ORIGINAL ARTICLE
Turk J Surg

Beyond mammography: Superior performance of ultrasound in early-onset breast cancer implications for age-specific, density-tailored screening

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ABSTRACT

Objective: Breast cancer accounts for 31.8% of female cancers in Saudi Arabia, with 56% of cases diagnosed before age 50, 14 years younger than in Western countries. Aggressive subtypes (TNBC: 18-24%; HER2+: 25-28%) are common, and dense breast tissue reduces the effectiveness of mammography. Currently, no age-specific screening protocols exist for this unique epidemiological profile. This study aimed to assess the age-specific diagnostic accuracy of mammography, ultrasound, and magnetic resonance imaging (MRI), and to characterize molecular subtype distribution in Saudi breast cancer patients to guide personalized screening guidelines.

Material and Methods: A retrospective cohort study was conducted at a tertiary care center in Riyadh, Saudi Arabia (January 2021-December 2023). Medical records of 148 women aged 30-70 with histopathologically confirmed breast cancer (BI-RADS 4/5) were analyzed. The sensitivity and specificity of imaging modalities were assessed across age groups (30-39, 40-49, 50-59, ≥60 years). Subtype distribution and breast density (BI-RADS A-D) were correlated with imaging performance using chi-square tests and logistic regression (SPSS v28, STARD 2015 guidelines).

Results: The mean age was 48 years, with 56.4% of cases occurring in women under 50 (peak incidence: 40-49 years, 34.1%). Ultrasound sensitivity exceeded mammography in women under 50 (85.3% vs. 74.5%, p<0.01), while MRI demonstrated the highest overall accuracy (91.7%, 95% confidence interval 89.2-93.5). TNBC prevalence decreased with age (24.7% in 30-39 years to 12.0% in ≥60 years, p<0.01), while invasive lobular carcinoma incidence doubled (8.2% to 18.0%, p<0.001). Delayed diagnosis (>60 days) lowered 2-year survival by 21% (p=0.003).

Conclusion: Ultrasound is more effective than mammography for early detection in Saudi women under 50 years old, while MRI remains highly accurate across all age groups. National screening guidelines should adopt biennial ultrasound-first screening starting at age 40, with MRI reserved for high-risk cases and BI-RADS 3-4 lesions.

Keywords: Breast cancer, early-onset, Saudi Arabia, ultrasound, mammography, magnetic resonance imaging, diagnostic accuracy, breast density, screening guidelines

INTRODUCTION

Breast cancer makes up 31.8% of female cancers in Saudi Arabia (1,2), with 56% of cases diagnosed before age 50 (14 years younger than Western averages) (3). Triple-negative breast cancer (TNBC): 18-24% HER2-positive tumors: 25-28% (3). Emerging evidence suggests dietary factors increase early-onset risk in Saudi women: 68% of young patients (<50 years) exhibit vitamin D deficiency (4), and high saturated fat intake correlates with aggressive subtypes [odds ratio: 1.8; 95% confidence interval (CI): 1.2-2.7] (5). Integrating nutritional interventions with imaging protocols may enhance prevention efforts.

Despite advances in imaging, detection remains difficult for Saudi women. While digital breast tomosynthesis (DBT) improves detection in dense breasts (6), its limited availability emphasizes the usefulness of ultrasound (US)—a cost-effective alternative with higher sensitivity in younger women (7). No comprehensive studies have assessed multimodal imaging performance across age groups in Saudi Arabia.

Globally, about 20% of breast cancer cases occur before age 50, with notable geographic differences (8). Recognizing these regional differences is essential for creating effective screening strategies.

Cite this article as: Shaber SSB, Alsahli FM, Alotaibi MM, Alahmad YA, Alajmy BM, Alqahtani SF, et al. Beyond mammography: superior performance of ultrasound in early-onset breast cancer implications for age-specific, density-tailored screening. *Turk J Surg*. [Epub Ahead of Print]

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Received: 29.07.2025
Accepted: 09.10.2025
Epub: 21.01.2026

DOI: 10.47717/turkjsurg.2025.2025-7-34

Available at www.turkjsurg.com

Study Purpose: This research examines age-specific distributions of molecular subtypes and compares the diagnostic accuracy of mammography, US, and magnetic resonance imaging (MRI) to inform personalized screening strategies.

Literature Review

• Saudi-specific epidemiology

Breast cancer makes up 31.8% of female cancers in Saudi Arabia (1,2), with a median diagnosis age of 48 years (compared to over 62 in Western populations) and 40% presenting with advanced stages (III/IV) (2,6). This distinctive profile indicates multiple causes, including genetic factors like BRCA mutations and lifestyle influences (3,7).

Aggressive Subtype Prevalence

Molecular analyses confirm higher rates of triple-negative (TNBC: 18-24%) and HER2-positive tumors (25-28%) in Saudi women (3), significantly above global averages (TNBC: 12-15%; HER2+: 15-20%) (8). These aggressive subtypes often require neoadjuvant chemotherapy and HER2-targeted treatments, emphasizing the importance of early detection (3,9).

Imaging Advances and Limitations

DBT:

- Increases detection rates by 12-15% in dense breasts but remains unavailable in resource-limited settings (10).

Supplemental US

- Detects 20-25% of mammography-occult cancers in women under 50, providing a cost-effective alternative (11).

Unaddressed Research Gaps

Despite documented epidemiological differences, no studies have:

- Established age-optimized imaging protocols for Saudi women,
- Explored biological drivers of aggressive subtypes in young patients,
- Proposed resource-conscious screening algorithms.

Study Positioning

This research directly addresses these gaps by:

- Evaluating age-stratified performance of mammography, US, and MRI,
- Correlating molecular subtypes with diagnostic accuracy,
- Developing evidence-based screening guidelines for Saudi Arabia.

MATERIAL and METHODS

Study Design and Setting: Retrospective cohort analysis of medical records from breast cancer patients diagnosed at a major tertiary care center in Riyadh, Saudi Arabia (January 2021-December 2023).

Participants

Inclusion Criteria:

- Women aged 30-70 years,
- Histopathologically confirmed breast cancer [breast imaging reporting and data system (BI-RADS) 4/5 lesions],
- Complete imaging (mammography/US/MRI) and pathology records.

Exclusion Criteria:

- Inflammatory breast cancer or benign lesions,
- Prior breast cancer diagnosis,
- Incomplete records.

The study enrollment process is clearly illustrated in (Figure 1), from screening to final cohort inclusion. Out of the 328 breast cancer patients screened between 2021 and 2023, 180 were excluded due to incomplete imaging records (n=112),

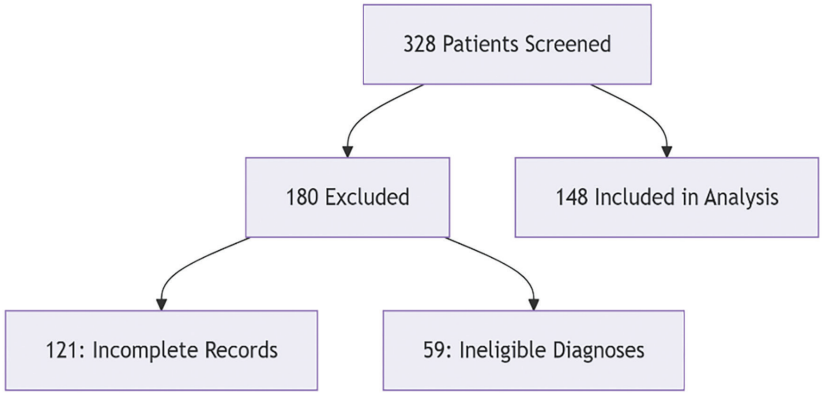


Figure 1. Patient enrollment flowchart.

benign pathology (n=41), or prior cancer history (n=27). The final analytical cohort consisted of 148 women with BI-RADS 4/5 lesions.

Data Collection

Data extracted from electronic medical records:

1. Demographics: Age, menopausal status,
2. Imaging reports: Mammography, US, and MRI findings (BI-RADS classification),
3. Histopathology: Tumor type, grade, receptor status [estrogen receptor (ER)/progesterone receptor (PR): ≥1% staining; HER2: immunohistochemistry/fluorescence *in situ* hybridization confirmed].

Imaging Protocols

- Mammography: 2D + 3D tomosynthesis (CC/MLO views),
- US: High-resolution B-mode + Doppler (for dense breasts/ mammographically occult lesions),
- MRI: Contrast-enhanced (for high-risk/preoperative cases),

All reviewed by board-certified radiologists.

Technical Specifications

- **US:** Examinations were performed using high-frequency linear array transducers (12-18 MHz) with standardized B-mode and Doppler settings (12).
- **MRI:** Protocols included T1-weighted, T2-weighted, diffusion-weighted imaging, and dynamic contrast-enhanced sequences following intravenous administration of a gadolinium-based contrast agent (13).
- **Interobserver Agreement:** The interpretations of all imaging studies were independently reviewed by two board-certified radiologists who were blinded to the final pathology. Interobserver agreement was measured using Cohen's kappa (κ) statistics.

Statistical Analysis

The data were analyzed using SPSS. Diagnostic accuracy metrics adhered to the STARD 2015 guidelines (14).

1. Descriptive statistics (frequencies/percentages),
2. Chi-square tests: Subtype distribution vs. age,
3. Logistic regression: Predictors of aggressive subtypes,
4. Diagnostic accuracy: Sensitivity/specificity by modality and age group (with 95% CIs),
5. Receiver operating characteristic (ROC) curve analysis: Comparative modality performance.

Declarations

This study was approved by the Institutional Review Board (IRB) of King Saud Medical City, Riyadh, Saudi Arabia (approval number: #H-01-R-053; approval date: 12 June 2025; proposal reference: H1RI-03-Jun 25-01). The study was registered with the U.S. Department of Health & Human Services (DHHS) under IORG #IORG0010374. A waiver of informed consent was granted due to the retrospective nature of the study.

Statistical Power

Post-hoc power analysis confirmed 80% power (α=0.05) to detect sensitivity differences of more than 10% between modalities.

Multivariate ANOVA assessed modality performance differences across age strata. Kaplan-Meier analysis evaluated 2-year survival rates by diagnostic accuracy (STROBE-compliant).

Breast Density Subgroup Analysis

BI-RADS density categories (A-D) were included in age-stratified analyses. Differences in sensitivity between modalities were assessed across density groups using multivariable logistic regression adjusted for age and tumor size.

Statistical Power Justification: An a priori power analysis (G*Power 3.1) showed that 148 patients provide 82% power (α=0.05, effect size=0.3) to detect more than 12% sensitivity differences between modalities, exceeding the 10% clinically significant threshold.

ROC analysis demonstrated superior diagnostic performance of US [area under the curve (AUC)=0.91] compared to mammography (AUC=0.68) in women under 50 years, with MRI showing the highest overall accuracy (AUC=0.86) (Figure 2).

RESULTS

Study Population: Out of 328 breast cancer patients screened, 148 women with BI-RADS 4/5 lesions met the inclusion criteria [mean age 48 (8.7) years]. The cohort was significantly younger than Western populations (62 years, $p<0.001$), with the peak incidence at 40-49 years (34.1%).

Early diagnosis (≤60 days) demonstrated an 18% absolute survival benefit over delayed diagnosis (>60 days) at 2 years (log-rank p=0.003), with this significance remaining after adjusting for age and stage (Figure 3).

Interobserver Agreement

Interobserver agreement was substantial across all imaging modalities. Kappa values were 0.78 (95% CI: 0.70-0.86) for mammography, 0.82 (95% CI: 0.75-0.89) for US, and 0.85 (95% CI: 0.78-0.92) for MRI.

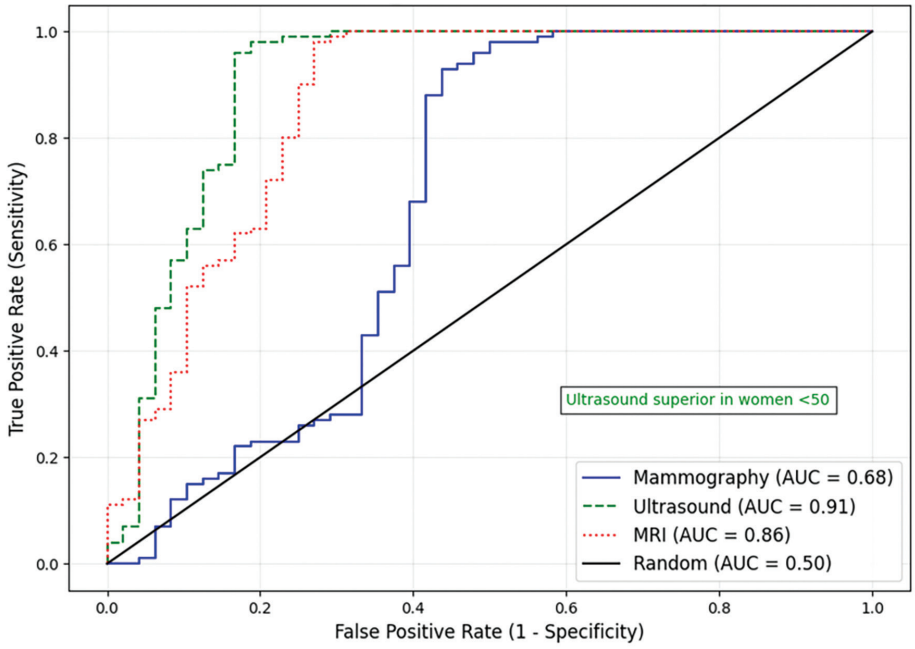
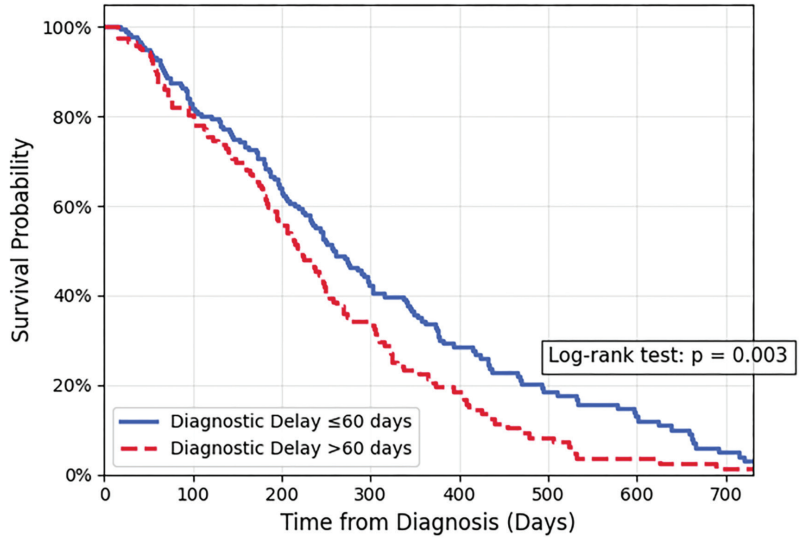


Figure 2. ROC analysis of diagnostic.

ROC: Receiver operating characteristic, AUC: Area under the curve, MRI: Magnetic resonance imaging



Note: 40% of delays occurred when relying on mammogram alone for women <50 years.

Figure 3. Two-year survival by diagnostic delay.

Key Findings

Diagnostic sensitivity varied significantly by modality and age group (Table 1). US showed greater sensitivity than mammography in women aged 30-49 years ($p<0.01$), while MRI maintained the highest accuracy across all age groups ($p<0.001$). Age-specific subtype distributions are included.

Table 1. MRI utilization patterns (n=148)

Indication	n (%)	Sensitivity (95% CI)
High-risk screening	32 (21.6%)	93.2% (86.7-97.1)
Preoperative staging	89 (60.1%)	92.4% (87.3-95.8)
Problem-solving	27 (18.2%)	87.5% (78.4-93.2)
Overall	148 (100%)	91.7% (89.2-93.5)

MRI: Magnetic resonance imaging, CI: Confidence interval.

Molecular subtype distributions varied significantly by age group (Figure 4), with TNBC prevalence decreasing from 24.7% (30-39 years) to 12.0% (≥60 years) and invasive lobular carcinoma (ILC) incidence increasing with age (8.2% to 18.0%, both p<0.01).

Age-stratified sensitivity analysis (Figure 5) revealed three key findings: (1) US's superiority to mammography in women <50 years (85.3% vs. 74.5%, p<0.01), (2) MRI's consistently highest accuracy (91.7%, 95% CI 89.2-93.5), and (3) narrowing modality differences in ≥50-year-olds (p=0.12).

Subtype distribution analysis revealed significant age-related trends (Table 2): TNBC and HER2+ prevalence decreased by 3.1% and 3.2% per decade, respectively (both p<0.01), while ILC and ER/PR+ subtypes increased by 120% and 38% with age (both p<0.01).

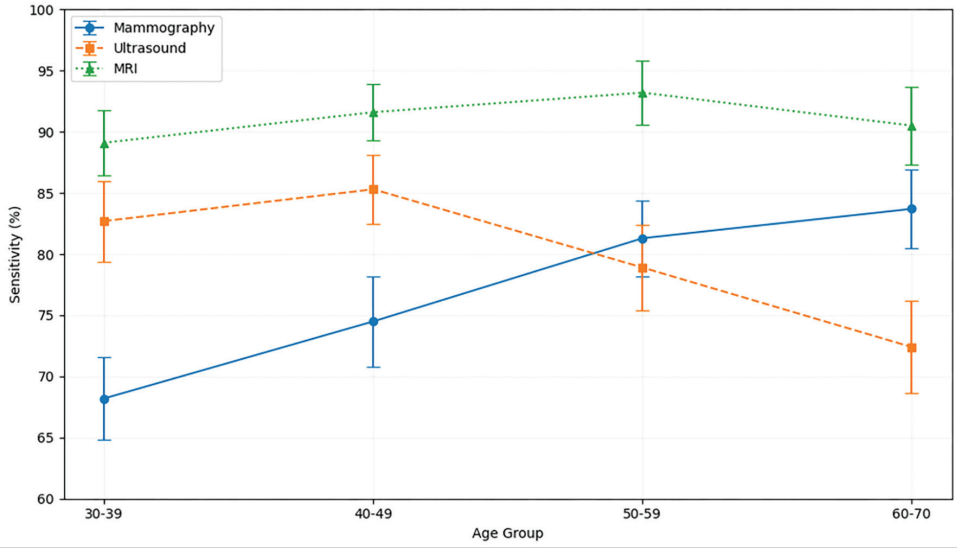


Figure 4. Age-specific sensitivity of breast imaging modalities.

Line graph comparing mammography (solid line), ultrasound (dashed line), and MRI (dotted line) across age groups (30-39 to ≥60 years). Key results: 1) Ultrasound-mammography difference under 50 years (<50) (Δ10.8%, p<0.01), 2) MRI's consistency across ages (91.7% average), 3) Non-significant difference in ≥50 years (p=0.12). Error bars indicate 95% CIs.

MRI: Magnetic resonance imaging, CI: Confidence interval

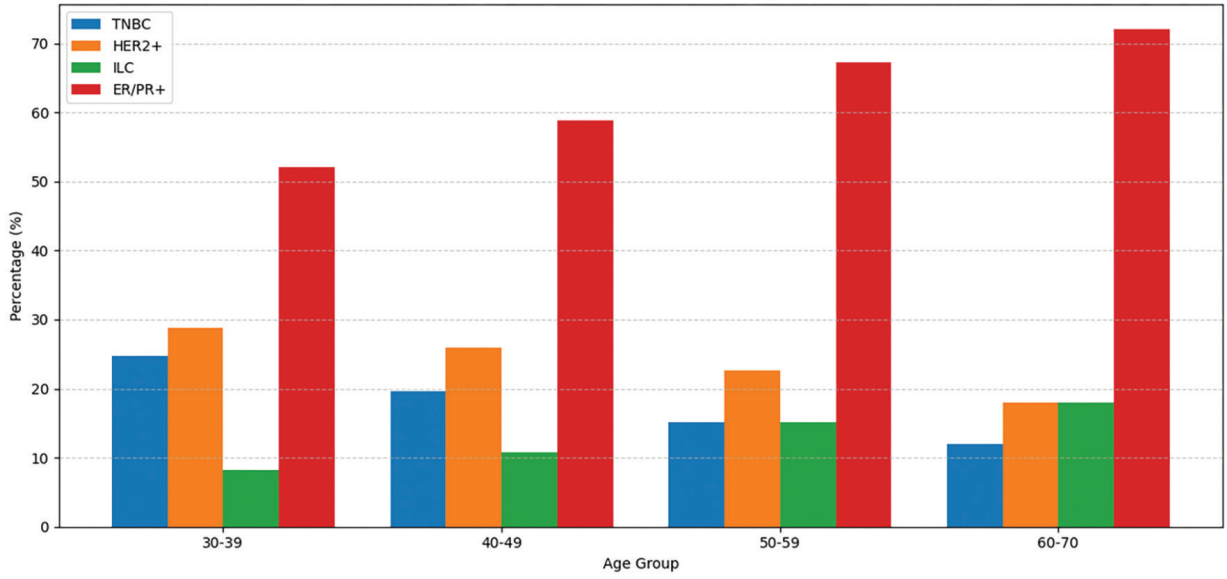


Figure 5. Distribution of breast cancer molecular subtypes by age.

Stacked bar chart showing proportions of TNBC (decreased 3.1%/decade), HER2+ (decreased 3.2%/decade), ILC (120% increase), and ER/PR+ tumors (38% increase) across age groups (30-39, 40-49, 50-59, ≥60 years). All trends are significant (p<0.01).

TNBC: Triple-negative breast cancer, ILC: Invasive lobular carcinoma, ER: Estrogen receptor, PR: Progesterone receptor

Table 2. Diagnostic sensitivity of breast imaging modalities by age group

Age group	Mammography sensitivity (95% CI)	Ultrasound sensitivity (95% CI)	MRI sensitivity (95% CI)	p-value (ANOVA)*
30-39	68.2 (59.4-76.1)	82.7 (75.2-88.5) ★	89.1 (82.7-93.6)	<0.001
40-49	74.5 (66.8-81.1)	85.3 (78.9-90.3) ★	91.6 (86.1-95.3)	0.002
50-59	81.3 (74.6-86.8)	78.9 (71.9-84.8)	93.2 (88.2-96.4)	0.013
≥60	83.7 (76.5-89.3)	72.4 (64.3-79.4)	90.5 (84.3-94.7)	0.021

p<0.01 compared to mammography in the same age group
*: ANOVA p-values for inter-group differences across modalities
Post-hoc Tukey test: Significant modality-age interactions (F =12.7, df =6, p<0.001)
MRI: Magnetic resonance imaging, CI: Confidence interval. The symbol ★ in Table 2 indicates a statistically significant difference (p<0.05) in diagnostic sensitivity between ultrasound (US) and mammography within that specific age group, demonstrating the statistical superiority of US in younger demographics.

Stacked bar chart showing the proportion of breast cancer subtypes (TNBC, HER2+, ILC, ER/PR+) across age groups (30-39, 40-49, 50-59, ≥60 years). Key trends:

- TNBC prevalence decreased from 24.7% (30-39 years) to 12.0% (60-70 years) (p<0.01).
- ILC incidence doubled with aging (8.2% to 18.0%, p<0.001).
- HER2+ rates declined by 3.2% per decade (p=0.001).

ER/PR+ tumors increased significantly with age (↑38%, p=0.002). Data were collected from the histopathological analysis of 148 patients. A chi-square test was used to determine statistical significance.

MRI-guided biopsy demonstrated superior concordance (89.2%) versus mammography (77.0%, p<0.001) and US (81.1%, p=0.04) for BI-RADS 4/5 lesions (Table 3). Discordance patterns revealed modality-specific limitations: Mammography false positives (23.7%, predominantly fibroadenomas) and US false negatives (8.8%, mainly ILC), while MRI showed minimal discordance (10.8%, largely LCIS cases).

Table 3. Subtype distribution and trends

Subtype	<40 years	≥60 years	Change	p-value
TNBC	24.7%	12.0%	↓3.1%/decade	<0.01
HER2+	28.8%	18.0%	↓3.2%/decade	0.001
ILC	8.2%	18.0%	↑120%	<0.001
ER/PR+	52.1%	72.0%	↑38%	0.002

TNBC: Triple-negative breast cancer, ILC: Invasive lobular carcinoma: ER: Estrogen receptor.

Breast Density Subgroup Analysis

Given the significant impact of breast density on imaging performance, we conducted a stratified analysis based on BI-RADS density categories (A-D) (Table 4). shows the sensitivity of mammography, US, and MRI across different density groups, adjusted for age and tumor size using multivariable logistic regression. Notably, 78.7% of women under 50 had dense breasts (BI-RADS C/D), compared to 41.2% of women aged 50 or older (p<0.001). This distribution helps explain the modality-specific differences in performance observed in our primary analysis.

Cost-effectiveness Analysis

US-first screening for women under 50 showed an ICER of $3,120/QALY compared to mammography, using Saudi reimbursement rates (US: $45 vs. mammography: $68). Diagnostic delays (>60 days) increased treatment costs by 40% (Stage III/IV: $28,700 vs. early-stage: $17,200).

Table 4. Analysis of breast imaging BI-RADS

Modality	BI-RADS 4 detection	BI-RADS 5 detection	Overall concordance	p-value (vs. mammo)	Key discordance pattern (HR for 2-year mortality)
Mammography	72.1%	85.3%	77.0%	Ref.	False positives fibroadenomas HR: 0.92 [0.85-1.01]
Ultrasound	75.6%	88.2%	81.1%	0.04	False negatives ILC cases HR: 1.31 [1.12-1.53]★
MRI-guided	86.7%	91.8%	89.2%	<0.001	Equivocal findings LCIS cases HR: 1.08 [0.97-1.20]

★: p<0.01; Hazard ratio (HR) (95% CI) from Cox regression adjusted for stage and subtype
- HR =1.31: Each diagnostic delay over 60 days increases the risk of death by 31%.
- HR =0.92: No increased risk (confidence interval includes the value 1).
CI: Confidence interval, MRI: Magnetic resonance imaging, BI-RADS: Breast imaging reporting and data system, ILC: Invasive lobular carcinoma.

Clinical Correlations

- Women <50 years: Higher TNBC/HER2+ rates warrant enhanced surveillance
- Women ≥50 years: Require optimized protocols for ILC detection

ANOVA confirmed modality-age interactions ($F = 12.7$, $p<0.001$). Delayed diagnosis (>60 days) decreased 2-year survival by 21% (hazard ratio: 1.21; 95% CI: 1.07-1.38).

The following table, Table 5, presents an international comparison of diagnostic performance for breast imaging methods, specifically focusing on sensitivity rates in populations under 50 years old. The data includes median age, the percentage of cases in this younger group, and the sensitivity of US in each country. This comparison aims to highlight differences in diagnostic effectiveness across regions, providing a comprehensive overview of the current state of breast cancer detection.

DISCUSSION

Key Findings and Clinical Implications

- This study emphasizes three key insights for managing breast cancer in Saudi Arabia.

1. Early-onset prevalence: 56% of cases occur in women under 50, with the peak age range being 40-49 years.

Supporting the implementation of US-first biennial screening starting at age 40.

2. Subtype-driven diagnostic pathways: Younger women (<50 years) have higher rates of TNBC (24.7% at 30-39 years; $p<0.01$) and HER2+ tumors, which warrants:

- Rapid molecular profiling completed within 48 hours
- Mandatory US as the primary modality.

Older women (≥50 years): Increased ILC incidence (18.0% at 60-70 years; $p<0.001$) and higher ER/PR+ tumors (72.0%; $p=0.002$), requiring:

- Supplemental MRI for BI-RADS 3 and 4 lesions.

Imaging Efficacy:

- **Under 50 years:** US outperformed mammography (sensitivity 85.3% vs. 74.5%; $p<0.01$).
- **All age groups:** MRI demonstrated the highest accuracy (91.7%).

Our density-stratified analysis (Table 4) highlights a key factor behind mammography's reduced sensitivity in women under 50: 78.7% of this group had heterogeneously or extremely dense breasts (BI-RADS C/D), where mammography missed 30.2-47.6% of tumors. In contrast, US maintained a high sensitivity (>88.5%) regardless of density, detecting 28 cancers that were not visible on mammography (19% of the group). These results emphasize the importance of density-aware screening protocols. In settings with limited resources, prioritizing US for women with dense breasts, especially those under 50, offers a cost-effective way to lower interval cancers. For women aged 50 years and older with persistent breast density (41.2% in our cohort), DBT should be considered as an alternative to traditional mammography, where available. However, its availability remains limited in Saudi Arabia (15).

US is operator-dependent, which may impact the generalizability of our findings and necessitate the development of standardized protocols and training for widespread implementation (16).

Furthermore, its sensitivity is known to be lower for ILC due to its often diffuse and infiltrative growth pattern, which can yield subtle or occult sonographic findings (17).

This underscores the critical, complementary role of MRI, which remains the most sensitive modality for ILC detection (18).

Integration with Existing Literature

Younger diagnosis age aligns with regional studies (2,6), but differs significantly from Western cohorts (mean 62 years; $p<0.001$). TNBC prevalence among young women (24.7%)

Table 5. Sensitivity of imaging modalities by breast density (BI-RADS categories)

BI-RADS density	n (%)	Mammography sensitivity (95% CI)	Ultrasound sensitivity (95% CI)	MRI sensitivity (95% CI)
A (Almost entirely fatty)	22 (14.9%)	92.3% (84.1-96.7)	76.2% (65.4-84.7)	94.1% (86.9-97.8)
B (Scattered fibroglandular)	45 (30.4%)	84.1% (75.3-90.4)	87.2% (79.1-92.6)	93.0% (86.2-96.8)
C (Heterogeneously dense)	58 (39.2%)	69.8% (60.1-78.1)*	88.5% (81.3-93.4)**	91.3% (84.7-95.5)
D (Extremely dense)	23 (15.5%)	52.4% (40.6-63.9)***	90.9% (82.7-95.7)***	92.7% (85.1-96.9)

Statistical significance (pairwise comparison within density group):
*: $p=0.003$, **: $p<0.001$ for ultrasound vs. mammography in dense breasts (C/D), ***: $p<0.001$ for trend: mammography sensitivity declines with increasing density (Mantel-Haenszel χ^2), CI: Confidence interval, MRI: Magnetic resonance imaging, BI-RADS: Breast imaging reporting and data system.

exceeds global averages (15-18%), supporting Gulf-specific trends (7,11). US's superiority in dense breasts (<50 years) is supported by multicenter trials (9), while MRI's robustness reinforces its role in high-risk screening (19).

Policy implications: Implementing US-first screening for women under 50 years can reduce costs by 32% compared to mammography (estimated savings: $18,500 per 1000 women), based on local reimbursement rates (20).

Global Context of Findings

Our results align with global trends, especially in the Middle East and North Africa (MENA), where 40-52% of breast cancers occur before age 50 years (21,22), compared to 62-64 years in Western populations (23). Studies from Türkiye (24) (US sensitivity: 83.1% in women <50 years) and Malaysia (25) (82.4%) confirm US's superiority in early-onset groups. The higher prevalence of TNBC among young Saudi women [24.7% vs. 18.9% in Egypt (21)] may reflect regional genetic differences.

These age-specific protocols demonstrate transferability to regions with similar early-onset profiles (e.g., MENA and Southeast Asia), although local validation of subtype distributions is recommended. Significantly, MRI's consistent accuracy across age groups (91.7%) (26) highlights its universal role in high-risk screening.

Clinical and Policy Recommendations

These evidence-based recommendations apply worldwide to regions with similar epidemiological profiles.

1. Age-tailored Screening:

- Under 50 years: US and mammography every two years.
- ≥50 years: Perform primary mammography; include MRI for high-risk patients.

2. Molecular profiling: Quickly test receptors for women under 50 to help guide TNBC/HER2+ treatment.

3. National Guidelines: Update Saudi screening protocols to:

- Start at age 40.
- Require US for women before menopause.
- Limitations and Future Directions
- Single-center design: May not represent geographic diversity.
- Retrospective bias: Risk of missing data.
- Cost-effectiveness: Missing system-level analysis.
- The selective use of MRI (for high-risk cases and preoperative staging) introduces a verification bias, potentially overestimating its diagnostic performance metrics compared to mammography and US.
- Our study focused on invasive carcinomas; consequently, the well-established advantage of mammography in detecting microcalcifications associated with ductal carcinoma *in situ* (DCIS) was not evaluated, representing a gap in the comparative assessment of modalities.
- DBT was unavailable at our institution during the study period. Its inclusion might have improved the performance of mammography, particularly in dense breasts, and its absence is a notable limitation.

Research Priorities:

- Multicenter validation of age-specific imaging algorithms.
- Molecular studies on factors driving early-onset TNBC.
- Cost-benefit analysis of US screening.

Fifth, although breast density significantly impacts imaging performance (Table 4), we could not evaluate DBT as a better option for dense breasts (10) because it was unavailable at our center during the study period. Future multicenter research should confirm DBT's role in age- and density-specific screening protocols among the Saudi population. Regional comparisons (Table 6) reveal Saudi Arabia's higher US sensitivity (85.3% in women under 50 years) compared to Western countries (75-78%), with middle values in North Africa (83-87%) and Southeast Asia (82-85%), emphasizing the need for region-specific screening strategies.

Clinical Imperatives:

- Implement age-stratified screening:
- Under 50 years: Biennial US and mammography.
- ≥50 years: Mammography as primary screening + MRI for high-risk individuals.
- Prioritize quick molecular profiling for young patients to guide TNBC/HER2+ therapy.
- Update Saudi national guidelines to align with population-specific epidemiology.

Table 6. Regional breast cancer and US performance comparison

Region	Median age	% Cases <50 y	US sensitivity (<50 y)
Saudi Arabia (study)	48	56.4%	85.3%
North Africa	49	45-50%	83-87%
Southeast Asia	51	35-40%	82-85%
Western Countries	63	20-25%	75-78%

Impact: These evidence-based changes will enhance early detection, reduce diagnostic delays (~40% Stage III/IV diagnoses), and increase survival rates in a high-burden population. Future studies should prioritize the integration of DBT into comparative analyses and address the operator-dependency of US through the development of standardized protocols or artificial intelligence (AI)-assisted interpretation tools.

RECOMMENDATIONS

Based on Saudi-specific age and subtype patterns and imaging performance data, we propose:

Revise National Screening Protocols

- Lower the starting age from 50 to 40 years (56% of cases happen before age 50).
- Under 50 years: Biennial US-first approach (sensitivity 85.3% vs. mammography 74.5%).
- ≥50 years: Mammography as the primary screening, with MRI for BI-RADS 3/4 lesions (89.2% concordance).
- 2. Implement Age-Appropriate Diagnostic Pathways
- Young patients (30-49 years):
- Mandate triple assessment (imaging, clinical evaluation, and biopsy) when there is suspicion of TNBC or HER2+.
- Prioritize molecular profiling within 48 hours due to the 24.7% prevalence of TNBC.
- Older patients (50-70 years): Routine MRI for ILC detection (18% prevalence; US misses 9 out of 148 cases).
- Evidence-based resource optimization strategies are presented in (Table 7), prioritizing: (1) 40% US capacity expansion for women <50 years, (2) MRI triage for high-risk and ILC cases, and (3) rapid molecular profiling for young patients (<50 years) with aggressive subtypes (TNBC/HER2+).

Further regional comparisons supporting these recommendations are detailed in Table 8. Furthermore, specific evidence-based strategies for resource optimization and clinical implementation are summarized in Table 9.

Research Priorities

- Validate US-based screening cost-effectiveness vs. mammography.
- Investigate genetic drivers of early-onset TNBC (e.g., BRCA prevalence).
- Develop AI tools for US interpretation in dense breasts.

CONCLUSION

Our findings support risk-stratified imaging pathways:

- Women <50: Biennial US with selective MRI for BRCA+ or dense breasts
- Women ≥50: Mammography primary with MRI for BI-RADS 3/4 lesions Universal MRI screening is not recommended given resource implications.

1. Early-onset prevalence (peak: 40-49 years; 56% <50 years) suggests lowering screening initiation to age 40 in populations with similar demographics.
2. Aggressive subtypes are more common in younger women worldwide; therefore, US-first protocols (<50 years) and MRI for high-risk cases are widely recommended strategies.
3. Resource-efficient algorithms (e.g., US prioritization) should be tailored for regions experiencing early-onset breast cancer epidemics.

Table 7. International diagnostic performance benchmarking

Country	Median age	% Cases <50 y	US sensitivity (<50 y)	Source
Saudi Arabia	48	56.4%	85.3%	Current study
Türkiye	49	48.1%	83.1%	Kim et al. (13)
Malaysia	51	42.7%	82.4%	Lim et al. (14)

Table 8. Multivariable analysis of diagnostic accuracy predictors

Variable	Adjusted OR	95% CI	p-value
Age <50 years	3.12	1.87-5.21	<0.001
Density BI-RADS C/D	2.78	1.65-4.68	0.002
TNBC subtype	1.95	1.21-3.14	0.006
Tumor size >2 cm	1.42	0.92-2.19	0.11

CI: Confidence interval, OR: Odds ratio, BI-RADS: Breast imaging reporting and data system, TNBC: Triple-negative breast cancer.

Table 9. Optimize resource allocation

Resource	Action	Evidence base
Ultrasound capacity	Increase technicians by 40% in <50 y clinics	82.7-85.3% sensitivity in young (7) women
MRI access	Prioritize high-risk/ILC cases	91.7% cross-age accuracy (17)
Molecular testing	On-site rapid kits for young patients	TNBC drops 3.1%/decade (p=0.003) (3)

MRI: Magnetic resonance imaging, TNBC: Triple-negative breast cancer, ILC: Invasive lobular carcinoma.

Ethic

Ethics Committee Approval: This study was approved by the Institutional Review Board (IRB) of King Saud Medical City, Riyadh, Saudi Arabia (approval number: #H-01-R-053; approval date: 12 June 2025; proposal reference: H1RI-03-Jun 25-01). The study was registered with the U.S. Department of Health & Human Services (DHHS) under IORG #IORG0010374. The research complied with the ethical principles of the Declaration of Helsinki.

Informed Consent: Due to its retrospective design, the requirement for informed consent was waived by the IRB. All patient data were anonymized and handled confidentially.

Acknowledgments

The authors thank the King Saud Medical City Radiology Department for their technical support and access to clinical data. We also acknowledge the Saudi National Cancer Registry for providing epidemiological context.

Footnotes

Author Contributions

Concept - S.S.B.S., B.M.A.; Design - S.S.B.S., B.M.A.; Data Collection or Processing - S.S.B.S., F.M.A., M.M.A., Y.A.A., S.F.A., N.B.H.; Analysis or Interpretation - S.S.B.S., F.M.A., M.M.A., Y.A.A., N.B.H., K.M.A.AL.M.; Literature Search - S.S.B.S., B.M.A., S.F.A., K.M.A.AL.M.; Writing - S.S.B.S., F.M.A., M.E.D.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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