Original Article

Frequency and covariates of molecular subcategories of breast carcinoma - a referral tertiary care center study in Khyber Pakhtunkhwa, Pakistan

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ABSTRACT

Objective: To assess the frequency of different molecular subcategories of breast cancer and establish correlations with clinical and pathological features at a tertiary care center in Khyber Pakhtunkhwa, Pakistan.

Material and Methods: This cross-sectional study was conducted at CMH, Peshawar, Pakistan (a tertiary care center of Khyber Pakhtunkhwa, serving as a referral center for Bannu, Mardan, Nowshera, Risalpur, Landikotal, and Kohat city) from January 2021 to December 2022. Non-probability consecutive sampling technique was used to collect breast cancer samples i.e., biopsies, lumpectomies, and mastectomies of 161 cases. Immunohistochemistry was applied to all cases using polyclonal antibodies for ER, PR, HER2, and Ki-67 stains by DAKO envision method. All the cases were classified into four molecular subtypes of breast carcinoma (Luminal A, Luminal B, Her2 enriched, and triple-negative) according to the 2011 St Gallen consensus report.

Results: In this study, 161 patients were enrolled, with a mean age of 51.20±13.20 yrs (range: 22 to 75 yrs). The distribution of molecular subtypes revealed Luminal A as the most prevalent (29.9%), followed by Luminal B (26.7%), Her2 enriched (25.5%), and Triple negative (18.0%). Luminal A subtype predominantly affected individuals aged 31-50 yrs and 51-70 yrs, while Luminal B was more common in the 51-70 yr age group. Her2 enriched subtype was prevalent among the elderly, whereas the Triple-negative subtype impacted younger individuals. Invasive ductal carcinoma was notably the most frequent subtype among Luminal A and Luminal B cases.

Conclusion: Our study found that the Luminal A subtype occurred in 48 cases (29.9%), followed by Luminal B with 43 cases (26.7%). We identified a notable association between increasing age and breast cancer incidence in this study.

Keywords: Breast cancer, Histological characteristics, Molecular classification, Treatment strategies

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INTRODUCTION

Breast cancer is a significant global health concern, accounting for a substantial number of new cases and deaths each year. In 2020, breast cancer surpassed lung cancer as the most common cancer worldwide, with 2.3 million newly diagnosed cases. Among female cancers, breast cancer accounts for 24.5% of all cases, highlighting its substantial impact.

Asia bears a significant burden of breast cancer, with an age-standardized incidence rate of 44.95% in this region [1]. Breast cancer poses a multifaceted public health challenge in Asia, demanding concerted efforts and effective interventions. The region's expansive population, diverse cultures, and abundant resources present both prospects and complexities in tackling this disease.

Pakistan, in particular, faces a considerable challenge, with a relatively high age-standardized incidence rate (38.4 per 100,000 population) and prevalence rate (87.6 per 100,000 population) for breast cancer [2]. The incidence and prevalence of breast cancer

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in Pakistan are notably significant, with a growing population of women susceptible to the disease. However, barriers such as delayed diagnoses and limited healthcare accessibility contribute to elevated mortality rates. Mitigating these challenges necessitates a steadfast focus on early detection, heightened public awareness, improved healthcare provisions, and the development of tailored treatment approaches.

Understanding the molecular subtypes of breast cancer is essential for effective management and personalized treatment. These subtypes exhibit variations in behavior, clinical features, and response to therapy. However, the frequency and covariates of molecular subtypes may vary among populations and geographical regions, emphasizing the need for local studies to determine the prevalence and clinical characteristics of different subtypes [3].

In this study, we aim to identify the clinical and pathological features that are associated with different molecular subcategories of breast cancer and to determine the frequency of each subcategory from patients of a tertiary care center in Khyber Pakhtunkhwa (KPK), Pakistan. To the best of our knowledge, this is the only study conducted in this province of Pakistan with a greater sample size and includes study samples from six cities of KPK. This study's findings could contribute to a better understanding of the molecular epidemiology of breast cancer in the Pakistani population, and it could help tailor personalized treatment approaches that are specific to the molecular subtype. Moreover, it could provide useful insights for future studies and contribute to improving breast cancer management and outcomes in Pakistan.

MATERIAL AND METHODS

The Cross-sectional study was conducted from January 2021 to December 2022 at CMH, Peshawar, Pakistan (a tertiary care center of Khyber Pakhtunkhwa, serving as a referral center for Bannu, Mardan, Nowshera, Risalpur, Landikotal, and Kohat city) after taking ethical approval from Institutional Ethical Review Board (IERB). Sample size was calculated by using WHO sample size calculator by using the prevalence of female breast cancers (24.5%) [1], 95% confidence level and 5% margine of error. All excisional biopsies, lumpectomies, and mastectomies were included by using non probability consecutive sampling. Male patients, patients with incomplete medical records, and cases that resulted in Her2 2+ results were excluded from the study.

Data of patients including age, menopausal status, size of tumor, and laterality of breast involved was retrieved. Histological details including histological type, histological grade, presence of ductal carcinoma in situ/lobular carcinoma in situ including grade of in situ component, presence of lymph vascular invasion, and nodal metastasis were collected. For the specimens in which nodes were not submitted with the specimen, radiological reports were used to retrieve this information.

Immunohistochemistry was applied to all cases using polyclonal antibodies for ER, PR, HER2, and Ki-67 stains by DAKO envision method. The pressure cooker method was used for heat-induced epitope retrieval. Positive and negative controls were used for interpretation. ER and PR stains were interpreted according to the Allred scoring system (Figure-I, II). ER low was defined as a total score of 3-4 and ER high as a score of 5-8. The Her 2 staining was done according to the CAP protocol 2020 (Figure-III). Ki-67 was interpreted according to the joint guidelines of the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP). All the cases were classified into four molecular subtypes of breast carcinoma (Luminal A, Luminal B, Her2 enriched, and triple-negative) according to the 2011 St Gallen consensus report. The data was analyzed using the Statistical Package for the Social Sciences (SPSS) version 22. Frequencies and percentages were computed for qualitative variables, while means and standard deviations were calculated for quantitative variables. The association was evaluated through chi-square test, considering a p-value of less than or equal to 0.05 as significant.

RESULTS

A total of 161 patients were included in this study with mean age 51.20±13.20 years range from 22 to 75 years. Among the molecular subtypes, Luminal A was found to be the most common (29.9%), followed by Luminal B (26.7%), Her2 enriched (25.5%), and Triple negative (18.0%). For less than 30 years, the most common molecular subtype was Triple-negative breast cancer (57.9%), for 31 to 50 years Luminal A (35.4%), for 51 to 70 years Luminal B (35.2%) and for more than 70 years again Luminal A (50%) breast cancer. Most of the patients were in the age range of 51-70 years. A positive association was found between the increasing age of the patient and breast carcinoma, as p-value = 0.010. However, regarding the menopausal status and age of the patient, no significant association (p value > 0.05) between the molecular subtypes and these two parameters was found (Table-I). Most of the postmenopausal women had Luminal B breast cancer (32.2%), while premenopausal patients had Luminal A type cancer (32.4%). Concerning breast laterality, no significant differences were observed among the molecular subtypes (p value >0.05). The proportions of left breast tumors (90/161) were more than right breast tumors (71/161). Tumor size was categorized into three groups: <2 cm, >2 cm but ≤5 cm, and >5 cm. The majority of tumors (90/161) diagnosed had a size of >2 cm but ≤5 cm, (24/161) cases diagnosed, were having a size of <2 cm, and (47/161) had a size of more than 5 cm at the time of diagnosis.

When considering the molecular profiles, the Luminal A subtype was observed in 48 cases (29.9%), followed closely by Luminal B with 43 cases (26.7%), Her2 enriched with 41 cases (25.5%), and Triple negative with 29 cases (18.0%). Regarding the histological subtypes, the most common was invasive ductal carcinoma, accounting for 122 cases (75.8%). This was followed by invasive lobular carcinoma with 19 cases (11.8%) and mixed ductal and lobular carcinoma with 8 cases (5%). There were smaller proportions of cases represented by invasive cribriform carcinoma, metaplastic carcinoma, mucinous carcinoma, encapsulated papillary carcinoma, and tubular carcinoma. Among the cases of invasive ductal carcinoma, the most common molecular subtype was Luminal A (31.1%), followed by Luminal B (26.2%). Invasive lobular carcinoma cases predominantly belonged to the Luminal B subtype (42.1%). Among the cases of mixed ductal and lobular carcinoma, the Her2 enriched subtype was most frequent (37.5%), while the Luminal A subtype was observed in cases of invasive cribriform carcinoma, mucinous carcinoma, and tubular carcinoma. Metaplastic carcinoma exhibited a Triple negative molecular profile, whereas encapsulated papillary carcinoma cases showed both Her2 enriched and Triple negative profiles (Table-II).

The histological characteristics showed no significant correlation with various molecular subtypes (p>0.05). 91.9% of cases exhibited grade II tumors, followed by 8.1% of grade I tumors. Most of the Triple-negative tumors (16, 55.2%) were of grade III. Notably, 90 cases of Luminal A, Luminal B and Her2 enriched cases were classified as Grade II. Ductal carcinoma in situ (DCIS) was predominantly found in Her2 enriched (36.4%) and Triple negative cases (27.3%), while it was notably absent in most Luminal A (46.6%) and Luminal B cases (34.2%). The prevalent grade of DCIS among all molecular subtypes was low. In terms of lymph node metastasis, Luminal A cases exhibited lymph node involvement in 11 cases (14.9%), Luminal B in 25 cases (33.8%), Her2 enriched in 21 cases (28.4%), and Triple negative in 17 cases (23%). The lymphovascular invasion was present in 14.8% of Luminal A, 31.8% of Luminal B, 28.4% of Her2 enriched, and 25% of Triple-negative cases (Table-III).

Table-I: Correlation of clinicopathologic parameters of Luminal A, Luminal B, Her 2 enriched and Triple negative carcinoma (n=161)

Clinicopathological parameters	Luminal A	Luminal B	Her2 enriched	Triple-negative	Total	p-value
Age groups						
≤ 30 yrs	3 (15.8%)	2 (10.5%)	3 (15.8%)	11 (57.9%)	19	0.23
31-50 yrs	23 (35.4%)	14 (21.5%)	16 (24.6%)	12 (18.5%)	65	0.58
51-70 yrs	19 (26.8%)	25 (35.2%)	22 (31%)	5 (7%)	71	0.43
70 > yrs	3 (50%)	2 (33.3%)	0 (0.0%)	1 (16.7%)	6	0.29
Menopause						
Pre-menopause	24 (32.4%)	15 (20.3%)	19 (25.7%)	16 (21.6%)	74	0.56
Post- menopause	24 (27.6%)	28 (32.2%)	22 (25.3%)	13 (14.9%)	87	0.47
Breast laterality						
Left	23 (25.6%)	24(26.7%)	26 (28.9%)	17 (18.9%)	90	0.71
Right	25 (35.2%)	19(26.8%)	15 (21.1%)	12 (16.9%)	71	0.51
Tumor size						
<2 cm	13 (54.2%)	6(25%)	4 (16.7%)	1 (4.2%)	24	0.33
>2 cm but ≤ 5 cm	25 (27.8%)	28(31.1%)	20 (22.2%)	17 (18.9%)	90	0.61
> 5 cm	10 (21.3%)	9(19.1%)	17 (36.2%)	11 (23.4%)	47	0.74

Table II: Distribution of histological types of breast carcinoma among Luminal A, Luminal B, Her 2 enriched and Triple negative carcinoma (n=161).

Sr #	Histological type	Total	Luminal A	Luminal B	Her2 enriched	Triple-negative
1	Invasive ductal carcinoma of no special type	122	38(31.1%)	32(26.2%)	30 (24.6%)	22 (18.3%)
2	Invasive lobular carcinoma	19	4 (21.1%)	8 (42.1%)	5 (26.3%)	2 (10.5%)
3	Mixed ductal & lobular carcinoma	8	1 (12.5)	2 (25.0%)	3 (37.5)	2 (25.0%)
4	Invasive cribriform carcinoma	3	2 (66.6%)	0	1 (33.4%)	0
5	Metaplastic carcinoma	3	0	0	1 (33.4%)	2 (66.6%)
6	Mucinous carcinoma	3	2 (66.6%)	1 (33.4%)	0	0
7	Encapsulated papillary carcinoma	2	0	0	1 (50.0%)	1 (50.0%)
8	Tubular carcinoma	1	1 (100.0%)	0	0	0
	Total	**161**	**48 (29.8%)**	**43 (26.7%)**	**41 (25.5%)**	**29 (18.0%)**

Note. 161 cases divided into 4 groups across 8 histological types of breast carcinoma. Frequency (percentage)

Table-III: Correlation of histological features of Luminal A, Luminal B, Her2 enriched, and Triple negative carcinoma (n=161).

Histological features	Luminal A	Luminal B	Her2 enriched	Triple-negative	Total	p-value
Histological grade						
Grade I	36 (85.7%)	2 (4.8%)	4 (9.5%)	0	42	0.52
Grade II	12(13.3%)	35(38.9%)	30 (33.3%)	13 (14.4%)	90	
Grade III	0	6(20.7%)	7 (24.1%)	16 (55.2%)	29	
DCIS						
Present	14 (15.8%)	18 (20.5%)	32 (36.4%)	24 (27.3%)	88	0.43
Absent	34 (46.6%)	25 (34.2%)	9 (12.3%)	5 (6.8%)	73	
DCIS grade						
Not applicable	34 (46.6%)	25 (34.2%)	9 (12.3%)	5 (6.8%)	73	0.08
Low	12 (21.1%)	12 (21.1%)	23 (40.1%)	10 (17.5%)	57	
High	2 (6.5%)	6 (19.4%)	9 (29%)	14 (45.2%)	31	
LVI						
Present	13 (14.8%)	28 (31.8%)	25 (28.4%)	22 (25%)	88	0.47
Absent	35 (47.9%)	15 (20.5%)	16 (21.9%)	7 (9.6%)	73	
Lymph node metastases						
Absent	32 (46.4%)	14 (20.3%)	16 (23.2%)	7 (10.1%)	69	0.44
Present	11 (14.9%)	25 (33.8%)	21 (28.4%)	17 (23%)	74	
Unclear	5 (27.8%)	4 (22.2%)	4 (32.2%)	5 (27.8%)	18	
Total	**48**	**43**	**41**	**29**	**161**	**-**

Note: Chi-square run through significance test of Phi and Cramer V values. DCIS (Ductal carcinoma in situ), LVI (Lympho-vascular invasion).

Table-IV: Distribution of molecular subtypes of breast carcinoma by immunohistochemistry in local studies from different cities of Pakistan.

Author	Setting	Number of patients	Years	Luminal A	Luminal B	Her2 enriched	Triple-negative
Current study	Peshawar	161	Jan 2021-Dec 2022	48	43	41	29
Sharif N, *et al*.	Peshawar	60	2012-2013	20	11	14	14
AA Hashmi, *et al*.	Karachi	1951	2011-2016	37%	63%	---	---
Alam S, *et al*.	Lahore	110	Jul 2016-Jan 2017	41	69	---	---
Akbar A, *et al*.	Islamabad	50	Jan 2015-oct 2016	15	17	14	4
Khokhar S, *et al*.	Lahore	261	Oct 2013-Mar 2015	54	72	32	50
Akbar M, *et al*.	Abbottabad	60	Jan2010-Dec 2010	17	15	18	10
Hashmi A, *et al*.	Karachi	1104	Jan 2010-Dec 2012	45.8%	17.8%	17.8%	18.6%
Mushtaq M, *et al*.	Islamabad	278	2016	10%	51%	18%	20%
Gulzar R, *et al*.	Karachi	285	Dec 2012-Dec 2015	60	139	54	32
Henna N, *et al*.	Lahore	83	2019	20.5%	9.6%	15.7%	27.7%
Sikandar B, *et al*.	Karachi	1247	2008-2012	28%	20%	10%	36%
Tabassum S, *et al*.	Karachi	119	Jan 2013-Dec 2014	17	38	16	30

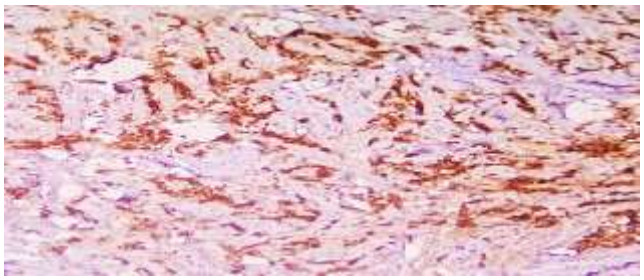

Figure-I: Immunostain for Estrogen receptor in Invasive Ductal Carcinoma (no special type), strong nuclear positivity, score 8/8

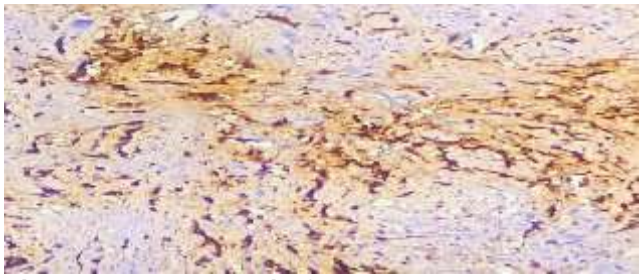

Figure-II: Immunostain for Progesterone receptor in Invasive Ductal Carcinoma (no special type), strong nuclear positivity, score 8/8

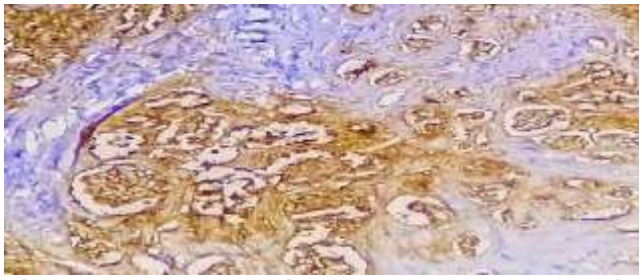

Figure-III: Immunostain for Her 2 receptors in Invasive ductal carcinoma (no special type), 3 + staining, strong, complete, membranous pattern.

DISCUSSION

Breast carcinoma is a heterogeneous disease with varying clinical and molecular characteristics. The identification and classification of molecular subtypes have revolutionized the field of breast cancer research and patient management. Additionally, histological features play a crucial role in understanding tumor behavior and guiding treatment decisions. In this study, we aimed to investigate the frequency of molecular subtypes in our population and the correlation between histological characteristics, molecular subtypes, and clinical parameters in breast carcinoma.

A total of 161 breast carcinoma cases were included in this study from CMH Peshawar Histopathology Laboratory. Our study showed that most of the cases of breast carcinoma were having an age range of 51-70 years with a mean age of 51.2 years ±13.2. Our findings are in accordance with several local and international studies [4-8]. However, they are in contrast to some recent local studies including a study by author Ullah Z, *et al* and Akbar F, *et al* [9,10].

Our study revealed that the Luminal A subtype of breast cancer was predominantly observed in the age group of 31 to 50 years (35.4%), with a secondary peak in the 50 to 70-

year age group (26.8%). These findings align with previous studies [11-13] conducted in this field. Notably, our study demonstrated an equal distribution of Luminal A cancer cases between premenopausal and postmenopausal patients, which contrasts with the findings of Dokcu Ş. *et al*. [14], who reported a higher prevalence of Luminal cancers among postmenopausal women and non-Luminal cancers among premenopausal patients. Histologically, Invasive ductal carcinoma was the most frequent subtype observed among Luminal A cases (38/48), followed by Invasive lobular carcinoma (4/48). Luminal A cancers are known to be hormone-responsive, typically exhibiting low-grade features and favorable prognoses [11, 15]. Consistent with this, our data indicated a significant proportion of Luminal A cases with absent lymphovascular invasion (13/48) and lymph node metastasis (32/48).

Our study showed most cases with a higher histological grade in comparison to Luminal A cancers, particularly with a predominant occurrence of invasive ductal carcinoma of no special type (32/43). Compared to the Luminal A subtype, the Luminal B subtype exhibits an intermediate prognosis and a higher likelihood of locoregional recurrence [16,17].

Her2-enriched carcinoma is characterized by genetic amplification and elevated expression of the HER2 protein. In our study, this subtype is prevalent in the older age group (50 -70 years) and comprising of most tumors with sizes> 2cm and > 5 cm. This molecular subtype is characterized by higher histological grade, increased proliferative index, and a higher propensity for metastasis, leading to shorter disease-free survival and poorer prognosis [18]. However, HER2-positive tumors have shown favorable responses to targeted therapies such as Trastuzumab (a humanized monoclonal antibody) and Lapatinib (a molecular receptor tyrosine kinase inhibitor) that specifically inhibit HER2 activity [19, 20]. Most cases in our data were invasive ductal carcinoma of no special type (30/41), followed by invasive lobular carcinoma (5/41) and mixed ductal and lobular carcinoma (3/41). This finding contrasts with a study by SM Fragomeni, stating that HER2 overexpression is exclusive to invasive lobular carcinoma [21]. Our study showed most cases with intermediate grade, lymph node metastasis as well as lymphovascular invasion.

Our study showed triple negative cases to be prevalent in the age range of less than 30 years and between 30 to 50 years. This finding is in accordance with other studies [22,23], where triple-negative breast cancer is more prevalent in younger patients. Triple-negative breast tumors were found more in the left breast, with most cases having sizes more than 2 cm and less than 5 cm, followed by cases of tumors having sizes more than 5 cm, indicating the aggressive behavior of this tumor. Indeed, triple-negative breast cancer is known for its invasive potential, poor prognosis, and relapsing potential [24]. In accordance with its ominous behavior, our findings showed most cases (22/29) having invasive ductal subtype with grade III. Ductal carcinoma in situ with high grade (24/29), lymphovascular invasion (22/29), and lymph node metastasis (17/29) were seen in most cases. Other histological subtypes having triple negative profile were invasive lobular, metaplastic carcinoma, and mixed ductal and lobular carcinoma. These findings are in agreement with other studies showing similar histological and pathological profiles for this molecular subtype [25, 26].

Microarray technology has helped classify these triple-negative tumors into basal-like subtype and breast-like subtype, through the interpretation of markers including CK5/6, CK14, CK17, and EGFR [27]. Triple-negative breast cancer poses a significant therapeutic challenge due to its highly invasive behavior and limited responsiveness to treatment, hence currently being under scrutiny of researchers to find alternate treatment modalities for this molecular subtype.

The most frequent molecular subtype in our study was Luminal A (48/161), followed by Luminal B (43/161) type cancer and Her2 enriched (41/161). Most studies in the Asian region have similar results with Luminal A type

cancer being the dominant subtype [11, 15, 28], however, few studies show Luminal B type cancer to have a higher prevalence than Luminal A [29, 30]. In comparative analysis with local studies conducted in Pakistan regarding molecular subtyping of beast carcinoma, two studies had Luminal A subtype predominance, one in Peshawar city and the other in Karachi (Table-IV). However, the majority of studies conducted in Pakistan show Luminal B subtype prevalence in various regions. A single study by Akbar M, *et al*. showed Her 2 enriched carcinoma majority, while studies by Sikandar B, *et al*. and Henna N, *et al*. showed Triple-negative breast cancer predominance in their study sample.

The presentation of 131/161 cases having sizes more than 2 cm and 119/161 cases with grade 2 and 3 cancers in our study sample enlightens the dire need for improvement in cancer diagnostics and breast cancer awareness in Pakistan. Pakistan has the highest incidence rate of breast cancer in Asia, affecting approximately one out of every nine women [31]. Between December 1995 and December 2009, breast cancer accounted for 45.9% of all diagnosed malignancies among adult women in Pakistan, with around 30% of cases being diagnosed at advanced stages (III or IV) [32]. Late diagnosis in Pakistan is primarily attributed to factors such as limited breast health awareness, personal modesty, and religious and cultural factors that contribute to the reluctance to seek medical attention from male doctors [33]. Addressing these challenges is crucial to improve early detection and treatment outcomes for breast cancer in Pakistan.

CONCLUSION

According to our study, the Luminal A subtype was observed in 48 cases (29.9%), followed by Luminal B with 43 cases (26.7%). A significant association between increasing age and breast cancer was found. Further investigations are warranted to explore the clinical implications and therapeutic considerations associated with specific subtypes of breast carcinoma.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

GRANT SUPPORT & FINANCIAL DISCLOSURE

Declared none

AUTHORS CONTRIBUTION

Hina Khan: Conceptualization, data curation, validation, Methodology, revisions
Abdul Qadir: Methodology, supervision
Sadia Khan: Data analysis, revisions
Shehla Akbar: Data interpretations, revisions

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