RESEARCH ARTICLE

Molecular subtypes of breast carcinoma and their association with clinicopathological parameters

Erum Khaliq, Summayya Shawana

Abstract

Objective: To evaluate the frequency of molecular subtypes of breast carcinoma, and to determine their association with clinicopathological parameters.

Method: The bi-directional, cross-sectional, analytical study was conducted from December 2022 to June 2023 at the Histopathology Department of Pakistan Naval Station Shifa Hospital, Karachi, and comprised 218 females aged 24-81 years with primary breast adenocarcinoma, including both prospective and retrospective cases. Immunohistochemistry was performed to categorise molecular subtypes. Allred scoring system was used to score oestrogen and progesterone receptors and human epidermal growth factor receptor-2. The cut-off value for proliferation index was set at 14%. Data was analysed using SPSS 27.

Results: Among the 218 females with mean age 49.15+-12.83 years, Luminal B was the most frequently observed molecular subtype with 95(42.2%) cases, followed by Luminal A 49(23.4%), triple-negative breast cancer 41(18.8%) and human epidermal growth factor receptor 2 positive 33(15.6%) cases. A significant association of molecular subtypes was identified with grade and Ki67 ($p<0.05$). A high proliferation index was observed in all breast cancer molecular subtypes except Luminal A. Stage III presentation was most common among Luminal A 12(50%) and HER2-positive 10(66.7%) cases, whereas the majority of Luminal B 22(57.9%) and triple-negative breast cancer 10(52.6%) cases presented at stage II. Among all molecular subtypes, Luminal B exhibited the highest frequency of lymphovascular invasion 20(48.8%) and lymph node metastases 23(60.5%) cases. Among the six cases exhibiting perineural invasion, five were identified as Luminal B molecular subtype.

Conclusion: Luminal B was found to be the predominant molecular subtype. Molecular subtype had a significant association with grade and proliferation index.

Key Words: Breast cancer, Molecular subtypes, Immunohistochemistry, Ki67, Lymph node metastases, Tumour infiltrating lymphocytes.

(JPMA 76: 346; 2026) **DOI: https://doi.org/10.47391/JPMA.22096**

Introduction

Breast cancer is the most frequently diagnosed cancer among women globally, accounting for 23.8% of all female cancers.[1] In 2020, there were 2.3 million diagnosed breast cancer cases, of which 43% were in Asia.[1,2] The 2022 Global Cancer Observatory (GLOBOCAN) statistics revealed that breast cancer had the highest incidence (31.1%) among all female cancers in Pakistan, and it was the leading cause of cancer-related deaths among females (26.1%).[1] According to Shaukat Khanum Memorial Cancer Hospital Annual Cancer Statistics 2023, breast cancer ranked first among the top 10 malignancies in adult females, accounting for 43% of all malignancies.[3] In Pakistan, one in every nine women is at risk of developing breast cancer in her lifetime.[4]

The persistently higher incidence and mortality of breast cancer, despite targetted and hormonal therapies, chemotherapy and radiotherapy, is attributed to its heterogeneous nature. Breast cancer exhibits a diverse range of clinical, histopathological and molecular features, and its heterogeneous behaviour depends on various factors, like tumour size, grade, stage and hormonal receptors, which not only influence the prognosis of tumour, but also have an impact on treatment implications.[5] Oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER2) have been used as predictive markers, which are further classified into molecular subtypes based on gene expression profiling.[5] According to the global gene expression profiling analysis, breast cancer has been classified into four molecular subtypes, namely luminal A, luminal B, HER2 overexpression and triple-negative breast cancer (TNBC).[6] Although luminal A and luminal B are both ER-positive cancers, the prognosis of luminal A breast cancer is more favourable than that of

Department of Pathology, Bahria University Health Sciences Campus, Karachi, Pakistan.

Correspondence: Erum Khaliq. . **Email:** erummirza34@gmail.com

ORCID ID: 0009-0004-4011-5678

Submission complete: 20-09-2024 **First Revision received:** 03-01-2025

Acceptance: 25-10-2025 **Last Revision received:** 24-10-2025

luminal B. The ER-negative breast cancer subtypes include HER2-positive and TNBC. HER2-positive breast cancer is an intermediate to high-grade tumour, while the TNBC molecular subtype manifests the worst prognosis.[7] The molecular classification helps predict tumour behaviour and, thus, prognosis of the patient, and also aids clinicians in selecting a precise treatment plan. Moreover, the information obtained from molecular classification is also valuable in offering an opportunity for novel targetted treatments aimed at specific molecular abnormalities driving the growth of individual tumours.

The current study was planned to determine the frequency of molecular subtypes luminal A, luminal B, HER2-positive and TNBC in the local population, and to evaluate their association with different clinicopathological parameters of breast cancer.

Patients and Methods

The bidirectional, cross-sectional, analytical study was conducted at the Department of Histopathology, Pakistan Naval Station (PNS) Shifa Hospital, Karachi, from December 2022 to June 2023. After approval from the ethics review committee of Bahria University Health Sciences Campus, Karachi, the sample size was calculated using OpenEpi version 3 using the formula: n = [DEFF*Np(1-p)]/ [(d2/Z21-α/2*(N-1)+p*(1-p)]), applying a two-sided test with significance level 0.05 and power 80%.[8] The sample was raised using non-probability convenience sampling technique. The samples included both prospective and retrospective cases. Informed consent was obtained from all participants of the study. Those included were females aged 24-81 years with primary breast adenocarcinoma. Cases with metastatic tumours and poorly fixed tissues were excluded. Clinical and histological parameters, like age, histological type, molecular subtype, grade, stage, lymph node (LN) status, lymphovascular invasion (LVI) and perineural invasion (PNI) were recorded.[5] Histological typing of breast cancer was carried out following the World Health Organisation (WHO) classification.[9] Grading was based on the Nottingham Grading System[10] and staging was determined using the Tumour-Node-Metastasis (TNM) Classification[11] as recommended by the American Joint Committee on Cancer (AJCC).[11]

All the specimens submitted to the histopathology laboratory were fixed in 10% buffered formalin, examined grossly, sectioned, stained with haematoxylin and eosin (H&E), and diagnosed by a histopathologist. Immunohistochemistry (IHC) analysis was performed according to the specifications provided by the manufacturer (Dako Agilent, USA), inclusive of positive and negative controls. Based on the hormone receptor positivity status, different molecular subtypes of breast carcinoma were identified and categorised into four main groups: 5 luminal A (ER+/PR+- HER2-, Ki67<14); luminal B (ER+/PR+-/ HER2+-/Ki67>14); HER2 (ER/PR- HER2+); and TNBC (ER/PR/HER2-)

The Allred system[12] was used to score ER, PR and HER2, which is a semi-quantitative method that combines the proportion of positively stained cells (scale of 0-5) with the intensity of staining (scale of 0-3). The scores for proportion and intensity were then summed up to yield the total score. The cut-off value for proliferation index (Ki67) was set at 14%.[13]

Data was analysed using SPSS 27. Mean +- standard deviation were calculated for quantitative variables, while frequencies and percentages were reported for qualitative variables. Chi-square/Fisher exact test was applied to determine the association between qualitative variables. P<0.05 was considered significant.

Results

Of the 218 females with mean age 48.58+-13.10 years

Table-1: Demographic and clinical characteristics (n=218).

	Frequency (percentage)
Age (years); mean± std. dev.	48.58±13.10
Age groups	
20-30 years	15 (6.9)
31-40 years	48 (22)
41-50 years	58 (26.6)
51-60 years	51 (23.4)
61-70 years	39 (17.9)
>70 years	7 (3.2)
Biopsy	
Modified radical mastectomy	95 (43.6)
Excisional	9 (4.1)
Incisional	12 (5.5)
Trucut	81 (37.2)
Needle	2 (0.9)
Skin	7 (3.2)
Not specified	12 (5.5)
Histology	
IBC-NST	193 (88.5)
ILC	11 (5)
DCIS	6 (2.8)
Others	7 (3.2)
No Residual Ca	1 (0.5)
Grade	
Grade-1	8 (3.7)
Grade-2	155 (71.1

Continue on next page..

Continue from previous page...

Grade-3	55 (25.2)
Stage	
Stage-0	2 (0.9)
Stage-I	9 (4.1)
Stage-II	44 (20.2)
Stage-III	42 (19.3)
Not specified	121 (55.5)
Receptor Status	
ER	22 (10.1)
ER/PR	85 (39)
ER/PR/HER2	23 (10.6)
TNBC	41 (18.8)
ER/HER2	9 (4.1)
PR/HER2	2 (0.9)
HER2	32 (14.7)
PR	4 (1.8)
Molecular Status	
Luminal A	49 (22.5)
Luminal B	95 (43.6)
HER2+ve	33 (15.1)
TNBC	41 (18.8)
Residual tumour	
<30%	8 (3.7)
31-50%	8 (3.7)
51-80%	8 (3.7)
>80%	11 (5)
No Treatment	183(83.9)
Laterality	
Right	104 (47.7)
Left	114 (52.3)
Ki67	
Low (<14%)	60 (27.5)
High (>14%)	158 (72.5)
Ductal carcinoma in situ	
Present	68 (31.2)
Absent	51 (23.4)
Not specified	99 (45.4)
Lymph vascular invasion	
Present	49 (22.5)
Absent	55 (25.2)
Not specified	114 (52.3)
Lymph node invasion	
Present	58 (26.6)
Absent	37 (17)
Not specified	123 (56.4)
Peri-neural invasion	
Present	6 (2.8)
Absent	90 (41.3)
Not specified	122 (56)
Tumour-infiltrating lymphocytes(n=105)	
Positive	24 (22.9)
Negative	18 (17.1)
Not specified	63 (60)

IBC-NST: Invasive breast carcinoma-no special type, ILC: Invasive lobular carcinoma, Ca: Carcinoma, DCIS: Ductal carcinoma in situ, HER2: Human epidermal growth factor receptor-2, TNBC: Triple-negative breast cancer, ER: Oestrogen receptor, PR" Progesterone receptor.

(range: 24 -81 years), 58(26.6%) were aged 41-50 years. Demographic and clinical characteristics of the sample were noted in detail (Table 1).

With respect to molecular subtypes, luminal B 95(43.6%)

Table-2: Association of molecular status with clinicopathological features.

	Molecular Status [n (%)]				p-value
	Luminal A	Luminal B	HER2+ve	Triple negative	
Age Groups					
20-30 years	3(6.1)	6(6.3)	2(6.1)	4(9.8)	0.11
31-40 years	11(22.4)	14(14.7)	8(24.2)	15(36.6)	
41-50 years	8(16.3)	33(34.7)	8(24.2)	9(22)	
51-60 years	11(22.4)	25(26.3)	8(24.2)	7(17.1)	
61-70 years	15(30.6)	12(12.6)	6(18.2)	6(14.6)	
>70 years	1(2)	5(5.3)	1(3)	0(0)	
Grade					
Grade-1	3(6.1)	5(5.3)	0(0)	0(0)	0.04*
Grade-2	40(81.6)	67(70.5)	23(69.7)	25(61)	
Grade-3	6(12.2)	23(24.2)	10(30.3)	16(39)	
Stage (n=97)					
Stage-0	2(8.3)	0(0)	0(0)	0(0)	0.23
Stage-I	2(8.3)	4(10.3)	1(6.7)	2(10.5)	
Stage-II	8(33.3)	22(56.4)	4(26.7)	10(52.6)	
Stage-III	12(50)	13(33.3)	10(66.7)	7(36.8)	
Residual Tumour					
<30%	6(12.2)	1(1.1)	0(0)	1(2.4)	0.11
31-50%	1(2)	5(5.3)	1(3)	1(2.4)	
51-80%	2(4.1)	3(3.2)	2(6.1)	1(2.4)	
>80%	1(2)	3(3.2)	3(9.1)	4(9.8)	
No Treatment	39(79.6)	83(87.4)	27(81.8)	34(82.9)	
Ki67					
Low (<14%)	49(100)	4(4.2)	4(12.1)	3(7.3)	
<0.001*					
High (>14%)	0(0)	91(95.8)	29(87.9)	38(92.7)	
Ductal carcinoma in situ (n=119)					
Present	18(54.5)	30(63.8)	12(63.2)	8(40)	0.30
Absent	15(45.5)	17(36.2)	7(36.8)	12(60)	
Lymph vascular invasion (n=104)					
Present	10(40)	20(48.8)	11(61.1)	8(40)	0.49
Absent	15(60)	21(51.2)	7(38.9)	12(60)	
Lymph Node Invasion (n=95)					
Present	15(62.5)	23(60.5)	10(71.4)	10(52.6)	0.74
Absent	9(37.5)	15(39.5)	4(28.6)	9(47.4)	
Peri-neural Invasion (n=96)					
Present	1(4)	5(13.5)	0(0)	0(0)	0.20
Absent	24(96)	32(86.5)	15(100)	19(100)	
Tumour-infiltrating lymphocytes (n=42)					
Positive	3(25)	9(64.3)	3(75)	9(75)	0.05
Negative	9(75)	5(35.7)	1(25)	3(25)	
Laterality					
Right	27(55.1)	43(45.3)	16(48.5)	18(43.9)	0.67
Left	22(44.9)	52(54.7)	17(51.5)	23(56.1)	

Chi-square/fisher exact test was applied*Significant at 0.05 levels.3

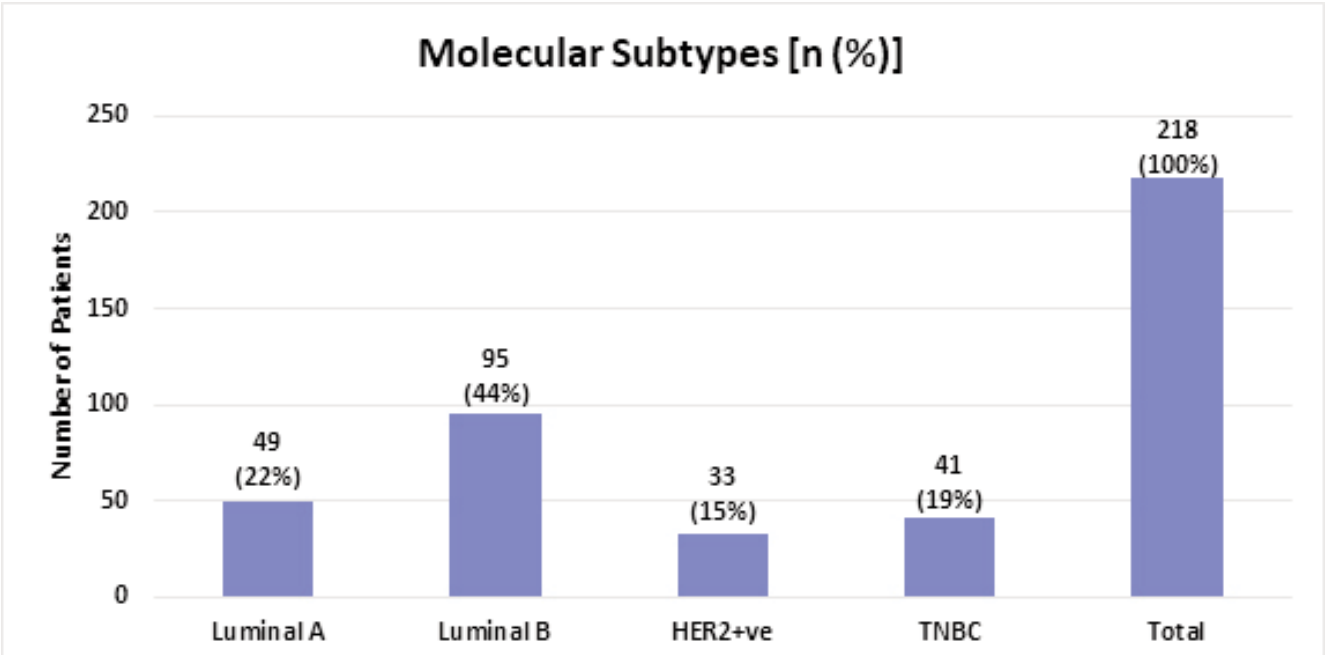

Figure: Distribution of molecular subtypes.

was the most frequent, followed by Luminal A 49(22.5%), TNBC 41(18.8%), and HER2-positive 33(15.1%) cases (Figure).

There was a significant association) of molecular subtypes with tumour grade (p=0.04 and Ki67 (p<0.001) (Table 2).

Discussion

Breast cancer is a leading cause of morbidity and mortality among women worldwide, with significant variations in incidence and outcome across different populations. This variation is attributed to the heterogeneous nature of breast cancer. The molecular classification of breast cancer has emerged as a pivotal tool in understanding its complexity, enabling more accurate prognostication and personalised treatment strategies. The concept of molecular classification was introduced by Perou and Sorlie based on gene expression profiling, but owing to its high cost, it has largely been replaced by IHC in routine practice.[14] The current study aimed at evaluating the frequency of molecular classification of breast cancer in the Pakistani population, and its association with different clinicopathological parameters.

The mean age in the current study was 48.58± 13.[10] years, similar to most of the studies conducted in Pakistan.[15,16] Conversely, women from different Asian countries have shown a mean age >50 years.[5,17,18] The peak age of incidence in the current study was 41-50 years (26.6%), similar to the study conducted by Nausheen et al. in Lahore, in which most of the breast cancer patients were <50 years of age.[15] On the contrary, studies conducted in Vietnam[17] and Scotland[19] revealed increased breast cancer incidence in older age groups. The young age of the population and lower life expectancy are the reasons for the younger age at presentation in developing countries. Many developing countries have a higher proportion of younger individuals. Since the population skews younger, the average age of breast cancer diagnosis is naturally lower. According to the Pakistan Bureau of Statistics (2020-21), approximately 78% population is aged <40 years.[20] Another reason is consanguineous marriages, which contribute to the appearance of the disease at a younger age. Consanguineous marriages can increase the likelihood of genetic mutations being passed down, which may contribute to hereditary cancers. Studies have been conducted in Pakistan[21,22], revealing the contribution of different genes in the development of hereditary breast cancer.

In the current study, the frequency of luminal B molecular subtype was the most common, followed by luminal A, TNBC and HER2-positive cases. Similar luminal B prevalence has also been observed in majority of other Pakistani studies[23,24] and in studies conducted in other countries.[17,18] However, some local studies[7,15,16] as well as the conducted in other parts of the world[25,26] showed higher prevalence of luminal A. The increased frequency of luminal cases (66%) in the current study is similar to that seen in the Western population (70%).[27] The variation

in most commonly observed breast cancer molecular subtype is seen not only among different populations, but also in the same population, which shows the heterogeneous nature of the disease, possibly due to differences in the genetic makeup. These findings warrant an individualised treatment strategy to help reduce the rising mortality rate among breast cancer patients.

The increased frequency of luminal B subtype and TNBC was noted in younger and youngest age groups, respectively, whereas luminal A was more predominant in older females. Similar age-specific frequency of molecular subtypes was assessed in studies conducted by Fatima et al.[25] and Atif et al.[7] These findings are contradictory to the studies conducted by Ramsha et al.[24] and Thi et al.[17] in Pakistan and Vietnam, respectively, showing increased frequency of luminal tumours and HER2-positive breast cancer in older age groups.

Most of the breast cancer patients in the current study population exhibited moderately differentiated tumours, a finding similar to many local studies.[23,16] On the contrary, Puneet et al.[14] and Seref et al.[18] revealed an increased frequency of grade 3 breast cancer in Indian and Turkish women, respectively. A significant association was identified between molecular subtypes and grade, showing all the molecular subtypes frequently presenting with grade 2. The findings are consistent with the studies conducted by Mehreen et al.[28] and Sana and Afshan,[29] whereas Puneet et al.[14] and Seref et al.[18] observed that all molecular subtypes, except Luminal A, presented as grade.[3] In the current study, luminal B exhibited the highest number of grade III cases, a finding similar to many studies,[14,17,23,28] and it corresponds to the aggressive behaviour of luminal B in the study population.

The majority of the tumours in the current study were stage II, followed by stage III. Similar results with increased stage II frequency have been reported by many local studies.[15,16,28] The increased frequency of advanced-stage tumours is likely due to late presentation during disease progression, a situation influenced by lack of self-awareness and screening programmes. Among different molecular subtypes, most of the luminal A and HER2-positive cases were stage III, while luminal B and TNBC were stage II at the time of presentation. Most studies have shown contradictory results, with Luminal A and HER2-positive cases presenting as stage II, and luminal B and TNBC presenting as stage III.[14,15,19] However, David et al.[30] showed similar findings of increased stage III frequency in luminal A breast cancer cases.

LN metastases is an important prognostic factor that helps determine the necessity of adjuvant chemotherapy and/or radiotherapy.[31] In the current study, the incidence of LN metastases and LVI was higher in luminal B breast cancer patients. The finding is compatible with the study conducted by Seref et al,[18] but it is contradictory to the results of increased nodal metastases in luminal A reported earlier.[25]

A significant association was also observed between molecular status and Ki67 expression ($p<0.001$), with luminal B, HER2-positive and TNBC cases displaying high proliferation rates, while luminal A cases largely exhibited low Ki67 expression. Similar results were reported by Mehreen et al.[28] and Seref et al.[18] Increased high Ki67 expression signify a higher frequency of aggressive tumours in the current study population, with rapid growth and spread, indicating the need for more aggressive treatments.

Tumour infiltrating lymphocytes (TILs) are the immunological biomarkers that add to the prognostic and predictive evaluation of breast cancer. The response of TILs varies across different subtypes of breast cancer. A positive correlation has been identified between TILs and treatment response in HER2-positive and TNBC cases, whereas the prognostic influence of TILs is limited in luminal tumours.[32] In the present study, luminal B showed the highest frequency of TILs, followed by TNBC. The enhanced immune response as evidenced by increased TILs might be a reaction to the aggressiveness of luminal B, and the presence of high TILs in luminal B tumours opens avenues for research into how these immune cells can be harnessed or boosted to improve treatment outcomes.

Most (60%) of the luminal A cases in the current study showed better treatment response (<30% residual tumour), whereas TNBC (>50%) and HER2-positive (50%) breast cancer cases had poor treatment response (>80% residual tumour). Most of the studies showed conflicting results of better pathological complete response after neoadjuvant chemotherapy in HER2-positive and TNBC cases compared to luminal A breast cancer cases in which the treatment response is comparatively low.[33,34] However, Shanmugam et al. revealed the best (90.5%) treatment response in HER2 breast cancer cases, followed by luminal A (81.2%) and the reduced treatment response in TNBC (66.6%).[35]

The current study has certain limitations, like being a single-centre study with a limited sample size. Multi-centre studies with large sample sizes are needed to validate the current findings. Furthermore, since trucut biopsies were also involved, the cases showing

pathological stage were further narrowed down, and, due to the lack of follow-up, the outcome could not be assessed. Finally, since the classification of luminal A and B was based on the proliferation index, a more robust diagnostic criterion was needed to minimise observer bias.

Conclusion

Most of the breast cancer patients were aged <50 years, and the presentation of the majority of patients at higher stages signifies lack of awareness and screening in the local population. Molecular subtypes had significant association with grade and Ki67 expression. Luminal B was the most predominant, and HER2-positive cases were the least frequent molecular subtypes observed. The predominance of luminal B breast cancer in the subset calls for further investigation with regard to underlying molecular mechanisms and associated predictive factors for disease outcome.

Disclaimer: The text is based on an MPhil thesis..

Conflict of Interest: None.

Source of Funding: None.

References

1. International Agency for Research on Cancer, World Health Organization (WHO). Cancer Today, GLOBOCAN Cancer Observatory. GLOBOCAN 2022 Version 1.1. Lyon, France: IARC; 2024. [Online] [Cited 2024 August 10]. Available from URL: https://gco.iarc.who.int
2. Lim YX, Lim ZL, Ho PJ, Li J. Breast cancer in Asia: incidence, mortality, early detection, mammography programs, and risk-based screening initiatives. Cancers (Basel) 2022;14:4218. doi: 10.3390/cancers14174218.
3. Mahmood S, Yousaf A, Faraz R, Quader A, Asif H, Atif A, et al. Annual Cancer Registry Report–2023. Lahore, Pakistan: Shaukat Khanum Memorial Cancer Hospital and Research Center; 2023.
4. Menhas R, Umer S. Breast cancer among Pakistani women. Iran J Public Health 2015;44:586–7.
5. Siddiqui B, Ahmed S, Sinha D, Sharma AVL. Molecular classification of breast carcinoma in a tertiary hospital of India: recent trends. Indian J Surg Oncol 2023;14:176–80. doi: 10.1007/s13193-022-01647-y.
6. Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, et al. Molecular portraits of human breast tumors. Nature 2000;406:747–52. doi: 10.1038/35021093.
7. Khalid F, Zafar G, Afzal S, Chughtai A, Fatima B, Chughtai AS. Frequency of different molecular subtypes of breast cancer in Pakistani population: a single-center study. Pak J Pathol 2020;31:50–4.
8. Dean AG, Sullivan KM, Soe MM. OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version: 3.01. [Online] 2013 [Cited 2024 August 10]. Available from URL: https://www.openepi.com/Menu/OE_Menu.htm
9. International Agency for Research on Cancer, World Health Organization (WHO). WHO classification of tumours of the breast, 5th ed. Lyon, France: IARC; 2019.
10. Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. Histopathology 1991;19:403–10. doi: 10.1111/j.1365-2559.1991.tb00229.x.
11. Giuliano AE, Edge SB, Hortobagyi GN. Eighth edition of the AJCC cancer staging manual: breast cancer. Ann Surg Oncol 2018;25:1783–5. doi: 10.1245/s10434-018-6486-6.
12. Allred DC, Harvey JM, Berardo M, Clark GM. Prognostic and predictive factors in breast cancer by immunohistochemical analysis. Mod Pathol 1998;11:155–68.
13. Alam S, Riaz S, Khan HA, Gardezi AB, Shehzad K, Anwar MF. Frequency of luminal A and luminal B breast cancers in Pakistani population. APMC 2019;13:296–9. doi: 10.29054/APMC/19.761.
14. Somal PK, Sancheti S, Sharma A, Sali AP, Chaudhary D, Goel A, et al. Clinicopathological analysis of molecular subtypes of breast cancer using immunohistochemical surrogates. South Asian J Cancer 2023;12:104–11. doi: 10.1055/s-0043-1761942.
15. Henna N, Shafqat F, Rehman M, Fakhr SA, Anjum S, Sameen S, et al. Clinicopathological characteristics of molecularly classified groups of invasive ductal breast carcinoma in Pakistani women. Pak J Med Dent 2022;11:3–8. doi: 10.36283/PJMD11-2/002.
16. Shirazi B, Niaz M, Khan MA. Characteristics and risk factors of breast cancer patients: distinctive regional differences. J Pak Med Assoc 2024;74:672. doi: 10.47391/JPMA.9360.
17. Nguyen TMT, Le RD, Nguyen CV. Breast cancer molecular subtype and relationship with clinicopathological profiles among Vietnamese women. Pathol Res Pract 2023;250:154819. doi: 10.1016/j.prp.2023.154819.
18. Dokcu S, Çaparlar MA, Başçeken SI, Eroğlu A. Distribution and clinicopathological characteristics of breast cancer molecular subtypes in Turkish women. EJ Clin Med 2022;3:14–20. doi: 10.24018/ejclinicmed.2022.3.6.220.
19. Mesa-Eguiagaray I, Wild SH, Rosenberg PS, Bird SM, Brewster DH, Hall PS, et al. Temporal trends in breast cancer incidence by molecular subtypes. Br J Cancer 2020;123:852–9. doi: 10.1038/s41416-020-0938-z.
20. Pakistan Bureau of Statistics (PBS). Percentage distribution of population by age, sex and area, 2020–21. Islamabad, Pakistan: PBS; 2021. [Online] 2021 [Cited 2024 August 10]. Available from URL: https://www.pbs.gov.pk
21. Akbar F, Siddiqui Z, Waheed MT, Ehsan L, Ali SI, Wiquar H, et al. Spectrum of germline pathogenic variants in suspected hereditary breast cancer in Pakistan. Hered Cancer Clin Pract 2022;20:24. doi: 10.1186/s13053-022-00232-2.
22. Saleem A, Akbar F, Zahid B, Nasir M, Kirmani S. CHEK2 variants contributing to hereditary breast cancer in Pakistan. Genet Med Open 2024;2:100979. doi: 10.1016/j.gimo.2024.100979.
23. Hashmi AA, Aijaz S, Khan SM, Mahboob R, Irfan M, Zafar NI, et al. Prognostic parameters of luminal A and B breast cancer subtypes. World J Surg Oncol 2018;16:1. doi: 10.1186/s12957-017-1299-9.
24. Khan R, Hashmi F, Bhatti AM, Memon AI, Nayab. Locally advanced breast cancer in Pakistani women. Pak J Health Sci 2023;4:31–4. doi: 10.54393/pjhs.v4i06.770.
25. Al-Thoubaity FK. Molecular classification of breast cancer: a retrospective cohort study. Ann Med Surg 2019;49:44–8. doi: 10.1016/j.amsu.2019.11.021.
26. Kurniawan BN, Djonny F, JP Jr. Breast cancer metastasis and mortality based on molecular subtype. Breast Dis 2022;41:427–32. doi: 10.3233/BD-229000.
27. Łukasiewicz S, Czeczelewski M, Forma A, Baj J, Sitarz R, Stanisławek A. Breast cancer: epidemiology, classification and prognostic markers. Cancers (Basel) 2021;13:4287. doi: 10.3390/cancers13174287.
28. Mushtaq M, Chaudry SS, Sheikh AK, Khan N, Khattak A, Akbar A, et al. Molecular subtypes with Ki-67 cut-off in Pakistani breast cancer patients. Arch Iran Med 2021;24:837–44. doi: 10.34172/aim.2021.124.
29. Shaikh S, Rasheed A. Predicting molecular subtypes of breast

cancer using imaging. Radiol Res Pract 2021;2021:6691958. doi: 10.1155/2021/6691958.
30. Nelson DR, Brown J, Morikawa A, Method M. Breast cancer-specific mortality in early breast cancer. PLoS One 2022;17:e0264637. doi: 10.1371/journal.pone.0264637.
31. Morkavuk SB, Güner M, Çulcu S, Eroğlu A, Bayar S, Ünal AE. Lymphovascular invasion and molecular subtypes in invasive breast cancer. Int J Clin Pract 2021;75:e13897. doi: 10.1111/ijcp.13897.
32. Ciarka A, Piątek M, Pęksa R, Kunc M, Senkus E. Tumor-infiltrating lymphocytes across breast cancer subtypes. Biomedicines 2024;12:763. doi: 10.3390/biomedicines12040763.
33. Atoui A, Zerdan MB, El Mahmoud A, Chamseddine N, Hamad L, Assi HI. Breast cancer molecular subtypes and Ki-67 as predictors of pathological complete response. Int J Breast Cancer 2022;2022:1218128. doi: 10.1155/2022/1218128.
34. Omair A, Alkushi A, Alamri G, Almojel T, Alsadun S, Masuadi E, et al. Correlation of pathological complete response and molecular subtypes. Cureus 2023;15:e37449. doi: 10.7759/cureus.37449.
35. Shanmugam S, Govindasamy G, Kumar PS, Muniasamy P. Molecular subtypes as predictors of response to neoadjuvant chemotherapy. Indian J Cancer 2017;54:652–7. doi: 10.4103/ijc.IJC_238_17.

AUTHOR'S CONTRIBUTION:
EK: Concept, data collection, acquisition, analysis, interpretation, drafting, revision and final approval.
SS: Concept, acquisition, analysis, interpretation, revision and final approval.