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Imaging Characteristics and Hormonal Receptor Correlations in Varieties of Breast Cancer

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Abstract

Background: While there is acknowledgment of the vital role of factors such as the status of histological grades and hormone receptor (HR) in shaping targeted treatment strategies for breast cancer (BC), comprehensive research that unifies the study of imaging features with the evaluation of HR characteristics and histopathological data is notably absent in Albania, creating a critical research gap that this study endeavors to fill. This study aimed to investigate the imaging characteristics observed in ultrasound and the possible correlations between expression levels of HRs in ductal and lobular types of BC to elucidate potential prognostic and therapeutic implications.

Methods and Results: This descriptive study, conceived as a series of cases, leveraged a prospective approach to scrutinize the dynamics of the study population over four years (2019-2023) in the Mother Teresa University Hospital Center and a private oncology clinic in Tirana. The convenience sampling strategy enlisted 238 female patients (mean age 60.5±12.5 years) diagnosed with BC who had been tested for HRs and consented to participate. Diagnostic imaging was facilitated using a Chison US equipped with a 10 MH linear probe. The results were adjudged based on the BI-RADS tumor classification. HR markers were discerned through rigorous immunohistochemical analyses. Utilizing SPSS version 21.0, statistical analyses incorporated a variety of tests, including Spearman's rho to assess correlations between hormonal receptors and imaging morphological characteristics and ordinal logistic regression to evaluate the relationships between hormonal receptors and cancer grades.

Analyzing the localization of the tumor revealed that a slightly higher proportion had it on the left side, accounting for 52.9% compared to 47.1% on the right side. Regarding the BI-RADS classification observed through echographic examination, a vast majority were classified as BI-RADS 5 (92.8%), followed by a smaller percentage distributed amongst BI-RADS 4 (5.9%), BI-RADS 3 (0.84%), and BIRADS 6 (0.42%). Examining the cancer grades determined that 68.3% were at Grade 2, whereas Grades 1 and 3 were noticeably less common, standing at 1.7% and 30.2%, respectively. Estrogen receptor (ER) and progesterone receptor (PgR) sensitivity were high in most patients, exhibiting 77.7% and 70.6% positivity, respectively, alongside a notable presence of high Ki67 levels in 75.2% of the individuals. The investigation into HER2 status demonstrated that a significant number were negative (76.1%), as opposed to 17.6% being positive and 6.3% equivocal. Remarkably, 5.5% of the patients had a triple-negative status upon biopsy evaluation. The Spearman's rho correlations displayed a moderate positive correlation between ER and PgR (rho=0.563) and a weak negative correlation between ER and Ki67 (rho=-0.343) (P<0.05 in both cases). PgR and Ki67 show a weak negative correlation (rho=-0.353, P<0.05), suggesting a tendency for higher PgR values to correspond with lower Ki67 values. The ordinal logistic regression analysis identified a statistically significant negative relationship between the ER variable and the outcome variable, denoted by a coefficient of -2.137, P<0.05. Additionally, Ki67 showcased a positive relationship with the outcome, as indicated by a coefficient of 5.150, P<0.05.

Conclusion: This study delineates the nuanced relationships between biomarkers such as ER, PgR, and Ki67 in different types of infiltrative cancers, pointing to a complex interplay that necessitates further exploration while also noting the independence of BI-RADS imagery in these correlations.**(International Journal of Biomedicine. 2024;14(1):20-25.)**

Keywords: breast cancer • hormonal receptor • BI-RADS imagery • Albania

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Abbreviations

BI-RADS, Breast Imaging Reporting and Data System; **BC**, breast cancer; **ER**, estrogen receptor; **HER2**, human epidermal growth factor receptor 2; **HR**, hormone receptor; **PgR**, progesterone receptor.

Introduction

Breast cancer (BC), silently developing and predominantly detected through routine screenings, is the most frequently diagnosed cancer in women globally, accounting for over a tenth of new annual diagnoses and standing as the second leading cause of cancer-related death among women.[1] In the nuanced pathway to predicting BC prognosis, the role of ultrasound emerges as critical, working in tandem with assessing histological grade and other characteristics, such as hormone receptor (HR) (estrogen receptor [ER] and progesterone receptor [PgR]) status and human epidermal growth factor receptor 2 [HER2] condition, to furnish a comprehensive picture that can guide targeted treatment strategies.[2] A study conducted in Albania indicated a promising Area Under the Curve value of 0.81 in the ROC curve analysis, underlining that utilizing ultrasound with BI-RADS categorization stands as a reliable instrument for identifying malignant breast tumors across all age groups, offering satisfactory precision for tertiary diagnostic services.[3] In Albania, there is a notable lack of studies that unify the examination of imaging features and HR characteristics, along with their potential intrinsic correlations or associations with histopathological data. Numerous differences by histological type—including lobular, ductal/lobular, tubular, and medullary histologies—are also observed by race/ethnicity. However, there was no clear evidence of substantial differences in a 21-gene recurrence score or ER1, PgR, or HER2 RNA expression.[4,5] Despite ethnicity or population-specific characteristics, it is critically important to meticulously analyze every potential correlation between these diagnostic-prognostic factors to forecast the prognosis of BC and inform treatment choices accurately. Evidence shows that ultrasound echo patterns in BC significantly correlate with ER, PR, and HER2/neu expression, potentially guiding prognosis and hormonal therapy responses.[6] Furthermore, a study analysis delineated significant associations between various molecular cancer subtypes, the presence of ER, PgR, and HER2, and elevated a proliferation marker Ki67 levels, revealing direct and inverse relationships.[7] Immunohistochemistry, essential in identifying biomarker expressions pivotal in breast pathology and predicting therapy responses using prevalent immunomarkers such as ER, PgR, HER2, and Ki67, offers a practical and cost-effective alternative to the more cumbersome and expensive gene profile analysis for determining BC prognoses and therapeutic strategies.[8]

This study aimed to investigate the imaging characteristics observed in ultrasound and the possible correlations between expression levels of HRs in ductal and lobular types of BC to elucidate potential prognostic and therapeutic implications.

Materials and Methods

The study was conceived as a series of cases, rigorously fitting the inclusion criteria. The guiding approach of the study was prospective, tracking the dynamics of the study population. However, the retained type of the study was descriptive, different from comparative cohort studies that still have a compelling analytical approach with two comparison groups. The study was conducted in the Oncology Service at the Mother Teresa University Hospital Center and Tirana's private oncological diagnostic clinic.

This study spanned from 2019 to 2023, according to the proper protocol, and employed a convenience sampling strategy, selecting cases until sufficient sample size was achieved to test various hypotheses and yield statistically significant results adequately. The sample size reached 238 female patients. The inclusion criteria were patients diagnosed with BC who had been tested for HRs and consented to participate.

Data Collection Instruments

The data accrued in the study hailed from a diversity of categories and utilized an array of tools. Diagnostic imaging was facilitated using a Chison US equipped with a 10 MH linear probe, administered by a skilled radiologist who later adjudged the results based on the BI-RADS tumor classification. A single anatomical pathologist affirmed the histopathological aspects. Moreover, HR markers were discerned through rigorous immunohistochemical analyses.

Variable Definitions and Measurements

In our study, we analyzed various patient variables and their clinical characteristics. The age of the patients is treated as a continuous variable, with statistics such as mean, median, standard deviation, and interquartile range elucidating the distribution. Tumor location and Ki67 level are binary variables differentiated as left versus right and high versus normal, respectively. Furthermore, we worked with categorical variables including BI-RADS classification (with categories BI-RADS 5, 4, 3, 6), cancer grade (categorized into Grades 1, 2, 3), estrogen and progesterone receptor sensitivity (each divided into positive, slightly positive, and negative), and HER2 status (divided into positive, equivocal, and negative). Triple-negative BC was characterized by the absence of three types of receptors (ER, PgR, and HER2).

Statistical Analysis

Data from the cases were initially processed in Microsoft Excel and subsequently in SPSS version 21.0. Absolute frequencies and corresponding percentages were calculated for all categorical variables. Central tendency measures (mean, median) and respective dispersion measures (standard deviation [SD], standard error [SE], percentile) were calculated for all numeric variables. Kolmogorov-Smirnov and Shapiro-Wilk tests assessed normal distribution for numeric variables like age, tumor size, and hormonal receptor values. The Student's t-test and ANOVA assessed the differences in hormone receptor values among cancer types and grades. The Chi-squared or Fisher's exact tests evaluated differences among cancer types, BI-RADS classification, and cancer localization. Spearman's correlation coefficient assessed connections between hormonal

receptors and imaging morphological characteristics and between the hormonal receptors themselves. Ordinal logistic regression assessed the relationship between independent variables (hormonal receptors) and cancer grades. Odds ratios (OR), 95% confidence intervals (95%CI), and statistical significance values were calculated in bivariate models of ordinal logistic regression. In all cases, values of $P<0.05$ were considered statistically significant.

Ethical Considerations

Data collection was conducted in accordance with the ethical principles set forth by the Helsinki Declaration for scientific research involving human subjects. Study participants were ensured confidentiality and privacy.

Results

A total of 238 patients were meticulously examined to gather pertinent data on their demographic details and health metrics. The average age among this population was 60.5 years, with a standard deviation of 12.5 years, indicating a moderate variability in the age of the patients. The median age stood at 61 years, offering a central tendency that is slightly higher than the mean age. When considering the interquartile range, the middle 50% of the data clustered between the ages of 53 and 68 years, highlighting the predominant age group in the study. It is noteworthy that the age of patients spanned a substantial range, with the youngest being 28 years and the oldest reaching 91 years, showcasing a wide generational gap in the study demographic. Furthermore, in assessing the normal distribution testing of the age variable using the Kolmogorov-Smirnov method, a *P*-value of 0.2 was derived, which suggests that the age distribution did not significantly deviate from a normal distribution at the conventional 0.05 threshold for statistical significance (Table 1).

Table 1.
Patient demographics and age (years) distribution normality test.

Parameter	Value	Normal Distribution Testing of the "Age" Variable (Kolmogorov-Smirnov), P Value
Patient Demographics		0.2
Number of patients studied	238	
Average age	60.5	
Standard deviation of age	12.5	
Median age	61	
Interquartile range of age	53-68	
Minimum age	28	
Maximum age	91	

A detailed examination of various critical aspects of the disease portrays a substantial variation in the cancer characteristics. Analyzing the localization of the tumor revealed that a slightly higher proportion had it on the left side, accounting for 52.9% compared to 47.1% on the right side. Regarding the BI-RADS classification observed through echographic examination, a vast majority were classified as BI-RADS 5 (92.8%), followed by a smaller percentage distributed amongst BI-RADS4 (5.9%), BI-RADS 3 (0.84%), and BIRADS 6 (0.42%). Examining the cancer grades determined that 68.3% were at Grade 2, whereas Grades 1 and 3 were noticeably less common, standing at 1.7% and 30.2%, respectively. Estrogen and progesterone receptor sensitivity were high in most patients, exhibiting 77.7% and 70.6% positivity, respectively, alongside a notable presence of high Ki67 levels in 75.2% of the individuals. The investigation into HER2 status demonstrated that a significant number were negative (76.1%), as opposed to 17.6% being positive and 6.3% equivocal. Remarkably, 5.5% of the patients had a triple-negative status upon biopsy evaluation, underscoring a critical area of focus in BC research and treatment (Table 2).

Table 2.
Clinical characteristics of BC patients.

Characteristics	Number of Patients	Percentage (%)
Tumor Location		
Left side	126	52.9
Right side	112	47.1
BI-RADS Classification		
BI-RADS 5	221	92.8
BI-RADS 4	14	5.9
BI-RADS 3	2	0.84
BI-RADS 6	1	0.42
Cancer Grade		
Grade 2	162	68.1
Grade 1	4	1.7
Grade 3	72	30.2
ER Sensitivity		
Positive	185	77.7
Slightly positive	10	4.2
Negative	43	18.1
PR Sensitivity		
Positive	168	70.6
Slightly positive	11	4.6
Negative	59	24.8
Ki67 Level		
High	179	75.2
Normal	59	24.8
HER2 Status		
Positive	42	17.6
Equivocal	15	6.3
Negative	181	76.1
Biopsy Results		
Triple negative (ER, PgR, HER2)	13	5.5

The presented Spearman's rho correlations between various variables, including ER, PgR, Ki67, and BI-RADS, provide insight into the strength and direction of the relationships between each pair of variables (Table 3). A noteworthy observation is the moderate positive correlation between ER and PgR (rho=0.563) and a weak negative correlation between ER and Ki67 (rho=-0.343) ($P<0.05$ in both cases), indicating that higher ER values are generally accompanied by higher PgR and lower Ki67 values,

respectively. Meanwhile, the ER and BI-RADS relationship manifests as a very weak correlation (rho=0.045), which isn't statistically significant, showcasing a negligible association between the two variables. Similarly, PgR and Ki67 show a weak negative correlation (rho=-0.353, P<0.05), suggesting a tendency for higher PgR values to correspond with lower Ki67 values. Regarding PgR and BI-RADS, a very weak correlation is observed (rho=0.038), representing a slight, non-significant association. Lastly, the Ki67 and BIRADS association is characterized by a very weak correlation (rho=0.018), further underscoring a non-significant relationship (Table 3).

Table 3.

Correlations among different variables (Spearman's Rho).

	ER	PgR	Ki67	BI-RADS
ER	-	0.563*	-0.343*	0.045
PgR	0.563*	-	-0.353*	0 .038
Ki67	-0.343*	-0.353*	-	0 .018
BI-RADS	0.045	0.038	0.018	-

*- P-value <0.05

Starting with the ER marker, ductal infiltrative cancer, with a substantial sample size of 103, shows a higher mean (0.7413) than the lobular infiltrative category, which had a mean of 0.6222 based on 9 observations. Though the ductal infiltrative type exhibits a higher mean, it is essential to consider the relatively wider confidence interval in the lobular category, reflecting a greater uncertainty around the mean estimate. Similarly, for the PgR marker, the ductal infiltrative type, analyzed across 98 cases, had a higher mean value (0.5791) than the lobular infiltrative category, which had a mean value of 0.3375 derived from 8 cases. The lobular infiltrative group here indicates a negative lower bound in the confidence interval, indicating a more substantial dispersion in the data and a potential for more extreme lower values.

Examination of the Ki67 marker found that the trend continues with the ductal infiltrative type having a higher mean (0.3230 from 80 cases) than the lobular infiltrative group, which stands at a mean of 0.3000, calculated from a much smaller sample size of 5 (Table 4).

Table 4.

Biomarker distributions across different histological types of breast cancer.

Variables	N	M	SD	SE	Lower	Upper
ER						
Ductal infiltrative	103	0.7413	0.39652	0.03907	0.6638	0.8188
Lobular infiltrative	9	0.6222	0.47376	0.15792	0.2581	0.9864
Mixed	3	0.4667	0.41633	0.24037	-0.5676	1.5009
Other	6	0.7667	0.38816	0.15846	0.3593	1.1740
Total	121	0.7269	0.40068	0.03643	0.6547	0.7990
PgR						
Ductal infiltrative	98	0.5791	0.40778	0.04119	0.4973	0.6608
Lobular infiltrative	8	0.3375	0.43732	0.15462	-0.0281	0.7031
Mixed	3	0.7333	0.30551	0.17638	-0.0256	1.4922
Other	5	0.5600	0.51284	0.22935	-0.0768	1.1968
Total	114	0.5654	0.41248	0.03863	0.4888	0.6419
Ki67						
Ductal infiltrative	80	0.3230	0.13689	0.01530	0.2925	0.3535
Lobular infiltrative	5	0.3000	0.07071	0.03162	0.2122	0.3878
Mixed	2	0.2250	0.10607	0.07500	-0.7280	1.1780
Other	4	0.3500	0.17321	0.08660	0.0744	0.6256
Total	91	0.3208	0.13441	0.01409	0.2928	0.3488

Turning our attention to the independent variables of Table 4, several biomarkers labeled HER2Plus with Grades from 0 to 3, ER, PGR, and Ki67 are presented. The HER2Plus Grade 3 category is indicated as a reference group. For other grades of HER2Plus, the coefficients represent the change in the logged odds of the outcome variable per unit increase in the predictor; however, none of these reach statistical significance (P>0.05).

The variable ER has a coefficient of -2.137 and a statistically significant P-value of 0.028, implying a negative relationship with the outcome variable, within a 95% CI of -4.045 to -0.230. The PGR variable, despite having a positive coefficient of 1.144, does not reach a conventional level of statistical significance with a P-value of 0.164. Conversely, the Ki67 variable displays a strongly positive relationship with the outcome variable, having a coefficient of 5.150 and a significant P-value of 0.025, showcasing a strong positive influence within a 95% CI of 0.655 to 9.645 (Table 5).

Table 5.

Ordinal Logistic Regression Analysis of Breast Cancer Biomarker Grades and Predictors.

		Coef.	Std. Error	Wald	df	P-value	Lower	Upper
Dependent variable	[Grade = 1]	-3.165	1.470	4.632	1	0.031	-6.047	-0.283
	[Grade = 2] (Border)	2.636	1.142	5.330	1	0.021	0.398	4.873
Independent variables	[HER2Plus=0]	1.420	0.962	2.178	1	0.140	-0.466	3.306
	[HER2Plus=1]	0.824	0.968	0.725	1	0.394	-1.073	2.722
	[HER2Plus=2]	0.946	1.239	0.584	1	0.445	-1.482	3.375
	[HER2Plus=3]	0[a]			0			
	ER	-2.137	0.973	4.822	1	0.028	-4.045	-0.230
	PgR	1.144	0.823	1.934	1	0.164	-0.468	2.756
	Ki67	5.150	2.294	5.042	1	0.025	0.655	9.645

Discussion

In the multifaceted landscape of BC research, understanding the interrelationships between various biomarkers, demographic details, and imaging characteristics stands pivotal in forging paths toward more personalized and effective treatments. The analysis presented encompassed a meticulous exploration of a cohort of 238 patients, diving deep into demographic patterns, pathological characteristics, and the intricate web of relationships between key biomarkers. The realm of focus spanned from age distributions to a fine-grained analysis of variables such as tumor localization, BI-RADS classification, and receptor sensitivities, navigating through correlations and dissecting the distribution patterns across different cancer types.

The data surrounding age distributions hinted at a moderately varied age range, with a substantive span between the youngest and the oldest individuals, painting a rich tapestry of generational diversity. The average and median ages of our study population are comparable to those in BC studies generally, as older age is a well-established risk factor for BC. Several studies have found the median age of diagnosis to be around the 60s, which aligns well with our results. A slightly higher prevalence of tumor localization on the left side raises questions on whether biological, genetic, or environmental factors play a role in this disparity. In fact, another study emphasized that left-sided BC is more common and is associated with more aggressive biology and poorer outcomes than right-sided BC.[11] The overwhelming presence of BI-RADS-5 (92.8%) indicates a cohort with largely high percentages of malignancy due to the inclusion criteria and the type of study population. A dominant percentage of patients with cancer Grade 2 (68.3%) show a moderate differentiation in the tumors. The stark contrast with Grade 1 patients could suggest a late diagnosis in many cases. High positivity rates for both ER (77.7%) and PgR (70.6%) sensitivities indicate that hormone therapy might be a viable treatment route for a substantial fraction of the cohort. Recent studies on current populations indicate a rise in the occurrence of BC that test positive for ER and PgR, with the overall rates now ranging between 79% and 84%.[12,13]

While representing a smaller fraction (5.5%), the triple-negative patients underline a crucial subgroup that generally faces limited treatment options and a poorer prognosis. In general, this cancer is responsible for more than 15%–20% of all BCs.[14]

In the same line, the prominent negativity in HER2 status in 76% of patients signals a predominant type of BC that traditionally responds well to certain therapies, albeit with a less aggressive disease course than HER2-positive types.

There is a moderate positive correlation between the ER and PgR variables (rho=0.563, $P<0.05$), indicating a generally concurrent increase in the values of ER and PgR. This might occur due to the modulation by the PgR of the ERα activity in BC; the PR is a target gene of ER that is upregulated, and its expression is dependent on estrogen.[15]

Furthermore, a weak negative correlation was observed between ER and Ki67 (rho=-0.343, $P<0.05$) and between PgR and Ki67 (rho=-0.353, $P<0.05$), suggesting a tendency that higher levels of ER and PgR are generally associated with lower Ki67 levels. Tumors that are ER-positive or PgR-positive tend to grow more slowly than ER-negative or PgR-negative tumors.[16] Therefore, ER-positive and PgR-positive tumors might exhibit a lower Ki67 index than ER-negative and PgR-negative tumors, indicating a slower proliferation rate. However, this is a general trend, and individual cases may vary significantly.

Our observations of elevated ER expression in ductal infiltrative cancer, as opposed to lobular infiltrative cancer, diverge from the established consensus in current literature, which generally affirms a higher propensity for ER expression in lobular types.[17,18]

This difference may be attributed to a variety of factors, including a potential selection bias due to the small sample size for lobular cancers, distinct geographic and demographic variables influencing receptor expression, unique histopathological characteristics potentially not represented evenly in the sample, advancements in technology altering the sensitivity and specificity of receptor detection over time, and inherent intra-tumor heterogeneity causing a diverse range of expressions even within the same cancer subtype.

However, in our study, and according to existing literature, there is no significant difference in ER and PgR expression levels between lobular and ductal carcinoma.[19] Ki67, a marker of proliferation, was found to be slightly higher in ductal infiltrative cancers in our study, consistent with the literature.[20] The other results establish that higher Ki67 levels are associated with increased logged odds of the outcome variable, underlining the crucial role of Ki67 as a marker for cancer proliferation and potentially indicating aggressive tumor characteristics, a finding that is in line with the extensive body of literature emphasizing Ki67 as a vital prognostic marker in cancer studies.[21] High-grade lesions, in general, are more likely to be ER and PR negative;[22] this explains why an increase in the ER level was associated with a decrease in the logged odds of the outcome variable.

The study analyzed a diverse patient cohort, revealing critical insights into age distributions, tumor localizations, and the prevalence of different cancer grades, thus laying a foundation for more personalized and effective treatments in BC. Furthermore, it challenged existing literature on ER expression in different cancer subtypes, opening avenues for fresh debates and encouraging deeper exploration in this sphere to offer nuanced perspectives in BC research.

Conclusion

Our study offers a profound glimpse into the intricate relationships between various biomarkers and their associations with different types of infiltrative cancers. By carefully analyzing patient demographics and tumor localizations, we elucidated potential trends and patterns that might guide future research. Our analysis revealed a discernable pattern of associations between ER levels with PgR and Ki67 markers, showcasing a complex interplay that warrants further exploration. BI-RADS, a radiological assessment, doesn't exhibit a significant correlation with any of the three markers, indicating it might be independent of the hormonal status and the proliferative index

of the tumor. Furthermore, when we delineated the trends across different cancer types, a discernible pattern emerged, with the ductal infiltrative category generally portraying higher mean values across all markers than the lobular infiltrative category. The negative coefficient for ER suggests a declining trend with increasing grades. At the same time, Ki67 demonstrates a strong positive relationship with higher cancer grades, underlining its role as a potent marker for cancer proliferation and potentially higher grades of cancer. This study lays substantial groundwork for future research, promising to foster more targeted and effective therapeutic avenues, nurturing hope for better, individualized cancer treatment strategies.

Competing Interests

The authors declare that they have no competing interests.

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