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Prognostic Value of Tumour-Stromal Ratio Using CD10 Expression in Primary Breast Carcinoma

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Abstract*— *Background: *When it comes to cancers affecting women, most common and second-leading cause of deaths related to cancer is Breast Cancer. The prognostic significance of tumor-stromal ratio (TSR) in primary breast carcinoma is reviewed, with a specific focus on its implications for disease prognosis and treatment in different histopathological subtypes.* ***Aim of Study:*** *Improving prognosis in breast cancer patients is needed to prevent over- and under-treatment with adjuvant chemotherapy.* ***Methodology:*** *This cross-sectional study examined Iraqi primary breast cancer. The Cancer Research Laboratory at Al-Sader General Hospital and private laboratories provided samples for immunohistochemistry analysis of CD10 expression. All data privacy and ethical requirements were observed. Sample preparation, staining, and microscopic examination were carefully detailed for accurate results. The investigation used scoring systems for HER2/Neu, estrogen, and Progesterone receptors to assess tumor cell staining intensity and pattern.* ***Results:*** *The findings revealed a similar distribution of breast cancer among different age groups, with a greater prevalence of grade II tumors. The majority of ER and PR statuses were positive, HER2/neu statuses were frequently negative, and Ki67 levels demonstrated variation.* ***Conclusion:*** *The study establishes tumor-stroma ratio (TSR) as a major independent predictive factor for breast cancer. Its simplicity and speed make it a promising tool for pathological evaluations and risk stratification in breast cancer management. To confirm TSR's predictive value, larger and more comprehensive studies are required.*

Keywords*— tumor-stroma ratio, CD10, breast cancer, immunohistochemistry.*

I. Introduction

Breast cancer (BC) is the second most prevalent cause of cancer mortality in women and most frequent malignancy in females. (1). One prognostic marker for BC is the tumor's stroma structure, which includes the extracellular matrix's density and rigidity (2). Thus, a new measurement has been implemented which is Tumor stroma ratio (TSR). It is defined as “the percentage of the neoplastic cell component relative to the stroma in tumor tissue” (3).

There was a strong correlation between the atypical ratio of TSR and certain clinical factors, including the clinical stage, the depth of invasion, and the lymph node metastases. Moreover, the stroma associated with tumors was shown to actively contribute to tumor growth via many pathways. Nevertheless, the precise mechanism responsible for the enhancing impact of stroma in solid tumors remains incompletely comprehended (4).

Thus, TSR has the potential to enhance the accuracy of predicting outcomes and identifying suitable patients for therapy. Results from Tumor-Stroma Ratio (TSR) may be generalized to BC, but specific types of tumors, e.g. invasive lobular and mucinous carcinomas, need particular consideration (2).

Presently, there are three approaches available to evaluate TSR: First approach is visual estimation, a manual technique using two stages to calculate TSR (5). The second approach is a partially automated point counting technique that was created by West et al. (6) and verified for BC by Downey et al. (7). Sections that are stained with HE and are four micrometers thick are scanned to identify the most invasive areas. Third approach is immunohistochemical (IHC) labelling of CD10.

The research hypothesis: Tumor-stromal ration is highly correlated to the outcome and prognosis in patients with primary breast carcinoma.

Aim of study:

- To determine if the tumor-stromal ratio is associated with a crucial role in the tumor pathogenesis of primary BC.
- To correlate the tumor-stromal ratio with various clinicopathological parameters including age, gender, tumor focality, and lymph node involvement.
- To assess diagnostic tumor-stromal ratio by CD10 immunohistochemistry in various types of primary BC.

II. Materials and Methods

The research was designed to be a retrospective cross-sectional study from (2020-2023) involving Iraqi patients diagnosed with primary breast carcinoma. No limitation on age or gender was proposed. All data was kept private; no information was divulged and only used for research. The study was done in the Najaf governorate, Pathology and Forensic Medicine Unit/ Alkufa University-Faculty of Medicine from 2020 to 2023.

Cases selection: The samples were collected from the archival materials in a laboratory for histopathology for Cancer Research in Al-Sader General Hospital and private laboratories in a convenient way. The inclusion criteria of this study were to include all cases diagnosed with primary breast carcinoma. The exclusion criteria include patients with mental deficits precluding proper follow-up and documentation and those with incomplete clinicopathological information. All included tumors were re-examined microscopically by two pathologists to confirm diagnosis by hematoxylin and eosin-stained

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sections. Cases were classified according to WHO classification of breast tumors.

This study has been approved by the scientific and ethical committee of College of Medicine / Kufa University under the registration number EAC: 17855 on 7th December 2021. The study has followed Helsinki Declaration standards. Full privacy guidelines protected patient data and private information like name and hospital number, and each patient's identity and profile were fully anonymized.

Microscopic Examination: Analyze the stained tissue sections using a microscope to evaluate the expression of CD10 in breast carcinoma samples.

Assess the staining intensity and distribution pattern of the markers HER2/Neu, Estrogen, and progesterone receptor proteins in tumor cells and compare them to adjacent normal breast tissue, if available.

Data Analysis and Interpretation: Once the staining procedure was completed, the stained slides were examined under a light microscope. CD10 expression levels were assessed based on staining intensity and localization in breast cancer tissue. The staining results were recorded, and scoring systems were applied to categorize the staining patterns.

Immunohistochemical Scoring Systems: These scoring systems assess HER2/Neu, Estrogen, and progesterone receptor proteins' expression levels in the tissue samples. Interpreting the staining results can help understand the role and significance of HER2/Neu and Estrogen receptor and progesterone receptor expression in the studied patients and their potential implications for diagnosis, prognosis, or treatment decisions (8).

III. Results

A total of fifty cases of breast cancer were gathered, with a mean age of 48.52 years with a standard deviation of 11 years and a median of 50.5 year. The age range was between 30 to 72 years, with 28 cases (54%) being 50 years and older. The majority of the tumors, which accounted for 37 (76%), were grade II. In 31 (62%) of the cases, the estrogen and progesterone receptors were positive.

On the other hand, HER2/neu was overexpressed in 15 (36%). A high proliferation index (more than 14%) was reported in 5 (10% of the cases), while the proliferation index (Ki67) was not available for 32 (64%) of the cases.

According to the molecular subtypes, luminal A and luminal B accounted for 5 (14%), and 13 (22%) respectively while 10 (24%) luminal cases were unclassified. HER2-enriched cases constituted 15 (24%) of all cases. Triple negative cases were the least frequent with a rate of 7(16%). Detailed information on the patient and the tumor may be found in Table 1

Tumor-stroma ratio

An estimation of the tumor-stroma ratio was made via calculating the stromal compartment using CD10. As can be seen in Figure 1, 24 of the tumors had a high stroma content (48%), whereas 26 of the tumors had a low stroma content (52%).

TABLE 1: Patients and tumor characteristics.

Characteristics		Frequency	Percentage
Age	<50	22	46
	≥50	28	54
Grade	I	1	2
	II	37	76
	III	12	22
ER status	Negative	17	38
	Positive	33	62
PR status	Negative	18	38
	Positive	32	62
HER2/neu expression	Negative	35	64
	Overexpressed	15	30
Ki67	≤14	13	26
	>14	5	10
	Not available	32	64
Molecular classification	Luminal A	5	14
	Luminal B	13	22
	HER2 enriched	10	24
	Triple negative	7	16
	Luminal A or B	15	24

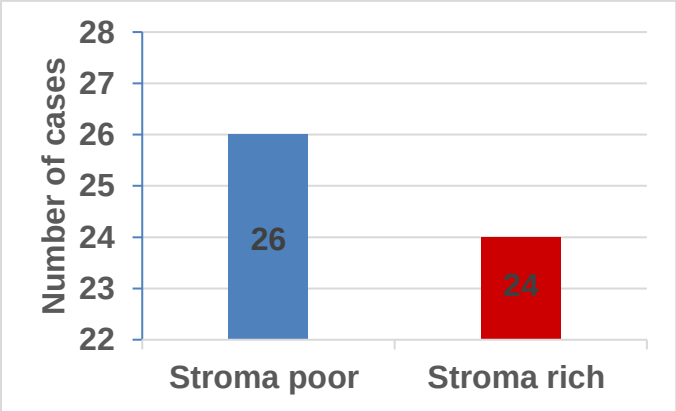

Figure 1: Tumor- stroma ratio in breast cancer.

Response to neoadjuvant therapy Complete response was observed in 31 (62%) of the cases. More than a quarter 13 (26%) had partial response and one case showed no response, as further illustrated in Figure 2.

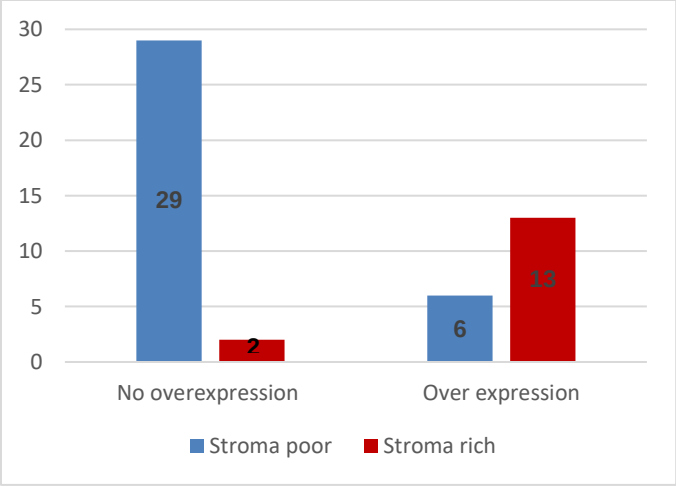

Figure 2: Response to neoadjuvant therapy.

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As Table 2 shows. out of stroma-rich tumors, 14 (61.5%) had partial pathological response compared to 4(8.3%) of stroma poor. Conversely, the majority of stroma-poor patients achieved complete pathological response 22 (91%) as compared to 9 (34.6%) of stroma-rich tumors, P<0.0001.

TABLE 2: The association between TSR and response to therapy

Response to NAT	Total	Tumor stroma ratio		P value
		Stroma poor No (%)	Stroma rich No (%)	
No response	1	0	1 (100)	<0.001
Partial	18	4 (8.3)	14 (61.5) *	
Complete	30	22 (91)	9 (34.6) *	

Association between tumor-stroma ratio and clinicopathological parameters and response to therapy Among patients younger than 50 years old, 14 (56.5%) had tumors that were poor in stroma, whereas 10 (43.4%) had tumors that were rich in stroma. Tumors of older women (≥50) were more frequently stroma-rich 14 (59.3%). According to Figure 3, the difference was not statistically significant.

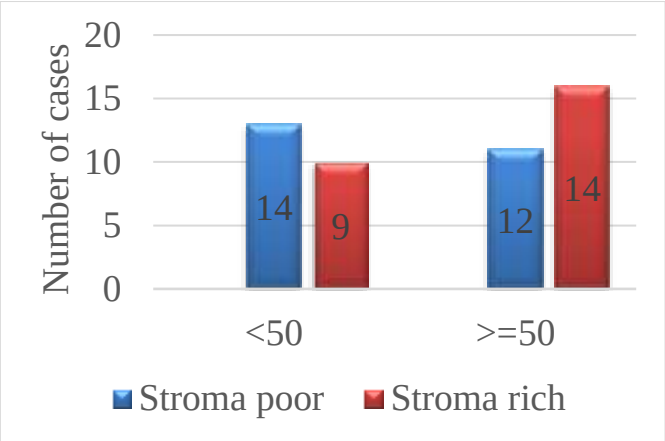

Figure 3: Association of patients age and tumor stroma ratio, P=0.395.

The association between response to therapy and tumor stroma ratio in each age group was compared in Table 3. Younger patients with stoma-rich tumors showed a significant association with partial response 6 (85.7%) compared to those with stroma poor who 12 (80%) of them experienced complete response, P=0.003.

Older patients had a similar pattern. The majority of patients with partial response 8 (90.9%) had stroma-rich tumors while more than two-thirds of those with complete response 10 (62.5%) had tumors poor in stroma.

TABLE 3: The association between patients age and response to neoadjuvant therapy with tumor-stroma ratio.

	Response to NAT	Total	Tumor stroma ratio		P value
			Stroma poor No (%)	Stroma rich No (%)	
<50	No response	1	0	1 (100)	0.003
	Partial	7	1 (14.3)	6 (85.7)*	
	Complete	14	12 (80)	2 (20)*	
≥50	Partial	11	3 (9.1)	8 (90.9)	0.008
	Complete	17	10 (62.5)	7 (37.5)	

Tumor grade: Out of the 11 grade III tumors, 9 (81.8%) were classified as stroma-rich, while 2 (18.2%) were classified as stroma poor. Out of the grade II tumors, 17 (44.7%) were characterized as rich stroma, whereas the remaining 21 (55.3%) had a poor stroma. There was a single grade I tumor which had a poor stromal content. Grade III tumors had a significantly higher rate of stroma-rich, Figure 4.

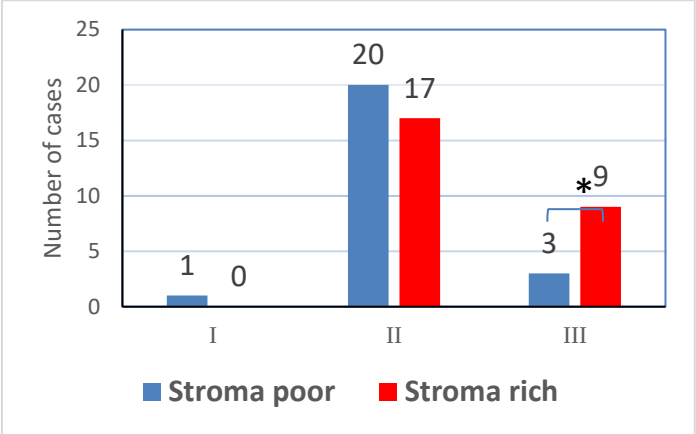

Figure 4: Association between tumor grade and tumor stroma ratio, *P=0.040.

The association between response to therapy and tumor stroma ratio in each tumor grade was compared in Table 4. The only GI patient who had stroma poor tumor achieved a complete pathological response. In grade II patients, tumors with stroma rich had a significantly lower rate of complete pathological response 8 (29.6%) compared to those with stroma poor 19 (70.4%). By contrast, stroma-rich tumors were more associated with partial response 9 (81.8%) compared to stroma-poor tumors 2 (18.2), P=0.005. Although all patients with stroma rich had partial responses 7 (100%) and 2 (66.7) in stroma poor achieved complete pathological response, the difference did not reach statistical significance.

TABLE 4: The association between tumor grade and response to neoadjuvant therapy with tumor-stroma ratio

	Response to NAT	Total	Tumor stroma ratio		P value
			Stroma poor No (%)	Stroma rich No (%)	
I	Partial	0	0	0	-
	Complete	1	1 (100)	0	
II	Partial	11	2 (18.2)	9 (81.8) *	0.005
	Complete	27	19 (70.4)	8 (29.6) *	
III	No response	1	0	1 (100)	0.109
	Partial	8	0	8 (100)	
	Complete	11	2 (66.7)	1 (33.3)	

Hormonal receptor status was significantly different in stroma-rich tumors. Approximately two-thirds of stroma-rich tumors 16 (61.5%) were ER and PR negative. By contrast, the majority of stroma-poor patients 21 (87.5%) were ER and PR positive, P < 0.001. Figure 5 and Table 5.

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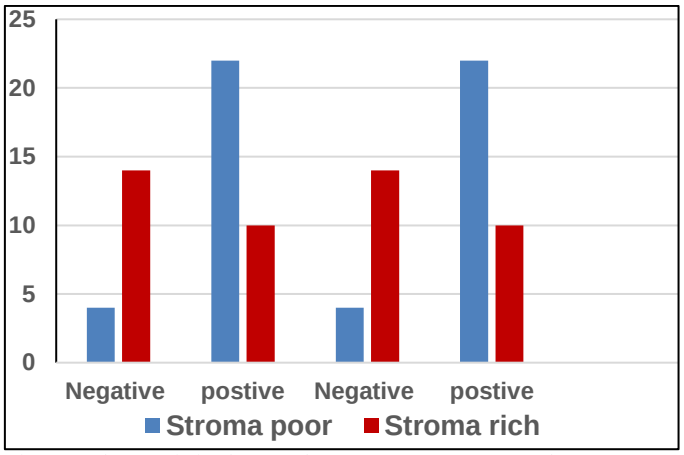

Figure 5: The association between hormone receptors status and tumor-stroma ratio, P<0.001.

TABLE 5: The association between hormone receptors status and tumor-stroma ratio.

Hormone status		Total	Tumor stroma ratio		P value
			Stroma poor No (%)	Stroma rich No (%)	
ER status	Negative	17	3 (12.5)	14 (61.5)	<0.001
	Positive	33	23 (87.5)	10 (38.5)	
PR status	Negative	18	4 (12.5)	14 (61.5)	<0.001
	Positive	32	22 (87.5)	10 (38.5)	

A significant association was also observed between HER2 neu expression and tumor-stroma ratio, Table 6 and Figure 6. Although stroma-rich tumors were equally distributed HER2 overexpression and HER2 negative; stroma poor tumors were significantly associated with HER2 negative expression 29 (79.2%), P=0.042.

TABLE 6: The association between HER2 neu expression and tumor-stroma ratio.

Characteristics		Total	Tumor stroma ratio		P value
			Stroma poor No (%)	Stroma rich No (%)	
HER2/neu expression	Negative	35	29 (79.2)	6 (50)	0.042*
	Overexpressed	15	2 20.8)	13 (50)	

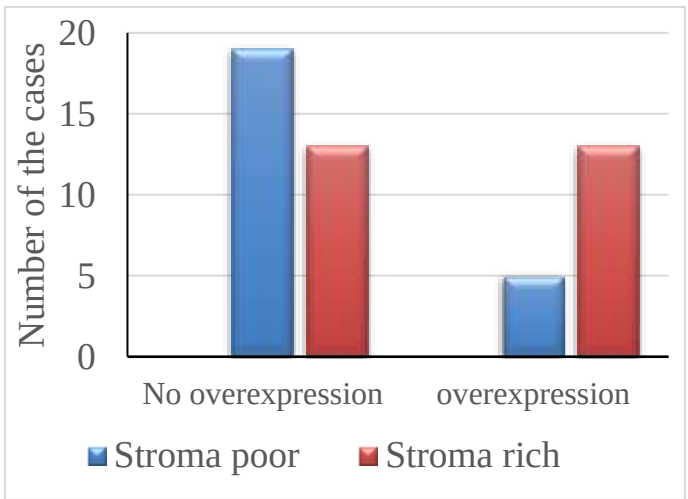

Figure 6: The association between HER2 neu expression and tumor-stroma ratio.

There was no significant difference in the proliferation index between stroma-rich and stroma-poor tumors, however, there were 32 tumors with unknown Ki67 expression more than half of them 18 (56.3%) were stroma-rich. Almost the same proportions of stroma rich 7 (26.9%) and stroma poor 6 (25%) showed low proliferation index. Although stroma-poor tumors seem to have a higher proliferation index of 4 (40%) vs 1(12.5%) the difference was not significant even after excluding cases with unknown Ki67 expression. Details are shown in Table 7 and Figure 7.

TABLE 7: The association between Ki67 proliferation index and tumor-stroma ratio

Characteristics		Total	Tumor stroma ratio		P value
			Stroma poor No (%)	Stroma rich No (%)	
Ki 67	≤14	13	6 (25)	7 (26.9)	0. 396
	>14	5	4 (16.7)	1 (3.8)	
	Unknown	32	13 (58.3)	19 (69.2)	

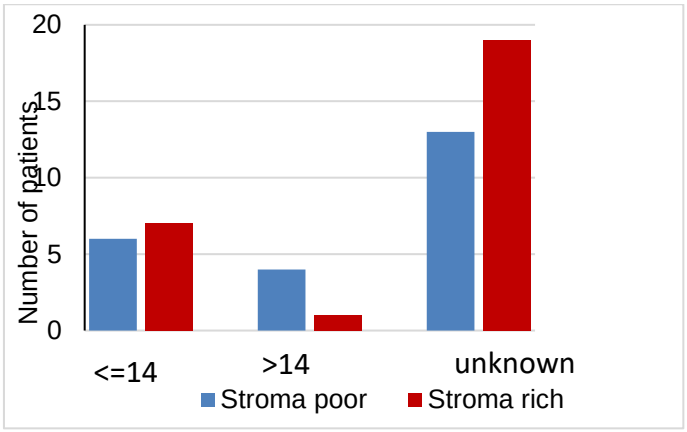

Figure 7: The association between Ki67 proliferation index and tumor-stroma ratio

A strong correlation was seen between both HER2-enriched tumors and luminal unclassified with stoma-rich tumors (P=0.008). Table 8 indicates that 10 out of 12 HER2 enriched tumors (83.3%) were stroma rich, whereas only 2 out of 12 luminal unclassified tumors (16.7%) were stroma rich, Figure 8.

TABLE 8: The association between molecular subtypes and tumor-stroma ratio

Molecular subtypes	Total	Tumor stroma ratio		P value
		Stroma poor No (%)	Stroma rich No (%)	
Luminal A	5	4(42.9)	1 (57.1)	0.008*
Luminal B	13	6 (63.6)	7 (36.4)	
Luminal (unknown A or B)	13	10 (83.3)	2 (16.7) *	
HER2/neu rich	10	2 (16.7)	8 (83.3) *	
Triple-negative	7	1 (25)	6 (75)	

The association between response to therapy and tumor stroma ratio in each molecular class was compared in Table 9, Figure 9. A significant correlation was observed between complete pathological response and patients with stroma-poor tumors in all luminal 18 (90%) and luminal unclassified 10

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(100%) with a P value of 0.007 and 0.015 respectively. In the triple-negative group, the single patient who did not show response to NAT, was stroma rich, while all patients with stroma poor achieved complete pathological response 2 (100%).

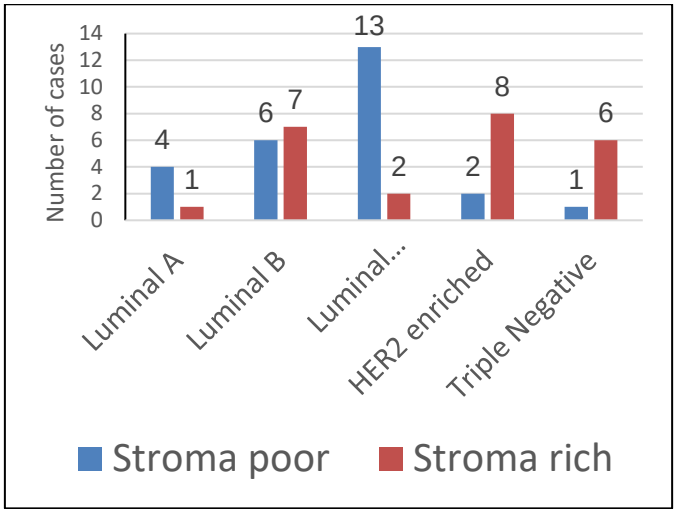


Figure 8: The association between molecular classification and tumor-stroma ratio, *P=0.008

TABLE 9: The association between molecular groups and response to neoadjuvant therapy with tumor-stroma ratio

Molecular groups	Response to NAT	Total	Tumor stroma ratio		P value
			Stroma poor No (%)	Stroma rich No (%)	
Luminal A	Partial	2	1 (33.3)	1 (75)	0.486
	Complete	3	3 (66.7)	0 (25)	
Luminal B	Partial	4	1 (14.3)	3 (25)	1.00
	Complete	9	5 (85.7)	4 (75)	
Luminal (unknown A or B)	Partial	3	2	1 (100)	0.015*
	Complete	12	11 (100)	1	
HER2/neu rich	Partial	5	0	5 (60)	0.455
	Complete	5	2 (100)	3 (40)	
Triple-negative	No response	1	0	1 (16.7)	0.214
	Partial	4	0	4 (66.7)	
	Complete	2	1 (100)	1 (16.7)	

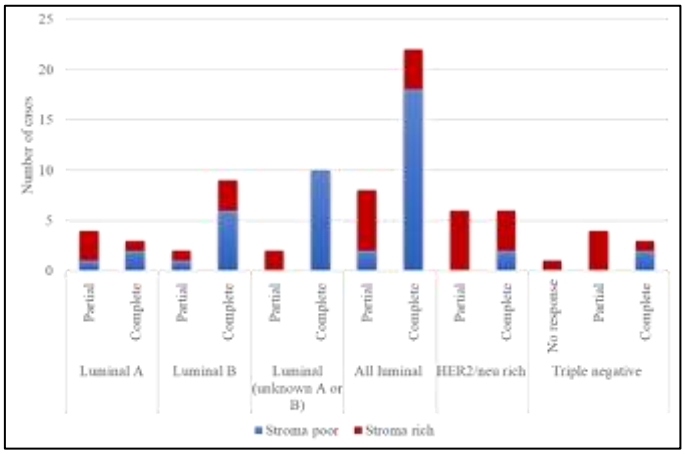


Figure 9: The association between molecular groups and response to neoadjuvant therapy with tumor-stroma ratio.

In HER2 enriched group, the complete pathological response was achieved in the tumors with stoma poor 2 (100%) whereas, 6 (60%) of those with stroma-rich tumors exhibited partial response, however, that was statically not significant.

Histological sections of rich and poor stromal tumors expressing CD 10 are shown below (Figures 10, 11,)

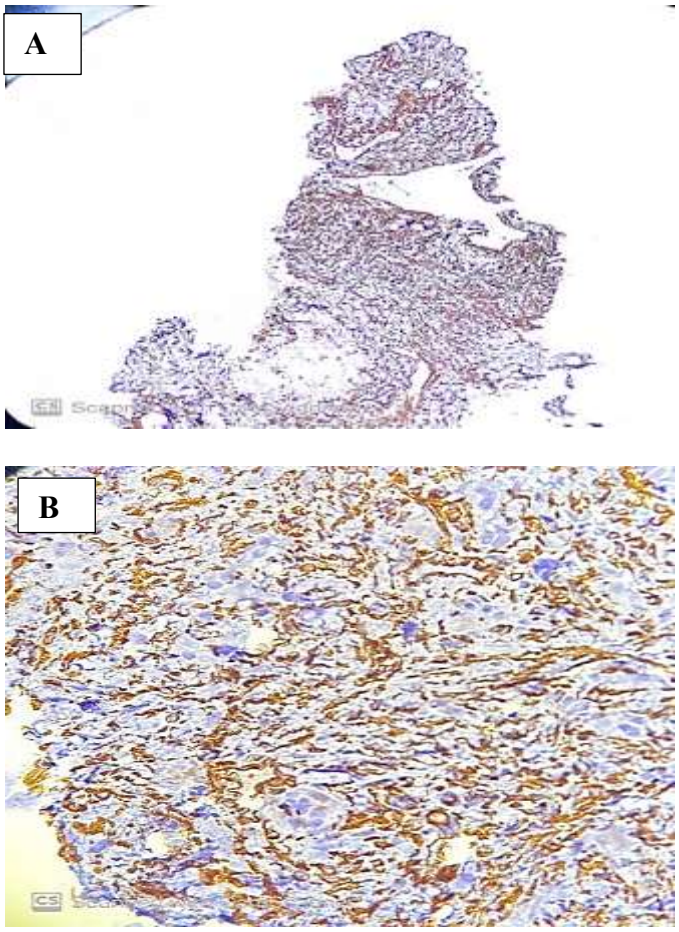
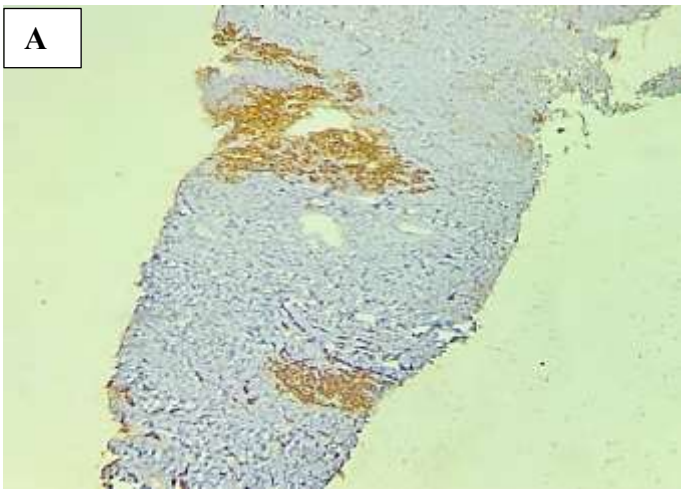


Figure 10: (A) Stroma rich 100x CD10, (B) Stroma rich 400x CD10



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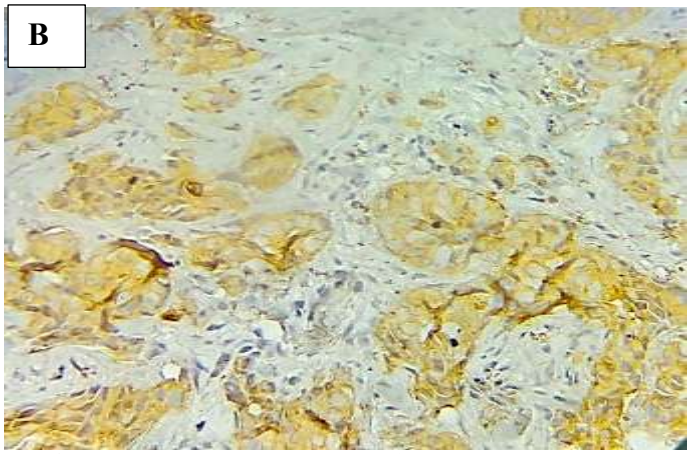

Figure 11: (A) Stroma poor 100x CD10, (B) Stroma poor 400x CD10

IV. Discussion

Breast cancer ranks fifth in female cancer-related fatalities worldwide and is the most prevalent form of cancer globally and nationally with growing incidence (9) (10). Breast tumor recurrence occurs in 30% of patients even after therapy, despite the consistent expanding of our understanding. Hence, it is believed that both the tumor cells and the stroma surrounding them have a role in the tumor's growth and treatment resistance (11). It has been acknowledged that the tumor stroma and microenvironment play a significant role in tumor progression (12). Nevertheless, clinical decision-making does not yet include tumor stroma markers. Tumor stromal ratio, a novel parameter that represents the composition of tumor-associated stroma, has been extensively documented as a valuable reservoir of prognostic data for a wide range of solid cancer subtypes (13). The biological function of TSR has been documented in breast cancer prognosis however data are inconsistent regarding the association with molecular subtypes (12, 14). In the current study, we examined the TSR in presurgical breast core biopsy specimens from women diagnosed with breast cancer. Additionally, we found a correlation between the TSR and molecular subtypes as well as the subsequent pathological response to neoadjuvant chemotherapy.

Patients and tumor features: The average age of breast cancer patients in the current study was 48.52±11 years with 46% of them being younger than 50 years. This is in agreement with previous Iraqi epidemiological studies. A large cross-sectional study involving 1093 from all over the country indicated that the median age was 46.4± 9.5 (15). Alwan et al (2010), in an earlier study, found that out of the 721 breast cancer patients studied, 580 of them, which accounts for 80.4%, were below the age of 60. The majority of patients (54.1%) were in the premenopausal age group, and 22.2% were less than 40 years old (16). A recent study conducted in Kurdistan included 429 patients with breast cancer has reported that the average age of 49.6 ± 11 years, 53.8% of women were of middle age or older (17). According to estimates from the World Health Organization, around 50% of malignancies in the Eastern Mediterranean region occur before the age of 55. Furthermore, as exposure to risk factors increases, the age-standardized incidence rates of all cancers in this area are projected to double (18). This depiction diverges from that which is presented in reports originating from developed and Western nations, which estimate the peak incidence rates to occur decades later (19).

The majority (76%) of patients with the current disease had grade II tumors and almost a quarter with high grade disease. A similar pattern has been illustrated by another local study (17), however, American cancer statistics in 2022 reported a higher prevalence of grade I and III compared to 21% and 29% respectively (20). Racial and environmental factors are established factors affecting tumor development and behavior (21).

The hormone receptor status along with Her2 and Ki67 categorized the tumors in our study as, luminal A (14%), Luminal B (22%), Her2 enriched (24%), and triple-negative (16%). However, in the current study, the molecular classification was constrained by the absence of Ki67 staining for (24%) luminal groups; thus, tumors within these groups were categorized as luminal unclassified when the proliferation index was available but attributed to the correct group otherwise. Studies that addressed the molecular classification of breast cancer in Iraqi patients are inconsistent, with the major variation observed in Luminal A and B distribution (22-24). For instance, the Luminal A group ranged between 29% (24), 45% (23), and 56% (22) while Luminal B ranged between 14% (23), 17% (22), and 53% (24). The variation was not limited to luminal subgroups, the overall luminal cases varied between these studies ranging 82%(24), 73%(24), and 59% (24). All luminal in our study were 60% which was within the range of what was previously reported. However, the rate of Her2 enriched cases was relatively higher compared to other local and international studies which ranged between 3% and 10.3% (20, 22-24).

Tumor stromal ratio: In the current research, more than half (52%) of the tumors were stroma-rich. Mallya et al. (2020) found in a cohort of 62 patients with a mean age of 48 (±11) years, that stroma-rich tumors constituted 45%/(25). A powered English study involving two retrospective cohorts and a total of 2412 breast cancers has found that out of 619 tumors in the first cohort, 415 (67%) were stroma rich as well as 1113 (61.5%) out of 1809 of the second cohort (26). By contrast, another large retrospective study conducted in the Netherlands involving 737 patients reported a lower rate of tumor rich (38.4%) (27). The median age of the patients in these two studies was 79 (26) and 53.6 (27) years respectively while the median age of patients in our study was 50.5 years. The discrepancy in the rate of stroma-rich tumors may in part be related to the variation in patients characteristics in each study particularly since there is compelling evidence that TSR has an association with age (26, 28). However, due to the relatively smaller sample size in the current study significant association with age was not observed.

We also observed that stroma-rich tumors were significantly associated with grade III tumors, hormone receptor-negative, and Her2 overexpression. This was in agreement with other studies. Stroma-rich association with higher tumor grades was reported by Karancsi et al. (2023) (28), and Elmhadi (2023)(29). In terms of tumor phenotype, data in the literature are conflicting. Meisel et al (2020) indicated, in agreement with

our findings, a significant association of stroma-rich tumor with low estrogen receptor and progesterone receptor expression, HER2 immunohistochemistry 3+ and also high Ki-67, high HER2/CEP17 ratio, and high HER2 copy number (30), in contrast, Roeke et al (2017) and one cohort in Vangangelt et al (2020) study did not show significant correlation with any of these predicting markers while the other cohort of Vangangelt et al (2020) showed a significant correlation of stroma rich with positive ER expression but not Her 2 (26). A significant correlation HR-positive breast cancer was also reported by Karancsi et al. (2023)(28). Whereas, Xu et al (2023) concluded that Stroma rich were significantly associated with Her2 over expressions, not hormone receptors (31)

A significant association with the surrogate molecular subtype was observed in the current study. Compared to stroma-poor, stroma-rich tumors were significantly lower in the Luminal group (unknown A or B) (83% vs 16.7%) and high in Her2 (16.7% vs 83.3%) enriched group. Additionally, 75% triple-negative tumors were stroma-rich. A good deal of studies failed to demonstrate a statistical association between TSR and molecular subtypes. This is expected when the study did not show a primary association between hormone receptors and Her2 expression (27, 32). Other studies find a significant association between TSR and molecular subtypes (28). Elmhadi et al. (2023) found that stroma-rich tumor was significantly associated with luminal B, however, the study included only ER+/HER2- operable breast cancer (29).

Tumor stroma ratio and response to neoadjuvant therapy: The present study has demonstrated a significant correlation between stroma-rich tumors and partial response to NAT, as well as stroma-poor and complete pathological response. The association between stroma-rich and partial pathological response was significant in older patients (P=0.008) and younger than 50 (P=0.003), grade II tumors (P=0.005), and luminal subtypes (P=0.007).

Similar findings have been reported by Mallya (2020) who observed only 3 (10%) of responders in the group of stroma-rich tumors while the majority 25 (90%) were nonresponses (25). TSR had a moderate negative correlation with residual cancer burden class, and it was deduced that high TSR (stroma poor) linked to minimal residual disease (25). Therapeutic drugs engage in cellular proliferation at an accelerated rate; therefore, as the percentage of cancer cells increases, so does the tumor's response to the drugs (33, 34). In a similar vein, Hagenaars et al. established a significant correlation between stroma-poor tumor status prior to neoadjuvant chemotherapy and a superior response in 375 HER2-negative patients. The significance of this relationship persisted in the ER negative subgroup (35)

V. Conclusions

1. Strom-rich tumor is an adverse prognostic factor associated with higher tumor grade, hormone receptor negative, and higher HER2 expression
2. Stroma-rich tumors are strongly associated with Her2-enriched molecular subtype while stroma-poor tumors are associated with Luminal subtypes.
3. Stroma-rich tumors were significantly associated with partial pathological response while the majority of patients with stroma-poor tumors achieved complete pathological response.
4. Significant correlations were observed between stroma-rich and partial pathological responses in patients who were younger than or older, had grade II tumors, and luminal subtypes.

References:

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-49.
2. Hagenaars SC, Vangangelt KMH, Van Pelt GW, Karancsi Z, Tollenaar R, Green AR, et al. Standardization of the tumor-stroma ratio scoring method for breast cancer research. Breast cancer research and treatment. 2022;193(3):545-53.
3. Smit MA, van Pelt GW, Terpstra V, Putter H, Tollenaar R, Mesker WE, et al. Tumour-stroma ratio outperforms tumour budding as biomarker in colon cancer: a cohort study. Int J Colorectal Dis. 2021;36(12):2729-37.
4. Wu J, Liang C, Chen M, Su W. Association between tumor-stroma ratio and prognosis in solid tumor patients: a systematic review and meta-analysis. Oncotarget. 2016;7(42):68954-65.
5. Hansen TF, Kjær-Frifeldt S, Lindebjerg J, Rafaelsen SR, Jensen LH, Jakobsen A, et al. Tumor–stroma ratio predicts recurrence in patients with colon cancer treated with neoadjuvant chemotherapy. Acta Oncologica. 2018;57(4):528-33.
6. West N, Dattani M, McShane P, Hutchins G, Grabsch J, Mueller W, et al. The proportion of tumour cells is an independent predictor for survival in colorectal cancer patients. British journal of cancer. 2010;102(10):1519-23.
7. Downey C, Simpkins S, White J, Holliday D, Jones J, Jordan L, et al. The prognostic significance of tumour–stroma ratio in oestrogen receptor-positive breast cancer. British journal of cancer. 2014;110(7):1744-7.
8. Iqbal BM, Buch A. Hormone receptor (ER, PR, HER2/neu) status and proliferation index marker (Ki-67) in breast cancers: Their onco-pathological correlation, shortcomings and future trends. Medical Journal of Dr DY Patil University. 2016;9(6):674-9.
9. Ministry of Health and Environment, Iraqi Cancer Board. Annual Report Baghdad; 2020.
10. Al-Hashimi MMY. Trends in breast cancer incidence in Iraq during the period 2000-2019. Asian Pacific journal of cancer prevention: APJCP. 2021;22(12):3889.
11. Öztürk Ç, Okcu O, Öztürk SD, Aşkan G, Şen B, Bedir R. A new practical method of estimating tumoral microenvironment parameters of possible prognostic significance in patients with invasive breast carcinoma: Combined microenvironment score. Ann Diagn Pathol. 2023;64:152128.
12. Insua-Rodríguez J, Oskarsson T. The extracellular matrix in breast cancer. Advanced drug delivery reviews. 2016;97:41-55.
13. Pyo JS, Kim NY, Min KW, Kang DW. Significance of Tumor-Stroma Ratio (TSR) in Predicting Outcomes of Malignant Tumors. Medicina (Kaunas). 2023;59(7).
14. Yan D, Ju X, Luo B, Guan F, He H, Yan H, et al. Tumour stroma ratio is a potential predictor for 5-year disease-free survival in breast cancer. BMC Cancer. 2022;22(1):1082.
15. Hashim HT, Ramadhan MA, Theban KM, Bchara J, El-Abed-El-Rassoul A, Shah J. Assessment of breast cancer risk among Iraqi women in 2019. BMC Women's Health. 2021;21(1):412.
16. Alwan NA. Breast cancer: demographic characteristics and clinico-pathological presentation of patients in Iraq. East Mediterr Health J. 2010;16(11):1159-64.
17. Abdulkareem AA, Ghalib HA, Rashaan MI. Factors causing delayed presentations of breast cancer among female patients in Sulaimani Governorate, Kurdistan region, Iraq. BMC Womens Health. 2023;23(1):612.
18. World Health O. Revised global burden of disease (GBD) 2002 estimates, 2005. Availa-ble from: http://www who int/healthinfo/global_burden_disease/en/index html[accessed on 2016 Dec 20]. 2009.

19. Freedman LS, Edwards BK, Ries LAG, Young JL. Cancer incidence in four member countries (Cyprus, Egypt, Israel, and Jordan) of the Middle East Cancer Consortium (MECC) compared with US SEER. Cancer incidence in four member countries (Cyprus, Egypt, Israel, and Jordan) of the Middle East Cancer Consortium (MECC) compared with US SEER. 2006.
20. Giaquinto AN, Sung H, Miller KD, Kramer JL, Newman LA, Minihan A, et al. Breast Cancer Statistics, 2022. CA: a cancer journal for clinicians. 2022;72(6):524-41.
21. Zavala VA, Bracci PM, Carethers JM, Carvajal-Carmona L, Coggins NB, Cruz-Correa MR, et al. Cancer health disparities in racial/ethnic minorities in the United States. Br J Cancer. 2021;124(2):315-32.
22. Al-Bedairy IH, AlFaisal AHM, Al-Gazali HR, Al H. Molecular Subtypes by Immunohistochemical for Iraqi Women with Breast Cancer. Iraqi journal of biotechnology. 2020;19(1).
23. Alwan NAS, Tawfeeq FN, Muallah FH. Breast cancer subtypes among Iraqi patients: identified by their Er, Pr and Her2 Status. Journal of the Faculty of Medicine Baghdad. 2017;59(4):303-7.
24. Al-Rawaq KJ, Al-Naqqash MA, Jassim MK. Molecular classification of Iraqi breast cancer patients and its correlation with patients' profile. Journal of the Faculty of Medicine Baghdad. 2016;58(3):197-201.
25. Mallya V, Singh V, Kaur N, Yadav P, Mandal S, Khurana N, et al. Does tumor stroma ratio of breast cancer trucut biopsy determine response to neoadjuvant therapy? Indian journal of pathology & microbiology. 2020;63(Supplement):S113-s6.
26. Vangangelt KMH, Kramer CJH, Bastiaannet E, Putter H, Cohen D, van Pelt GW, et al. The intra-tumoural stroma in patients with breast cancer increases with age. Breast cancer research and treatment. 2020;179(1):37-45.
27. Roeke T, Sobral-Leite M, Dekker TJA, Wesseling J, Smit VTHBM, Tollenaar RAEM, et al. The prognostic value of the tumour-stroma ratio in primary operable invasive cancer of the breast: a validation study. Breast cancer research and treatment. 2017;166(2):435-45.
28. Karancsi Z, Hagenaars SC, Németh K, Mesker WE, Tőkés AM, Kulka J. Tumour-stroma ratio (TSR) in breast cancer: comparison of scoring core biopsies versus resection specimens. Virchows Archiv : an international journal of pathology. 2023.
29. Elmhadi C, Allaoui M, Zerrik M, Oukabli M, Tanz R, Ichou M. Tumor-Stroma Ratio in ER+/HER2- Breast Cancer: Is it a Tool for Treatment Decision? Gulf J Oncolog. 2023;1(42):14-21.
30. Meisel JL, Zhao J, Suo A, Zhang C, Wei Z, Taylor C, et al. Clinicopathologic Factors Associated With Response to Neoadjuvant Anti-HER2-Directed Chemotherapy in HER2-Positive Breast Cancer. Clin Breast Cancer. 2020;20(1):19-24.
31. Xu Q, Chen YY, Luo YH, Zheng JS, Lin ZH, Xiong B, et al. Proposal of an automated tumor-stromal ratio assessment algorithm and a nomogram for prognosis in early-stage invasive breast cancer. Cancer medicine. 2023;12(1):131-45.
32. Öztürk Ç, Okcu O, Şen B, Bedir R. An easy and practical prognostic parameter: tumor-stroma ratio in Luminal, Her2, and triple-negative breast cancers. Rev Assoc Med Bras (1992). 2022;68(2):227-33.
33. Öhlund D, Elyada E, Tuveson D. Fibroblast heterogeneity in the cancer wound. Journal of Experimental Medicine. 2014;211(8):1503-23.
34. Wang M, Zhao J, Zhang L, Wei F, Lian Y, Wu Y, et al. Role of tumor microenvironment in tumorigenesis. Journal of Cancer. 2017;8(5):761.
35. Hagenaars SC, de Groot S, Cohen D, Dekker TJA, Charehbili A, Meershoek-Klein Kranenbarg E, et al. Tumor-stroma ratio is associated with Miller-Payne score and pathological response to neoadjuvant chemotherapy in HER2-negative early breast cancer. International journal of cancer. 2021;149(5):1181-8.