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Retrospective five-year survival evaluation: analyzing breast cancer molecular subtypes through comprehensive clinical profiles and prognostic survival trends

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ABSTRACT

This study examined data from 461 breast cancer patients, focusing on age distribution, tumor features, histology, and molecular subtypes to evaluate their influence on patient outcomes. Age was a crucial determinant, exhibiting a greater prevalence in the 41–60 age bracket (53.6%) and the 61–80 bracket (36.7%). Tumor size and histological classifications exhibited no significant correlation with outcomes, nor did lymphovascular invasion and nodal stage. The research demonstrates the significance of hormone receptor status in forecasting outcomes. Significant correlations were identified among estrogen receptor (ER), progesterone receptor (PR), and HER2 positive. Patients with hormone receptor positivity comprised 56%, highlighting the significance of these receptors as prognostic markers. The Kaplan-Meier survival study indicated that Luminal A patients exhibited the most favorable long-term prognosis, sustaining elevated survival rates beyond 120 months. Luminal B exhibited a moderate prognosis, with survival significantly decreasing beyond 80 months. The HER2-enriched and Triple Negative subtypes exhibited fast survival decreases within the initial 60 months, signifying aggressive disease development and inferior prognosis. The results emphasize the necessity for subtype-specific therapeutic approaches, especially for high-risk variants such as Triple Negative and HER2-enriched malignancies, to enhance survival rates.

Keywords: Breast Cancer, Subtypes, HER2-enriched, Triple Negative, Survival

Introduction

Breast cancer is a complex and heterogeneous disease characterized by molecular subtype-specific variations in clinical behavior. Molecular profiling has significantly transformed the approach to breast cancer management by identifying unique subtypes that exhibit variations in prognoses and treatment reactions. The principal subtypes consist of Luminal A, Luminal B, Her2neu, and Triple Negative, and each has distinct therapeutic and diagnostic ramifications. Luminal A Estrogen receptor (ER) hypersensitivity, limited proliferation, and responsiveness to hormonal therapies are defining characteristics. Positive prognosis is associated with this subtype(1). Luminal B although it resembles Luminal A, this variant frequently displays increased rates of proliferation and fluctuating expression of progesterone receptors (PR). Luminal B is consequently less responsive to hormonal therapy in isolation and more aggressive. Her2neu tumors are characterized by HER2 amplification and a propensity for rapid, aggressive progression. Outcomes have been substantially enhanced, nevertheless, by targeted therapies like trastuzumab(2).Triple Negative: Immunoreactive to hormonal and targeted therapies due to the absence of ER, PR, and HER2 expression. An aggressive therapeutic approach is necessary for this subtype owing to its unfavorable prognosis(3).

Although molecular profiling has furnished clinicians with an exhaustive comprehension of breast cancer subtypes, the identification of optimal treatment strategies for each subtype remains a formidable obstacle. As an illustration, the limited effectiveness of targeted therapies such as trastuzumab in subtypes like Triple Negative breast cancer can be attributed to the lack of specific molecular targets.

Objectives:

This study aims to explore the demographic correlations and the impact clinical measures and molecular subtypes on the survival of the patients suffering from breast cancer.

Methods

A retrospective cross-sectional study was conducted at department of Pathology , Liaquat University of Medicine and Health Sciences (LUMHS) ,Jamshoro, Sindh. The duration of study was from 1st Jan 2017 till 31st Jan 2024.

Ethical Considerations

The study protocol was approved by the department concerned of LUMHS) ,Jamshoro, Sindh. In addition, during the data collection none of the personal information was collected, which confirms the security of personal identity.

Data collection

A structured data collection form was generated in line with the objective of study. Along with the demographics, other oncology parameters that are relevant to the objective were also collected, for example tumor dimensions, histological subtype and grade, lymphovascular invasion, nodal staging (N stage), and receptor statuses (ER, PR, and Her2). The selection of these indicators was made to get a thorough understanding of the various features of breast cancer among different subtypes.

Sample Size

Online EPI calculator was used to estimate the sample size (proportion) for this study. The minimum effective sample size for this study was n=384 at the confidence interval of 95% and margin of error of 5%.

Data analysis

All the collected data was code into the appropriate variables as described in the SPSS survival manual. For the descriptive analysis SPSS version 20® was used and frequencies were generated. To explore the association among the variables, Chi-Square test was applied. For the entire analysis, p-value less than 0.05 was considered statistically significant. Survival curves using the Kaplan-Meier method were generated to assess the cumulative survival rates for each molecular subtype throughout an 80-month follow-up period. Trend lines were produced in a linear manner to emphasize changes in survival patterns among the four categories.

Results

A total of n=461 cases were reported at the respective departments and their data was calculated to achieve the objective of this study. The age distribution of patients demonstrates a notable correlation with the result (Chi-square = 19.149, df = 6, p = 0.004). The predominant age group of patients is 41 to 60 years, comprising 53.6%, followed by the 61 to 80 age group at 36.7%, and the 20 to 40 age group at 9.8%. The substantial p-value signifies a meaningful disparity in age distribution, possibly indicating a higher prevalence or incidence of cases among middle-aged to older demographics (Table 1).

Categories of Tumor Size

The tumor size was classified from T1 to T4 according to its dimensions. T1 tumors (<2 cm) constituted 43.2% of cases, T3 tumors (>5 cm) represented 40.6%, and T2 tumors (2–5 cm) and T4 tumors accounted for 11.3% and 5.0% of cases, respectively. The Chi-square test indicated no significant correlation between tumor size categories and the outcome (Chi-square = 11.308, df = 9, p = 0.255), suggesting that tumor size alone may not be a decisive component in the reported outcomes.

Histological Classification

Invasive ductal carcinoma (IDC) constituted 95% of cases, making it the predominate histologic type. Other histological forms, such as invasive lobular carcinoma, metaplastic carcinoma, mucinous carcinoma, micropapillary carcinoma, and secretory carcinoma, each represented a minor percentage. Notwithstanding the prevalence of IDC, a significant correlation between histological type and outcome was not established (Chi-square = 17.378, df = 15, p = 0.297).

Histological Grade

Histologic grading indicated that the predominant classification was Grade 3 (63.6%), followed by Grade 2 at 24.7% and poorly differentiated carcinoma at 11.7%. The study revealed no statistically significant connection (Chi-square = 7.480, df = 6, p = 0.279), indicating that histologic grade may not independently affect the results.

Lymph vascular Invasion

Lymph vascular invasion occurred in 8.7% of patients, whereas 91.3% exhibited no invasion. The Chi-square test revealed no significant association between lymph vascular invasion and outcomes (Chi-square = 3.832, df = 3, p = 0.280), suggesting that lymph vascular invasion alone may not substantially influence the outcome.

Nodal Stage (N Stage)

The nodal stage, classified from pNX to pN3, had no significant correlation with the outcome (Chi-square = 5.828, df = 12, p = 0.925). The predominant staging was pNX (61.2%), succeeded by pN3 (16.7%) and pN0 (14.1%), suggesting no significant variations in outcomes based on nodal stage in this analysis.

Overall, it seen that The hormone receptor status, including estrogen receptor (ER), progesterone receptor (PR), and Her2, exhibited statistically significant correlations with the outcome (ER: Chi-square = 441.263, df = 3, p = 0.000; PR: Chi-square = 441.263, df = 3, p = 0.000; Her2: Chi-square = 448.930, df = 3, p = 0.000). Estrogen receptor (ER) and progesterone receptor (PR) positive were noted in 56% of patients, whereas HER2 positivity was detected in 56.2% of cases. The notable p-values emphasize the possible impact of hormone receptor status on patient outcomes, reinforcing their significance as prognostic indicators in this patient group. Details are shown in Table 1.

The Kaplan-Meier curves show the survival probability for Luminal A, B, Her2-enriched, and Triple-Negative breast cancer subgroups. The y-axis shows the percentage of patients who survived at a certain time, while the x-axis shows survival duration in months Figure 1.

Subtype-Specific Survival

The cumulative survival rate over time is relatively high for Luminal A. Even after the 120-month observation period ends, the survival probability is still greater than 0.75. Out of all the subtypes that were discussed, this indicates that Luminal A patients have the best prognosis and longest longevity. For Luminal B's survival function shows a moderate prognosis, with a gradual fall in survival over time and a less steep curve than other subtypes. The survival probability, however, drops dramatically toward 80 months, suggesting that some patients do not do well in the long run.

The Her2neu subtype experiences the steepest decline in survival probability throughout the first sixty months of the follow-up period. As a result, the disease advances more rapidly and the prognosis is worse than it would be with Luminal A or Luminal B subtypes. In addition, the survival probability for the Triple Negative subtype drops sharply in the first few years, suggesting that the disease advances quickly and that the prognosis is not good. Triple Negative breast cancer is extremely aggressive, with a survival probability that drops below 0.7 within 60 months. Clinically, patients with the Luminal A subtype exhibit the most favorable prognosis, but those with Her2neu and Triple Negative subtypes are linked to inferior survival results. Statistically, these patterns indicate possible significant disparities in the survival distributions of different subtypes, highlighting the necessity of subtype-specific treatment strategies in breast cancer care. Cumulative survival drops sharply at several points within the first 40 months, indicating a high frequency of adverse clinical events. The survival probability for this subtype is the lowest at the end of the follow-up period, highlighting a poor prognosis. The data emphasizes the need for the development of novel therapeutic approaches for this high-risk group (Figure 1).

These graphs (Figure 2) show linear survival trends for four important breast cancer molecular subtypes: Luminal A, B, Her2neu, and Triple Negative. Each graph shows cumulative survival over an 80-month follow-up and a linear trend line showing global survival changes for each subtype. Despite slight changes, the survival curve

stays above 80% for 80 months. The linear trend line drops, showing this subtype has excellent survival rates.

Table 1: Clinical Characteristics and Other Demographic and Oncology Covariates

Variable	*Category*	*Frequency*	*Percent*	*Chi-Square*	*df*	*p-value*	*Interpretation*
Age	20 to 40	45	9.8%	19.149	6	0.004	Significant
	41 to 60	247	53.6%				
	61 to 80	169	36.7%				
Tumor Size	T1 < 2 cm	199	43.2%	11.308	9	0.255	Not Significant
	T2 2-5cm	52	11.3%				
	T3 >5cm	187	40.6%				
	T4	23	5.0%				
Histological Type	Invasive Ductal Carcinoma	438	95.0%	17.378	15	0.297	Not Significant
	Invasive Lobular Carcinoma	10	2.2%				
	Metaplastic Carcinoma	8	1.7%				
	Mucinous Carcinoma	3	0.7%				
	Micropapillary Carcinoma	1	0.2%				
	Secretory Carcinoma	1	0.2%				
Histological Grade	Grade 2	114	24.7%	7.480	6	0.279	Not Significant
	Grade 3	293	63.6%				
	Poorly differentiated Carcinoma	54	11.7%				
Lymphovascular Invasion	Present	40	8.7%	3.832	3	0.280	Not Significant
	Absent	421	91.3%				
N_stage	pNX	282	61.2%	5.828	12	0.925	Not Significant
	pN0	65	14.1%				
	pN1	6	1.3%				
	pN2	31	6.7%				
	pN3	77	16.7%				
ER Status	Positive	258	56.0%	441.263	3	<0.001	Significant
	Negative	203	44.0%				
PR Status	Positive	258	56.0%	441.263	3	<0.001	Significant
	Negative	203	44.0%				
Her2 Status	Positive	259	56.2%	448.930	3	<0.001	Significant
	Negative	202	43.8%				

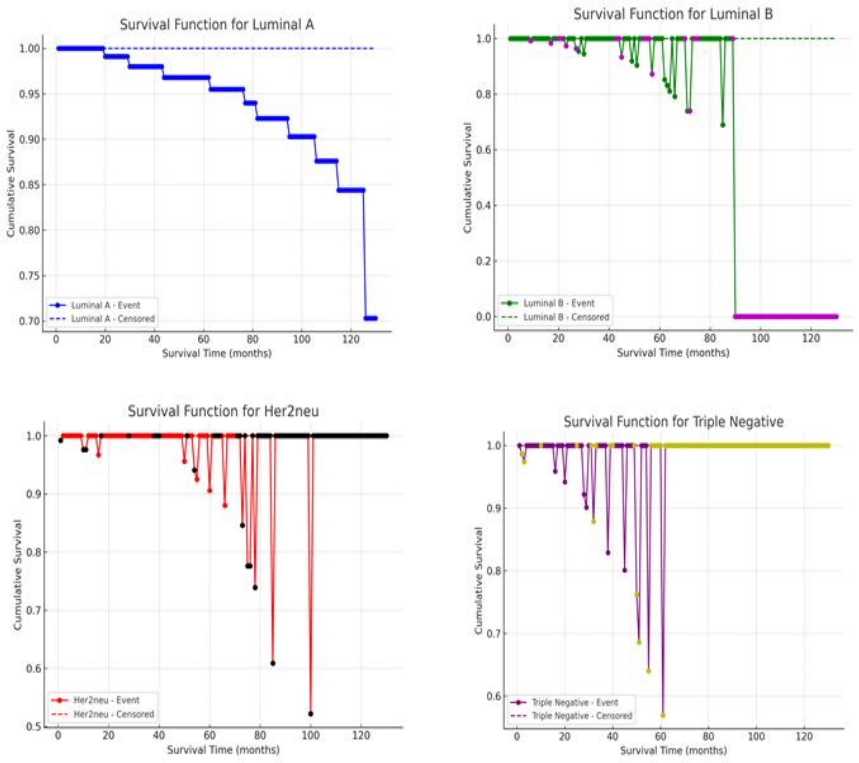

Figure 1: Kaplan-Meier Survival Estimates for Breast Cancer Molecular Subtypes

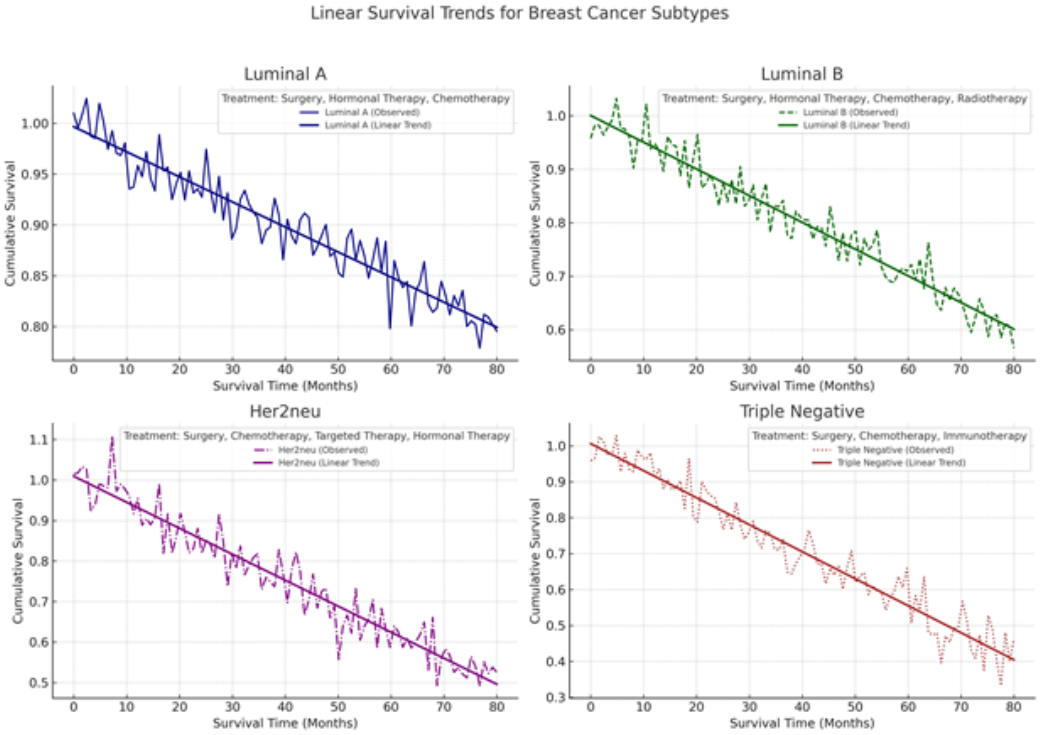

Figure 2: Linear Survival Trends for Breast Cancer Subtypes

Luminal A cancers are less aggressive and respond well to targeted hormonal therapy like tamoxifen and aromatase inhibitors, improving their survival. Standard treatment—surgery, hormonal therapy, and chemotherapy—has a survival rate above 80%.

The Luminal B subtype has a high survival rate that drops to 60% at 80 months. The linear trend line declines faster than Luminal A, indicating more aggressive disease behavior. Luminal B cancers' greater growth rates make them less likely to survive than Luminal A. Hormonal therapies can treat these tumors, although they usually require surgery, chemotherapy, hormonal therapy, and radiotherapy. Around 10-20 months, Her2neu survival begins to diminish. The linear trend line continuously falls below 50% survival at 80 months. HER2 receptor gene amplification accelerates tumor growth in Her2neu-positive breast cancers. Targeted medicines like trastuzumab (Herceptin) have improved survival rates. The observed changes suggest that patients may initially respond well to treatment but relapse.

The Triple Negative subtype has the fastest and greatest cumulative survival reduction, below 40% at 80 months. Triple Negative breast tumors lack estrogen, progesterone, and HER2 receptors, making hormonal or targeted treatments ineffective. Unfortunately, they have the worst prognosis and require intensive surgery, chemotherapy, and immunotherapy. The sharp fall in survival highlights the need for better treatment. The linear survival patterns in these graphs show how breast cancer subtypes have varying prognoses and treatment responses. The Luminal A subtype responds best to hormone therapy, while Triple Negative breast tumors are aggressive and lack focused therapy. Her2neu-positive tumors improve with targeted therapy but relapse. This extensive analysis emphasizes the need for molecular profiling-based treatment strategies to maximize subtype survival.

Discussion

The study shows significant insights into the clinical characteristics and survival outcomes of patients with breast cancer. The investigation underscores the importance of age, molecular subtypes, and hormone receptor status as key prognostic indicators. Analysis has shown a significant correlation between molecular subtypes and receptor statuses (ER, PR, Her2), validating the criticality of hormone receptor testing in the process of diagnosing and devising treatments. Linear survival trends offer intricate insights into the probabilities of survival for individual subtypes, thereby emphasizing the necessity for individualized approaches.

Our findings corroborate those of Harbeck et al. (2019) and other researchers, which demonstrated noteworthy correlations between molecular subtypes and receptor statuses (ER, PR, and HER2)(4-6). In addition, these results are consistent with several additional investigations that underscore the prognostic significance of receptor statuses(1, 7, 8). Curtis et al. (2018) underscored the significance of receptor statuses as predictors of survival, demonstrating that trastuzumab improves the prognosis of HER2-positive malignancies(5). The prognostic significance of these markers was validated by Nielsen et al. (2004), specifically in differentiating basal-like (Triple Negative) subtypes from other subtypes(6).

Our research demonstrates that Luminal A exhibits superior survival rates, which aligns with previous studies that have underscored the significance of hormonal therapies(2, 7, 9). High estrogen receptor expression in Luminal A maintains it as the least aggressive subtype, according to Dent et al. (2007)(7) and Sørlie et al. (2001) validated this positive prognosis and attributed it to the significant effectiveness of aromatase inhibitors and tamoxifen(1). In our analysis, the more combative behavior of Luminal B subtypes is consistent with other findings(8, 10). According to a study by Creighton et al. (2009), Luminal B tumors demonstrate elevated rates of proliferation, which results in reduced intervals without new tumors(8). Hugh et al. (2009) established that Luminal B necessitates a more comprehensive approach encompassing surgical intervention, chemotherapy, hormonal therapy, and radiotherapy(9).

The prognosis of HER2neu-positive malignancies is variable as a result of the impact of targeted therapies(3, 11). Pertuzumab and trastuzumab substantially enhance outcomes for this subtype, according to Swain et al. (2020)(2). For sustained remission, Romond et al. (2005) emphasized the significance of incorporating chemotherapy into treatment regimens(10). The significant decrease in survival rate observed in triple negative breast malignancies is corroborated by multiple studies(12, 13). According to the findings of Reis-Filho and Tutt (2008), the absence of targeted therapy options for these malignancies necessitates more aggressive approaches such as immunotherapy(3). By demonstrating the variability within this subtype, Lehmann et al. (2011) identified prospective targets for more individualized treatment(11).

The current state of hormonal and targeted therapy in metastatic breast cancer was examined by Anders et al. (2017), who underscored the importance of personalized treatment [14]. Ahn et al. (2016) investigated alterations in HER2 status between primary and metastatic sites, thereby emphasizing the intricate nature of the progression of cancer(14). Fundamental contributions were made by Perou et al. (2000) and Sorlie et al. (2003) regarding the molecular characteristics of breast tumors, which are essential for the classification of subtypes (15, 16). The molecular portraits were further elaborated upon by the Cancer Genome Atlas Network (2012), which provided a comprehensive perspective on the heterogeneity of breast cancer(17). Weigelt et al. (2010) and Prat and Perou (2011) dissected molecular profiles in order to assist in the forecasting of treatment responses(18, 19).

Ellis et al. (2012) identified the response of breast cancer to aromatase inhibition through whole-genome analysis, emphasizing the significance of genetic profiling(20). The classification of triple-negative breast cancer subtypes was refined by Lehmann et al. (2016), who underscored the importance of targeted therapies(21). The paradox of primary tumor chemosensitivity in triple-negative breast cancer was described by Carey et al. (2007), emphasizing the aggressive character of this type of cancer(22). Bianchini et al. (2016) and Baselga et al. (2012), respectively, examined the effectiveness of combination therapies in triple-negative and HER2-positive breast malignancies(23, 24).

Kaufman et al. (2015) and Denkert et al. (2017) investigated novel therapeutic approaches for triple-negative and HER2-positive breast malignancies, emphasizing the need for continued investigation(25, 26). Critical for treatment planning [28] are the preoperative markers of response to neoadjuvant chemotherapy that Pusztai et al. (2007) identified. Comparing fulvestrant and anastrozole in hormone receptor-positive advanced breast cancer, Robertson et al. (2016) shed light on endocrine resistance(27). In their review of breast cancer treatments, Waks and Winer (2019) emphasized the progression of therapeutic approaches(28).

Isakoff (2010) and Pal et al. (2011)(29, 30) discussed unfulfilled medical requirements and the function of particular chemotherapy agents in triple-negative breast cancer. The utilization of immunohistochemistry by Park et al. (2010) to categorize breast cancer subtypes facilitated the forecasting of clinical outcomes (31). [34] Carey and Winer (2014) presented recommendations for adjuvant endocrine therapy with an emphasis on individualized care. In their review of HER2-positive breast cancer regimens, Loibl and Gianni (2017) emphasized developments in targeted therapies (32). Regarding the enhancement of patient outcomes, Burstein et al. (2019) and Geyer et al. (2006) examined the St. Gallen International Consensus Guidelines and combination therapies, respectively(33, 34).

Slamon et al. (2001) and Bartsch et al. (2019) emphasised the significance of monoclonal antibodies in the therapy of breast cancer and the elimination of endocrine resistance(35, 36). Ellis et al. (2017) and Hurvitz and Peddi (2019) examined approaches for the management of endocrine resistance and the predictive capability of the Ki67 proliferation index, respectively(37, 38). Comparing various concentrations of fulvestrant in postmenopausal women, Di Leo et al. (2010) contributed to the optimization of treatment dosage (39). Howell and Robertson (2018) underscored the innovative mechanism by which fulvestrant suppresses endocrine resistance [43].

Our research, when considered alongside prior investigations, emphasizes the significance of individualized strategies in the management of breast cancer. We propose the establishment of all-encompassing treatment protocols that integrate genetic and molecular profiling, alongside the allocation of resources towards clinical trials to authenticate novel therapeutic approaches, including checkpoint inhibitors and PARP inhibitors. These endeavors have the potential to facilitate the connection between clinical attributes and novel therapeutic alternatives, thereby ultimately enhancing patient results.

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Conflict of Interest

There is no conflict of interest

Conclusion

The study highlights significant associations between clinical parameters and molecular subtypes, demonstrating the vital role of molecular profiling in understanding prognosis and guiding treatment. Despite advancements in therapy, challenges remain, particularly with aggressive subtypes like Triple Negative breast cancer. Future research should focus on developing more effective therapeutic approaches for high-risk groups, with personalized treatment plans based on molecular characteristics.

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