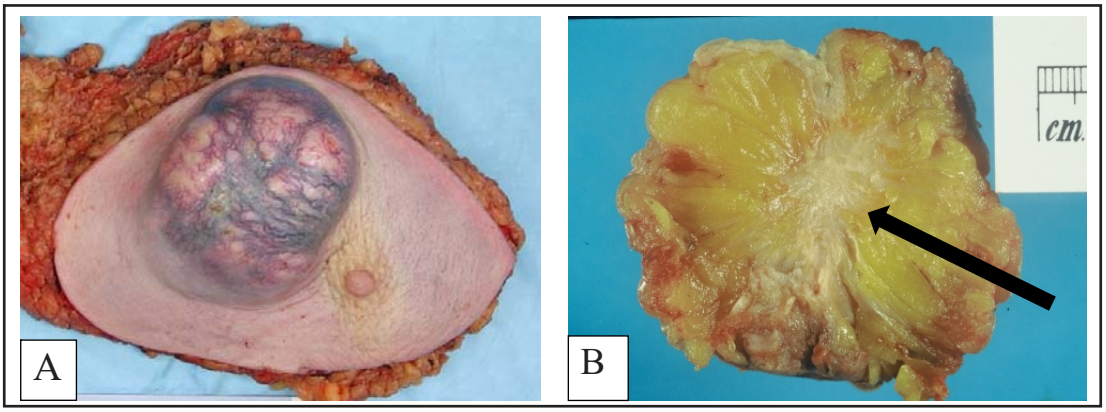

Figure 1 Gross pathology of breast cancer. (A): External appearance of a mastectomy specimen containing a very large invasive ductal carcinoma. (Emmanuelm, 2009). (B): Excised human breast tissue, showing a stellate area of cancer 2cm in diameter (arrowed). The histology was that of a moderately well differentiated ductal carcinoma. (John Hayman, 2007)

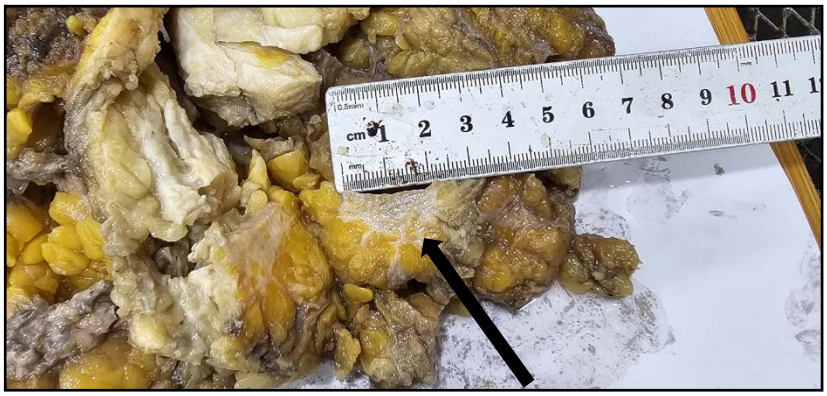

Figure 2 Macroscopic appearance of invasive lobular carcinoma of breast. The mass has an approximate diameter of 2cm (arrowed). Image by the author

https://doi.org/10.15218/zjms.2025.050

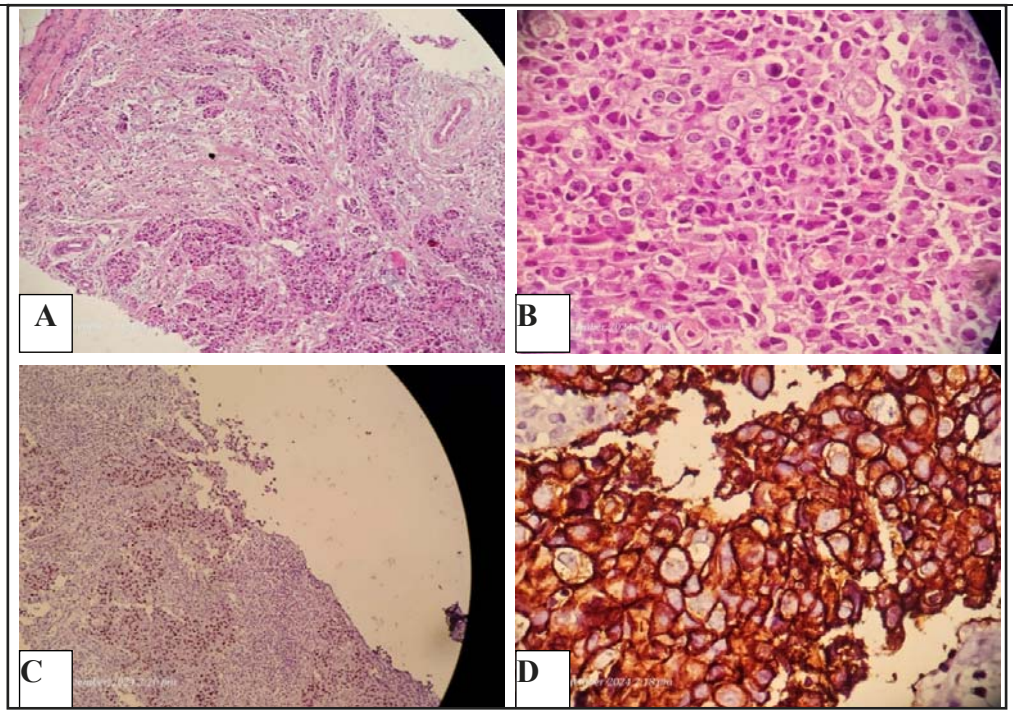

Figure 3 Microscopic appearance of high-grade invasive duct carcinoma. (A): H&E staining x100 magnification. (B): H&E staining x400 magnification. (C): Estrogen receptor strong positive by immunohistochemistry. (D): HER-2 receptor strong positive by immunohistochemistry. Image by the author

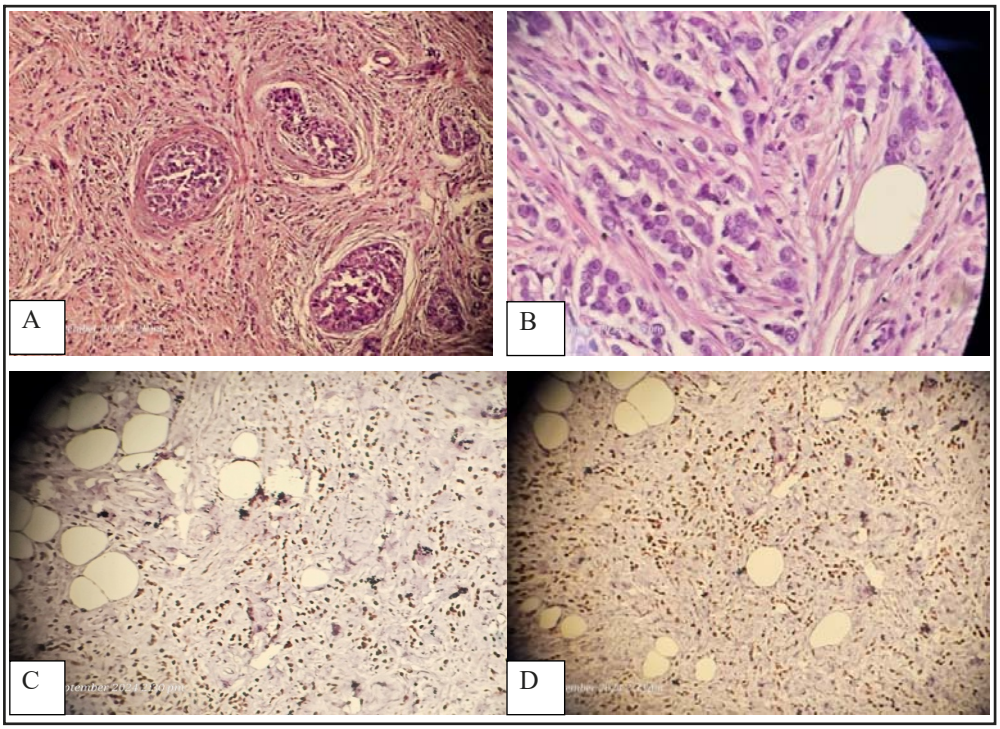

Figure 4 Microscopic appearance of intermediate grade invasive lobular carcinoma. (A): H&E staining x100 magnification. (B): H&E staining x400 magnification. (C): Estrogen receptor positive by immunohistochemistry. (D): Progesterone receptor positive by immunohistochemistry. Image by the author

https://doi.org/10.15218/zjms.2025.050

Likewise, according to the St. Gallen Consensus 2011, molecular subtypes of breast cancer can be classified into four subtypes:
(1) Luminal A (ER+/PR+/HER2-/low Ki-67).
(2) Luminal B (ER+/PR+/HER2-/+/high Ki-67)
(3) HER2-overexpression (ER-/PR-/HER2+); and (4) Basal like/triple negative breast cancer (ER-/PR-/HER2-).[11,12]
Notably, different breast cancer subtypes have distinct therapeutic and prognostic implications.[13] For example, luminal-A patients typically have low-grade tumors and a favorable prognosis, while luminal-B, HER2, and triple-negative types are known to have poorer survival rates and higher-grade tumors.[14,15] Hormone therapy is commonly used to treat hormone receptor-positive (HR+) breast cancer, such as Luminal-A and Luminal-B subtypes.[16]
HER2 inhibitors like trastuzumab and pertuzumab are administered to HER2-positive breast cancer subtypes.[17] Whereas for triple-negative breast cancer patients, chemotherapy remains the primary treatment option.[18]
The main objective of this study was to perform a retrospective analysis on the medical records to investigate the prevalence of various breast cancer molecular subtypes. The second objective was to determine the association between molecular subtypes and some important prognostic characteristics in breast cancer such as histological subtype, tumor grade, primary tumor size and axillary lymph node status.

Methods

Data collection and study design:
Breast cancer data was retrospectively collected from the case-notes of patients diagnosed with breast cancer and registered at the Oncology Center in Rizgary Teaching Hospital, Erbil, Iraq. The study included all women diagnosed with and treated for breast cancer over a 12-month period from January to December 2021. Out of a total of 195 recorded breast cancer patients, 187 of them, who had readily accessible data in their medical records, were included in the study.
The study included the impact of the patient's age on the distribution of molecular subtypes of breast cancer. For this purpose, the cases were divided into three age subgroups: young age (≤40 years), middle age (41-60 years) and old age (>60 years). The clinicopathological, immunohistochemical (IHC), and in situ hybridization (ISH) data, in addition to common important breast cancer prognostic parameters such the histological subtype, tumor grade and disease stage, based on AJCC TNM staging, were extracted from the included pathology reports in the patients' hospital records. Based on the St Gallen classification, using someof the mentioned breast cancer parameters such as hormone receptor status, HER2 receptor status, and Ki-67 index score, the molecular subtypes of breast cancer among the studied patients were categorized into four main types: luminal A, luminal B, HER2-enriched, and triple-negative breast cancer (TNBC).
Histopathologically, the recorded breast cancer cases were classified into two main subtypes: common histological subtypes such as invasive ductal carcinoma and invasive lobular carcinoma, and rare/ special histological subtypes like medullary and papillary carcinomas. Likewise, the breast cancer grading system included three levels based on the degree of cellular differentiation (how closely tumor cells resemble normal breast cells): grade I (low differentiation), grade II (moderate differentiation), and grade III (poor differentiation), reflecting low, moderate, and high histological tumor grades, respectively. Besides, the diagnostic medical imaging reports such as CT-scan, MRI and PET/CT scans, that were also included in the patients' case-notes, were used to assess clinical disease staging.

The clinical staging of breast cancer was done based on eighth edition of the American Joint Committee on Cancer (AJCC), which is based on extent of cancer as defined by tumor size (T), lymph node status (N), and distant metastasis (M).[19]

Statistical Analysis: The Statistical Package for Social Sciences software version 25 was used for statistical analyses. In descriptive statistics, frequency and percentages of categorical variables were reported. The associations between the different molecular subtypes and tumor characteristics, such as tumor grade and TNM disease stage, were calculated using Pearson's Chi-square test, Monte Carlo significance test and Fisher's exact test for categorical variables. The latter was used when more than 20% of expected values in the cells were less than five. A two-tailed *P*-value of less than 0.05 was regarded as statistically significant.

Ethical considerations: The study received approval from the Research Ethics Committee of the College of Dentistry at Hawler Medical University in May 2023. Since the study was retrospective, ethical implications were minimal, and participants' identities were safeguarded by assigning each patient a unique serial number.

Results

The final analysis of the records of 187 confirmed breast cancer patients, as illustrated in Table 1, revealed that the frequency distribution of the breast cancer molecular subtypes was as follows: About three quarters of the patients had luminal-type breast cancer, luminal-B was the most frequent subtype at about 45%, and just less than one-third of the patients had luminal-A disease. Meanwhile, only 10.2% of the patients were HER2-enriched, and the remaining 12.8% had triple-negative (TNBC) breast cancer.

The impact of age on the frequency of breast cancer molecular subtypes at the time of diagnosis is demonstrated in Table 2. As the table reveals, despite some numerical variations, there was no significant association between the age of the patient and incidence of molecular subtype of breast cancer. *P* = 0.384.

Table 1 Distribution of breast cancer molecular subtypes (n=187)

Category	Frequency	Percentage (%)
Luminal-A	59	(31.5)
Luminal-B	85	(45.5)
HER2-enriched	19	(10.2)
TNBC	24	(12.8)
Total	187	(100)

Table 2 Effect of age on the distribution of breast cancer molecular subtype

Age Group	Molecular Subtype					*P*-value*
	Luminal-A No. (%)	Luminal-B No. (%)	HER2-enriched No. (%)	Triple-negative No. (%)	Total No. (%)	
Young age (≤40 yrs.)	9 (24)	17 (45)	7 (18)	5 (13)	38 (20)	0.384
Middle age (41-60 yrs.)	37 (36)	45 (43)	7 (7)	15 (14)	104 (56)	
Old age (>60 yrs.)	13 (29)	23 (51)	5 (11)	4 (9)	45 (24)	
Total	59 (32)	85 (45)	19 (10)	24 (13)	187 (100)	

*Pearson's Chi-square test

https://doi.org/10.15218/zjms.2025.050

Regarding the distribution of important clinicopathological characteristics, such as histological subtypes and their association with breast cancer molecular subtypes, Table 3 shows that the most frequent histological subtype of breast cancer was invasive ductal carcinoma (IDC) at almost 80%; the second most common subtype was invasive lobular carcinoma (ILC) at 7.5%, followed by inflammatory breast cancer (IBC) at 4.3%. Rare special histological subtypes, such as medullary, papillary, mucinous and malignant phyllodes tumor, constituted only about five percent of the breast cancer cases in total.

Concerning the relationship between breast cancer molecular subtype and the histological subtype, based on Table 4, the study findings indicated that, despite some numerical differences, there were no statistically significant associations between molecular subtypes and their presenting histological subtypes, with the two-sided *P*-value of 0.164.

Table 3 The frequency distribution of breast cancer histological subtypes

Breast Cancer Histological Subtype		Frequency	Percentage (%)
Common Subtypes	Invasive ductal carcinoma (IDC)	149	(79.7)
	Invasive lobular carcinoma (ILC)	14	(7.5)
	Inflammatory breast cancer (IBC)	8	(4.3)
	Ductal carcinoma in situ (DCIS)	6	(3.2)
Special Subtypes	Medullary carcinoma (Med.)	5	(2.7)
	Papillary carcinoma (Pap.)	3	(1.6)
	Mucinous carcinoma (Muc.)	1	(0.5)
	Phyllodes tumor (Phy.)	1	(0.5)
Total		187	(100)

Table 4 The associations between molecular subtype and histological subtype

Molecular Subtype	Histological Subtype						*P*- value*
	IDC No. (%)	ILC No. (%)	IBC No. (%)	DCIS No. (%)	Special subtypes No. (%)	Total No. (%)	
Luminal-A	47 (80)	7 (11)	1 (2)	2 (3.5)	2 (3.5)	59 (34)	0.164
Luminal-B	71 (83)	4 (5)	3 (3.5)	3 (3.5)	4 (5)	85 (43)	
HER2-E	14 (74)	1 (5)	3 (16)	1 (5)	0 (0)	19 (10)	
TNBC	17 (72)	2 (8)	1 (4)	0 (0)	4 (16)	24 (13)	
Total	149 (79)	14 (8)	8 (4.5)	6 (3.5)	10 (5)	187 (100)	

*Fisher's exact test

https://doi.org/10.15218/zjms.2025.050

Meanwhile, there was a highly statistically significant association between breast cancer molecular subtype and the presenting tumor grade, the latter being regarded as an important prognostic factor in breast cancer. As it is seen in Table 5, 12% of luminal-A patients had low grade (grade I) disease compared to none of the patients with HER2-enriched or TNBC subtypes. On the other hand, only 12% of luminal-A patients had high grade (grade III) disease, compared to about half of the patients with luminal-B and HER2-enriched subtypes, and two-thirds of patients with triple negative disease (TNBC). The *P*-value was <0.001.

The study also addressed whether different molecular subtypes were associated with varying staging parameters in breast cancer, such as primary tumor status/size (T) and axillary lymph node status (N) according to AJCC TNM Staging System. Table 6 reveals that nearly 90% of patients with luminal-A disease had early-stage (Tis, T1, T2) tumors, while only 4% had advanced (T4) disease. This can translate to a good prognostic characteristic of luminal-A breast cancer in relation to the tumor size. Oppositely, more than half of the patients with HER2-enriched and more than one-third of patients with triple negative breast cancer (TNBC) were presented with advanced (T3 or T4) disease. The differences were statistically significant with a two-sided *P*-value of 0.017.

Table 5 The association between breast cancer molecular subtype and tumor grade

Molecular subtype	**Tumor Grade**				***P*-value***
	I	**II**	**III**	**Total**	
	n (%)	**n (%)**	**n (%)**	**n (%)**	
Luminal-A	7 (12)	45 (76)	7 (12)	59 (31)	<0.001
Luminal-B	6 (7)	40 (47)	39 (46)	85 (46)	
HER2-E	0 (0)	8 (42)	11 (58)	19 (10)	
TNBC	0 (0)	8 (33)	16 (67)	24 (13)	
Total	13 (7)	101 (54)	73 (39)	187 (100)	

*Fisher's exact test

Table 6 The association between molecular subtype with the primary tumor size

Molecular Subtype	**Primary Tumor Size (T)**						***P*- value***
	Early			**Advanced**		**Total**	
	Tis	**T1**	**T2**	**T3**	**T4**		
	No. (%)	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	
Luminal-A	1 (2)	15 (25)	37 (62)	4 (7)	2 (4)	59 (32)	0.017
Luminal-B	3 (4)	15 (17)	47 (55)	9 (11)	11 (13)	85 (45)	
HER2-E	0 (0)	2 (11)	6 (31)	5 (27)	6 (31)	19 (10)	
TNBC	0 (0)	3 (13)	12 (50)	6 (24)	3 (13)	24 (13)	
Total	4 (2)	35 (19)	102 (54)	24 (13)	22 (12)	187 (100)	

*Monte Carlo significance test

https://doi.org/10.15218/zjms.2025.050

Finally, about the association between breast cancer molecular subtype and the axillary lymph node status, Table 7 shows that there was a statistically significant influence of breast cancer molecular subtype on the axillary lymph nodal status of the patient – whether free from malignancy (negative) or involved by malignancy (positive). For example, at the time of breast cancer diagnosis, only four in ten of patients with luminal-A subtype had positive axillary lymph node status, meanwhile, around three quarters of patients with either HER2-enriched or TNBC subtypes had axillary lymph nodes involved by malignancy. Also, about two-thirds of luminal-B patients presented with positive axillary lymph nodes. The *P*-value was 0.002. This means that, compared to luminal-A breast cancer, luminal-B, HER2-enriched and TNBC have associated significantly with more advanced axillary lymph node stage at the time of breast cancer diagnosis.

Discussion

The study examined the distribution of breast cancer molecular subtypes and their associations with various prognostic characteristics, such as tumor grade and disease stage, in patients visiting the Oncology Center at Rizgary Teaching Hospital in Erbil during the year of 2021.

The findings of the present study revealed that the median age of breast cancer presentation was 49 years. This was in concordance with data from the surrounding counties such as Saudi Arabia and Oman.[20,21] Meanwhile, the age distribution results differed from observations in some other countries, for instance in the United States, where 65.1% of the reported breast cancer cases were found in women older than 55 years of age, according to the Surveillance Epidemiology and End Results (SEER) Cancer Statistics Review.[22]

This difference in age distribution and its earlier onset in our regions may be due to inadequate health awareness and health care systems in the Middle East compared to advanced Western countries. Life style, genetics, and early detection also contribute greatly to this difference.[23]

Regarding the distribution of breast cancer molecular subtype, similar to our study, some comparable studies reveal that luminal-B was the most evident molecular subtype, and invasive duct carcinoma was the most common histological subtype.[24,25] Nonetheless, some other studies revealed some obvious differences in this distribution. For instance, a number of studies done in the United States and Norway showed that luminal-A was by far much more common than other molecular subtypes, at about 70%.[26,27] Additionally, studies done in Saudi Arabia and Tunisia also found that luminal-A formed the majority of subtypes at just more than half

Table 7 The association between molecular subtype and axillary lymph node status

Molecular Subtype	Axillary Nodal Status (N)			*P*-value*
	Negative No. (%)	Positive No. (%)	Total No. (%)	
Luminal-A	35 (59)	24 (41)	59 (32)	0.002
Luminal-B	29 (34)	56 (66)	85 (45)	
HER2-enriched	4 (21)	15 (79)	19 (10)	
TNBC	7 (29)	17 (71)	24 (13)	
Total	75 (40%)	112 (60%)	187 (100%)	

*Pearson's Chi-square test

https://doi.org/10.15218/zjms.2025.050

of the cases, followed by TNBC, luminal-B and HER2-enriched subtypes in order of decreasing frequency.[23,28]

The observed differences in subtype-specific incidence across various geographical regions could result from some kinds of genetic variations. For example, data from the United States indicate that mutations in the breast cancer susceptibility genes BRCA1 and BRCA2 may be more prevalent among African-American women than non-Hispanic White women,[29] while mutations in other breast cancer genes may be less common in African-Americans.[30] There is some evidence, though not entirely consistent, that BRCA mutation carriers are more likely to develop triple-negative breast cancer (TNBC).[31]

In regard to the associations between molecular subtypes and clinico-pathological/prognostic characteristics of breast cancer such as the tumor grade and disease stage, similar to our study, several studies showed that molecular subtype was significantly associated with histological tumor grade. For instance, grade III pathology was mostly found in luminal-B, TNBC and HER2 disease, while lower grades, such as grades I and II, were predominated in luminal-A disease, which may explain a less aggressive behavior of luminal-A breast cancer compared to the other molecular subtypes.[24,25,32]

Furthermore, concerning the relationship between molecular subtype and TNM disease stage at the time of breast cancer diagnosis, similar to our results, many other studies done worldwide found a significant association between breast cancer molecular subtype and tumor burden including primary tumor size and axillary lymph node status. Luminal subtypes were generally associated with smaller tumor sizes and less lymph node involvement compared to non-luminal breast cancer subtypes. For instance, a study by Isheden et al found that Her2-enriched breast cancer was associated with 1.53 times faster tumor spread than luminal A cancer.[33] Also, another study by Li J et al concluded that lower tumor grades and disease stages were found in luminal cancers compared to TNBC and HER2-enriched subtypes.[34] These findings could translate to the conclusion that HER2-enriched and triple-negative breast cancers generally behave more aggressively than luminal breast cancer subtypes.

Concerning the limitations of the present study, although a sample size of 187 records offers a valuable insight; however, being retrospective and reliant on hospital records, introduces certain limitations. In retrospective observational studies, the data's completeness and accuracy are contingent upon the records available; this can potentially lead to information gaps. Furthermore, inherent to retrospective designs, selection bias may affect the representativeness of the findings. Controlling for all potential confounding variables is challenging, and the generalizability of the results beyond the studied population may be limited.

Conclusion

This study aimed to determine the distribution of breast cancer molecular subtypes and explore their relationships with staging and prognostic features in breast cancer. Although it acknowledges the limitations of hospital-based retrospective studies, the findings highlight significant connections between molecular subtypes and key staging and prognostic factors, including tumor grade, primary tumor size, and axillary lymph node status. Future research is needed to elucidate the mechanisms linking different subtypes with tumor characteristics and to enhance understanding of how these subtypes influence breast cancer behavior, aggressiveness, treatment, and prognosis. This study provides valuable insights, laying the groundwork for future targeted interventions and personalized treatment approaches in oncology.

Competing interests

The author declares that he has no competing interests.

References

1. Carvalho FM, Bacchi LM, Pincerato KM, Van de Rijn M, Bacchi CE. Geographic differences in the distribution of molecular subtypes of breast cancer in Brazil. BMC Womens Health. 2014; 14:102. doi: 10.1186/1472-6874-14-102. PMID: 25174527; PMCID: PMC4153008.
2. Acheampong T, Kehm RD, Terry MB, Argov EL, Tehranifar P. Incidence Trends of Breast Cancer Molecular Subtypes by Age and Race/Ethnicity in the US From 2010 to 2016. JAMA Netw Open. 2020; 3(8):e2013226. doi: 10.1001/jamanetworkopen.2020.13226. PMID: 32804214; PMCID: PMC7431997.
3. Emmanuelm. External appearance of a mastectomy specimen containing a very large invasive ductal carcinoma. 2009. Licensed under the Creative Commons Attribution 3.0 Unported license. (https://upload.wikimedia.org/wikipedia/commons/3/3f/BreastCancer.jpg)
4. Hayman John. Human breast tissue, showing a stellate area of cancer 2 cm in diameter. The histology was that of a moderately well differentiated ductal carcinoma. 2007. Released into the public domain. (https://upload.wikimedia.org/wikipedia/commons/8/80/Breast_cancer.JPG)
5. Zubair M, Wang S, Ali N. Advanced Approaches to Breast Cancer Classification and Diagnosis. Front Pharmacol. 2021; 11:632079. doi: 10.3389/fphar.2020.632079. PMID: 33716731; PMCID: PMC7952319.
6. Masood S. Breast cancer subtypes: morphologic and biologic characterization. J Womens Health (Lond). 2016; 12(1):103-19. doi: 10.2217/whe.15.99. PMID: 26756229; PMCID: PMC5779568.
7. Eliyatkın N, Yalçın 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 Breast Health. 2015; 11(2):59-66. doi: 10.5152/tjbh.2015.1669. PMID: 28331693; PMCID: PMC5351488.
8. Li Y, Wang S, Yang W, Liu H. Prognostic significance of molecular subtype, metastatic site and primary tumor surgery for survival in primary metastatic breast cancer: A SEER-based study. Medicine (Baltimore) 2021; 100(27):e26619. doi: 10.1097/MD.0000000000026619. PMID: 34232220; PMCID: PMC8270584.
9. Orrantia-Borunda E, Anchondo-Nuñez P, Acuña-Aguilar LE, Gómez-Valles FO, Ramírez-Valdespino CA. Subtypes of Breast Cancer. In: Mayrovitz HN, editor. Breast Cancer [Internet]. Brisbane (AU): Exon Publications 2022. Chapter
10. Zhao L, Lee VHF, Ng MK, Yan H, Bijlsma MF. Molecular subtyping of cancer: current status and moving toward clinical applications. Brief Bioinform. 2019; 20(2):572-84. doi: 10.1093/bib/bby026. PMID: 29659698.
11. Goldhirsch A, Wood WC, Coates AS, Gelber RD, Thürlimann B, Senn HJ; Panel members. Strategies for subtypes--dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. Ann Oncol. 2011; 22(8):1736-47. doi: 10.1093/annonc/mdr304. PMID: 21709140; PMCID: PMC3144634.
12. Vasconcelos I, Hussainzada A, Berger S, Fietze E, Linke J, Siedentopf F, et al. The St. Gallen surrogate classification for breast cancer subtypes successfully predicts tumor presenting features, nodal involvement, recurrence patterns and disease free survival. Breast. 2016; 29:181-5. doi: 10.1016/j.breast.2016.07.016. PMID: 27544822.
13. Hennigs A, Riedel F, Gondos A, Sinn P, Schirmacher P, Marme F, et al. Prognosis of breast cancer molecular subtypes in routine clinical care: a large prospective cohort study. BMC Cancer. 2016; 16:734. doi: 10.1186/s12885-016-2766-3.
14. Tran B, Bedard PL. Luminal-B breast cancer and novel therapeutic targets. Breast Cancer Res. 2011; 13. doi: 10.1186/bcr2904. Article 221.
15. TečićVuger A, Šeparović R, Vazdar L, Pavlović M, Lepetić P, Šitić S, et al. Characteristics and prognosis of triple-negative breast cancer patients: a croatian single institution retrospective cohort study. Acta Clin Croat. 2020; 59(1):97-108. doi: 10.20471/acc.2020.59.01.12. PMID: 32724280; PMCID: PMC7382886.
16. Tremont A, Lu J, Cole JT. Endocrine Therapy for Early Breast Cancer: Updated Review. Ochsner J. 2017; 17(4):405-11. PMID: 29230126; PMCID: PMC5718454.
17. Kim J, Pareja F, Weigelt B, Reis-Filho JS. Prediction of Trastuzumab benefit in HER2-positive breast cancers: is it in the intrinsic subtype? J Natl Cancer Inst. 2017; 109(2). doi: 10.1093/jnci/djw218. Article djw218.
18. Lebert JM, Lester R, Powell E, Seal M, McCarthy J. Advances in the systemic treatment of triple-negative breast cancer. Curr. Oncol. 2018; 25:S142–S150. doi: 10.3747/co.25.3954.
19. AJCC Teichgraeber DC, Guirguis MS, Whitman GJ. Breast Cancer Staging: Updates in the AJCC Cancer Staging Manual, 8th Edition, and Current Challenges for Radiologists, From the AJR Special Series on Cancer Staging. AJR Am J Roentgenol. 2021; 217(2):278-90. doi: 10.2214/AJR.20.25223. PMID: 33594908.
20. Shawarby M, Al-Tamimi D, Ahmed A. Molecular classification of breast cancer: an overview with emphasis on ethnic variations and future

perspectives. Saudi J Med Sci. 2013;1:14–19.
21. Mehdi I, Monem AA, Al Bahrani B, Ramadhan FA. Breast cancer molecular subtypes in Oman: correlation with age, histology, and stage distribution - analysis of 542 cases. Gulf J Oncolog. 2014; 1(15):38-48. PMID: 24610287.
22. Ries LAG, Melbert D, Krapcho M. SEER Cancer Statistics Review 1975- 2021. National Cancer Institute, Bethesda, MD.
23. Al-Thoubaity FK. Molecular classification of breast cancer: A retrospective cohort study. Ann Med Surg (Lond). 2019; 49:44-8. doi: 10.1016/j.amsu.2019.11.021. PMID: 31890196; PMCID: PMC6926136.
24. Mohammed AA. The clinical behavior of different molecular subtypes of breast cancer. Cancer Treat Res Commun. 2021; 29:100469. doi: 10.1016/j.ctarc.2021.100469. PMID: 34624832.
25. Joute Z, Debnath M, Pukhrambam G, Khuraijam S, Sarangthem B. Molecular subtypes of breast carcinoma and its relation with clinicopathological features: A single-center initial experience. J Med Soc. 2021; 35(3):103-7. DOI: 10.4103/jms.jms_5_22.
26. Acheampong T, Kehm RD, Terry MB, Argov EL, Tehranifar P. Incidence Trends of Breast Cancer Molecular Subtypes by Age and Race/Ethnicity in the US From 2010 to 2016. JAMA Netw Open. 2020; 3(8):e2013226. doi: 10.1001/jamanetworkopen.2020.13226. PMID: 32804214; PMCID: PMC7431997.
27. Hjerkind KV, Johansson ALV, Trewin CB. Incidence of breast cancer subtypes in immigrant and non-immigrant women in Norway. Breast Cancer Res. 2022; 24:4. https://doi.org/10.1186/s13058-021-01498-5
28. Fourati A, Boussen H, El May MV, Goucha A, Dabbabi B, Gamoudi A, et al. Descriptive analysis of molecular subtypes in Tunisian breast cancer. Asia Pac J Clin Oncol. 2014; 10(2):69-74. doi: 10.1111/ajco.12034. PMID: 23176549.
29. Pal T, Bonner D, Cragun D, Monteiro AN, Phelan C, Servais L, et al. A high frequency of BRCA mutations in young black women with breast cancer residing in Florida. Cancer. 2015; 121 (23):4173-80. doi: 10.1002/cncr.29645. PMID: 26287763; PMCID: PMC4666784.
30. Domchek SM, Yao S, Chen F, Hu C, Hart SN, Goldgar DE, et al. Comparison of the Prevalence of Pathogenic Variants in Cancer Susceptibility Genes in Black Women and Non-Hispanic White Women with Breast Cancer in the United States. JAMA Oncol. 2021; 7(7):1045-50. doi: 10.1001/jamaoncol.2021.1492. PMID: 34042955; PMCID: PMC8160931.
31. Oluwagbemiga LA, Oluwole A, Kayode AA. Seventeen years after BRCA1: what is the BRCA mutation status of the breast cancer patients in Africa? - a systematic review. SpringerPlus. 2012; 1(1):83. doi: 10.1186/2193-1801-1-83. Epub 2012
32. Setyawati Y, Rahmawati Y, Widodo I, Ghozali A, Purnomosari D. The Association between Molecular Subtypes of Breast Cancer with Histological Grade and Lymph Node Metastases in Indonesian Woman. Asian Pac J Cancer Prev. 2018; 19(5):1263-8. doi: 10.22034/APJCP.2018.19.5.1263. PMID: 29801411; PMCID: PMC6031822.
33. Isheden G, Grassmann F, Czene K, Humphreys K. Lymph node metastases in breast cancer: Investigating associations with tumor characteristics, molecular subtypes and polygenic risk score using a continuous growth model. Int J Cancer. 2021; 149(6):1348-57. doi: 10.1002/ijc.33704. PMID: 34097750.
34. Li J, Chen Z, Su K, Zeng J. Clinicopathological classification and traditional prognostic indicators of breast cancer. Int J Clin Exp Pathol. 2015; 8(7):8500-5. PMID: 26339424; PMCID: PMC4555752.