

HER2 Status in Breast Cancer in Relation to Age and Tumor Category: A Cross-Sectional Clinicopathological Study from Karbala, Iraq

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ABSTRACT

Background: Human epidermal growth factor receptor 2 (HER2) overexpression defines an aggressive, biologically distinct subset of breast carcinomas with critical therapeutic relevance. Epidemiological and pathological profiles from central Iraq, particularly Karbala Province, remain scarce. This study evaluates HER2 immunohistochemical (IHC) expression profiles across age cohorts and clinicopathological tumor categories in Iraqi breast cancer patients.

Materials and Methods: In this retrospective cross-sectional study, clinicopathological data from 99 consecutive women with histologically confirmed invasive breast carcinoma diagnosed at a tertiary diagnostic center in Karbala Province were evaluated. Patients were categorized into four age deciles (28–39, 40–49, 50–59, and 60–69 years). Tumor category was documented based on standardized diagnostic practice incorporating histological types (invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC), clinical stage/extent (locally advanced breast cancer (LABC), metastatic breast cancer (MBC), and receptor-defined molecular subtype (triple-negative breast cancer (TNBC)). HER2 expression was scored by IHC according to 2013 ASCO/CAP guidelines (0, 1+, 2+, 3+). Categorical distributions were analyzed using Pearson χ^2 and exact Monte Carlo tests. Multivariable logistic regression and continuous-age sensitivity analyses were conducted to identify independent predictors of HER2 3+ positivity.

Results: The median cohort age was 48 years, with the 40–49-year decile representing the largest patient stratum (33.3%, 33/99). Invasive ductal carcinoma was the predominant tumor category (56.6%, 56/99), followed by LABC (16.2%, 16/99), ILC (12.1%, 12/99), MBC (8.1%, 8/99), and TNBC (7.1%, 7/99). Overall, 47.5% (47/99) of tumors scored IHC 0 and 13.1% (13/99) scored IHC 1+ (total HER2-negative = 60.6%), while 13.1% (13/99) were equivocal (IHC 2+), and 26.3% (26/99) exhibited definitive HER2 3+ overexpression. Accounting for unresolved equivocal cases, potential cohort HER2 positivity ranges from 26.3% to 39.4%. HER2 IHC score demonstrated no significant association with patient age ($\chi^2 = 3.43$, $df = 9$, $p = 0.94$). In contrast, tumor category distribution varied significantly across age cohorts ($\chi^2 = 151.50$, $df = 12$, exact Monte Carlo $p < 0.00001$), reflecting earlier presentation for IDC and clustering of advanced/TNBC cases in older cohorts. In multivariable logistic regression, neither age group nor tumor category independently predicted HER2 3+ status (IDC adjusted OR = 1.67, 95% CI: 0.20–14.05, $p = 0.64$; age 40–49 adjusted OR = 0.90, 95% CI: 0.25–3.28, $p = 0.87$).

Conclusions: Over half of the cohort exhibited detectable HER2 expression, with a definitive IHC 3+ rate of 26.3% that aligns with regional Middle Eastern series and exceeds Western historical averages. The presence of 13.1% unresolved equivocal cases underscores the clinical imperative for establishing onsite reflex in-situ hybridization (ISH). Tumor category varied significantly across age groups, whereas HER2 expression was age-independent. Standardized synoptic reporting and multi-center molecular profiling are warranted.

Keywords: Breast Cancer; HER2 Neu; Immunohistochemistry; ASCO/CAP Guidelines; Karbala; Iraq; Molecular Oncology



INTRODUCTION:

Breast carcinoma remains the most frequently diagnosed malignancy and the leading cause of cancer-related mortality among women worldwide, accounting for approximately 2.3 million new diagnoses and over 660,000 deaths annually [1,2]. In response to this expanding global burden, the World Health Organization (WHO) Global Breast Cancer Initiative has prioritized early detection, rapid tissue diagnosis, and universal access to multimodal therapy to avert preventable global mortality [3]. In transitional healthcare environments and low-to-middle-income countries (LMICs), however, cancer control is heavily impacted by late clinical presentation, infrastructural gaps in pathology diagnostics, and restricted availability of personalized targeted therapeutics [4,5]. In Iraq, breast cancer constitutes approximately one-third of all female malignancies and continues on an upward trajectory [6,7].

Human epidermal growth factor receptor 2 (HER2/neu), encoded by the ERBB2 proto-oncogene localized on chromosome 17q12, plays a pivotal oncogenic role when amplified or overexpressed, promoting cell proliferation, angiogenesis, and metastatic dissemination [8]. Historically, HER2-overexpressing tumors comprised 15%–20% of invasive breast carcinomas in Western populations and portended a markedly aggressive clinical course [9,10]. The advent of humanized anti-HER2 monoclonal antibodies, led by trastuzumab and subsequently supplemented by pertuzumab, antibody-drug conjugates (e.g., trastuzumab emtansine [T-DM1] and trastuzumab deruxtecan [T-DXd]), and tyrosine kinase inhibitors, has fundamentally revolutionized the natural history of this disease [11–13]. Furthermore, contemporary therapeutic developments have established the clinical significance of the ‘HER2-low’ phenotype (IHC 1+ or IHC 2+ with non-amplified in-situ hybridization [ISH]), offering targeted therapeutic opportunities to a substantially broader patient population [13,15].

Accurate, standardized determination of HER2 status is paramount for clinical decision-making. The joint American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) clinical practice guidelines provide strict, validated criteria for immunohistochemical (IHC) scoring and algorithmic reflex in-situ hybridization (ISH/FISH) testing for equivocal (IHC 2+) cases [14–16]. Epidemiological series

from Arab nations, including Baghdad cohorts (Alwan et al., reporting 29.4% positivity) and Jordanian data (Saleh et al., reporting 23.8% positivity), consistently report higher rates of HER2 overexpression than those documented in North American and European registries, accompanied by a markedly younger median age at diagnosis [17–20].

Despite these known regional characteristics, comprehensive clinicopathological and molecular epidemiological data from Karbala Province—a major demographic and healthcare center in central Iraq—remain unexplored. This study was undertaken to evaluate HER2 IHC status across age deciles and clinicopathological tumor categories in 99 consecutive breast cancer patients from Karbala, to characterize the distribution of equivocal cases in the absence of onsite reflex ISH, and to benchmark these findings against regional and international standards.

MATERIALS AND METHODS

Study Design and Setting: This single-center retrospective cross-sectional investigation was conducted at a specialized clinicopathological oncology diagnostic center serving Karbala Province, Iraq. Karbala represents a prominent central Iraqi governorate with an estimated population exceeding 1.2 million and one of the country’s highest age-standardized breast cancer incidence rates (approximately 94.6 per 100,000 females) according to Iraqi National Cancer Registry reports [6,7]. The study protocol received formal institutional ethical approval from the Institutional Ethics Committee of the College of Medicine, University of Kerbala. Informed patient consent was waived by the institutional review board due to the fully anonymized, retrospective nature of archival record analysis.

Patient Cohort and Variable Definitions: Archival pathology records and formalin-fixed paraffin-embedded (FFPE) tumor tissue blocks from 99 consecutive female patients diagnosed with primary invasive breast carcinoma between 2022 and 2024 were reviewed. Inclusion criteria comprised adult females (≥ 18 years) with confirmed primary invasive carcinoma and evaluable tissue blocks for immunohistochemistry. Patients with recurrent disease, incomplete diagnostic documentation, or inadequate tissue cores were excluded. Patients were stratified into four 10-year age deciles (28–39, 40–49, 50–59, and 60–69 years) in alignment with previous Iraqi and Middle Eastern epidemiological cohorts [17,18]. To ensure absolute pathological precision, tumor categories

were systematically recorded from archival institutional records representing three clinicopathological dimensions: true histological diagnoses (invasive ductal carcinoma of no special type [IDC-NST] and invasive lobular carcinoma [ILC]), clinical stage/extent of disease (locally advanced breast cancer [LABC, Stage III] and metastatic breast cancer [MBC, Stage IV]), and receptor-defined molecular phenotype (triple-negative breast cancer [TNBC, estrogen receptor/progesterone receptor/HER2-negative]).

Immunohistochemical Assessment: Serial 4- μ m sections were cut from representative FFPE blocks, mounted on positively charged slides, deparaffinized in xylene, and rehydrated through graded ethanol series. Heat-induced epitope retrieval was performed in citrate buffer (pH 6.0) using an automated platform. HER2 protein expression was evaluated using a validated rabbit monoclonal anti-HER2/neu primary antibody in an automated immunostainer alongside batch-matched positive (known HER2 3+ breast carcinoma) and negative controls. Staining was evaluated by a board-certified anatomical pathologist blinded to clinical parameters. HER2 scoring strictly adhered to the validated 2013 ASCO/CAP guideline criteria [14]: IHC 0 (no staining or faint/incomplete membrane staining in $\leq 10\%$ of tumor cells; negative); IHC 1+ (faint/barely perceptible incomplete membrane staining in $>10\%$ of tumor cells; negative); IHC 2+ (weak-to-moderate complete circumferential membrane staining in $>10\%$ of tumor cells; equivocal, requiring reflex ISH); and IHC 3+ (intense, circumferential complete membrane staining in $>10\%$ of tumor cells; positive). Modern 2023 ASCO/CAP focused updates and HER2-low paradigms [13,15] are utilized strictly as contemporary clinical context in the Discussion and were not used for case classification.

Statistical Analysis: Categorical data are presented as absolute counts and percentages. Cross-tabulated associations between patient age cohorts, HER2 IHC expression tiers, and tumor categories were evaluated using Pearson's chi-square test (χ^2). For contingency tables where $>20\%$ of cells contained expected frequencies <5 (Table 2), exact p-values were computed using the Monte Carlo method (Fisher-Freeman-Halton formulation; 200,000 resamples). Multivariable logistic regression analysis was conducted using maximum likelihood estimation with definitive HER2 positivity (IHC 3+) as the binary dependent variable, adjusting for age groups (28–39 years as reference) and tumor category (IDC vs. others), reporting adjusted odds ratios

(aOR), 95% confidence intervals (CI), and two-sided p-values. Sensitivity analysis evaluated patient age as a continuous variable using univariate continuous logistic regression and Mann-Whitney U testing. Statistical calculations were executed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY) and the Python statsmodels library, with a two-tailed $p < 0.05$ defining statistical significance.

RESULTS

Demographic and Tumor Characteristics: The study cohort comprised 99 women with primary invasive breast cancer aged 28 to 69 years (mean age 48.6 ± 10.4 years). The age distribution was dominated by the 40–49-year cohort (33.3%, 33/99), followed by women aged 60–69 years (30.3%, 30/99), 50–59 years (19.2%, 19/99), and 28–39 years (17.2%, 17/99). In overall tumor categorization, invasive ductal carcinoma accounted for 56.6% of cases (56/99), followed by locally advanced breast cancer (16.2%, 16/99), invasive lobular carcinoma (12.1%, 12/99), metastatic breast cancer (8.1%, 8/99), and triple-negative breast cancer (7.1%, 7/99).

HER2 Expression Profiles by Age Group: Evaluation of HER2 immunostaining across the full cohort revealed that 47.5% of tumors (47/99) scored IHC 0 and 13.1% (13/99) scored IHC 1+, yielding an overall ASCO/CAP-defined HER2-negative rate of 60.6% (60/99). Equivocal staining (IHC 2+) was identified in 13.1% (13/99) of patients, while definitive HER2 overexpression (IHC 3+) was demonstrated in 26.3% (26/99). Over half of the cohort (52.5%, 52/99) exhibited detectable HER2 membrane immunoreactivity (IHC scores 1+, 2+, or 3+). Cross-tabulation of HER2 IHC tiers across age deciles (Table 1, Figure 1) demonstrated no statistically significant association between patient age and HER2 expression level (Pearson $\chi^2 = 3.43$, $df = 9$, $p = 0.94$). Definitive IHC 3+ cases were distributed across all age brackets, peaking in absolute frequency in the 40–49-year cohort (9/26, 34.6%).

Tumor Category Variation Across Age Groups: Cross-tabulation of tumor categories across age deciles (Table 2, Figure 2) revealed marked and statistically significant variations (Pearson $\chi^2 = 151.50$, $df = 12$, exact Monte Carlo $p < 0.00001$). IDC predominated entirely in patients aged <50 years (17/17 in 28–39 years; 33/33 in 40–49 years) and was diagnosed in 6 patients aged 50–59 years, but was absent as a standalone classification in the 60–69-year cohort. Invasive lobular carcinoma presented exclusively in the postmenopausal 50–59-year decile

Table 1. HER2 immunohistochemistry (IHC) score by age group among 99 Iraqi women with breast cancer.

HER2 IHC Score	28–39 y	40–49 y	50–59 y	60–69 y	Total (%)
0 (Negative)	8	16	11	12	47 (47.5%)
1+ (Negative)	2	4	2	5	13 (13.1%)
2+ (Equivocal)	2	4	1	6	13 (13.1%)
3+ (Positive)	5	9	5	7	26 (26.3%)
Total (%)	17 (17.2%)	33 (33.3%)	19 (19.2%)	30 (30.3%)	99 (100.0%)

Values are presented as counts (percentages). Pearson $\chi^2 = 3.43$, $df = 9$, $p = 0.94$; no statistically significant association was observed between age and HER2 expression.

IHC scores 0 and 1+ are classified as HER2-negative, 2+ as equivocal (requiring ISH), and 3+ as HER2-positive per ASCO/CAP 2013 guidelines.

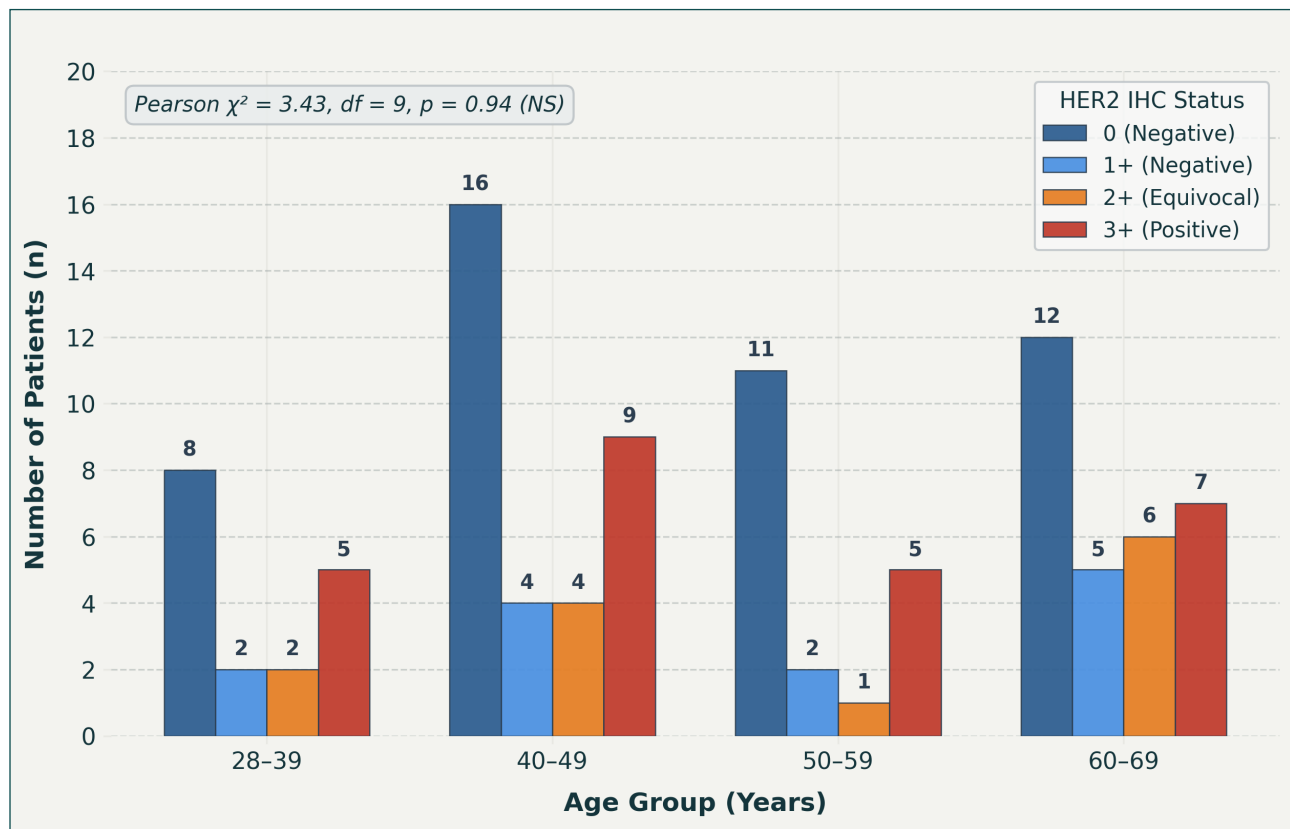


Figure 1: Distribution of HER2 immunohistochemistry (IHC) score (0, 1+, 2+, 3+) by age group among 99 Iraqi women with invasive breast cancer, Karbala, Iraq. Bars represent absolute patient counts across 10-year age deciles. No statistically significant association was observed between age and HER2 expression level (Pearson $\chi^2 = 3.43$, $df = 9$, $p = 0.94$).

Table 2. Distribution of tumor categories across age groups (N = 99).

Tumor Category	28–39 y	40–49 y	50–59 y	60–69 y	Total (%)
Invasive ductal carcinoma (IDC)	17	33	6	0	56 (56.6%)
Invasive lobular carcinoma (ILC)	0	0	12	0	12 (12.1%)
Locally advanced breast cancer (LABC)	0	0	1	15	16 (16.2%)
Metastatic breast cancer (MBC)	0	0	0	8	8 (8.1%)
Triple-negative breast cancer (TNBC)	0	0	0	7	7 (7.1%)
Total (%)	17 (17.2%)	33 (33.3%)	19 (19.2%)	30 (30.3%)	99 (100.0%)

Values are counts (percentages). Pearson $\chi^2 = 151.50$, $df = 12$, exact Monte Carlo $p < 0.00001$; distribution varied significantly by age. IDC/ILC denote histological type, LABC/MBC denote clinical stage/extent, and TNBC denotes receptor-defined molecular subtype.

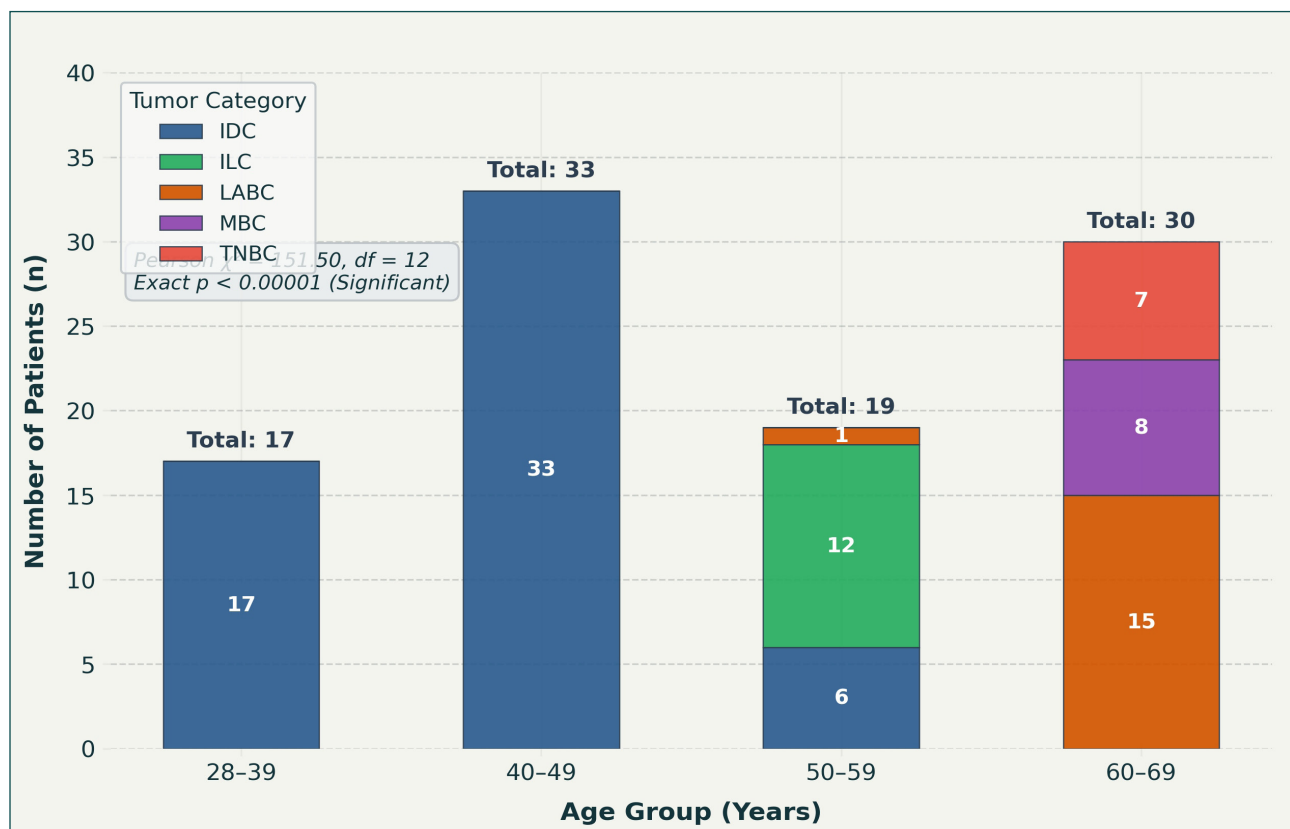


Figure 2: Distribution of breast cancer tumor categories by age group among 99 Iraqi women with invasive breast cancer, Karbala, Iraq. IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; LABC = locally advanced breast cancer; MBC = metastatic breast cancer; TNBC = triple-negative breast cancer. Tumor category distribution varied significantly across age cohorts (Pearson $\chi^2 = 151.50$, $df = 12$, exact Monte Carlo $p < 0.00001$).

(12/12, 100.0%). Locally advanced breast cancer was heavily concentrated in older patients (15/16 in 60–69 years; 1/16 in 50–59 years), as were metastatic breast cancer (8/8 in 60–69 years) and triple-negative breast cancer (7/7 in 60–69 years).

Multivariable Logistic Regression and Sensitivity Analysis: In multivariable logistic regression analysis modeling definitive HER2 3+ positivity (Table 3), neither age group nor tumor category exhibited a statistically significant independent predictive association. Compared to the referent 28–39-year age decile, the adjusted odds ratio (aOR) for the 40–49-year cohort was 0.90 (95% CI: 0.25–3.28, $p = 0.87$), for 50–59 years was 1.20 (95% CI: 0.16–8.80, $p = 0.86$), and for 60–69 years was 1.22 (95% CI: 0.10–15.13, $p = 0.88$). Invasive ductal carcinoma showed a non-significant trend toward higher HER2 3+ positivity compared to other categories (aOR = 1.67, 95% CI: 0.20–14.05, $p = 0.64$). Sensitivity analysis evaluating age as a continuous covariate similarly confirmed an absence of association (univariate continuous logistic regression OR = 1.01, 95% CI: 0.96–1.06, $p = 0.74$; Mann-Whitney U test $p = 0.82$).

DISCUSSION

This cross-sectional clinicopathological investigation provides the first systematic characterization of HER2 expression profiles in Karbala Province, Iraq. Three principal findings emerge from our analysis: (1) definitive HER2 3+ overexpression was identified in 26.3% (26/99) of patients, with an additional 13.1% (13/99) presenting with equivocal (IHC 2+) status, establishing that over half of the cohort (52.5%) possesses detectable HER2 immunoreactivity; (2) HER2 expression tiers exhibited no significant association with patient age cohorts ($\chi^2 = 3.43$, $p = 0.94$); and (3) clinicopathological tumor

category varied significantly across age cohorts (exact $p < 0.00001$), characterized by prominent early-stage ductal presentation in younger women and late-stage or triple-negative disease in older cohorts.

The definitive HER2 3+ rate of 26.3% observed in this Karbala cohort aligns closely with regional Middle Eastern reports while substantially exceeding the historical 15%–20% baseline described in Western cancer registries [9,10]. Specifically, our findings corroborate the landmark Baghdad series by Alwan et al. (29.4% HER2 positivity in 686 Iraqi patients) [17], large Saudi Arabian cohorts (28.0%–30.5%) [18], and Jordanian registry analyses by Saleh et al. (23.8%) [19]. Furthermore, if equivocal (IHC 2+) cases in our cohort are accounted for, the potential biological positivity rate spans 26.3% to 39.4%. Several intertwined biological and epidemiological factors may explain this elevated prevalence in Arab populations. First, distinct oncogenic drivers, including germline polymorphisms and somatic alterations in ERBB2 transcriptional modulators, may be enriched in Eastern Mediterranean populations [8,20]. Second, the younger median age at presentation observed across Arab cohorts (48.6 years in our series vs. >62 years in Western registries) coincides with reproductive determinants, such as early parity and high fertility, which have been linked to hormone-receptor-negative and HER2-driven tumorigenesis [18,21,22]. A vital diagnostic challenge highlighted by our study is the 13.1% (13/99) prevalence of equivocal (IHC 2+) cases. Under 2013 ASCO/CAP guidelines, all IHC 2+ cases mandate reflex in-situ hybridization (FISH/CISH) to determine ERBB2 gene amplification [14,16]. Due to severe logistical and financial constraints, onsite reflex ISH was unavailable at our center, and referral pathways to centralized facilities in Baghdad faced documented socio-economic barriers [5]. This diagnostic impasse

Table 3. Multivariable logistic regression analysis of factors associated with HER2 3+ positivity (N = 99).

Predictor Variable	Reference Group	Adjusted OR (95% CI)	p-value
Age 40–49 years	28–39 years	0.90 (0.25–3.28)	0.87
Age 50–59 years	28–39 years	1.20 (0.16–8.80)	0.86
Age 60–69 years	28–39 years	1.22 (0.10–15.13)	0.88
Invasive ductal carcinoma	Other categories	1.67 (0.20–14.05)	0.64

OR: Odds ratio; CI: Confidence interval. Model dependent variable: HER2 IHC 3+ status (n = 26).

Multivariable logistic regression model demonstrates no statistically independent predictors of HER2 3+ positivity ($p > 0.05$).

carries profound therapeutic consequences. Without reflex ISH, a substantial subset of women with truly amplified tumors may be denied life-saving trastuzumab-based regimens. Conversely, in the contemporary era shaped by the 2023 ASCO/CAP update and DESTINY-Breast04 clinical trial, non-amplified IHC 2+ tumors are categorized as 'HER2-low' and qualify for novel antibody-drug conjugates such as trastuzumab deruxtecan [13,15]. Thus, establishing accessible, state-funded reflex ISH testing infrastructure in central Iraq represents an urgent clinical priority.

Our evaluation of tumor categories demonstrated dramatic age-dependent clustering ($\chi^2 = 151.50$, exact $p < 0.00001$). We emphasize, however, that this statistical significance must be interpreted in light of the composite nature of this variable in routine Iraqi practice. In our center, invasive ductal carcinoma (56.6%) and invasive lobular carcinoma (12.1%) represent true WHO histological entities, whereas locally advanced (16.2%) and metastatic (8.1%) disease represent clinical stage/disease extent, and TNBC (7.1%) denotes a receptor-defined subtype. The exclusive manifestation of ILC in postmenopausal women (50–59 years) perfectly matches the established biological predilection of lobular histology [24,25]. The marked concentration of locally advanced, metastatic, and triple-negative cases in the 60–69-year age bracket reflects the pervasive reality of delayed clinical presentation, diagnostic fear, and lack of population-based mammographic screening among older Iraqi women [4-6].

In multivariable logistic regression modeling, neither age nor ductal histology emerged as independent predictors of HER2 3+ positivity. Although ductal carcinomas exhibited an adjusted OR of 1.67 (95% CI: 0.20–14.05, $p = 0.64$), the wide confidence intervals reflect the limited sample size ($N = 99$, 26 events), indicating that the lack of statistical significance represents constrained statistical power (risk of Type II error) rather than confirmed biological equivalence. These findings should be regarded as exploratory and hypothesis-generating.

STUDY LIMITATIONS

Several limitations must be acknowledged. First, the modest sample size ($N = 99$) from a single provincial center restricts the statistical power of multivariable subgroup analyses. Second, routine clinical records lacked standardized synoptic reporting for estrogen receptor (ER), progesterone receptor (PR), and Ki-67 proliferation index across all cases, precluding formal St.

Gallen surrogate intrinsic molecular subtyping (Luminal A, Luminal B, HER2-enriched, Basal-like) [31,32]. Third, the absence of onsite reflex FISH/ISH precluded final adjudication of the 13 equivocal (IHC 2+) cases. Fourth, composite clinicopathological classification in archival records combined histological diagnoses with clinical stage and molecular labels. Finally, the retrospective, cross-sectional design lacked longitudinal survival follow-up. Standardizing digital synoptic pathology reporting across Iraqi provinces will address these infrastructural limitations.

CONCLUSIONS

In this inaugural study from Karbala Province, Iraq, 52.5% of invasive breast carcinomas exhibited detectable HER2 protein expression, with a definitive IHC 3+ overexpression rate of 26.3% and an equivocal (IHC 2+) rate of 13.1%. HER2 IHC status was biologically independent of patient age, whereas clinicopathological tumor categories exhibited profound age-dependent variation characterized by late-stage presentation in older cohorts. These findings underscore the pressing clinical necessity for expanding reflex ISH diagnostic infrastructure and implementing organized screening and synoptic reporting across central Iraq.

DECLARATIONS

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Data Availability Statement: The de-identified dataset supporting the findings of this study is available from the corresponding author upon reasonable academic request.

References:

1. Sung H, Ferlay J, Siegel RL, 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):209-249. doi:10.3322/caac.21660
2. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2024;74(3):229-263. doi:10.3322/caac.21834
3. World Health Organization. Global Breast Cancer Initiative (GBCI). Geneva: WHO; 2021. Available at: <https://www.who.int/initiatives/global-breast-cancer-initiative>
4. Anderson BO, Cazap E, El Saghir NS, et al. Optimisation of breast cancer management in low-resource and middle-resource countries: executive summary of a Breast Health Global Initiative consensus, 2010. *Lancet Oncol.* 2011;12(4):387-398. doi:10.1016/S1470-2045(11)70031-5
5. Abood RA, Al-Jaf J, Al-Mousa A, et al. HealthCare Access Barrier (HCAB) framework for the barriers to cancer care in Iraq. *BMJ Oncol.* 2024;3(1):e000252. doi:10.1136/bmjonc-2023-000252
6. Al-Hashimi MMY. Trends in Breast Cancer Incidence in Iraq During the Period 2000-2019. *Asian Pac J Cancer Prev.* 2021;22(12):3889-3896. doi:10.31557/APJCP.2021.22.12.3889
7. Iraqi Cancer Registry. Annual Report. Baghdad: Iraqi Ministry of Health; 2024. Available at: <https://moh.gov.iq>
8. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science.* 1987;235(4785):177-182. doi:10.1126/science.3798106
9. Perou CM, Sorlie T, Eisen MB, et al. Molecular portraits of human breast tumours. *Nature.* 2000;406(6797):747-752. doi:10.1038/35021093
10. Howlader N, Altekruse SF, Li CI, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. *J Natl Cancer Inst.* 2014;106(5):dju055. doi:10.1093/jnci/dju055
11. World Health Organization. WHO Model List of Essential Medicines – 22nd List (2021). Geneva: WHO; 2021.
12. Hwang J, Shon HS, Lee KH. Barriers to the Use of Trastuzumab for HER2+ Breast Cancer and Biosimilar Replacement Strategies: A Narrative Review. *Pharmaceuticals (Basel).* 2014;7(9):943-958. doi:10.3390/ph7090943
13. Modi S, Jacot W, Yamashita T, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer (DESTINY-Breast04). *N Engl J Med.* 2022;387(1):9-20. doi:10.1056/NEJMoa2203690
14. Wolff AC, Hammond MEH, Hicks DG, et al. Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update. *J Clin Oncol.* 2013;31(31):3997-4013. doi:10.1200/JCO.2013.50.9984
15. Wolff AC, Somerfield MR, Dowsett M, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: ASCO/CAP Clinical Practice Guideline Focused Update. *J Clin Oncol.* 2023;41(28):3867-3872. doi:10.1200/JCO.22.02864
16. Wolff AC, Hammond MEH, Allison KH, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. *J Clin Oncol.* 2018;36(20):2105-2122. doi:10.1200/JCO.2018.77.8738
17. Alwan NAS, Tawfeeq FN, Muallah FH. Breast Cancer Subtypes among Iraqi Patients: Identified By Their ER, PR and HER2 Status. *J Fac Med Baghdad.* 2018;59(4):303-307. doi:10.32007/jfacmedbaghdad.v59i4.164

18. Alnegheimish NA, Alshatwi AA, Alhudairy SE, et al. Molecular subtypes of breast carcinoma in Saudi Arabia: A retrospective study. *Saudi Med J*. 2016;37(5):506-512. doi:10.15537/smj.2016.5.15000
19. Saleh BO, Al-Shammari F, Al-Juboori A, et al. Changing Trends in Estrogen Receptors/Progesterone Receptors/Human Epidermal Growth Factor Receptor 2 Prevalence Rates Among Jordanian Patients With Breast Cancer Over the Years. *JCO Glob Oncol*. 2022;8:e2100359. doi:10.1200/GO.21.00359
20. Chouchane L, Boussen H, Sastry KS. Breast cancer in Arab populations: molecular characteristics and disease management. *Lancet Oncol*. 2013;14(10):e417-e424. doi:10.1016/S1470-2045(13)70243-7
21. Besharat S, et al. Age at diagnosis of breast cancer in Iranian women: a systematic review and meta-analysis. *Iran J Public Health*. 2021;50(7):1305-1314.
22. Othman RT, et al. Clinicopathological profile of breast cancer in Iraqi Kurdistan. *Breast Dis*. 2015;35(4):217-222.
23. American Cancer Society. Breast Cancer Facts & Figures 2023-2024. Atlanta: American Cancer Society; 2023.
24. Li CI, Anderson BO, Daling JR, Moe RE. Trends in incidence rates of invasive lobular and ductal breast carcinoma. *JAMA*. 2003;289(11):1421-1424. doi:10.1001/jama.289.11.1421
25. Surveillance, Epidemiology, and End Results (SEER) Program. Cancer Stat Facts: Female Breast Cancer Subtypes. National Cancer Institute; 2024.
26. Dietze EC, Sistrunk C, Miranda-Carboni G, Seewaldt VL. Triple-negative breast cancer in African-American women: disparities versus biology. *Nat Rev Cancer*. 2015;15(4):248-254. doi:10.1038/nrc3896
27. Eniu A, Carlson RW, El Saghir NS. Guideline implementation for breast cancer in low- and middle-income countries. *J Glob Oncol*. 2016;2(1):1-14. doi:10.1200/JGO.2016.006213
28. Knaul FM, Atun R, Arreola-Ornelas H, et al. Access to Cancer Therapeutics in Low- and Middle-Income Countries. *Am Soc Clin Oncol Educ Book*. 2018;38:521-532. doi:10.1200/EDBK_155975
29. Dent R, Trudeau M, Pritchard KI, et al. Triple-negative breast cancer: clinical features and patterns of recurrence. *Clin Cancer Res*. 2007;13(15):4429-4434.
30. Al-Azri M, et al. Breast Cancer in the Arabian Gulf: clinical and pathological characteristics. *Gulf J Oncolog*. 2020;1(33):14-23.
31. Goldhirsch A, Winer EP, Coates AS, et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. *Ann Oncol*. 2013;24(9):2206-2223. doi:10.1093/annonc/mdt303
32. Cheang MCU, Chia SK, Voduc D, et al. Ki67 Index, HER2 Status, and Prognosis of Patients With Luminal B Breast Cancer. *J Natl Cancer Inst*. 2009;101(10):736-750. doi:10.1093/jnci/djp082