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Research Article

Pathologic Response and Survival After Neoadjuvant Chemotherapy Among Breast Cancer Subtypes: Clinicopathologic and Survival Analysis from Azerbaijan

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Abstract

Objectives: Neoadjuvant chemotherapy (NACT) has become a cornerstone in the management of locally advanced breast cancer, offering tumor downstaging, increased rates of breast-conserving surgery, and in vivo assessment of treatment response. Pathologic complete response (pCR) serves as a key prognostic indicator, with significant variability observed across molecular subtypes. However, limited data exist on survival outcomes and clinicopathological differences among these subtypes following NACT.

Methods: This retrospective study analyzed 151 patients with stage II-III breast cancer treated with NACT at a tertiary referral center between 2016 and 2023. Patients were stratified by St. Gallen subtypes: luminal A (5%), luminal B HER2-negative (40%), luminal B HER2-positive (17%), HER2-positive (17%), and triple-negative (21%). The primary endpoint was pCR predictors, while secondary outcomes included overall survival (OS) analysis.

Results: Results demonstrated significant subtype-dependent differences in pCR rates (p=0.001), with luminal B HER2-positive (42%) and HER2-positive (39%) achieving the highest responses, whereas luminal A (0%) and luminal B HER2-negative (12%) showed minimal response. Multivariate analysis identified younger age (<65 years), absence of lymphovascular invasion, and HER2-enriched subtypes as independent predictors of pCR (p<0.001). Survival analysis revealed subtype-dependent OS disparities (p<0.001), with triple-negative tumors exhibiting the worst prognosis (HR 18.2 vs. luminal B HER2-negative), while luminal B HER2-negative demonstrated the most favorable outcomes.

Conclusion: These findings underscore the critical influence of molecular subtypes on treatment response and survival, reinforcing the need for subtype-specific NACT optimization. Despite limitations including retrospective design and sample size constraints, this study contributes valuable real-world data to guide therapeutic decision-making in breast cancer management

Keywords: Breast cancer subtypes, pathologic complete response, overall survival

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Over the past years, Neoadjuvant chemotherapy has become an essential part of the oncologist's armamentarium, reducing the tumor size and increasing the number of breast-conserving surgeries performed. Furthermore, it has several advantages in evaluating the response of the primary tumor and lymph nodes to systemic therapy. Pathologic complete response (pCR), also known as excellent response to neoadjuvant chemotherapy (NACT), is a strong predictor of survival in breast cancer patients.[1] Several valuable papers in the literature state significant differences in pCR rates between the breast cancer subtypes.[1,2]

Breast cancer subtypes are defined by St. Gallen International Breast Cancer Expert Consensus according to their immunohistochemical properties: luminal A, luminal B, HER2-positive, triple-negative. Estrogen (ER), Progesterone (PR), and HER2 receptor status combined with Ki-67 % levels differ among these subtypes.[3,4] Luminal A tumors can be defined as any ER or PR positivity with <14% Ki-67, and they are clinically low-grade, slow-growing subtypes with the best prognosis with higher disease-free and overall survival rates. For these types of carcinomas, hormone therapy (aromatase inhibitors or tamoxifen) has more favorable outcomes than chemotherapy.[5] Luminal B subtype tumors are also ER or PR positive but with high Ki-67% (≥14%) levels. Luminal B is divided into two subgroups due to HER2 expression:HER2- negative Luminal B and HER2-positive Luminal B. Because of the high Ki-67 rates, tumors in this subgroup are more aggressive and have a worse prognosis compared to luminal A variants with high visceral recurrence rates.[6] In addition to hormone therapy, chemotherapy is also a treatment option in the luminal B subtype with a better response than luminal A.[7]

On the other hand, HER2-positive are fast-growing and more aggressive tumors compared to luminals. They are defined as ER/PR negative but HER2-positive tumors regardless of the Ki-67% status. Chemotherapy plus HER2/neu protein-directed drugs (trastuzumab combined with pertuzumab, trastuzumab combined with emtasin (T-DM1), and trastuzumab combined with deruxtecan) is the treatment option for this subtype.[8] Triple-negative breast cancer is characterized by a lack of ER, PR, and HER2 expression and is distinguished by its aggressiveness, early relapse, and a greater tendency to present in advanced stages. Although with the latest advances in the molecular oncology field, the unique molecular pathophysiology of triple-negative tumors is enigmatic.[9]

There is still limited research on the survival and clinicopathological differences among patients with various molecular subtypes of breast cancer who receive neoadjuvant chemotherapy. In this context, investigation of the differences among breast cancer subtypes was necessary.

The aim of this study was to evaluate clinicopathological and survival differences among breast cancer subtypes in patients receiving NACT, thereby contributing real-world evidence to the existing literature.

Methods

This is an ethics board-approved (Liv Bona Dea Hospital ethics committee, approval no: 202401012) single-arm, retrospective cohort study. Patients with clinical stage II or III breast cancer treated with neoadjuvant chemotherapy at the oncology department of a tertiary referral center (Liv Bona Dea Hospital) from December 12, 2016, to December 27, 2023 were included with no selection based on clinical details. Patients who did not have subsequent surgery were removed from the study. Relevant data on patient demographics, tumor location, TNM stage, Ki-67 percent, HER2, ER, PR status, postoperative pathological response, and survival outcomes were collected retrospectively. All of the patients were treated and followed by high-volume oncologists. In our setting, patients with luminal breast cancer received four cycles of doxorubicin (60mg/m^2) combined with cyclophosphamide (600mg/m^2) every three weeks or dose-dense (dd) adriamycin and cyclophosphamide (AC) every two weeks with granulocyte colony-stimulating factor support. Following this, patients received either four cycles of docetaxel (100mg/m^2) every three weeks, 12 rounds of weekly paclitaxel (80mg/m^2), or paclitaxel 175 mg/m^2 every two weeks four cycles. Patients with the triple-negative subtype received four cycles of doxorubicin (60mg/m^2) combined with cyclophosphamide (600mg/m^2) every three weeks or dose-dense (dd) AC every two weeks with granulocyte colony-stimulating factor support followed by docetaxel 75 mg/m^2 every three weeks or Paclitaxel 175 mg/m^2 Carboplatin Auc 5 every three weeks four cycles or Paclitaxel 175 mg/m^2 every two weeks four cycles. Patients with HER2-positive tumors (n=26) received AC followed by docetaxel with anti-HER2 therapy. Among them, 13 patients received trastuzumab alone (8 mg/kg loading dose followed by 6 mg/kg every three weeks), while 9 patients received dual blockade with trastuzumab and pertuzumab (trastuzumab as above, plus pertuzumab 840 mg loading dose followed by 420 mg every three weeks). Treatment modifications were made based on the patient's age and comorbidities. Statuses of ER, PR, and HER2 were determined from initial core biopsy findings. Subtypes were defined according to the St. Gallen International Breast Cancer Expert consensus and ASCO guidelines. Tumors with low Ki-67 index (less than 14%) and with ER or PR positivity were defined as Luminal A (Fig. 1). Tumors with ER or PR

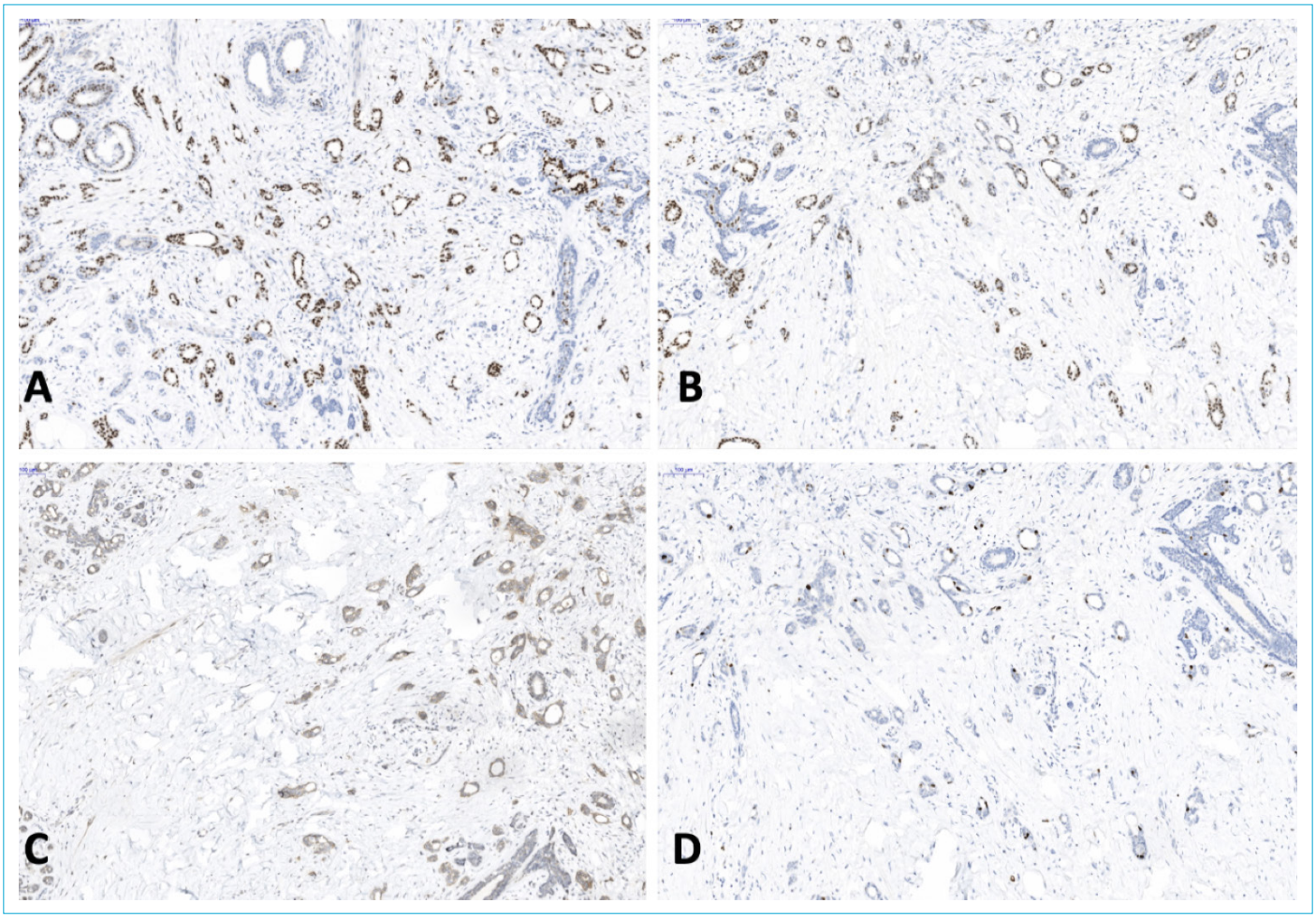

Figure 1. Luminal A. Immunohistochemistry of luminal A invasive breast carcinoma. A, estrogen receptor positive, nuclear staining. B, progesterone receptor positive, nuclear staining. C, HER-2 1+ negative, membrane staining. D, Ki-67 positive 5%, nuclear staining.

positivity but higher degree Ki-67 index (equal or greater than 14%) were classified as luminal type B. Whereas luminal B subtype is divided into two subgroups according to its HER2 status: luminal B HER2-negative (Fig. 2) and luminal B HER2-positive (Fig. 3). HER2 subtype was defined as HER2-positive and ER and PR negative tumors (Fig. 4). Lastly, tumors that demonstrate neither HER2 nor ER and PR positivity were defined as triple-negative subtypes (Fig. 5).

Pathologists determined the hormone receptor status of the tumors in formalin-fixed, paraffin-embedded tissue sections by immunohistochemistry (IHC). Only nuclear staining is considered positive. ASCO/CAP guidelines recommend that ≥1% positive cell carcinomas be considered positive for ER and PR. We used appropriate internal and external positive controls to prevent false negative results.[10]

Regarding the HER2 status, a score of 0 and 1 (+) indicated a HER2 negative tumor, whereas a score of 3 (+) indicated HER2 positive. Tumors scoring 2 (+) for HER2 underwent further analysis by either fluorescence in situ hybridization (FISH), chromogenic in situ hybridization (CISH), or silver-enhanced in situ hybridization (SISH) for HER2 to determine the presence or absence of gene amplification. If analysis revealed HER2 amplification, they were considered HER2-positive.

Treatment response was evaluated according to the final pathology assessment on the resected specimen. Pathological complete response was decided by pathologists, according to the residual cancer burden (RCB) score.[11] RCB score uses the diameter of residual disease, percentage of vital tumor cells, and diameter of the largest involved lymph node to calculate the amount of residual disease and is the most commonly used assessment to determine the pCR in our hospital. RCB-0 is defined as pCR, whereas RCB-1, RCB-2, AND RCB-3 are considered no pCR.

Statistical Analysis

The primary outcome was to determine the predictors of pCR, and the secondary outcome was to show the investigate the overall survival.

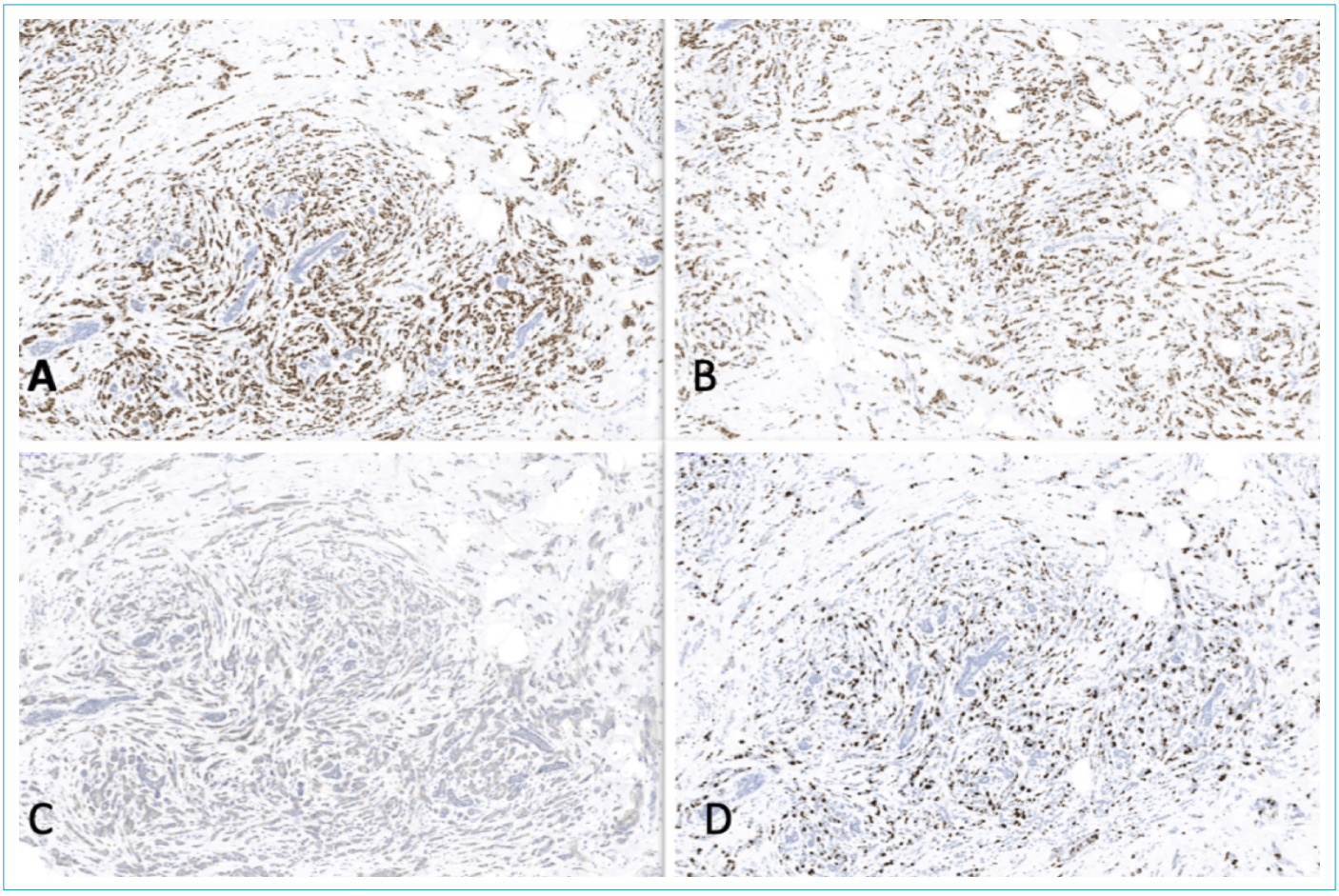

Figure 2. Immunohistochemistry of luminal B HER2 negative invasive breast carcinoma. A, estrogen receptor positive, nuclear staining. B, progesterone receptor positive, nuclear staining. C, HER2 0+ negative, membrane staining. D, Ki-67 positive 25%, nuclear staining.

Using the chi-square and Fisher's exact tests, the association between clinicopathological variables and pCR differences among the breast cancer subtypes was assessed. Overall survival (OS) was calculated from the initial diagnosis to the date of the patient's death or last known follow-up. The Kaplan-Meier survival plots were utilized for survival analysis. The log-rank test was used to compare survival curves during the Kaplan-Meier survival analysis method. Univariate Cox regression analysis methods were used to assess the predictive importance of clinicopathological characteristics regarding survival outcomes. Variables with p≤0.2 in univariate analysis were included in the Cox proportional hazards model. Hazard ratios (HRs) and 95% confidence intervals (CIs) were used to express the results.

In addition, univariate and multivariate logistic regression analyses were used to identify independent variables that might be associated with pCR. The results are shown as odds ratios (ORs) with 95% confidence intervals (CIs) attached. Categorical variables are reported as percentages and continuous variables are reported as medians (interquartile range). Descriptive statistical analyses were performed using JMP, version 17.1.0 software (SAS Institute Inc).

Results

Patient Characteristics & Breast Cancer Subtypes

In total, the cohort included 151 patients with clinical stage II or III breast cancer, with a median age of 47 (IQR, 38-59). The median body mass index was 28.2 kg/m^2 (IQR, 24.5-32.5) among the patients. Of the 151 patients, 68% (n=103) had stage III tumor, while 32% (n=48) had stage II tumor. Only 3% of the patients had grade I tumor (n=4), while 37% had grade III tumor (n=57), and the majority of the patients had grade II tumor (60%, n=90).

The most common subtypes in the cohort were luminal B HER2 - (40%, n=60) and triple-negative (21%, n=31), followed by HER2 positive (17%, n=26) and luminal B HER2 positive (17%, n=26) subtypes, the least common subtype was luminal A (5%, n=8). Significant differences between the subtypes were found in grade (p=<0.0001), Ki-67 index

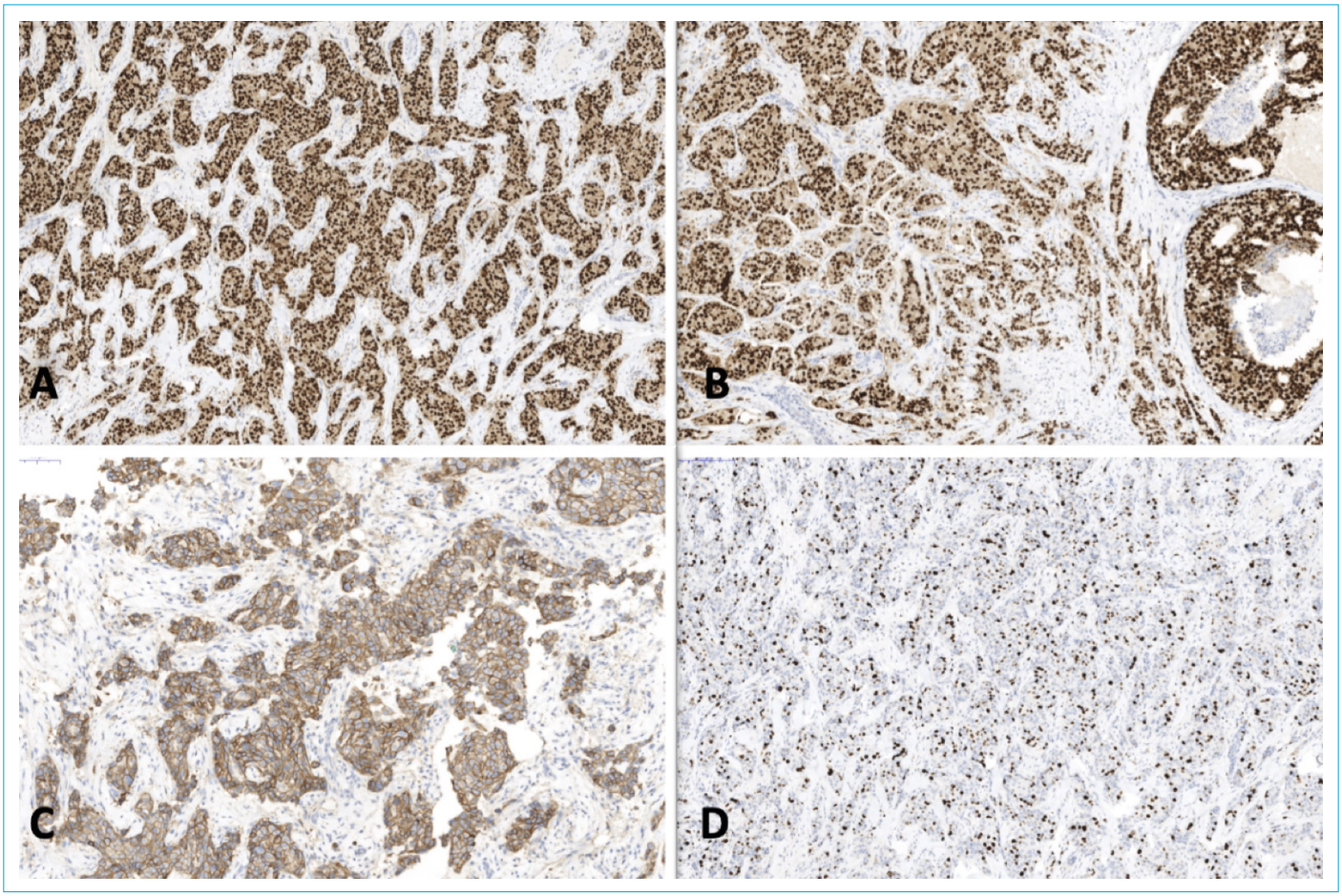

Figure 3. Immunohistochemistry of luminal B HER2 positive invasive breast carcinoma. A, estrogen receptor positive, nuclear staining. B, progesterone receptor positive, nuclear staining. C, HER2 3+ positive, membrane staining. D, Ki-67 positive 20%, nuclear staining.

(p=<0.0001), and pCR (p=0.001). Demographical and clinical details of the study patients were summarized in Table 1.

Survival Outcomes

The median follow-up after the diagnosis was 18 months (IQR, 11-35 months). Death occurred in 27 patients (18%). On univariate survival analysis, subtypes (p=<0.001) and BMI (p=0.01) were found to be the only factors affecting overall survival. Patients with a triple-negative subtype and a high BMI were the ones with the worst survival. After putting the variables with <p=0.2 into the Cox proportional hazards model, subtypes were found to be the sole predictor of the overall survival in our cohort (p=<0.001). The hazard ratio of the triple-negative subtype in contrast with luminal B HER2-negative was 18.2, the HER2-positive subtype was 3.62, to luminal B HER2-positive 1.89 and luminal A 1.51.

Table 2 displays the results of univariate and multivariate analyses of factors predicting OS. Kaplan-Meier survival plot of the breast cancer subtypes is shown in Figure 6.

Independent Predictors of pCR

Univariate and multivariate logistic regression analyses demonstrated that the predictors of the pCR were age (p=0.01 and p=0.01, respectively), lymphovascular invasion (p=0.01 and p=0.02, respectively), and subtypes in our study (p=0.01 and p=<0.001, respectively). Patients with age lower than 65 and absent lymphovascular invasion in pre-treatment biopsy had higher odds ratios to achieve pCR (1.65 and 3.94, respectively). Among the subtypes, luminal B HER2-positive patients had the best response to NACT with a 42% pCR rate, HER2 patients had 39%, and triple-negative patients had a 23% pCR rate.

In the univariate logistic regression model, the odds ratios of achieving the pCR in luminal B HER2-positive subtype in contrast to luminal B HER2-negative was 5.55 (95% CI,1.83-16.8), to triple-negative was 2.51 (95% CI, 0.79-7.91), and to HER2-positive was 1.17 (95% CI, 0.38-3.55). In the multivariate logistic regression model, the odds of achieving pCR were even more prominent as luminal B HER2-positive subtype to luminal B HER2-negative was

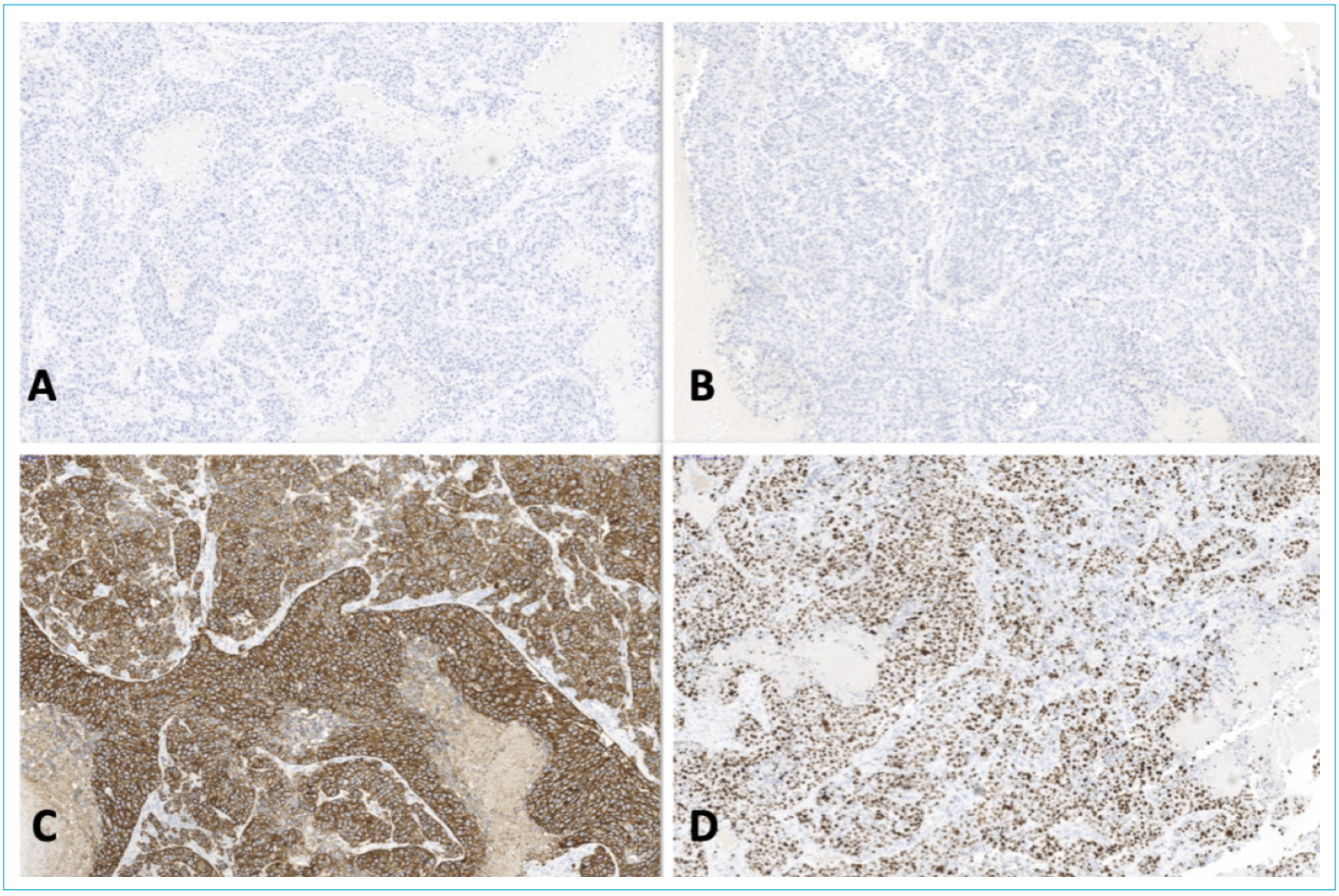

Figure 4. Immunohistochemistry of HER2 positive invasive breast carcinoma. A, estrogen receptor negative. B, progesterone receptor negative. C, HER2 3+ positive, membrane staining. D, Ki67 positive 70%, nuclear staining.

8.18 (95% CI, 2.24-29.9), to triple-negative was 5.64 (95% CI, 1.38-23.01), and to HER2-positive subtype was 1.44 (95% CI, 0.40-5.23). Table 3. shows the univariate and multivariate logistic regression models of the factors predicting pCR.

Discussion

Breast cancer is divided into four subgroups based on gene expression: luminal A, luminal B, HER2-positive, and triple-negative. Luminal B is then divided into two groups: luminal B HER2-negative and luminal B-HER2 positive. These subtypes can assist doctors in grouping patients based on morphology, response to therapy, and clinical outcomes.[12,13] NACT has become an essential part of breast cancer treatment because of several advantages, such as down-staging the disease, decreasing the extent of surgery, establishing an in vivo assessment of the treatment response, and obtaining an in vivo assessment of treatment sensitivity and providing comprehensive information about a patient's clinical outcome.[14] Patients with pCR after NACT have better long-term prognosis than those with residual disease (RD), especially in aggressive tumor subtypes.[15]

Nonetheless, the pCR rates after neoadjuvant chemotherapy vary across different molecular subtypes of breast cancer. Reports suggest that HER2-positive patients have a pCR rate of around 40%, triple-negative breast cancer exhibits a pCR rate of approximately 23%, and Hormone receptor positive /HER-2 negative breast cancer has a notably low pCR rate of only 9.1%.[1,16,17] Our cohort also shows similar results, luminal B HER2-positive patients had a 42% pCR rate, HER2-positive patients had 39%, and triple-negative patients had a 23% pCR rate. In comparison, none of the luminal A patients obtained a pCR after the NACT, and only 12% of the luminal B HER2-negative patients had pCR. These findings may suggest a potential positive relationship between HER2-positivity and pCR.

Several similar studies in the literature suggest that there are differences in age, survival rates, Ki-67 expression, lymphovascular invasion, tumor grade, pCR rate, and survival among the breast cancer subtypes.[1,2] Although our study

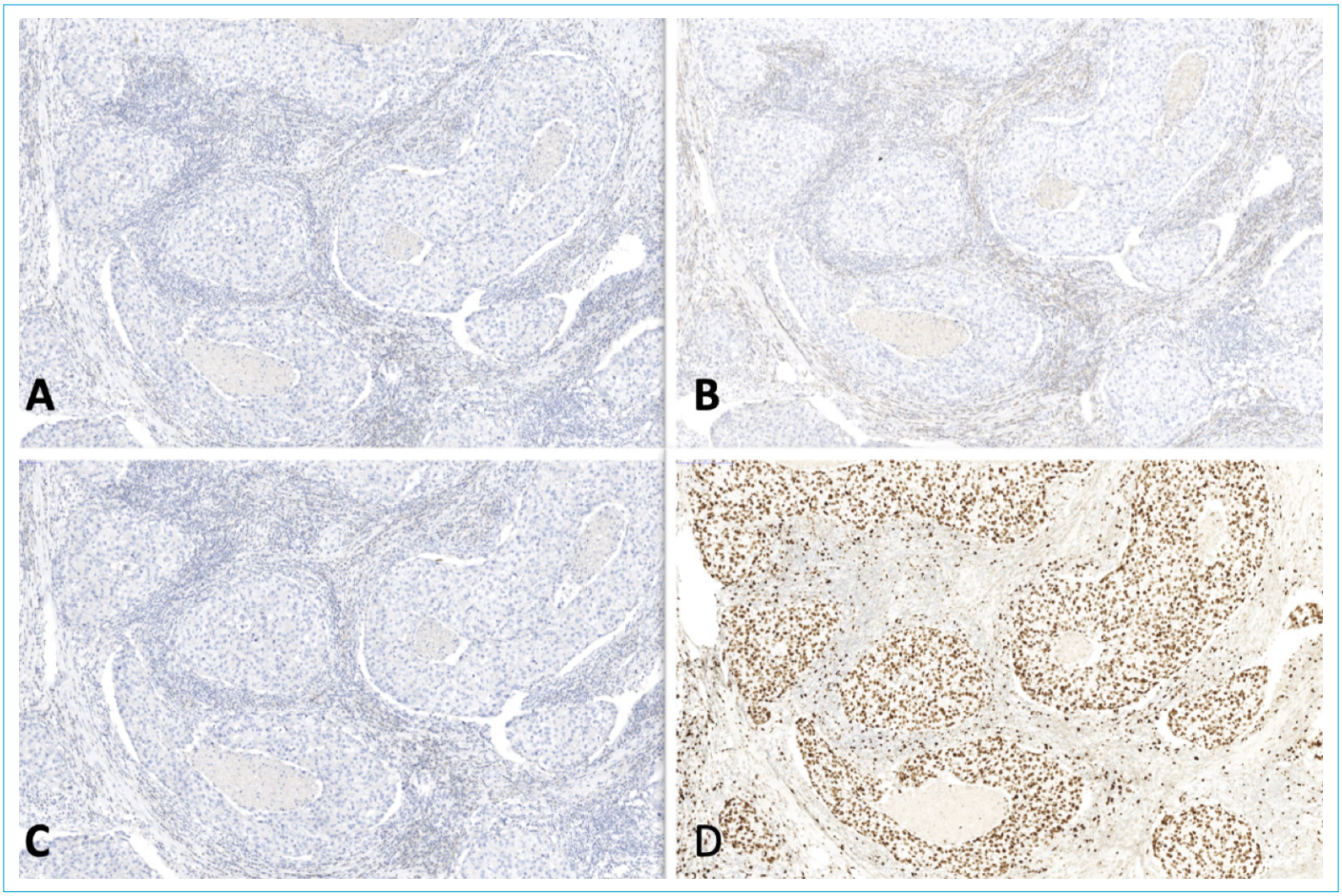

Figure 5. Immunohistochemistry of triple-negative invasive breast carcinoma. A, estrogen receptor negative. B, progesterone receptor negative. C, HER2 negative, membrane staining. D, Ki67 positive 80%, nuclear staining.

agrees with some of these findings, as overall survival, pCR, tumor grade, and Ki-67 index vary between subtypes, no relationship was found between subtypes and age or lymphovascular invasion.

Our study suggests that tumors with triple-negative or luminal B HER2-positive subtypes have the worst grade, while tumors with HER2 and triple-negative subtypes have the highest Ki-67 index, aligning with the findings from previous studies.[1,2,18–20]

Regarding overall survival, our findings suggest that the sole predictive factor of the overall survival is tumor subtype. Our investigations show the best survival outcome was observed in luminal B HER2-negative subtype while the worst outcome was in triple-negative. The higher chemosensitivity observed in HER2-positive tumors may be attributed to their rapid proliferation and intrinsic responsiveness to anti-HER2 targeted therapies, whereas triple-negative tumors, despite achieving moderate pCR rates, often exhibit aggressive biology, genomic instability, and lack of targeted therapies, contributing to poorer long-term survival outcomes. Such biological differences may partly explain the variability in treatment response and survival outcomes observed across molecular subtypes. However, considering the fact that the luminal A subtype group had only eight patients involved, this finding may be subject to criticism. This small sample size limits the statistical power for detecting reliable associations, and the outcomes for this group should therefore be interpreted with caution.Some studies show similar findings to ours,[1,6,12] while Yildiz A. et al. did not find any significant difference regarding overall survival among the subtypes in a relatively small cohort similar to this study.[2]

The primary outcome of this study was pCR. After the univariate and multivariate logistic analyses, our study revealed that the predictor of pCR are breast cancer subtypes, age, and lymphovascular invasion in our cohort, mostly correlating with the findings from various studies over the world.[2,21–23] Although some studies report a correlation between Ki-67 and pCR rates, we preferred not to use the Ki-67 index in the analysis because of the overlap with breast cancer subtypes.

Table 1. Clinicopathological data of breast cancer subtypes

Parameter	Luminal A HER2- negative	Luminal B HER2- positive	Luminal B	HER2- positive	Triple- negative	p
Total n=151, n (%)	8 (5)	60 (40)	26 (17)	26 (17)	31 (21)	
Age, years	53 (47-58)	45 (38-56)	45 (33-56)	49 (37-61)	48 (38-63)	0.42
BMI, kg/m^2	24,6 (24.1-32.9)	27.5 (25.1-31.9)	28.2 (25.1-31.7)	28.8 (24.9-33.3)	28.5 (25.4-36.3)	0.4
Menopause status, n (%)						
Premenopausal	5 (63)	36 (40)	18 (69)	14 (54)	18 (58)	0.84
Postmenopausal	3 (38)	24 (60)	8 (31)	12 (46)	13 (42)	
Tumor localization, n (%)						
Right	1 (13)	33 (55)	17 (65)	14 (54)	15 (48)	0.1
Left	7 (87)	27 (45)	9 (35)	12 (46)	16 (52)	
Clinical stage, n (%)						
II	3 (38)	17 (28)	11 (42)	10 (38)	6 (19)	0.36
III	5 (62)	43 (72)	15 (58)	26 (62)	25 (81)	
Ki-67 %	10 (8.5-12)	30 (20-42)	28 (24-36)	40 (27-50)	50 (30-75)	**<0.0001**
Grade, n (%)						
I	2 (25)	2 (3)	0 (0)	0 (0)	0 (0)	
II	5 (63)	43 (72)	14 (54)	19 (73)	9 (29)	
III	1 (12)	15 (25)	12 (46)	7 (27)	22 (71)	**<0.0001**
Lymphovascular invasion, n (%)						
Present	4 (50)	21 (35)	10 (39)	7 (27)	4 (13)	0.08
Absent	4 (50)	39 (65)	16 (61)	19 (73)	27 (87)	
pCR, n (%)						
Achieved	0 (0)	7 (12)	11 (42)	10 (39)	7 (23)	
Not achieved	8 (100)	53 (88)	15 (58)	16 (61)	24 (77)	**0.001**

Numbers are given as median and interquartile range (IQR) for continuous variables and as total number and percentage for categorical variables. BMI – Body Mass Index, pCR – Pathological Complete Response. Bold represents statistically significant values.

Table 2. Univariate analysis of factors affecting overall survival

Parameter	p
Age	0.35
<65	
≥65	
BMI	**0.01**
<35	
≥35	
Menopause Status	0.79
Premenopause	
Postmenopause	
Tumor Stage	0.54
II	
III	
Tumor Grade	0.20
I	
II	
III	
Lymphovascular Invasion	0.47
Present	
Absent	
Subtypes	**0.001**
Luminal A	
Luminal B HER2-negative	
Luminal B HER2-positive	
Triple negative	
HER2-positive	

Bold represents statistically significant values.

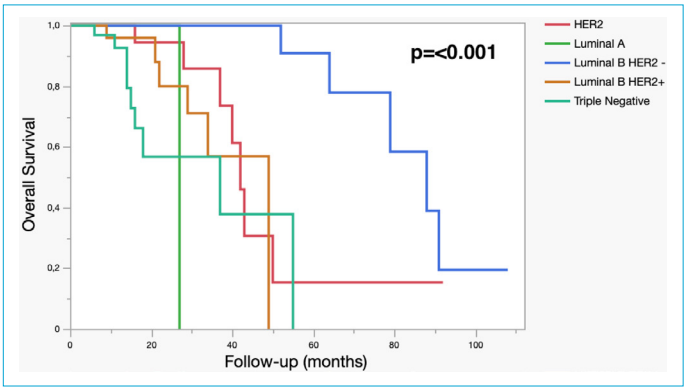

Figure 6. Kaplan-Meier analysis comparing the overall survival between breast cancer subtypes.

In addition, a novel study from Hussain L. et al. reported a machine learning model that predicts the pCR by evaluating the MRI images of breast cancer patients.[24] This finding is promising for the future of NACT customization in breast cancer patients.

This study has certain limitations that should be mentioned. First of all, the retrospective nature of the study makes it prone to data collection bias. Secondly, this is a single-center study with a limited number of patients in

Table 3. Multivariate Cox proportional hazard model on overall survival

Parameter	Hazard Ratio	95% CI	p
BMI (≥35 vs)			1.46
<35	0.9-2.39	0.12	
Grade (III vs)			0.42
I	2.12	0.61-7.2	
II	1.07	0.73-1.58	
Subtypes (Triple negative vs)			**0.01**
Luminal B HER2*negative	1.95	1.16-3.28	
HER2-positive	1.67	0.94-2.99	
Luminal B HER2-positive	1.19	0.68-2.09	
Luminal A	0.62	0.26-1.44	

Bold represents statistically significant values.

some breast cancer subtypes and a relatively small total sample size. In addition, since the cut-off for the date of diagnosis was 2023, OS analysis does not show strong results. Nevertheless, the relatively short median follow-up of 18 months limits the ability to draw firm conclusions regarding long-term survival outcomes, and the survival estimates presented here should be interpreted as preliminary until validated by studies with extended follow-up durations. It should also be noted that treatment heterogeneity existed within the HER2-positive subgroup, as some patients received trastuzumab alone, while others received dual blockade with trastuzumab and pertuzumab. This variability may have influenced both pCR and survival outcomes, limiting the comparability of results across subgroups. Eventually, the study was conducted in a developing country, Azerbaijan, with limited access to novel treatment advances in NACT, such as pertuzumab and pembrolizumab. This limited access to novel therapies may have contributed to lower pCR rates or differences in survival outcomes compared to international benchmarks, where dual HER2 blockade or immunotherapy are more widely available.

Conclusion

In conclusion, these findings emphasize the critical role of molecular subtyping in predicting NACT response and long-term survival in breast cancer. The contrast in outcomes between subtypes supports the need for tailored therapeutic strategies, particularly for HER2-positive and TNBC patients. Future research should focus on prospective validation and novel treatment approaches to improve pCR rates and survival. Ultimately, precision oncology guided by tumor biology remains essential for optimizing breast cancer management.

Table 4. Pathological complete response univariate and multivariate logistic regression analyses

	Univariate Logistic Regression			Multivariate Logistic Regression		
Parameter	**Odds ratio**	**95% CI**	**p**	**Odds ratio**	**95% CI**	**p**
Age (<65 vs)						
≥65	1.73	1.21-3.89	**0.01**	1.65	1.16-3.78	**0.01**
BMI (<35 vs)						
≥35	0.82	0.31-2.47	0.72	0.60	0.16-2.22	0.45
Menopause status (premenopausal vs)						
Postmenopausal	1.59	0.72-3.67	0.24	1.33	0.27-2.06	0.58
Stage (II vs)						
III	1.36	0.6-2.99	0.44	1.14	04.3-3.01	0.79
Grade (I vs)						
II	1.54	0.07-12.9	0.16	7.41	0.35-153.3	0.15
III	0.72	0.03-6.08		3.30	0.16-68.9	
Lymphovascular invasion (absent vs)						
Present	3.28	1.27-10.19	**0.01**	3.94	1.21-12.90	**0.02**
Subtypes (Luminal B HER2-positive vs)						
Luminal A	No value	No value	**0.001**	No value	No value	**<0.001**
Luminal B HER2- negative	5.55	1.83-16.8		8.18	2.24-29.9	
Triple negative	2.51	0.79-7.91		5.64	1.38-23.01	
HER2-positive	1.17	0.38-3.55		1.44	0.40-5.23	

Bold represents statistically significant values.

Disclosures

Ethics Committee Approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the ethics committee of the Liv Bona Dea Hospital (2024-1015). Patient consent was waived owing to the retrospective data selection. This was approved by the ethics committee of the Liv Bona Dea Hospital (2024-1015).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Design – C.İ., A.Y.; Supervision – A.İ.; Materials – F.A.; Data collection &/or processing – M.A., P.A.; Analysis and/or interpretation – T.H., I.B.; Literature search – M.A., A.I., A.A.; Writing – A.A.; Critical review – E.S.

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