Association of tumor volume with molecular phenotypes in breast cancer: A study at a tertiary care hospital

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Abstract. Breast cancer is a common cause of mortality among women worldwide. The incidence of this disease is higher in developing countries than in Western countries. Variations are noted in the distribution of breast cancer subtypes between Eastern and Western populations. Breast cancer is a heterogeneous lesion at the molecular level, and its prognosis is dependent on multiple factors. The present study aimed to determine the distribution of various molecular phenotypes of breast cancer and its association with tumor volume in patients presenting to a tertiary care hospital. The present observational cross-sectional study was conducted at a tertiary care medical college hospital. Following analysis using immunohistochemistry for estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2 (HER2), and Ki67, all patients with breast cancer were classified into the luminal A, luminal B, HER2-enriched and triple-negative breast cancer (TNBC) groups. In addition, the age and tumor volume of the patients were compared among the different subtypes of breast cancer. Of the 165 patients with infiltrating ductal carcinoma (type not otherwise specified), the most common molecular phenotype was TNBC (39.4%), followed by luminal B (24.2%). The HER2-enriched and luminal A subtypes constituted 20.6 and 15.8%, respectively. There was no significant difference in the average age of the patients among the different molecular phenotypes. The smallest median tumor volume was observed in the luminal A (4.5 cm^3) group, followed by the HER2-enriched (8.0 cm^3), TNBC (24.0 cm^3) and luminal B (29.94 cm^3) groups. TNBC was the most common molecular phenotype. The tumor volume was the smallest in the patients with the luminal A subtype. As tumor volume has prognostic value, the poor prognosis of patients with TNBC and HER2-enriched breast cancer may be improved via targeted therapy. It is hoped that the findings of the present study may prove useful in the management of patients with breast cancer.

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Introduction

Breast cancer is one of the most common malignancies among women worldwide and one of the most common causes of cancer-related mortality among women in both developed and developing countries (1). According to the GLOBOCAN 2020 data, >2 million cases and ~685,000 deaths were registered in 2020 globally (2). In Asia, the incidence of new breast cancer cases was 1,026,171 and the associated mortality rate was 346,009 cases. In India, there were 178,361 new breast cancer cases (26.3%), and the mortality rate was 90,408 cases (21.9%). Owing to the increasing incidence of female breast cancer (11.7%), it has surpassed lung cancer as the most common type of cancer worldwide (11.4%), followed by lung (11.4%) and colorectal (10.0%) cancer. The age-standardized incidence rate of invasive breast cancer in women in Asia was 36.8 per 100,000, whereas in Western populations, such as North America and Europe, it was 89.4 and 74.3 per 100,000 women, respectively, which is ~50% of that in the Western population (2).

The incidence of breast cancer is higher in developing countries than in Western countries; however, globally, there has been a change in the prevalence of breast cancer among women in South America, Africa and Asia (3). GLOBOCAN has estimated that the incidence of breast cancer will double by the year 2050 (4).

Clinical and pathological examinations play crucial roles in the diagnosis and understanding of complex diseases, such as breast cancer. However, the published literature reveals that there is a paucity of epidemiological data on breast cancer in India (5). Variations are noted in the distribution of breast cancer subtypes between the Indian (6-10) and Western populations (11-15).

The prognosis of patients with breast cancer is dependent on various factors, such as the tumor histological type, grade, lymph node involvement, hormonal receptor [estrogen receptor (ER), progesterone receptor (PR)] and human epidermal growth factor receptor 2 (HER2) status and the proliferative index (6,11,16).

Over the past two decades, microarray-based gene profiling and The Cancer Genome Atlas network have established refined subtypes of breast cancer via the extensive profiling of various protein levels, microRNAs and DNA (17).

Breast cancer exhibits diverse clinical and molecular features. Therefore, on the basis of its molecular characteristics, patients can be categorized into four groups as follows: i) Luminal A (ER^+, PR^+ and $HER2^-$ with a low Ki67 expression); ii) luminal B (ER^+, PR^+, $HER2^{+/-}$ and a high Ki67 expression); iii) HER2-enriched (ER^-, PR^- and $HER2^+$); iv) and triple-negative breast cancer (TNBC; ER^-, PR^- and $HER2^-$) (12,18).

Each molecular subtype of breast cancer has been associated with a different prognosis, preferential metastatic organs and response to therapy, as well as different recurrence or disease-free survival rates (19,20).

One of the most distinct features of cancer is the uncontrolled proliferation of cells, and all proliferating cells exhibit the Ki67 antigen, which indicates that it is a key biomarker for the estimation of cell proliferation. Hence, the rate of cell proliferation can be estimated by assessing the Ki67 antigen using immunohistochemical techniques (21). Moreover, Ki67 plays a crucial role in determining the relative prognosis of the disease, resistance to chemotherapy or endocrine therapy, and the residual risk assessment of patients receiving standard therapy. In addition, assessing treatment efficacy, specifically that of endocrine therapy, is pertinent for patients receiving neoadjuvant therapy (22).

Of the various molecular subtypes of breast cancer, TNBC and HER2-enriched breast cancer are highly aggressive and are associated with short survival periods. Although they respond well to chemotherapy (23), patients with TNBC with tumor-infiltrating lymphocytes have a better prognosis and survival rate than those without lymphocyte-infiltrating tumors (24). Thus, breast cancer lesions of the same histological type may respond differently to therapy and exhibit varying prognoses. Therefore, molecular characterization has become a key factor in deciding the targeted therapy for patients (12). However, the prevalence of molecular subtypes of breast cancer has not been studied extensively in developing countries. Furthermore, the fact that tumor volume plays a critical prognostic role in breast cancer should be considered. Hence, the present study was performed in an aim to determine the distribution of molecular phenotypes of ductal carcinoma of the breast in patients who presented to a tertiary care hospital of Northern Delhi, India. In addition to the molecular subtypes, clinicopathological factors, such as age and tumor volume, were compared among the patients with the various molecular phenotypes.

Patients and methods

The present study is an observational cross-sectional study performed at the Department of Pathology of a tertiary care medical college hospital in Delhi. The study was conducted after obtaining approval from the Institutional Ethics Committee, vide letter no. IEC/NDMC/2022/109 (dated June 17, 2022). The present study conformed to the tenets of the Declaration of Helsinki, and good clinical practice guidelines were followed. Moreover, written informed consent was obtained from the patients for their participation.

Patients. A total of 165 patients with breast cancer were included in the present study. All women with infiltrating ductal carcinoma-not otherwise specified (IDC-NOS) who presented from June, 2022 to December, 2023 to the hospital were included in the study. All males, patients with IDC-NOS for whom complete tumors were not available, such as via needle biopsy, and those who underwent surgery after neoadjuvant therapy were excluded from the study.

Immunohistochemistry. The immunohistochemistry (IHC) staining procedure was performed on formalin-fixed paraffin-embedded (FFPE) tissue blocks utilizing an optimized IHC protocol. Sections of FFPE tissue were sliced at a 4 μm thickness and subsequently dewaxed, followed by rehydration in water. Heat-induced epitope retrieval was performed using a domestic pressure cooker with retrieval buffer (Tris-EDTA buffer, pH 9.0, Merck KGaA) for ER, PR, HER2, and Ki67. The slides underwent a 10-min incubation at room temperature with peroxidase-blocking solution (1% hydrogen peroxide), followed by a wash with phosphate-buffered saline (PBS, pH 7.2-7.4).

The slides were then incubated for 1 h at room temperature with specific ready-to-use mouse monoclonal primary antibodies ER, PR, HER2 and Ki67 (cat. no. AN710-5ME, AN711-5ME, AN471-5ME and AM297-5M, respectively; BioGenex), followed by overnight incubation at 4-6˚C in a refrigerator. Subsequently, the slides were washed with PBS solution, followed by a 30-min incubation at room temperature with a secondary antibody (polymer HRP; cat. no. HK595-50KN, BioGenex). Following another wash with PBS solution, the DAB chromogen with substrate (cat. no. HK124-025KN, BioGenex) was applied for 5 min. The slides were counterstained with hematoxylin (Merck KGaA) for 30 sec at room temperature and then mounted with DPX and a cover slip. Assessment of the IHC stained sections was conducted using a compound light microscope (Olympus Corporation) by an experienced pathologist.

All the studied patients were classified as luminal A [ER^+, PR^+ and HER2 with a low (<14%) Ki67 expression]; luminal B [ER^+, PR^+ and $HER2^{+/-}$, with a high (>14%) Ki67 expression]; HER2-enriched (ER^-, PR^- and $HER2^+$); and TNBC (ER^-, PR^- and $HER2^-$). The tumor volume in cm^3 was estimated from the histological specimens of all patients included in the study.

Statistical analysis. Statistical analyses were performed using the Python language package V3.0 (https://www.python.org) and Jupyter V5.0 (https://jupyter.org) as the IDE for the Python language. To assess the significance of differences in age and tumor volume among the different molecular subtypes of breast cancer, the Kruskal-Wallis (non-parametric) test was used. In the case that the Kruskal-Wallis test result was significant, Dunn's post hoc test was then performed. A P-value of <0.05 was considered to indicate a statistically significant difference.

Results

All the cases were infiltrating ductal carcinoma, NOS type. The age range of the patients was 25-75 years, with a mean age of 47.1 years (SD ±11.5 years), and the median age was 45 years. The majority of the patients with breast cancer were in the age

Table I. Age distribution of the patients in the present study.

Age group (years)	Luminal A (n)	Luminal B (n)	HER2-enriched (n)	TNBC (n)	Total (n)	Percentage
Up to 30	1	3	3	3	10	6.06
31-40	7	13	11	22	53	32.1
41-50	7	12	7	17	43	26.1
51-60	5	8	9	16	38	23.0
61-70	4	4	4	6	18	10.9
>70	2	0	0	1	3	1.82
Total	26	40	34	65	165	100

Data were analyzed using the Kruskal Wallis test (P=0.686).

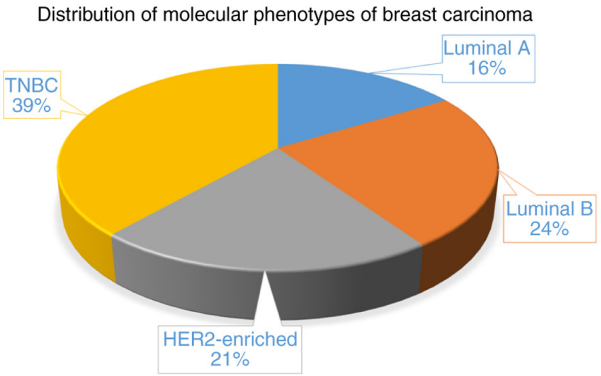

Figure 1. Distribution of molecular subtypes of breast cancer. TNBC, triple-negative breast cancer; HER2, human epidermal growth factor receptor 2.

group of 31-40 years (32.1%), followed by 41-50 years (26.1%), 51-60 years (23%), 61-70 years (10.9%), <30 years (6.1%) and >70 years (1.8%) (Table I).

The most common molecular phenotype was TNBC (65 cases, 39.4%) with a median age of 45 years (range, 25-71 years), followed by luminal B (40 cases, 24.2%) with a median age of 45 years (range, 28-70 years), HER2-enriched (34 cases, 20.6%) with a median age of 46 years (range, 25-70 years), and luminal A (26 cases, 15.8%) with a median age of 48.5 years (range, 30-75 years) (Figs. 1 and 2). The difference in age among the patients with different molecular subtypes of breast cancer was not statistically significant (P=0.686, Kruskal-Wallis test; Table I).

The average tumor volume was 44.16 cm^3 (SD ±71.96 cm^3) and ranged from 0.13 to 440 cm^3. The mean tumor volume was 14.6 cm^3 (SD ±27.56 cm^3) in the luminal A subgroup with a median of 4.5 cm^3 (range, 1.13-110.0 cm^3), 69.4 cm^3 (SD ±78.23 cm^3) in the luminal B subgroup with a median of 29.94 cm^3 (range, 4.0-224.0 cm^3), 36.15 cm^3 (SD ±47.66 cm^3) in the HER2-enriched cohort with a median of 8.0 cm^3 (range, 1.8-162.5 cm^3) and 51.31 cm^3 (SD ±91.1 cm^3) in TNBC with a median of 24.0 cm^3 (range, 1.15-440.0 cm^3) (Fig. 3).

The tumor volume differed significantly among the molecular subtypes of breast cancer (P=0.001, Kruskal-Wallis test). The difference in tumor volume between the luminal A and luminal B subtype, as well as between the luminal A and TNBC groups was statistically significant (P=0.001 and P=0.001, respectively, Dunn's test). Similarly, the difference in tumor volume between the luminal B and HER2-enriched, as well as between the luminal B and TNBC subtype was statistically significant (P=0.001 and P=0.001, respectively, Dunn's test). Furthermore, the difference in tumor volume between the HER2-enriched and TNBC subtype was also statistically significant (P=0.001, Dunn's test) However, the difference in tumor volume between the luminal A and HER2-enriched subtype was not statistically significant (P=0.158, Dunn's test) (Table II).

Discussion

Breast cancer remains a leading cause of cancer-related mortality among women worldwide. Breast cancer is a highly heterogeneous and complex disease and can be attributed to various clinical, pathological and biological factors that vary from one population to another. Identifying these factors is crucial as many of these factors have prognostic significance and play a key role in the successful treatment of the disease. Hence, the molecular classification of breast cancer has emerged as a vital tool for the optimal management of patients.

In the present study, the mean age of the patients was 47.1 years (SD ±11.5 years). The age of the patients ranged from 25 to 75 years, which was very close to that reported in the study by Sharma *et al* (7), in which the mean age was 48.14 years and the median age was 47 years. This finding is unlike that of other studies, as for instance in the studies of Jain *et al* (8), Kumar *et al* (18) and Pereira *et al* (9), in which the mean age of the patients was slightly higher.

However, in a study by Pandit *et al* (10), the median age of the patients was 50.02 years, ranging from 22 to 100 years, and the majority of the patients were in the age group of 41-50 years (31.3%), followed by 51-60 years (27.6%). In the present study, the majority of the patients were in the age group of 31-40 years (32.1%), followed by 41-50 years (26.1%). The findings of the present study are similar to those of the study by Gupta *et al* (6), in which a total of 60 patients were included. The most prevalent age group was 31-40 years (41.7%), followed by 41-50 years (26.7%) (6). In the study by Sharma *et al* (7), the majority of the patients were >40 years (73.4%) and 26.6% were <40 years. Jain *et al* (8) also reported that 41-70 years was the predominant age group, accounting

Table II. Differences in tumor volume among the different molecular subtypes of breast cancer.

	Molecular subtype, median tumor volume (range), cm^3			
Molecular subtype	Luminal A 4.5 (1.13-110.0)	Luminal B 29.94 (4.0-224.0)	HER2-enriched 8 (1.8-162.5)	TNBC 24.0 (1.15-440.0)
Luminal A	0.999	0.001	0.158	0.001
Luminal B	0.001	0.999	0.001	0.001
HER2-enriched	0.158	0.001	0.999	0.001
TNBC	0.001	0.001	0.001	0.999

Data were analyzed using the Kruskal-Wallis test (P=0.001) followed by Dunn's post hoc test (P-value illustrated above).

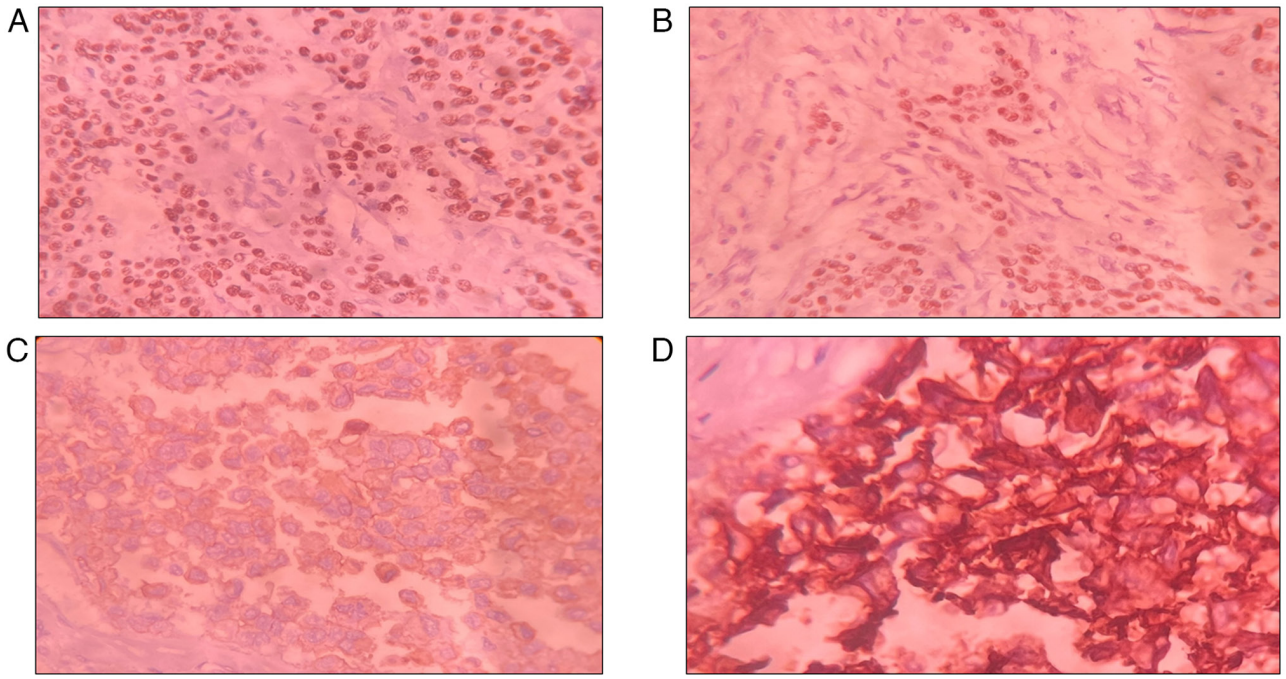

Figure 2. Photomicrographs from IHC illustrating (A) estrogen receptor positivity (IHC for ER, DAB; magnification, x40), (B) progesterone receptor positivity (IHC for PR, DAB; magnification, x40), (C) HER2 positivity (2+) (IHC for HER2, DAB; magnification, x40), and (D) HER2 positivity (3+) (IHC for HER, DAB; magnification, x40). IHC, immunohistochemistry; HER2, human epidermal growth factor receptor 2.

for 76.1% of breast cancer cases; 13.9 and 10% of the patients were <41 years and >70, respectively.

In the present study, TNBC was the most common subtype of breast cancer, followed by luminal B, HER2-enriched and luminal A. This finding agrees to a certain extent with the findings presented in the study by Pereira *et al* (9) in Mangalore (South India), in which TNBC was the most prevalent subtype, followed by the luminal B, luminal A and HER2-enriched subtypes.

By contrast, in the study by Pandit *et al* (10) performed in Maharashtra (West India), the most common molecular subtype of breast carcinoma was luminal A, followed by TNBC (26%), HER2-enriched (11%) and luminal B (8%). In that study, the remaining 18% of the total 2,062 patients were unclassified owing to an equivocal HER2 status (10). Similarly, another study from North India was performed by Gupta *et al* (6), in which luminal A was the most common subtype, followed by the TNBC, HER2-enriched and luminal B subtypes. However, in the studies by Jain *et al* (8) and Sharma *et al* (7) performed in Ludhiana (North India) and Guwahati (North-East India), respectively, luminal B was the most prevalent subtype, followed by the TNBC, luminal A and HER2-enriched subtypes. According to the findings of various Indian studies, there is heterogeneity in the distribution of molecular subtypes of breast cancer in the Indian population (7,8). However, studies from other countries have revealed a predominance of the luminal A subtype of breast cancer. The studies performed in Thailand (Asia) and Morocco (North Africa) by Tubtimhin *et al* (13) and Elidrissi *et al* (14), respectively, reported similar findings, with luminal A being the most common subtype, followed by the luminal B, TNBC and HER2-enriched subtypes.

In the study performed in Saudi Arabia (the Middle East) by Alnegheimish *et al* (12), the most common subtype was luminal A, followed by the TNBC, luminal B and HER2-enriched subtypes. The study conducted by Lin *et al* (15)

Table III. Prevalence of molecular subtypes of breast carcinoma among the different populations.

Authors (country)	Luminal A (%)	Luminal B (%)	HER2-enriched (%)	TNBC (%)	Total no. of cases	(Refs.)
Pandit *et al* (India)	37	08	11	26	2,062	(10)
Jain *et al* (India)	19.7	47.2	11.4	21.7	360	(8)
Pereira *et al* (India)	17	33.4	15.3	34.3	300	(9)
Sharma *et al* (India)	18.7	43	15.5	22.8	568	(7)
Gupta *et al* (India)	60.6	3.3	10	26.7	60	(6)
Tubtimhin *et al* (Thailand)	31.6	15.6	9.9	11.3	523	(13)
Elidrissi *et al* (Morocco)	61.1	16.1	8.6	14.2	2,260	(14)
Lin *et al* (Taiwan)	62	9	12	13	978	(15)
Alnegheimish *et al* (Saudi Arabia)	58.5	14.5	12.3	14.8	359	(12)
AlZaman *et al* (Bahrain)	41.3	22	23	13.7	109	(11)
Present study (India)	15.8	24.2	20.6	39.4	165	

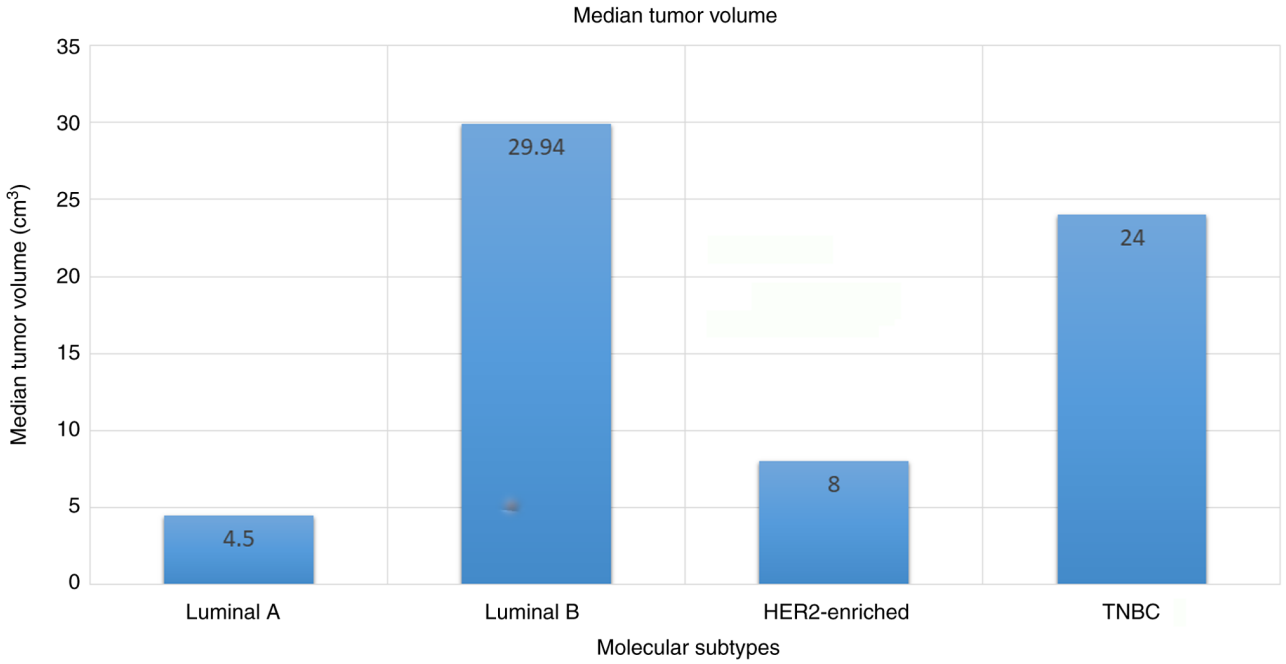

Figure 3. Median volume of the tumors in the patients with different molecular subtypes of breast cancer. TNBC, triple-negative breast cancer; HER2, human epidermal growth factor receptor 2.

in Taiwan (Asia) also documented that luminal A was the most prevalent subtype, followed by the TNBC, HER2-enriched and luminal B subtypes. Furthermore, yet another study from Bahrain (Asia) performed by AlZaman *et al* (11) observed that luminal A was the most common subtype, followed by the HER2-enriched, luminal B and TNBC subtypes (Table III).

All the surveyed studies considered only the largest dimension of the tumor in terms of tumor size; however, in the present study, the tumor volume (cm^3) was instead considered, which is considered more appropriate for assessing the clinicopathological features of patients. The findings presented herein indicated that the average tumor volume was 44.16 cm^3 (SD ±71.96 cm^3), ranging from 0.13 to 440 cm^3. Furthermore, luminal A tumors were found to have the smallest median tumor volume (4.5 cm^3), followed by HER2-enriched tumors (8 cm^3), TNBC tumors (24 cm^3) and luminal B tumors (29.94 cm^3). The differences in the median tumor volume between the luminal A and luminal B groups, and between the luminal A and TNBC groups were statistically significant (P=0.001 and P=0.001, respectively). Similarly, the difference in tumor volume between the luminal B and both HER2-enriched and TNBC subtype was also found statistically significant (P=0.001 for both). Moreover, a statistically significant difference in tumor volume was also found between the HER2-enriched and TNBC subtypes (P=0.001).

In the study by Jain *et al* (8), the mean tumor size was 3.7 cm and ranged from 0.8 to 10 cm, with a median of 3 cm. The mean tumor size was the least in the luminal A subgroup

(3.2 cm) and the highest in the HER2-enriched subgroup (4 cm) (8). Their study further demonstrated that there was a significant difference in the mean tumor size between luminal A breast cancer and other subtypes of breast carcinoma (luminal B, HER2-enriched and TNBC, P=0.03) (8).

In the study by Kumar *et al* (18), the mean tumor size was 3.4 cm and ranged from 1.1 to 7.8 cm. According to their study, the luminal A subtype had the maximum percentage of tumors <2 cm (smallest), whereas the TNBC subtype had the maximum percentage of tumors >5 cm (largest). In addition, there was a significant difference in the mean tumor size among all molecular subtypes of breast cancer (P=0.004) (18).

In the study by Pereira *et al* (9), the mean tumor size was 3.4 cm (SD ±1.6 cm), with luminal A having the maximum percentage of tumors <2 cm in size and TNBC having the maximum percentage of tumors >5 cm in size. Moreover, there was no significant difference between the molecular subtypes of breast cancer and tumor size (9).

Of note, a limitation of the present study is the small sample size of 165 patients, which resulted in a small number of cases in all four molecular subtypes of breast carcinoma.

In conclusion, in the present study, it was found that TNBC was the most common molecular phenotype of breast cancer in Delhi (North India). The tumor volume was the smallest in the luminal A, followed by the HER2-enriched subtype, than in the other molecular subtypes of breast cancer. As tumor volume has prognostic significance, patients with TNBC have a poor prognosis, and those with HER2-enriched breast cancer can be treated using targeted therapy. The findings of the present study may prove to be useful for the management of patients with breast cancer.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

All authors (SKS, SS and SK) contributed to the conception and design of the study. Material preparation was performed by SKS and SS. Data collection and analysis were performed by SKS and SS. Analysis was performed by SKS and SS. The first draft of the manuscript was written by SKS, and all authors commented on previous versions of the manuscript. SS and SK confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was conducted after obtaining approval from the Institutional Ethics Committee, NDMC Medical College and Hindu Rao Hospital, Delhi (vide letter No. IEC/NDMC/2022/109 dated June 17, 2022), and written informed consent was obtained from the patients for participation in the study. The present study was conducted in accordance with the Declaration of Helsinki.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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