High-Risk HPV Testing in ASC-US Cytology: Clinical Outcomes and Implications for Cervical Cancer Prevention in Japan

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COI Disclosure

The author declares no conflict of interest.

Background

Atypical squamous cells of undetermined significance (**ASC-US**) represent cytological findings that are suggestive but not diagnostic of low-grade squamous intraepithelial lesions (LSIL). ASC-US is the most common abnormal result, yet its clinical significance is highly variable.

Current Japanese Guidelines for ASC-US Management

hrHPV Reflex Testing

High-risk HPV testing is the recommended first-line triage strategy for all ASC-US cytology results in Japan.

Immediate Colposcopy if HPV+

Women who test positive for hrHPV should be referred immediately for colposcopic examination to assess for underlying CIN or carcinoma.

Alternative: Repeat Cytology

Repeat cytology at 6 months is an acceptable alternative pathway, particularly when HPV testing is not immediately available.

⚠ Despite these standardized recommendations, clinical management of ASC-US varies considerably in real-world practice, highlighting a gap between guideline intent and implementation.

Study Objectives

This retrospective institutional study was designed to rigorously assess the clinical significance of hrHPV testing in women diagnosed with ASC-US cytology at a single gynecologic practice in Nagano, Japan.

HPV Positivity Rate

Determine the proportion of ASC-US cases testing positive for high-risk HPV genotypes across screening and clinically indicated populations.

Histopathological Outcomes

Characterize the distribution of histological diagnoses — from cervicitis to CIN3 and invasive carcinoma — among HPV-positive ASC-US cases.

One-Year Follow-Up Results

Evaluate cytological outcomes at 12 months and assess rates of regression, persistence, and progression stratified by HPV status.

Materials and Methods

Study Period

April 2014 – March 2019
Single-institution retrospective cohort study
Horiuchi Ladies Clinic, Nagano, Japan

Study Population

Screening Group: 8,152 cases
Clinically Indicated Group: 10,997 cases

The clinically indicated group comprised patients presenting with symptoms such as abnormal genital bleeding or discharge.

Evaluations Performed

- ASC-US detection rate by patient group
- hrHPV positivity rate among ASC-US cases
- Age-specific HPV distribution and stratification
- Histopathological diagnosis in HPV-positive cases
- Cytological follow-up at 1 year post-diagnosis

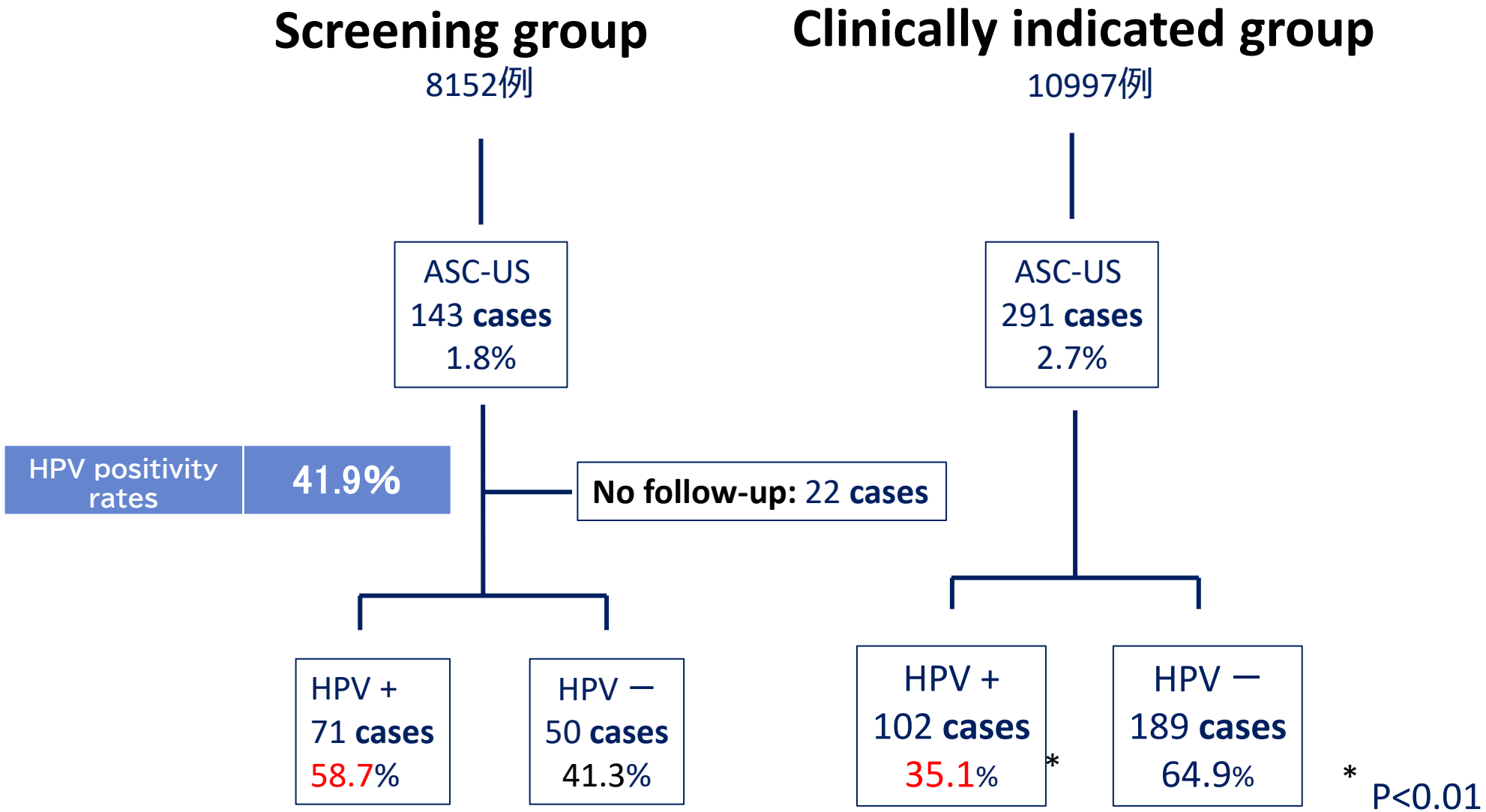
HPV genotyping was performed using standard validated assays. Histological diagnosis was obtained via colposcopy-directed biopsy.

ASC-US frequency

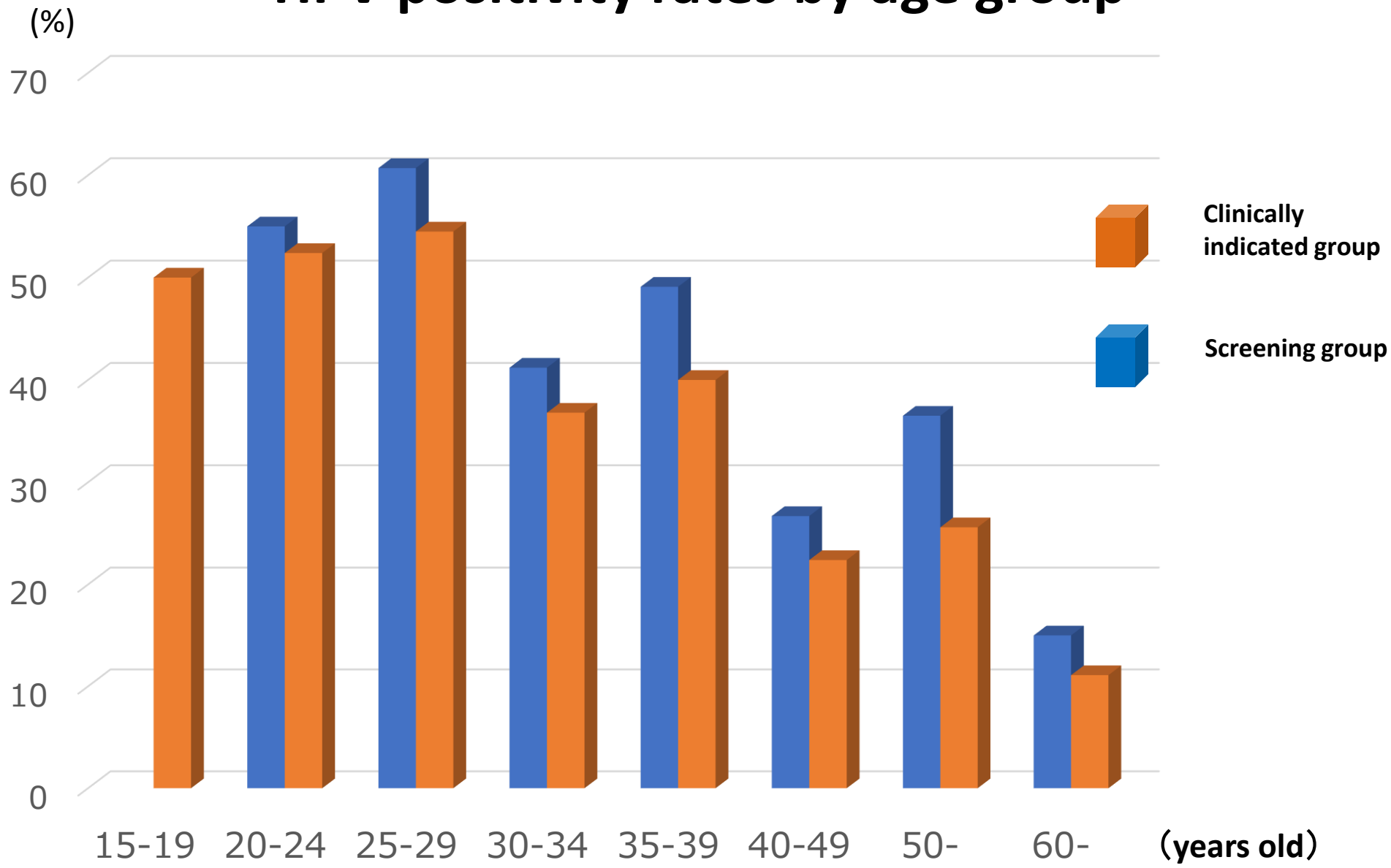
	ASC-US	%
Screening group (8152 cases)	143	1.8
Clinically indicated group (10997 cases)	291	2.7 *

(p<0.01)

HPV positivity rates in ASC-US cases

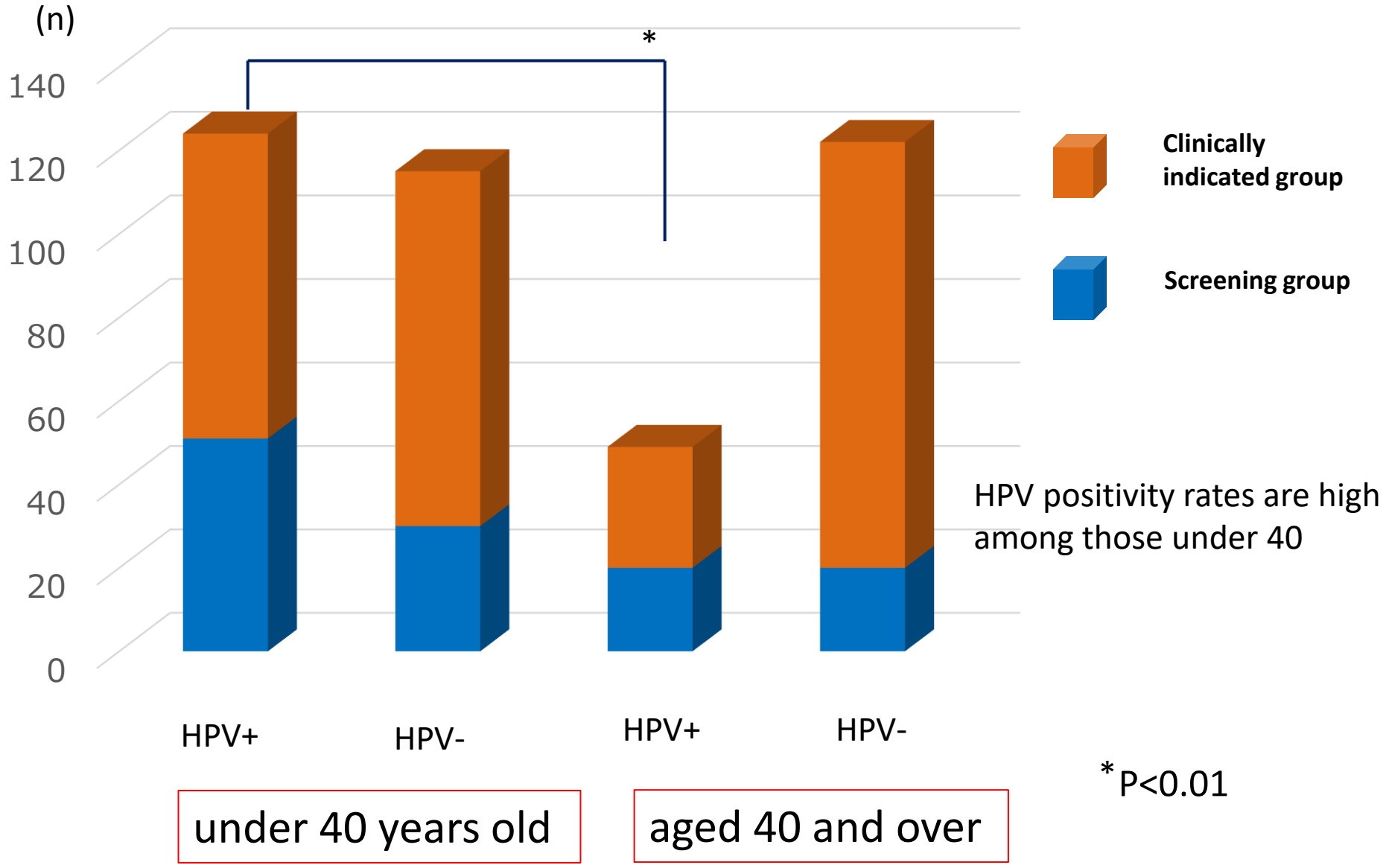


HPV positivity rates by age group



No significant difference between the two groups

HPV positivity rates
Comparison between those under 40 and those aged 40 and over



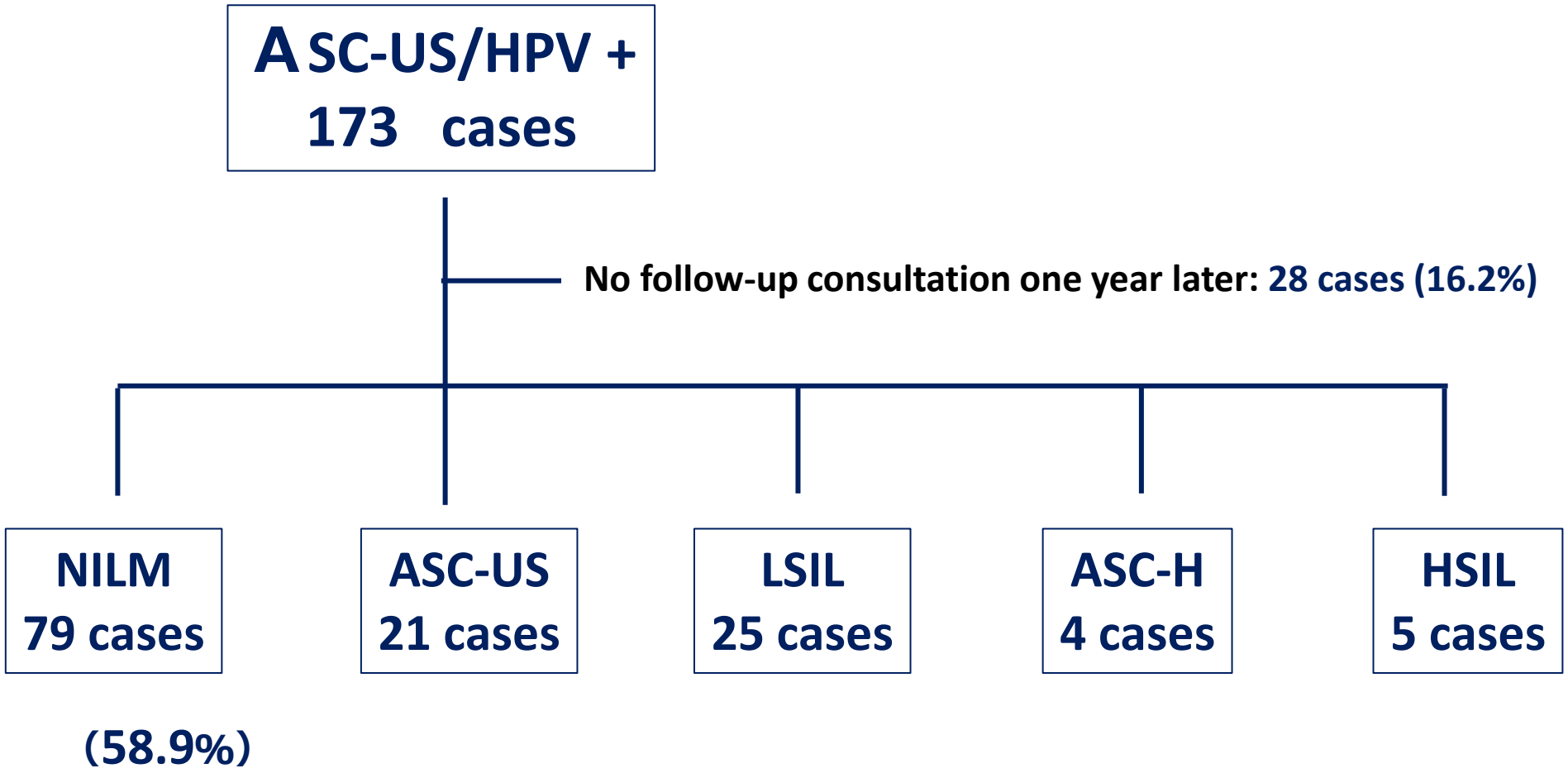
HPV positivity rates are high among those under 40

*P<0.01

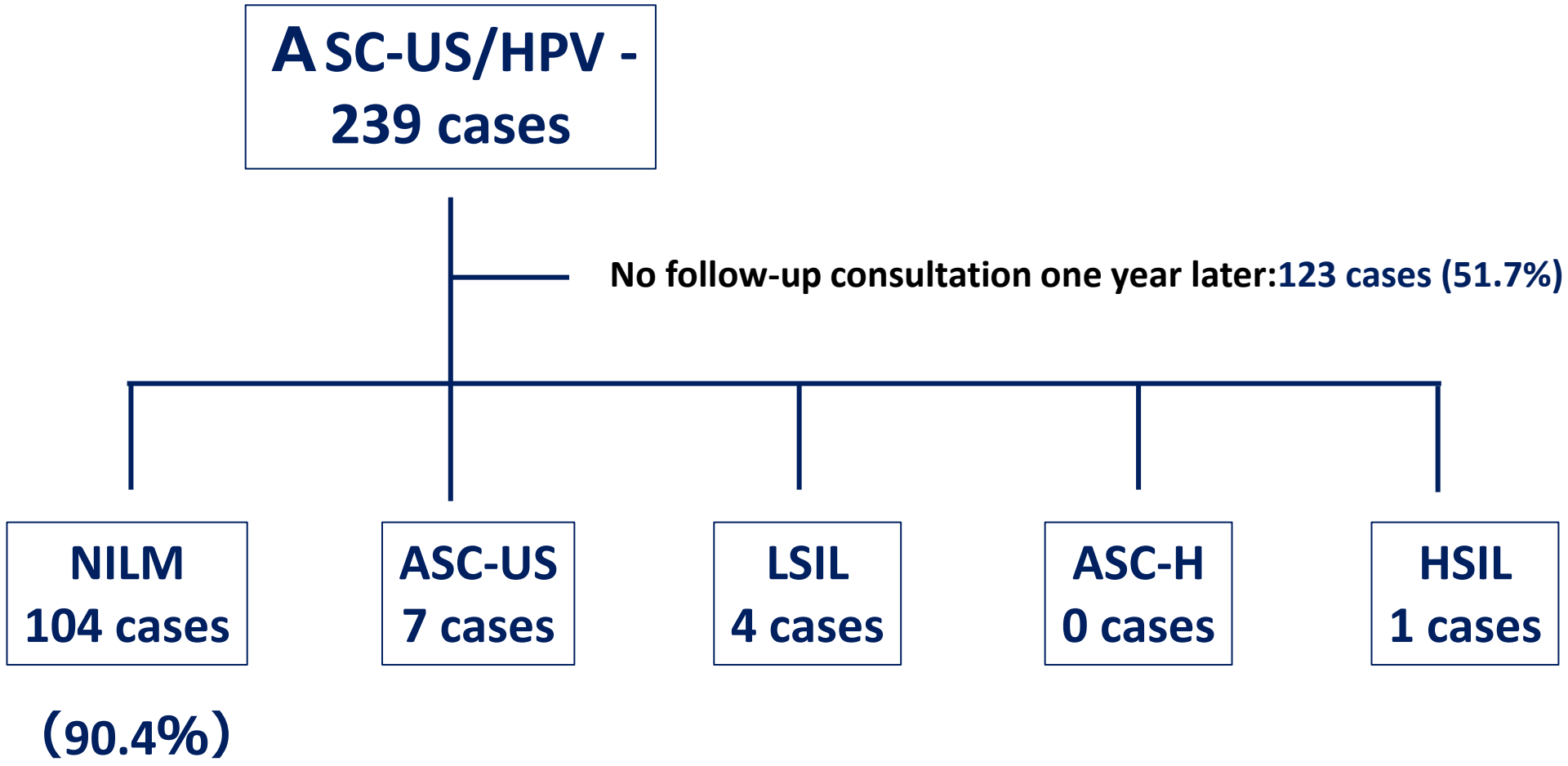
Pathological diagnosis in ASC-US/HPV+ cases

Pathological diagnosis	No of cases	%
Cervicitis	48	27.7
CIN1	85	49.7
CIN2	29	16.8
CIN3	10	5.2
Microinvasive carcinoma	1	0.5

Cytological findings one year after ASC-US/HPV+



Cytological findings one year after ASC-US/HPV-



Cytological findings one year after ASC-US cases (comparison of HPV-positive / HPV-negative cases)

	NILM	ASCUS	LSIL	ASCH	HSIL
ASCUS/HPV+	79	21	25	4	5
ASCUS/HPV-	104 *	7	4	0	1

* P<0.01

Discussion

Previous studies have demonstrated that ASC-US is a heterogeneous category, with HPV status serving as a key determinant of clinical risk. The 5-year risk of CIN3+ in ASC-US/HPV-positive cases has been reported to be approximately 6–7%, supporting immediate colposcopic evaluation. In addition, cohort studies have shown that the cumulative incidence of CIN2+ in HPV-positive ASC-US cases can exceed 30%, whereas HPV-negative cases have a risk comparable to NILM. These findings highlight the clinical utility of HPV testing as an effective triage tool.

- Comparison of three management strategies for patients with atypical squamous cells of undetermined significance: baseline results from a randomized trial. Solomon D, et.al., J Natl Cancer Inst 2001; 93: 293-299.
- Clinicopathologic significance and treatment of ASC-US in cervical cytology. Abdulaziz, et.al., Int J Clin Exp Pathol 2020;13(2):307-316
- Five-year risks of CIN2+ and CIN3+ for women with HPV-positive and HPV-negative LSIL Pap results. Katki, et.al., Published in final edited form as: J Low Genit Tract Dis. 2013 April ; 17(5 0 1): S43–S49.

Results

1 Higher ASC-US Frequency in Symptomatic Patients

ASC-US was detected in 1.8% of the screening group vs. 2.7% of the clinically indicated group ($p<0.01$), reflecting the higher pre-test probability of cytological abnormality in symptomatic women.

2 Overall HPV Positivity: 41.9%; Higher in Women Under 40

The institutional hrHPV positivity rate among ASC-US cases was 41.9%, with significantly higher rates in women under 40 years of age across both study groups.

3 CIN2+ Found in 22.5% of HPV-Positive Cases

Histology revealed CIN2 in 29 cases, CIN3 in 10, and one microinvasive carcinoma. Eleven patients subsequently underwent conization for high-grade disease.

4 One-Year Follow-Up: Marked Divergence by HPV Status

Regression to NILM occurred in 58.9% of hrHPV-positive vs. 90.4% of hrHPV-negative cases. Loss to follow-up was substantially higher in the HPV-negative group (51.7% vs. 16.2%), a critical public health concern.

Conclusion

ASC-US with hrHPV positivity carries a clinically meaningful risk of cervical intraepithelial neoplasia — supporting active colposcopic evaluation for all HPV-positive cases without delay.

Given Japan's comparatively low HPV vaccination coverage and suboptimal cervical cancer screening participation rates, these findings carry significant public health implications. The substantial loss to follow-up observed in this cohort — particularly among HPV-negative cases — underscores the urgent need for:

Enhanced Patient Education

Clear communication of HPV status and its implications for CIN risk to improve patient engagement and adherence.

Improved Follow-Up Adherence

Systematic recall programs and reminder strategies to reduce unacceptable rates of loss to follow-up in both HPV-positive and HPV-negative cohorts.

Refined Triage Strategies

Integration of age-specific risk data and population-level HPV epidemiology into evolving national guidelines to optimize cervical cancer prevention in Japan.