

Risk stratification for malignant upgrade in breast atypical hyperplasia: a Korean multi-institutional analysis from academic hospitals

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Purpose: Atypical hyperplasia (AH) management remains controversial due to variable malignant disease progression rates. While Western studies report 10% to 25% upgrade rates, data from Asian populations, particularly from referral academic centers, are limited. We aimed to identify predictive factors for malignant upgrade in Korean women with AH at academic hospitals.

Methods: This retrospective multi-institutional study analyzed 340 patients diagnosed with AH on initial biopsy who underwent subsequent excision at five Korean academic hospitals from 2000 to 2022. Malignant upgrade was defined as ductal carcinoma *in situ* or invasive cancer on the final pathology. Multivariate logistic regression was used to identify independent predictors of upgrades.

Results: Among 340 patients (319 atypical ductal hyperplasia, 20 atypical lobular hyperplasia, and 1 mixed), 128 (37.6%) experienced a malignant upgrade, 98 (76.6%) to ductal carcinoma *in situ*, and 30 (23.4%) to invasive cancer. In multivariate analysis, multifocal atypia (odds ratio [OR], 25.61; 95% confidence interval [CI], 11.20–58.55; $P < 0.001$) and Breast Imaging-Reporting and Data System 4c-5 lesions (OR, 11.02; 95% CI, 1.43–84.86; $P = 0.021$) were significant predictors. Multifocal atypia showed an 84.4% upgrade rate. Core needle biopsy had higher upgrade rates than vacuum-assisted biopsy (45.2% vs. 20.0%; $P < 0.001$). The upgrade rates decreased from 50% to 25% over the study period ($P < 0.05$).

Conclusion: The 37.6% upgrade rate in this tertiary referral cohort exceeded that in Western reports, with multifocal atypia emerging as the strongest predictor. These findings support immediate excision for multifocal atypia while allowing individualized management for unifocal lesions with favorable imaging in Korean tertiary care settings.

Keywords: Breast neoplasms, Risk factors, Precancerous conditions, Carcinoma, intraductal, noninfiltrating

INTRODUCTION

Atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH) are breast lesions characterized by abnormal cellular

proliferation within the ductal and lobular epithelium, respectively. These lesions are regarded as high-risk for breast cancer development, necessitating complete tissue analysis of the entire lesion due to their potential to be reclassified as malignant upon further in-

Received: Jul 11, 2025 Revised: Dec 17, 2025 Accepted: Jan 5, 2026

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vestigation. Histologically, differentiating between low-grade ductal carcinoma *in situ* (DCIS) and ADH can be challenging, often requiring excision for a definitive diagnosis.

Initial diagnoses of ADH or ALH are typically made through core needle biopsies (CNBs), but the limited sample size inherent to these procedures can lead to underestimation of lesion severity [1,2]. This diagnostic uncertainty has led to the American Society of Breast Surgeons recommending surgical excision for comprehensive evaluation of the entire lesion to rule out malignancy [3]. However, these recommendations are being challenged by emerging evidence suggesting that not all patients with atypical hyperplasia (AH) require surgical intervention. The rate at which AH upgrades to DCIS or invasive breast cancer upon excisional biopsy varies considerably, with previous studies reporting upgrade rates ranging from 0% to 37.5%, depending on many factors [4-9]. The controversy arises from the observation that the majority of ADH lesions do not upgrade to malignancy after surgical excision. The reported upgrade rates were lower in carefully selected low-risk patients [10,11]. While several studies have attempted to identify predictive factors for malignant upgrade, the results have been inconsistent. The applicability of these findings to Asian populations, including Korean patients, remains unclear because of potential differences in breast cancer biology, healthcare systems such as screening, and genetic factors. Asian women often have breasts that are smaller and denser than those of Western women, which makes it more difficult to detect and treat these lesions.

Previous studies in Korea investigating AH have been limited by single-center cohorts and relatively small sample sizes [12,13]. We conducted a multi-institutional retrospective cohort study to analyze data from five academic tertiary medical centers in Korea, where patients presented after initial evaluation and filtering through primary and secondary healthcare facilities. This patient cohort raises questions about whether the known characteristics of AH can be applied. We aimed to analyze factors that can guide clinical decision-making for Korean patients with AH who visited tertiary hospitals.

METHODS

Study design and patient selection

This retrospective multi-institutional cohort study collected data from five academic hospitals across Korea from January 2000 to December 2022. Patients were included in this study if they had: (1) a diagnosis of ADH or ALH on initial biopsy, and (2) subsequent excision by surgery or vacuum assistance. We excluded patients with (1) concurrent diagnosis of malignancy (DCIS or invasive carcinoma) in the ipsilateral breast at initial biopsy, (2) previ-

ous history of breast cancer, and (3) insufficient pathological or clinical information for analysis. One hospital had only 10 cases, and all these cases were excluded during the exclusion process. As a result, data from four hospitals were ultimately included in the statistical analysis. One case with both ADH and ALH features was classified as ADH based on the predominant pattern.

Data collection and definitions

We collected demographic data (age, body mass index [BMI], menopausal status, and reproductive history), lesion characteristics (size, location, and multifocality), diagnostic information (biopsy method and imaging findings), and pathological outcomes. Radiological findings were categorized according to the Breast Imaging-Reporting and Data System (BI-RADS) classification. Malignant upgrade was defined as the presence of DCIS or invasive breast cancer in the final excision specimen following an initial tissue diagnosis of AH. Multifocal atypia was defined as AH with multiple foci within the same breast.

Statistical analysis

Statistical analyses were performed using R software (version 4.3.1; R Core Team, 2023). Missing data ranged from 2.1% (age) to menopausal age (83.8%), variables with excessively high missing rates were excluded from the analysis. Additionally, univariate and multivariate analysis was performed by excluding missing data for each variable individually. Chi-square or Fisher exact tests were used for categorical variables, and Student t-test or Mann-Whitney U test for continuous variables. For BI-RADS categorization, we used a three-tier system (0-3/4a-b/4c-5) based on clinical relevance. Univariate logistic regression identified factors associated with upgrade, and variables with $P < 0.1$ were included in multivariate analysis. We analyzed temporal trends using the year of diagnosis as a continuous variable and examined operation delay effects by categorizing patients into < 31 , $31-70$, and > 70 days. Statistical significance was defined as $P < 0.05$.

RESULTS

Study population and patient characteristics

Of the 589 initially collected cases, 340 met the inclusion criteria (Fig. 1). The cohort included 319 (93.8%) patients with ADH, 20 (5.9%) with ALH, and one (0.3%) with both features. Overall, the initial pathology remained unchanged in 212 patients (62.4%), whereas 128 patients (37.6%) experienced malignant upgrades: 98 (76.6%) to DCIS and 30 (23.4%) to invasive cancer (Fig. 2). The baseline characteristics are shown in Table 1. The median age at operation was 47 years (IQR, 41–54 years). Significant differences

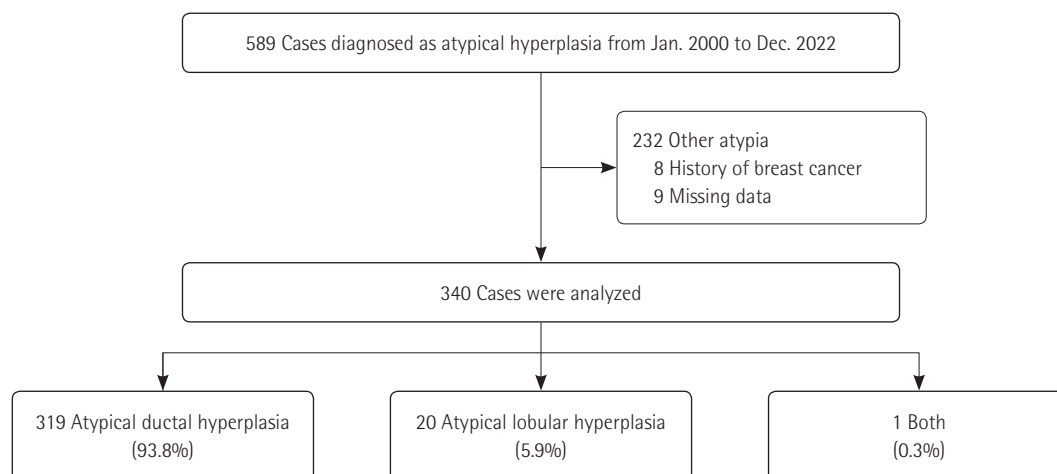


Fig. 1. Flowchart for selecting final analysis cases according to exclusion criteria.

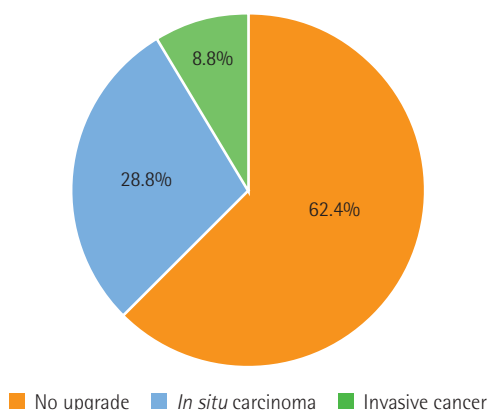


Fig. 2. Proportional chart of atypia patients upgraded to *in situ* carcinoma and invasive cancer.

between the upgrade and no-upgrade groups were observed for postmenopausal status ($P = 0.002$), age > 55 years ($P < 0.001$), *BRCA* mutation positive ($P = 0.043$), ultrasonography (USG) BI-RADS 4c, 5 ($P < 0.001$), and multifocal atypia ($P < 0.001$). In addition, ADH cases had significantly higher upgrade rates than ALH cases (39.2% vs. 15.0%; $P = 0.030$). Among 295 cases with tissue sampling, CNB was associated with higher upgrade rates than vacuum-assisted biopsy (VAB) (45.2% vs. 20.0%; $P < 0.001$).

Risk factor analysis

Univariate analysis identified several factors associated with a malignant upgrade (Table 2). Significant predictors included BMI ≥ 25 kg/m² (odds ratio [OR], 1.74; $P = 0.047$), age > 55 years (OR, 2.83; $P = 0.007$), postmenopausal status (OR, 2.24; $P < 0.001$), CNB (OR, 3.30; $P = 0.020$), BI-RADS 4c-5 (OR, 13.50; $P < 0.001$), and multifocal atypia (OR, 14.85; $P < 0.001$). In multivariate analysis,

only two factors remained independently associated with upgrade (Table 3): multifocal atypia (OR, 25.61; 95% confidence interval [CI], 11.20–58.55; $P < 0.001$) and BI-RADS 4c-5 (OR, 11.02; 95% CI, 1.43–84.86; $P = 0.021$). Multifocal atypia was present in 91 cases (28.8%), with an upgrade rate of 81.3%.

Time trends and operation delay

Upgrade rates significantly decreased over the study period, from approximately 50% in the early 2000s to 25% in recent years (P for trend < 0.05) (Fig. 3). Operation delay analysis showed no significant impact of timing on upgrade rates when comparing < 31 , 31–70, and > 70 -day intervals (Table 4).

Difference in upgrade rates by the stepwise categories

Upgrade rates according to stepwise categories of predictive factors had identified in this study, including age, USG BI-RADS, and operation time delay (Fig. 4). The upgrade rate was highest in patients age > 55 (58.6%) years, BI-RADS 4c, 5 (81.8%), and in the group with a delay of 31–70 days from diagnosis to surgery (50.0%).

Sensitivity analysis for missing data handling

To evaluate the stability of the results under different approaches to handling missing data, we compared original analysis with complete case analysis for multivariate logistic regression (Supplementary Table 1). Among 340 cases, 211 cases (62.1%) were available for complete case analysis. The two independent predictors—multifocal atypia (OR, 40.12; 95% CI, 15.19–105.99; $P < 0.001$) and BI-RADS 4c-5 (OR, 8.78; 95% CI, 1.04–74.13; $P = 0.046$)—remained statistically significant with consistent direction of effect in the complete case analysis. However, the overall upgrade rate was higher in complete cases, compared to original analysis (44.5% vs. 37.6%).

Table 1. Baseline characteristics of the study participants

Characteristics	No. (%)			P-value
	Overall (n = 340)	No upgrade (n = 212)	Upgrade (n = 128)	
BMI (kg/m ²)				0.150
< 18.5	17 (5.3)	13 (6.4)	4 (3.4)	
18.5–22.9	159 (49.7)	107 (52.5)	52 (44.8)	
23.0–24.9	61 (19.1)	39 (19.1)	22 (19.0)	
≥ 25.0	83 (25.9)	45 (22.1)	38 (32.8)	
Menopausal status				0.002
Premenopause	188 (63.9)	130 (71.0)	58 (52.3)	
Postmenopause	106 (36.1)	53 (29.0)	53 (47.7)	
Age at operation (yr)				< 0.001
< 40	45 (15.4)	30 (17.1)	15 (12.7)	
40–55	161 (55.0)	109 (62.3)	52 (44.1)	
> 55	87 (29.7)	36 (20.6)	51 (43.2)	
Age of first delivery (yr)				0.473
< 30	75 (66.4)	51 (63.0)	24 (75.0)	
30–35	28 (24.8)	22 (27.2)	6 (18.8)	
> 35	10 (8.8)	8 (9.9)	2 (6.2)	
Alcohol history				0.936
No	258 (96.3)	164 (95.9)	94 (96.9)	
Yes	10 (3.7)	7 (4.1)	3 (3.1)	
Smoking history				0.246
Never	268 (98.2)	171 (97.2)	97 (100.0)	
Former	4 (1.5)	4 (2.3)	0	
Smoker	1 (0.3)	1 (0.6)	0	
HRT history				0.575
No	302 (97.1)	190 (96.4)	112 (98.2)	
Yes	9 (2.9)	7 (3.6)	2 (1.8)	
Familial history of breast cancer				0.691
No	291 (91.8)	184 (91.1)	107 (93.0)	
Yes	26 (8.2)	18 (8.9)	8 (7.0)	
Breast biopsy history				0.960
No	278 (88.8)	177 (88.5)	101 (89.4)	
Yes	35 (11.2)	23 (11.5)	12 (10.6)	
History of high-risk lesion (atypia or LCIS)				0.415
No	301 (97.7)	191 (97.0)	110 (99.1)	
Yes	7 (2.3)	6 (3.0)	1 (0.9)	
BRCA mutation				0.043
No	327 (96.2)	208 (98.1)	119 (93.0)	
Yes	13 (3.8)	4 (1.9)	9 (7.0)	
USG BI-RADS				< 0.001
0, 1, 2, 3	48 (15.9)	36 (19.5)	12 (10.3)	
4a, 4b	231 (76.7)	145 (78.4)	86 (74.1)	
4c, 5	22 (7.3)	4 (2.1)	18 (15.5)	
Multifocal atypia				< 0.001
No	225 (71.2)	174 (91.1)	51 (40.8)	
Yes	91 (28.8)	17 (8.9)	74 (59.2)	
Initial pathology				0.030
ADH	319 (93.8)	194 (91.5)	125 (97.7)	
ALH	20 (5.9)	17 (8.0)	3 (2.3)	
Both	1 (0.3)	1 (0.5)	0	
Diagnostic method				< 0.001
Vacuum-assisted biopsy	25 (8.5)	20 (11.9)	5 (3.9)	
Core needle biopsy	270 (91.5)	148 (88.1)	122 (96.1)	

BMI, body mass index; HRT, hormonal replacement therapy; LCIS, lobular carcinoma *in situ*; USG, ultrasonography; BI-RADS, Breast Imaging-Reporting and Data System; ADH, atypical ductal hyperplasia; ALH, atypical lobular hyperplasia.

Table 2. Univariate analysis of variables associated with malignant upgrade

Variable		OR (95% CI)	P-value
BMI (kg/m ²)	< 18.5	0.63 (0.20–2.04)	0.443
	18.5–22.9	1 (reference)	
	23.0–24.9	1.16 (0.62–2.15)	0.637
	≥ 25.0	1.74 (1.01–3.00)	0.047
Age at operation (yr)	< 40	1 (reference)	
	40–55	0.95 (0.47–1.93)	0.896
	> 55	2.83 (1.33–6.01)	0.007
Age of first delivery (yr)	< 30	1 (reference)	
	30–35	0.58 (0.21–1.61)	0.297
	> 35	0.53 (0.10–2.69)	0.445
Menopausal status	Premenopause	1 (reference)	
	Postmenopause	2.24 (1.37–3.66)	< 0.001
Alcohol history	No	1 (reference)	
	Yes	0.75 (0.19–2.96)	0.679
BRCA mutation	No	1 (reference)	
	Yes	0.76 (0.32–1.82)	0.543
HRT history	No	1 (reference)	
	Yes	0.48 (0.10–2.37)	0.372
Breast biopsy history	No	1 (reference)	
	Yes	0.91 (0.44–1.91)	0.812
USG BI-RADS	0, 1, 2, 3	1 (reference)	
	4a, 4b	1.78 (0.88–3.60)	0.110
	4c, 5	13.50 (3.81–47.84)	< 0.001
Diagnostic method	Vacuum-assisted biopsy	1 (reference)	
	Core needle biopsy	3.30 (1.20–9.04)	0.020
Multifocal atypia	No	1 (reference)	
	Yes	14.85 (8.05–27.40)	< 0.001
Intraductal lesion	No	1 (reference)	
	Yes	1.05 (0.55–2.01)	0.881
Symptomatic	No	1 (reference)	
	Yes	1.25 (0.80–1.95)	0.333
Lesion number	1	1 (reference)	
	≥ 2	1.57 (0.84–2.90)	0.154
History of high-risk lesion (atypia or LCIS)	No	1 (reference)	
	Yes	0.29 (0.03–2.43)	0.254
Lesion size		1.26 (0.81–1.96)	0.294

OR, odds ratio; CI, confidence interval; BMI, body mass index; HRT, hormonal replacement therapy; USG, ultrasonography; BI-RADS, Breast Imaging-Reporting and Data System; LCIS, lobular carcinoma *in situ*.

DISCUSSION

The management of AH remains challenging due to variable upgrade rates and inconsistent risk assessment criteria [11,14]. In this multi-institutional cohort of 340 patients, we observed a 37.6% upgrade rate and identified multifocal atypia as the strongest predictor of malignant upgrade.

The overall upgrade rate of 37.6% falls within the higher range of

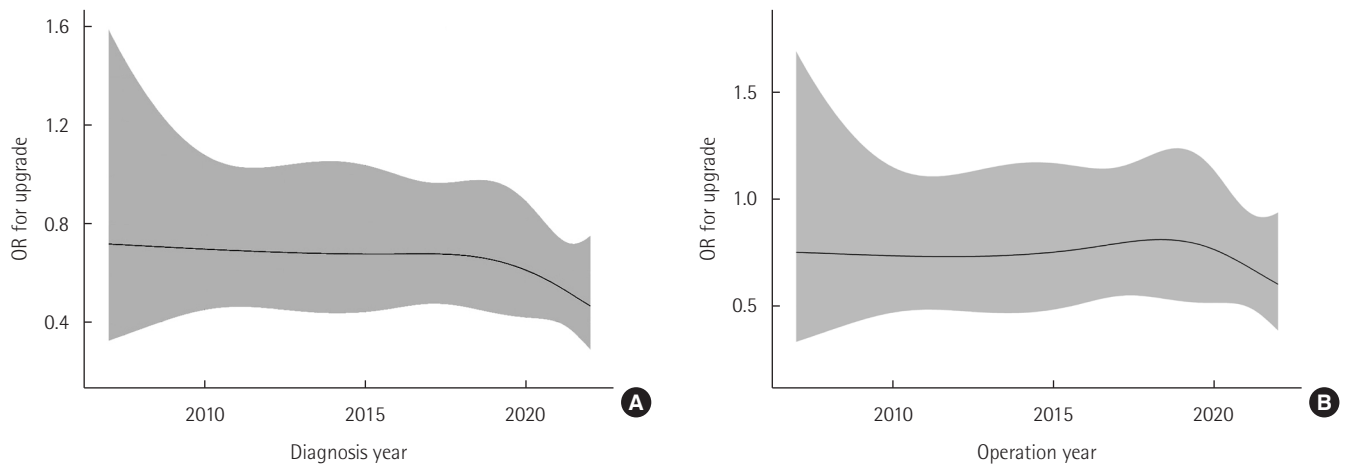
previously reported rates (0%–37.5%) but exceeds recent Western studies reporting 10% to 25% [15,16]. This difference likely reflects our tertiary center population, where patients were referred after the initial evaluation at primary and secondary facilities, representing a preselected higher-risk cohort.

Our multivariate analysis identified multifocal atypia as the strongest independent predictor (OR, 25.61; $P < 0.001$), representing one of the most powerful associations reported in the literature

Table 3. Multivariate logistic regression analysis of variables associated with malignant upgrade

Variable		Adjusted OR (95% CI)	P-value
BMI (kg/m ²)	< 18.5	0.36 (0.03–4.04)	0.411
	18.5–22.9	1 (reference)	
	23.0–24.9	0.38 (0.13–1.11)	0.077
	≥ 25.0	1.02 (0.43–2.40)	0.969
Age at operation (yr)	< 40	1 (reference)	
	40–55	0.71 (0.26–1.97)	0.513
	> 55	2.26 (0.50–10.27)	0.290
Menopausal status	Premenopause	1 (reference)	
	Postmenopause	1.17 (0.33–4.06)	0.810
USG BI-RADS	0, 1, 2, 3	1 (reference)	
	4a, 4b	1.65 (0.35–7.81)	0.526
	4c, 5	11.02 (1.43–84.86)	0.021
Diagnostic method	Vacuum-assisted biopsy	1 (reference)	
	Core needle biopsy	2.08 (0.41–10.65)	0.379
Multifocal atypia	No	1 (reference)	
	Yes	25.61 (11.20–58.55)	< 0.001

OR, odds ratio; CI, confidence interval; BMI, body mass index; USG, ultrasonography; BI-RADS, Breast Imaging-Reporting and Data System.

**Fig. 3.** (A) Risk of malignant upgrade according to the year of diagnosis. (B) Risk of malignant upgrade according to the year of operation. OR, odds ratio.

[17]. This suggests that the spatial distribution of atypical lesions is more predictive than individual lesion characteristics. High-suspicion ultrasonographic findings (BI-RADS 4c-5) also showed a significant association (OR, 11.02; 95% CI, 1.43–84.86; $P = 0.021$), consistent with previous studies demonstrating the importance of imaging characteristics in predicting upgrade risk [18,19]. In the sensitivity analysis for 211 complete cases without missing values, multifocal atypia (OR, 40.12; 95% CI, 15.19–105.99; $P < 0.001$) and BI-RADS 4c-5 (OR, 8.78; 95% CI, 1.04–74.13; $P = 0.046$) remained statistically significant, supporting the robustness of our findings. However, the higher upgrade rate in complete cases (44.5%) compared with the overall cohort (37.6%) suggests an MNAR (missing

not at random) pattern, where patients with complete data may represent a higher-risk subgroup. This pattern may have influenced the magnitude of effect estimates, although the direction and significance of key predictors remained consistent across analytical approaches.

The wide CIs observed for BI-RADS 4c-5 in both analyses reflect sparse data bias. Although the BI-RADS 4c-5 category contained few cases, the upgrade rate in this subgroup was disproportionately high, resulting in inflated ORs with wide CIs. Consequently, uncertainty and reduced reliability in the results were inevitable.

CNB demonstrated a significantly higher upgrade rate than VAB (OR, 3.30; $P = 0.020$) in the univariate analysis, but this signif-

Table 4. Upgrade rates by operation delay groups

Variable		OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Operation delay days	No operation	0.24 (0.12–0.51)	< 0.001	0.70 (0.19–2.57)	0.587
	< 31	1 (reference)		1 (reference)	
	31–70	1.34 (0.71–2.55)	0.364	1.13 (0.44–2.90)	0.795
	> 70	0.75 (0.24–2.30)	0.612	2.20 (0.46–10.43)	0.322

OR, odds ratio; CI, confidence interval.

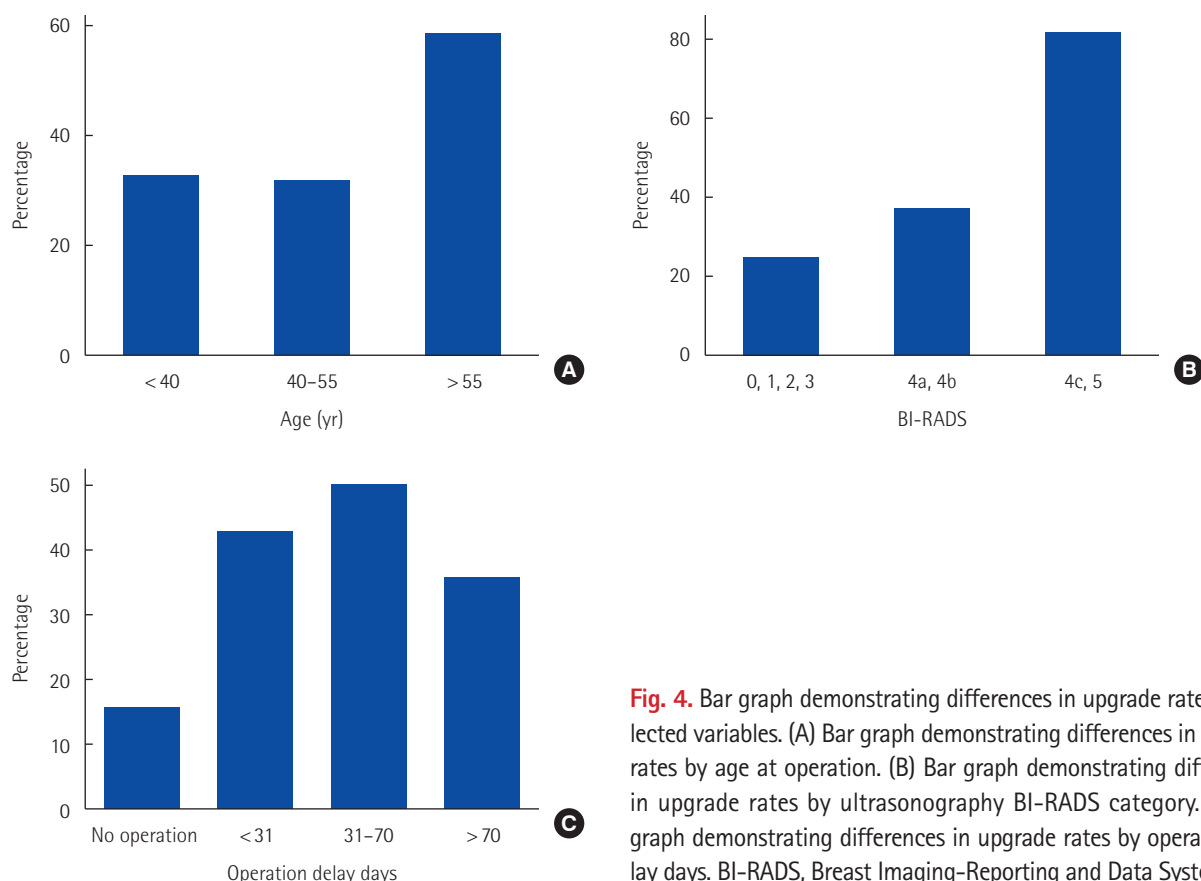


Fig. 4. Bar graph demonstrating differences in upgrade rates by selected variables. (A) Bar graph demonstrating differences in upgrade rates by age at operation. (B) Bar graph demonstrating differences in upgrade rates by ultrasonography BI-RADS category. (C) Bar graph demonstrating differences in upgrade rates by operation delay days. BI-RADS, Breast Imaging-Reporting and Data System.

ificance was attenuated in the multivariate model (OR, 2.08; $P=0.379$). This change in significance is attributable to multicollinearity among the independent variables, which interferes with the independent estimation of each predictor. In clinical practice, lesions with BI-RADS 4c or higher are more frequently diagnosed by CNB rather than VAB. Additionally, the small number of VAB cases (8.5%) relative to CNB (91.5%) caused the separation effect, which has further increased estimation uncertainty.

Consistent with prior studies, we confirmed that ADH has significantly higher upgrade rates than ALH (39.2% vs. 15.0%) [20]. However, several previously recognized risk factors did not maintain significance in this analysis. Age, which has been positively associated with upgrade risk in previous studies, lost significance when adjusted for other factors [21]. Similarly, palpable masses, le-

sion size, and microcalcifications were not independently associated with upgrade in this cohort [22,23]. This discrepancy may reflect the tertiary referral nature of our population, where patients may have been preselected based on high-risk imaging characteristics. The absence of significance for factors such as co-existing columnar cell lesions and detailed histopathological characteristics may be attributed to missing data and variations in pathological reporting across institutions and time periods [21].

The significant decline in upgrade rates from approximately 50% in the early 2000s to 25% in recent years likely reflects improvements in imaging technology and biopsy techniques [24–26]. Enhanced imaging resolution and larger tissue sampling may contribute to a more accurate initial diagnosis, reducing the likelihood of missed concurrent malignancy [26,27]. The finding that opera-

tion delay did not impact upgrade rates provides reassurance that reasonable delays for multidisciplinary consultation do not compromise outcomes.

This study has several limitations. The retrospective design inherently carries the risks of selection and information bias. Missing data were substantial for several key variables: menopausal age (83.8%), reproductive history including parity (59.1%), mammographic findings (71.8%), sonographic characteristics (64.1%), and pathologic lesion size (62.6%). Variables with excessively high missingness were inevitably excluded from the analysis, which have limited our ability to identify additional risk factors and develop more robust prediction models. The small number of ALH cases ($n = 20$, 5.9%) restricts the generalizability of the findings to this subgroup and limits the statistical power for meaningful comparisons with ADH cases.

The declining upgrade rates over time may introduce temporal bias, as cases diagnosed in earlier years may have different baseline characteristics and diagnostic criteria than more recent cases. Variations in pathological interpretation between institutions and across the study period may have influenced diagnostic consistency, particularly given the subjective nature of distinguishing AH from low-grade DCIS. The exclusion of cases initially diagnosed by surgical excision, while methodologically appropriate, may have excluded high-risk lesions that warranted immediate excision based on imaging characteristics, potentially underestimating the upgrade rates in the highest-risk population.

Furthermore, our findings may not be generalizable to community practice settings or screening-detected lesions, as the tertiary referral nature of our cohort likely represents a preselected higher-risk population. The upgrade rates ranged from 4.5% to 60.2% across institutions (sample size range: $n = 44$ to $n = 129$), showing the differences in upgrade rates among the hospitals. There may be variations depending on the tendencies of pathologists, but formal statistical comparison was not performed due to the relatively small sample size at each institution. Future studies should focus on standardized data collection across multiple academic centers to develop more robust risk assessment models specific to referred patient populations.

In conclusion, this multi-institutional study demonstrated that multifocal atypia is the strongest independent predictor of malignant upgrade in Korean women with AH diagnosed in tertiary care settings. The 37.6% upgrade rate reflects the preselected nature of patients referred to academic hospitals. These results provide evidence-based guidance for AH management in referred care settings, supporting immediate excision for multifocal atypia while allowing individualized management for unifocal lesions with favorable imaging characteristics. Standardized data collection

across academic centers is required to develop reliable decision-making criteria for this specific patient population.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Funding

This study was supported by a research grant from the Korean Society of Surgical Oncology (KSSO-24-07).

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Institutional Review Board Statement

This study was approved by the Institutional Review Board of Catholic Medical Center (IRB No. XC24RADI0019) and performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was waived by the IRB.

Supplementary Materials

Supplementary materials are available at the Korean Journal of Clinical Oncology website (<http://www.kjco.org/>).

Data Availability Statement

Data analyzed in this study are available from the corresponding author upon reasonable request.

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