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ORIGINAL ARTICLE

Correlation between Multiparametric Magnetic Resonance Imaging (MRI) Descriptors and Breast Cancer Molecular Subtypes

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ABSTRACT

Background and Objectives: Breast cancer is a variable group of diseases with different genotypic and phenotypic subtypes. Identifying the breast cancer molecular subtype is important in directing the type of treatment.

The aim of this work: Our study aimed to evaluate the role of multiparametric MRI in prediction of molecular subtypes of breast cancer.

Patients and Methods: A retrospective study included 135 female patients with pathologically proven invasive ductal carcinoma (IDC). Clinicopathological findings, morphological features, and dynamic contrast enhanced MRI (DCE-MRI) features were evaluated and correlated with the breast cancer molecular subtypes based on Immunohistochemistry classification.

Results: We found that the most common histological grade (61.5%) was grade I &II (low grade) of invasive ductal carcinoma (IDC). There were 110 (81.5%) masses and 25 (18.5%) non-mass lesions. The luminal A-like (Lum A-like) was the most common subtype seen in 57 (42.2%), then luminal B-like (Lum B-like) in 46 (34.1%), human epidermal growth factor receptor2 (HER2) positive in 14 (10.4%), and triple-negative (TN) was the least common subtype seen in 18 (13.3%) of the lesions. Irregular or Spiculated mass margins and irregular shape were significantly associated with Luminal A-like subtype (87.7%&80.7%) and Luminal B-like (85%&100%), respectively (P=0.002). Larger mass size, multifocality, and non-mass enhancement were reliably associated with HER2-enriched subtype (78.6% ,50% & 50%) respectively. The mass with oval shape, circumscribed margin, intra-tumoral high signal intensity on T2WI, rim enhancement, and higher histological grade was highly significant detected in TN breast cancer (P<0.001). The edema pattern was not significantly related to any molecular subtype.

Conclusions: Morphological features of breast cancer, intra-tumoral T2WI signal intensity, the pattern of enhancement determined by multiparametric MRI, as well as the histological grade of the tumor could be helpful to predict and differentiate breast cancer molecular subtypes and hormone receptors.

Keywords: multiparametric MRI; Breast cancer; Molecular subtypes

INTRODUCTION

Breast cancer is a disease have wide variation in clinical behaviors, histological subtypes, and response to therapy. So, personalized management is needed [1]. The traditional criteria for treatment selection were the tumor size, histopathologic grading, local invasion, involvement of lymph nodes, and distant metastasis. Women having the same histopathologic features and the same cancer stage

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may have variation in the clinical behavior and the treatment outcome [2]. Immunohistochemistry (IHC)is a reliable test that can detect molecular subtypes based upon the expression of progesterone receptor (PR), the estrogen receptor (ER), and HER2, and on the level of Ki-67 index. According to IHC, clinicopathological molecular subtypes were identified: luminal A-like, luminal B-like (luminal B-like HER2 negative, luminal B-like HER2 positive), HER2-enriched, and triple-negative (TN)[3]. Every molecular subtype has shown variable incidence, therapeutic response, prognosis, rate of recurrence, and disease-free survival outcome [4]. Multiparametric magnetic resonance imaging (MRI) is a non-invasive imaging modality that is highly sensitive, and efficacious for preoperative evaluation of breast cancer patients, as well as planning of treatment, and prediction of its efficacy [5]. Detection of the molecular markers by features obtained from multiparametric MRI without invasive biopsy helps guide treatment plans for patients [6]. We aimed to evaluate the accuracy of multiparametric MRI in prediction of different breast cancer molecular subtypes.

PATIENTS AND METHODS

1. Study type and population:

This was a retrospective study conducted at a tertiary hospital and included all female patients referred to department of radio-diagnosis for imaging of breast lesion(s) and histopathologically proved malignant mass during the period from June 2020 to April 2022, the medical records of all patients were revised. In addition to the MRI data, the variables collected included the patients' demographics, medical history, and clinical characteristics. The exclusion criteria included pathologically proved benign breast tumor (n=82), history of prior neo-adjuvant chemotherapy or previous cancer surgery (n=68), recurrent breast cancers (n=6), patients with missed histopathologic, and IHC biomarkers data (n=18), cases with motion artifact (n=13). Finally, 135 patients were met the inclusion criteria and included in the study, their age ranged from 22 to 75 years with the mean age of 42 years. The study has been carried out in accordance with the code of ethics of the World Medical Association (Declaration of Helsinki) — Ethical Principles for Medical Research Involving Human Subjects. Approval was obtained from the institution review board and the patient's informed consent was waived. All patients were subjected to multiparametric MRI of the breast mass in addition to histopathologic and IHC examinations of the excised mass or the biopsy.

2. MRI Examination

All examinations were done using MRI system, 1.5 Tesla [Achieva-class IIa, Philips Medical Systems, and Optima 450GEM, GE healthcare]. The examination was preferred to be done in the second week of menstrual cycle to reduce the background parenchymal enhancement. The patient lies prone, and a bilateral breast surface coil was used.

3. Imaging acquisition protocol:

- Pre-contrast sequences: T1-weighted turbo spin-echo(T1-TSE) (TR/TE = 500/ 5.5 ms) axial cuts. T2-weighted image turbo spin-echo (T2-TSE) (TR/TE = 120/5 ms) axial and sagittal cuts, and pre-contrast fat-saturated T2WI. Short-time inversion recovery (STIR) (TR/TE = 80/6.3 ms) axial cuts.
- Axial diffusion-weighted image (DWI) was obtained by the following parameters: TR/TE = 7000/85 msec, b-values= 0 and 1000 s/mm^{2,} slice thickness= 3 mm, FOV= 34 cm, flip angle= 90°, matrix= 255 – 205, pixel bandwidth= 1196 Hz, in-plane resolution=1.5 × 1.5 mm^2.
- Dynamic contrast-enhanced (DCE) sequences: A bolus of 0.1 mmol per kilogram body weight (0.1 mmol/kg) contrast media (gadolinium-diethylene tri amino Penta-acetic acid, Gd-DTPA) (Magnavist, Schering AG Berlin, Germany) was injected intravenously (IV) with a rate of 2 mL/sec then followed by 20 mL saline flush. Six dynamic phases were obtained: one phase before and five phases were obtained after IV injection of contrast media, 80 seconds for each phase acquisition. The total time of DCE-MRI protocol was 20 minutes, using axial three-dimensional (3D) gradient-echo (GRE) T1 High Resolution Isotropic Volume Examination (THRIVE) sequence with fat suppression (TR/TE = 2.8/9 ms) and FOV= 34 cm, flip angle= 10, slice thickness = 1.5 mm, interslice gap= 0.3 mm, matrix= 348 - 338., and fat-suppressed fast spin-echo sequence (repetition time msec/echo time msec, 5500–7150/85; field of view, 20 × 20 cm; matrix size, 256 × 160; section thickness, 1.5 mm with no gap)

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- Time-signal intensity curve (TIC) was performed by applying a region of interest (ROI) manually on the intensely enhancing region of the mass (its size is about 3 pixels). The ROI placement was repeated about three times and the most suspicious TIC was obtained.

4. Histopathological examination:

True cut image-guided biopsy (82 patients) or surgical excision (53 patients) was done to obtain a tissue sample, followed by histopathologic study, and IHC surrogate was done for estimation of hormone receptors (HR), and HER2 over expression, and Ki-67 status, and Fluorescence in situ hybridization (FISH) test for HER2 equivocal cases. Immunohistochemical detection was performed to obtain the status of ER, PR, HER2 overexpression, and Ki-67 index. Pathologists assess the nuclear ER and PR expression on stained slides based on the guidelines of the American Society of Pathologists (positive cut-off value ≥ 1%). Ki-67 index <14% means low expression, and ≥ 14% means high expression. The detection of HER2 expression in IHC based on staining pattern of the cell membrane. Grade 1+ or 0 means negative, grade 3+ means positive, and grade 2+ means equivocal. Fluorescence in situ hybridization was used to further analyze all equivocal samples, where FISH ratios above 2.2 or HER2 gene copies > than 6.0 were count positive. According to St. Gallen 2011 consensus surrogate definition,[10] breast cancers were divided into 4 molecular subtypes: Luminal A-like subtype (HR +ve, HER2 -ve, and Ki-67 < 14%), Luminal B-like subtype either Lum B HER2 neg. (HR +ve, HER2 -ve, and Ki-67 ≥ 14%) or Lum B HER2 pos. (HR +ve and HER2 +ve), HER2-enriched type (HR -ve and HER2 +ve), TNBC (HR, and HER2 -ve).

5. Image analysis:

Obtained MR images were evaluated by an experienced radiologists (more than 10 years) using the 5th edition of the American College of Radiology (ACR) breast imaging reporting and data system (BI-RADS) MR lexicon (2013)[11] on a separate session.. The radiologists were blinded for the histopathological results. In each case the image were evaluated for site and number of lesions, the margin, shape, intra-tumoral signal intensity on the T2WI, the pattern of enhancement and distribution of cases with non-mass lesions, time-signal intensity curve (TIC) pattern kinetics, edema patterns were subclassified into five patterns (no edema, skin edema, perilesional edema, combined skin + perilesional, perilesional + pre pectoral edema, or skin + perilesional + pre pectoral patterns. All obtained data were correlated to the histopathological data to determine the relation between multiparametric MRI characteristics, and the breast cancer molecular subtypes.

Statistical analysis:

Using SPSS version 20.0 for windows (SPSS Inc., Chicago, IL, USA) & MedCalc 13 for windows (MedCalc Software bvba, Ostend, Belgium), the obtained data were collected, tabulated, and statistically analyzed. Qualitative data were expressed as an relative frequency (percentage) and absolute frequency (number). The Chi-square test or Fisher's exact test were used for comparison of categorical data. P-value was evaluated as < 0.001 highly statistically significant (HS), < 0.05 statistically significant (S), and P-value ≥ 0.05 non statistically insignificant (NS).

RESULTS

This study included 135 patients aged between 22 and 75 years (mean 42 years), breast cancer subtypes were classified as 57 patients (42.2 %) were Lum A-like subtype **(Figure 1),** 46 patients (34.1%) were Lum B-like subtype (of the LB subgroup, 46 % were Lum B HER2 -ve , while,54% were Lum B HER2 +ve) **(Figure 2),** 14 patients (10.4%) were HER2-enriched **(Figure 3),** and 18 patients (13.3%) were TNBC **(Figure S1).** The histological grade in our patients the low grade (I &II) tumors were more common detected in 83 (61.5 %) patients compared to the high grade tumors (grade III) found in 52 (38 .5%) patients **(Table 1).** TNBC were found to be more common in premenopausal female (61.1%), however there was no significant differences in the patient age (P-value = 0.654) among different tumor subtypes (**Table 2).** Analysis of the MRI finding, we found 110 (81.5%) patients had mass lesions, and 25 (18.5%) had non-mass lesions and there was a significant difference between both lesion types and molecular subtypes (P-value =0.005). Mass lesion was highly related to TN breast cancer (18/18, 100%), Lum A-like (53/57, 93 %), and Lum B-like (32/46, 69.6 %) subtypes. While non-mass like lesions were significantly frequent in the HER2-positive subtype (7/14, 50 %).

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Regarding the size of the examined breast masses there was no statistical significance in tumor size among the molecular subtypes (P-value = 0.598), however the larger diameter seen more encountered in HER2-enriched subtype. The mass with oval shape was highly significant associated with TNBC (14/18, 78 %) compared to other breast cancer subtypes (P-value = 0.002) and masses with irregular shape was more commonly noted in luminal A-like (46/57, 80.7%), and luminal B-like lesions (46/46, 100%) than TN lesions (4/18, 22%) (P-value =0.002). Analysis of the mass margin we found a statistically significant difference between the mass margins and different molecular subtypes (P-value < 0.001). TNBC more frequently had well-circumscribed margins (14/18, 78). While the irregular or spiculated mass margins were highly associated with Lum A-like lesions (50/57, 87.7%), and Lum B-like lesions (46/46, 100%). HER2-enriched breast cancer tended to be multifocal lesions (7/14, 50 %), followed by Lum B-like subtype that had (7/46, 15.2 %) multifocal, and (7/46, 15.2 %) multi-centric. High T2WI signal intensity was significantly higher in TN cancers (14/18, 78%) than in Lum B-like cancers (7/46, 15.2%) with P-value = 0.001. The difference between the enhancement and TIC patterns of different molecular subtypes was statistically significant (P = 0.021), Heterogenous enhancement was more detected in Lum A-like (46/57, 80.7%), Lum B-like (36/46, 78.3%), and HER2-enriched (14/14, 100%), while Rim enhancement was significantly related to TNBC (11/18, 61.1%). TIC III (washout pattern) was intimately related to TNBC (18 /18, 100%), while TIC II (Plateau pattern) was common in Lum A-like (43/57, 75.4%). No significant association was founded between the pattern of edema and breast cancer subtypes (P = 0.882) Perilesional edema was commonly associated with Lum A-like (21/57, 36.8%), Lum B-like (25/46, 54.3%), HER2 (7/14, 50%), and TNBC (11/18, 61.1%). Axillary lymph nodes involvement was founded more in TNBC (11/18, 61.1%), however no statistically significant difference were founded between axillary LNs involvement and molecular subtypes (P-value = 0.289) **(Table 3).** The recorded sensitivity, specificity, PPV, and NPV for multiparametric MRI in the prediction of LA, LB, HER2-enriched and TNBC molecular subtypes respectively was (87.5%,81.8%, 77.77%, 90%), (69.2%, 96%, 90%, 85.71%), (75%, 97.05%, 75%, 97.05%) and (80%, 93.9%, 66.66%, 96.87%) **(Table 4).**

Table 1. Pathological data of the included patients.

Pathological findings	Number (NO.)	%
Grade of IDC		
Low (grade I & II)	83	**61.5%**
High (grade III)	52	**38.5%**
ER		
Negative	32	**23.7%**
Positive	103	**76.3%**
PR		
Negative	49	**36.3%**
Positive	86	**63.6%**
HER2 status		
Negative	96	**71%**
Positive	39	**29%**
Ki-67		
Low	57	**42.2%**
High	78	**57.8%**
Molecular subtype		
Luminal A-like	57	**42.2%**
Luminal B-like	46	**34.1%**
HER2-enriched	14	**10.4%**
Triple negative	18	**13.3 %**

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Table 2. Relationship between menopausal status and molecular subtypes among the studied patients

Menopausal status	Included patients (n=135)		Molecular subtype								Test a	p-value
			Luminal A-like (n=57)		Luminal B-like (n=46)		HER2 Enriched (n=14)		Triple-negative (n=18)			
	N.	%	N.	%	N.	%	N.	%	N.	%		
Pre-menopausal	49	36.3 %	18	31.6%	17	37 %	3	21.4%	11	61.1%	1.623a	**0.654**
Postmenopausal	86	63.7 %	39	68.4%	29	63 %	11	78.6%	7	38.9%		

Table 3. MRI features different breast cancer molecular subtypes.

MRI features	Studied patients (n=135)		Molecular subtype								Test a	p-value (Sig.)
			Luminal A-like (n=57)		Luminal B-like (n=46)		HER2 Enriched (n=14)		Triple negative (n=18)			
	No.	%	No.	%	No.	%	No.	%	No.	%		
Mass size												
≤ 20 mm	75	55.6%	36	63.2 %	25	54.3%	3	21.4%	11	61.1%	1.877	**0.598**
>20mm	60	44.4%	21	36.8 %	21	45.6%	11	78.6%	7	38.9%		**(NS)**
Distribution												
Mass form	110	81.5%	53	93%	32	69.6%	7	50%	18	100%	21.130	**0.012**
Non-mass form												
Segmental	14	10.3%	4	7%	10	21.7%	0	0%	0	0%		**(NS)**
Regional	7	5.2%	0	0%	4	8.7%	3	21.5%	0	0%		
Multiple regions	4	3%	0	0%	0	0%	4	28.5%	0	0%		
Multiplicity												
Absent	110	81.5%	53	93%	32	69.6%	7	50%	18	100%	6.680	**0.083**
Present	25	18.5%	4	7%	14	30.4%	7	50%	0	0%		**(NS)**
Multifocality												
Absent	121	89.6%	57	100%	39	84.8%	7	50%	18	100%	9.414	**0.024**
Present	14	10.4%	0	0%	7	15.2%	7	50%	0	0%		**(S)**
Multicentricity												
Absent	124	92.1%	53	93.8 %	39	84.8%	14	100%	18	100%	1.834	**0.608**
Present	11	7.9%	4	6.2%	7	15.2%	0	0%	0	0%		**(NS)**
Shape												
Oval	32	23.7%	11	19.3 %	0	0%	7	50%	14	78%	14.556	**0.002**
Irregular	103	76.3%	46	80.7 %	46	100%	7	50%	4	22%		**(S)**

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MRI features	Studied patients (n=135)		Molecular subtype								Test a	p-value (Sig.)
			Luminal A-like (n=57)		Luminal B-like (n=46)		HER2 Enriched (n=14)		Triple negative (n=18)			
	No.	%	No.	%	No.	%	No.	%	No.	%		
Margin												
Circumscribed	24	17.7%	7	12.3 %	0	0%	3	21.4%	14	78%	27.638	**<0.001**
Irregular	68	50..4%	18	31.6 %	35	76.1%	11	78.6%	4	22%		**(HS)**
Spiculated	43	31.9%	32	56.1 %	11	23.9%	0	0%	0	0%		
Intra-tumoral SI on T2WI												
Low	110	81.5%	57	100%	39	84.8%	11	78.6%	4	22%	16.424	**0.001**
High	25	18.5%	0	0%	7	15.2%	3	21.4%	14	78%		**(S)**
Internal enhancement												
Homogenous	14	10.4%	11	19.3 %	3	6.5%	0	0%	0	0%	14.303	**0.026**
Heterogenous	103	76.3%	46	80.7 %	36	78.3%	14	100%	7	38.9%		**(S)**
Rim enhancement	18	13.3%	0	0%	7	15.2%	0	0%	11	61.1%		
TIC												
Plateau curve (Type II)	68	50.4%	43	75.4 %	18	39%	7	50%	0	0%	9.692	**0.021**
Washout curve (Type III)	67	49.6%	14	24.6 %	28	61%	7	50%	18	100%		**(S)**
Edema												
Absent	28	20.7%	14	24.6 %	11	24%	0	0%	3	16.7%	8.917	**0.882**
Perilesional	64	47.4%	21	36.8 %	25	54.3%	7	50%	11	61.1%		**(NS)**
Skin	4	3%	4	7%	0	0%	0	0%	0	0%		
Perilesional + skin	28	20.7%	14	24.6 %	7	15.2%	3	21.4%	4	22.2%		
Perilesional+ pre pectoral	4	3%	4	6.2%	0	0%	0	0%	0	0%		
Perilesional+ pre pectoral + skin	7	5.2%	0	0%	3	6.5%	4	28.6%	0	0%		
Lymph node												
Negative	82	60.7%	43	75.4 %	21	45.7%	11	78.6%	7	38.9%	3.759	**0.289**
Positive	53	39.3%	14	24.6 %	25	54.3%	3	21.4%	11	61.1%		**(NS)**

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Table 4. Diagnostic accuracy of multiparametric MRI in differentiating between different breast cancer molecular subtypes.

	Luminal A-like	Luminal B-like	HER2-enriched	Triple negative
SN (95%CI)	87.50% (61.65 – 98.44)	69.23% (38.57 – 90.90)	75% (19.41 – 99.36)	80% (28.35 – 99.49)
SP (95%CI)	81.81% (59.71 – 94.81)	96% (79.64 – 99.89)	97.05% (84.67 – 99.92)	93.93% (79.77 – 99.25)
PPV (95%CI)	77.77% (58.59 – 89.64)	90% (56.04 – 98.45)	75% (19.41 – 99.36)	66.66% (32.74 – 89.15)
NPV (95%CI)	90% (70.80 – 97.09)	85.71% (72.56 – 93.15)	97.05% (84.67 – 99.92)	96.87% (84.27 – 99.44)
Accuracy (95%CI)	84.21% (68.74 – 93.97)	86.84% (71.91 – 95.58)	94.73% (82.25 – 99.35)	92.10% (78.62 – 98.34)

SN: Sensitivity; SP: Specificity; PPV: Positive Predictive Value; NPV: Negative Predictive Value; CI: Confidence Interval.

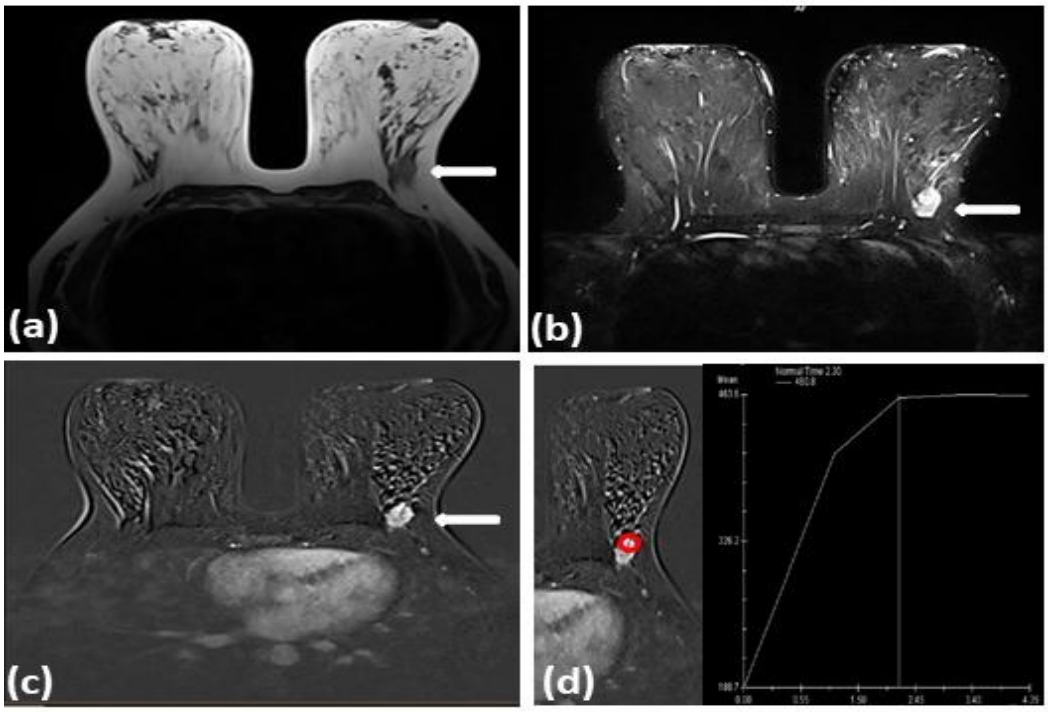

Figure 1. Lum A-like breast cancer (IDC grade II) of 59 years old female left breast. A- Axial T2WI TSE shows low SI non circumscribed irregular breast mass seen at the upper outer quadrant. B- Axial STIR Shows high SI in STIR. C- Axial dynamic examination post-contrast subtracted image display intense heterogeneous enhancement, D- Time-intensity curve present type II (plateau kinetics).

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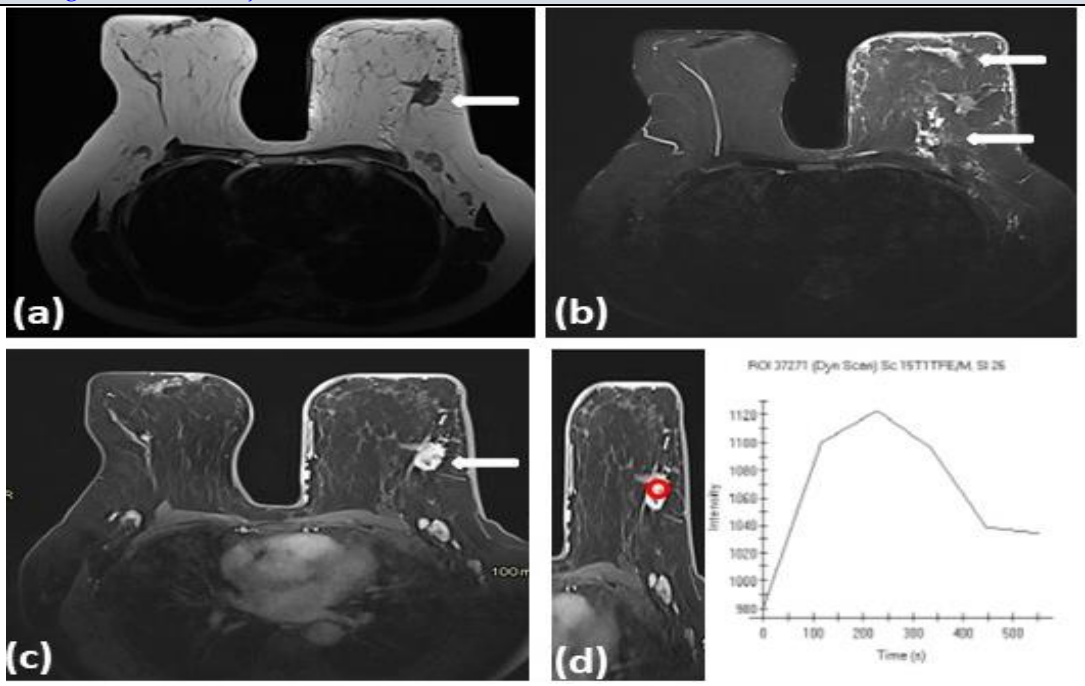

Figure (2): Lum B-like HER2 -ve breast cancer (IDC grade II) in 52 years old female left breast. A- Axial T2WI TSE shows low SI non-circumscribed spiculated breast mass seen at the upper outer quadrant. B- Axial STIR Shows skin thickening, perilesional and pre pectoral edema. C- Axial contrast-enhanced 3D GE T1 high-resolution isotropic volume sequence (THRIVE) display intense heterogeneous enhancement, D- TIC present a type III TIC (washout kinetics).

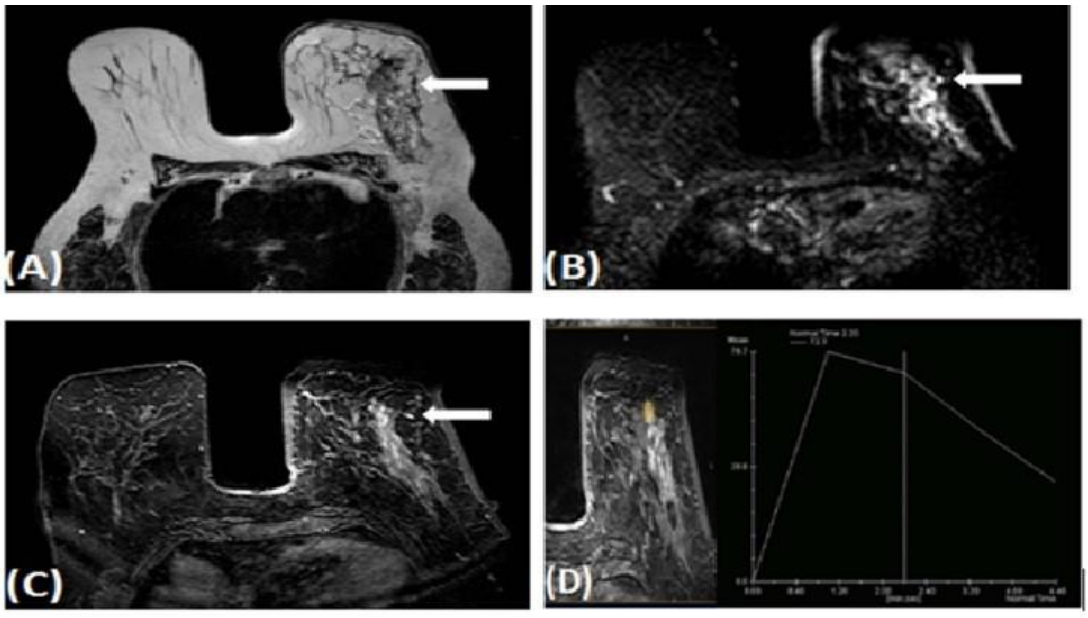

Figure (3): Lum B-like HER2 +ve breast cancer (IDC grade III) in 59 years old female left breast. A- Axial T2WI TSE shows a non-mass lesion seen at upper & lower outer quadrants. B- Axial DWI Shows restricted diffusion. C- Axial contrast-enhanced 3D GE T1 high-resolution isotropic volume sequence (THRIVE) shows heterogeneous enhancement, D- Time-intensity curve shows a type III TIC (washout kinetics).

DISCUSSION

Breast cancer is a disease that has variable genotypic and phenotypic subtypes. This has valuable prognostic and therapeutic impact as the molecular subtypes become a major requirement for therapeutic managments [11]. Each molecular subtype of breast cancer has variable manner of presentation and metastatic behavior as well as the response to chemotherapy and radiotherapy [12].

Our study aimed to correlate the relationship between breast cancer molecular subtypes, ER,

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PR status, HER2neu expression with imaging characteristics of multiparametric MRI, that would improve the presurgical personalized medical care.

We found no statistically significant relation between the age of the patients and the molecular subtypes, although the luminal A-like subtype was more common in older age group (postmenopausal state) (68.4%), and TNBC commonly presented in younger age group (premenopausal females) (61.1%). This was in agree with *Issar et al. Dogan et al., and Fan et al.* [2,13,14,], who concluded that there was no valuable association between age group and molecular subtypes. While, in studies of *Costantini et al. and Osman et al.* [5,15], they concluded that the TNBC was significantly associated the younger age females, this statistics difference attributed to the higher number of their patient with TNBC. In the current study, we found that the most common presenting form of IDC of breast cancer is the mass lesion occurring in 110 cases (81.5 %) of our patients and 25 cases (18.5 %) were presented by non-mass lesion and this consistent with *Dogan et al., Temiz et al., also with Chen et al.* [13,16,17]. We recorded that the mass size was larger in HER2-positive groups (78.6%) compared to Lum A-like (36.8%), Lum B-like (45.6%), and TNBC (38.9%), but the result was statistically non-significant. This is agree *with Fan et al.* [14], they found that the larger mass diameter was related to the HER 2-positive type.

The present study revealed that there was a statistically significant difference in the shape, margin of the mass lesions, intra-tumoral T2WI signal intensity, pattern of enhancement, and time-intensity curve. We found that Lum A-like and Lum B-like masses were more encountered as mass with irregular-shape and spiculated/ irregular margin (87.7 &100%) respectively, while mass with oval shape and well-circumscribed margin was significantly linked with TNBC (78%). *Algazzar et al.* [18] found that HR-negative breast masses was differ from HR-positive tumor regarding the tumor margin, with a well circumscribed lesions more with HR-negative tumors. This was the same as *Dogan et al*. and *Navarro et al.* [13,19] who found that spiculated margin was related to luminal A-like subtype compared to TN breast cancers. We reported that the HER2-enriched subtype tends to be multifocal (50%), followed by Lum B-like mass lesions where (15.2%) were multifocal, and (15,2%) were multi-centric. On the other hand, TNBC tends to be unifocal (100%). We agree with *Elias et al.* [8] who stated that the multifocal lesions were related to the HER2 subtype when considering only mass lesions. This was the same as *Grimm et al.* [9] revealed that multifocal or multi-centric lesions were reliably more common in Lum B-like and HER2-positive subtypes. *Uematsu et al.* [20] reported that two-thirds of TN breast cancers were unifocal. *Issar et al.* [2] reported that 81.82 % of TN breast cancers were unifocal. High intra-tumoral T2WI signal intensity corresponded to intra-tumoral necrosis, which is considered as a prognostic factor in invasive breast carcinoma. A mass with central necrosis presented by rapid clinical course and early systemic metastasis [15].

Our study recorded that the percentage of intra-lesional high T2WI SI is highly associated with TNBC (78%) than the other types due to necrosis as the TNBC has the most aggressive behavior and is mostly associated with high-grade tumors. We agree with *Dogan et al*. [13] who noted that TNBC type was more commonly linked to the high tumor grade, circumscribed mass margin, oval mass shape, and higher signal intensity on T2WI. In our study, regarding the lesion enhancement at DCE-MRI, we found that the pattern of tumor enhancement and molecular subtypes has a statistically significant association, where the majority of Lum A-like (80.7%), Lum B-like (78.3%), and HER2-enriched (100%) had heterogeneous enhancement and the rim enhancement was associated with TNBC (61.1%), and to a lesser degree in Lum B-like cases (15.2%). It may be because Lum B-like is more aggressive than Lum A-like. In line with our results *Dogan et al. Angelini et al. & Moffa et al.* [13,21,22] concluded that the rim enhancement was reliably correlated to TN tumors, also *Algazzar et al.* [18], stated that; there was a significant difference in the enhancement pattern with the molecular subtypes. Rim pattern of enhancement was predominantly found in TNBC subtype compared to the heterogeneous pattern of enhancement more reported with other molecular subtypes. This may be due to higher rate of internal breakdown in TNBC. Also our results were in accordance with *Issar et al., Navarro et al., Azzam et al. and Youk et al.* [2,19,23,24] where they reported similar findings.

As regards time-intensity curve kinetics we reported a statistically significant difference amongst different molecular subtypes. We reported that type II kinetic curve was reliably associated with Lum A-like (75%), and type III kinetic curve was ultimately related to TNBC

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(100%) (P-value =0.021). Our results were in agree with DiLorenzo et al. and Lee et al. [25, 26].*Also, Algazzar et al.* [18] reported that HR-negative breast cancers tended to show type III (washout) curve, and this agrees with our study.

In contrast to *Dogan et al.* [13], who found that the dynamic curve was accurately used to discriminates between benign and malignant breast masses and also concluded that different curve kinetics were reported in each breast cancer molecular subtypes, however, there was no significant data realize that dynamic curve can differentiate breast cancer molecular subtypes. *Issar et al. & Navarro et al.* [2,19], in their research concluded that no significant difference between dynamic curve and different molecular subtypes as plateau and washout curves were seen in all malignant groups.

About the edema pattern, we found that the perilesional edema was noted in (61.1%) of TNBC, (50 %) of HER2-enriched, (54.3 %) of Lum B-like, and (36.8%) of Lum A-like and was the most common form of edema in different molecular subtypes of invasive breast cancers. But we found no significant relationship between the form of edema, and molecular subtypes.

In contrast to *Dogan et al.* [13], they stated that (perilesional + pre pectoral) edema and (skin + perilesional + pre pectoral) edema were commonly seen with HER2-positive cancers in comparison to Lum A-like type. *Alili et al.* [27] in their study concluded that perilesional edema pattern commonly linked to HER2-type.

In our study, we found that axillary LNs affection was more commonly associated with TNBC (61.1%) than other types (Lum A-like (24.6%), and HER2-enriched (21.4%)) but this was non-significant statistically (*P*-value= 0.289).

Temiz et al. [16], reported a relation between axillary LNs metastasis and tumor with larger size, high-grade, and high Ki-67 index.

Our study had many limitations as; we did not assess if there is a relation between nipple/ skin invasion or chest wall invasion and breast cancer molecular subtypes, also we did not correlate with breast cancer staging at time of the diagnosis which might influence imaging characteristics and also we not including the relation between ADC value and different molecular subtypes.

CONCLUSION

From the obtained results we concluded that multiparametric MRI is a noninvasive rapid and accurate modality for predicting the molecular subtypes of breast cancers. Morphological features, intra-tumoral T2WI signal intensity, the pattern of enhancement as well as the histological grade of the tumor would be helpful to differentiate molecular subtypes of breast cancers. Multiparametric MRI can predict the luminal group, HER2-enriched, and TNBC but cannot ideally differentiate between Lum A-like and Lum B-like subtypes as they share common imaging characteristics.

REFERENCES

1. **Harbeck, N.; Gnant, M.** Breast cancer. Lancet 2017, 389, 1134–50.
2. **Issar P, Sinha S, Ravindranath M, Issar SK.** MRI Features of Different Molecular subtypes of Breast Cancer. *Indian J Appl Radiol*. 2020;6(1): 151.
3. **Goldhirsch A, Wood WC, Coates AS, Gelber RD, Thürlimann B, Senn HJ;** Strategies for subtypes—dealing with the diversity of breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. *Ann. Oncol*. 2011;22(8):1736-47.
4. **Ng CK, Schultheis AM, Bidard FC, Weigelt B, Reis-Filho JS..** Breast Cancer Genomics from Microarrays to Massively Parallel Sequencing: Paradigms and New Insights. *JNCI: Journal of the National Cancer Institute*. 2015;107(5).
5. **Melania Costantini, Paolo Belli, Daniela Distefano, Enida Bufi, Marialuisa Di Matteo, Pierluigi Rinaldi, et al.;** Magnetic Resonance Imaging Features in Triple-Negative Breast Cancer: Comparison with Luminal and HER2-Overexpressing Tumors. *Clin Breast Cancer*. 2012;12(5):331-9.
6. **Li W, Yu K, Feng C, Zhao D..** Molecular Subtypes Recognition of Breast Cancer in Dynamic Contrast-Enhanced Breast Magnetic Resonance Imaging Phenotypes from Radiomics Data. *Comput Math Methods Med.* 2019;1-14.
7. **Kawashima H, Inokuchi M, Furukawa H , Kitamura S.** Triple-negative Breast Cancer. *Acad Radiol*. 2011;18(8):963-9.
8. **Sjoerd G. Elias, Arthur Adams, Dorota J. Wisner, Laura J. Esserman, Laura J. van't Veer, Willem P.Th.M. Mali, et al.;** Imaging Features of HER2 Overexpression in Breast Cancer: A Systematic Review and Meta-analysis. *Cancer Epidemiol. Biomark. Prev*. 2014;23(8):1464-83.

https://doi.org/10.21608/zumj.2023.246436.2994 Volume 30, Issue 1.2, February 2024, Supplement Issue

9. **Lars J. Grimm, Karen S. Johnson, P. Kelly Marcom, Jay A. Baker, and Mary S. Soo.** Can Breast Cancer Molecular Subtype Help to Select Patients for Preoperative MR Imaging? *Radiology*. 2015;274(2):352-58.
10. **American College of Radiology Breast Imaging Reporting and Data System (BI-RADS Atlas)** MRI-Lexicon. 5th ed. Reston: American College of Radiology; VA2013.
11. **Edge S, Byrd D, Compton C.** ***AJCC Cancer Staging Manual.*** 7th ed. New York: Springer; 2009:347–76.
12. **rop I, LeBlanc SM, David J, Lalonde L, Tran-Thanh D, Labelle M, El Khoury MM.** Molecular Classification of Infiltrating Breast Cancer: Toward Personalized Therapy. *Radiographics*. 2014;34(5):1178-95.
13. **Dogan S., Ozmen S., Oz B., Imamoglu H., Kahriman G., Zararsiz G., et al.,** Comparison of Different Dynamic Contrast Enhanced-Magnetic Resonance Imaging Descriptors and Clinical Findings Among Breast Cancer Subtypes Determined Based on Molecular Assessment. *Iranian Journal of Radiology*, 2018;15(4):e64889. https://doi.org/10.5812/iranjradiol.64889.
14. **Fan M, He T, Zhang P, Cheng H, Zhang J, Gao X, et al.** Diffusion-weighted imaging features of breast tumours and the surrounding stroma reflect intrinsic heterogeneous characteristics of molecular subtypes in breast cancer. *NMR Biomed*. 2017;31(2): e3869.
15. **Osman N, Chalabi N, Raboh N.** Triple negative breast cancer: MRI features in comparison to other breast cancer subtypes with correlation to prognostic pathologic factors. *Egypt J Radiol Nucl Med*. 2014;45(4):1309-16.
16. **Temiz K, Oztekin P, Hucumenoglu S , Koseoglu EN& Kosar PN.** Correlation of prognostic factors with MRI findings in malignant breast lesions. *Egypt J Radiol Nucl Med.*. 2020;51(1)1-7.
17. **Chen JH, Baek HM, Nalcioglu O, Su MY.** Estrogen receptor and breast MR imaging features: A correlation study. *JMRI*. 2008;27(4):825-33.
18. **Algazzar M, Elsayed E, Alhanafy A & Mousa WA,** Breast cancer imaging features as a predictor of the hormonal receptor status, HER2neu expression and molecular subtype. *Egypt J Radiol Nucl Med.*. 2020;51(1)1-10.
19. **Navarro Vilar L, Alandete Germán SP, Medina García R, Blanc García E, Camarasa Lillo N, Vilar Samper J.** . MR Imaging Findings in Molecular Subtypes of Breast Cancer According to BIRADS System. Breast J. 2017 Jul;23(4):421-8.
20. **Uematsu T, Kasami M, Yuen S.** Triple-Negative Breast Cancer: Correlation between MR Imaging and Pathologic Findings. *Radiology*. 2009;250(3):638-47.
21. **Angelini, G.; Marini, C.; Iacconi, C.; Mazzotta, D.; Moretti, M.; Picano, E.; et al.** Magnetic resonance (MR) features in triple negative breast cancer (TNBC) vs receptor positive cancer (nTNBC). *Clin. Imaging* 2018, 49, 12-6.
22. **Moffa G, Galati F, Collalunga E, Rizzo V, Kripa E, D'Amati G, et al.,** Can MRI Biomarkers Predict Triple-Negative Breast Cancer? *Diagnostics*. 2020;10(12):1090.
23. **Azzam, H., Kamal, R., El-Assaly, H., Metwally L. I. A.** The value of dynamic contrast-enhanced MRI in differentiating triple-negative breast cancer from other subtypes. *Egypt J Radiol Nucl Med*. 2019; 50 (106).
24. **Youk JH, Son EJ, Chung J, Kim JA, Kim EK.** Triple-negative invasive breast cancer on dynamic contrast-enhanced and diffusion-weighted MR imaging: comparison with other breast cancer subtypes. *Eur Radiol*. 2012;22(8):1724-34.
25. **ilorenzo G, Telegrafo M, La Forgia D, Stabile Ianora AA, Moschetta M.** Breast MRI background parenchymal enhancement as an imaging bridge to molecular cancer sub-type. *Eur J Radiol*. 2019; 113:148-52.
26. **Lee SH, Cho N, Kim SJ, Cha JH, Cho KS, Ko ES, et al.** Correlation between High Resolution Dynamic MR Features and Prognostic Factors in Breast Cancer. *Korean J Radiol*. 2008;9(1):10.
27. **Alili C, Pages E, Curros Doyon F, Perrochia H, Millet I, et al.** Correlation between MR imaging – prognosis factors and molecular classification of breast cancers. *Diagn Interv Imaging*. 2014;95(2):235-42.

https://doi.org/10.21608/zumj.2023.246436.2994 Volume 30, Issue 1.2, February 2024, Supplement Issue

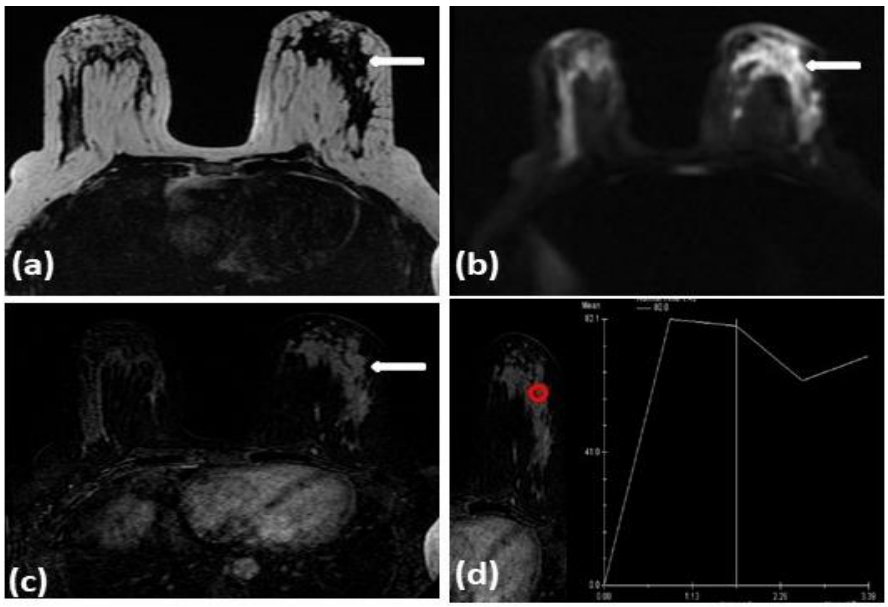

Figure S1. HER2-enriched breast cancer (IDC grade II) in 38 years old female right breast. A- Axial T2WI TSE shows large ill-defined area of regional non-mass at UOQ & LOQ. B- Axial DWI shows restricted DWI of the non-mass lesion. C- Axial contrast-enhanced 3D GE T1 high-resolution isotropic volume sequence (THRIVE) shows moderate heterogeneous enhancement. D- Time-intensity curve shows type II TIC (plateau Kinetic).

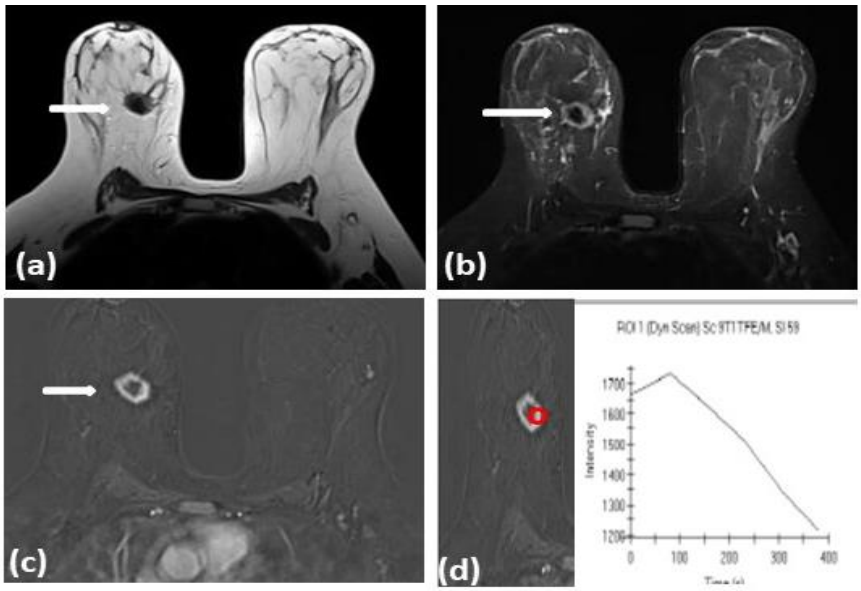

Figure S2. TN breast cancer (IDC grade III) in 42 years old female right breast. A- Axial T2WI TSE shows upper inner quadrant low SI rounded well-circumscribed mass. B- Axial STIR Shows perilesional edema. C- Axial post-contrast dynamic examination subtracted image of display rim enhancement, D- Time-intensity curve present a type III TIC (washout kinetics).

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