







# Evaluation of Three Models of Follow-up of Patients with Cervical Cytological Abnormalities in a Peruvian's Largest Teaching Women's Hospital

Jeel Moya-Salazar <sup>1,2,3\*</sup> , Jennifer Huarcaya <sup>2</sup> , Víctor Rojas-Zumaran <sup>2</sup> , Diana L. Vásquez <sup>4</sup> ,  
Karina Chicoma-Flores <sup>3</sup> , Hans Contreras-Pulache <sup>1,5\*\*</sup> 

<sup>1</sup>School of Medicine, Faculties of Health Science, Universidad Privada Norbert Wiener, Lima, PERU

<sup>2</sup>Department of Pathology, Hospital Nacional Docente Madre Niño San Bartolomé, Lima, PERU

<sup>3</sup>Oncology Unit, NESH Hubbs, Lima, PERU

<sup>4</sup>Department of Pathology, Instituto Nacional de Enfermedades Neoplásicas, Lima, PERU

<sup>5</sup>South America Center for Education and Research in Public Health, Universidad Norbert Wiener, Lima, PERU

\*Corresponding Author: [jeel.moya@gmail.com](mailto:jeel.moya@gmail.com)

\*\*Corresponding Author: [hans.contreras@uwiener.edu.pe](mailto:hans.contreras@uwiener.edu.pe)

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## ABSTRACT

**Introduction:** The follow-up of squamous intraepithelial lesions (SIL) allows us to understand their progression and regression, however squamous cell atypia (ASC) can generate confusing follow-up results. We aimed to describe the evolution of ASC and SIL during cyto-histopathological follow-up in a tertiary-care hospital.

**Materials and methods:** we conducted a retrospective study during 2016 in 156 Papanicolaou test (PAP) results under three models: 1) with  $\geq 1$  PAP and biopsies, 2) 1 PAP followed by  $\geq 1$  biopsy, and 3)  $\geq 1$  PAP and a confirmatory biopsy. Progression was defined as ASCUS to low-grade SIL (LSIL) or higher, and LSIL to high-grade SIL (HSIL) or higher; and regression as HSIL to LSIL or lower; and LSIL to ASCUS or lower.

**Results:** In PAP, 57 (36.5%) cases were ASC and in histopathology 56 (39.9%) cases of grade 1 cervical intraepithelial neoplasia. Twenty-nine (18.6%) results were followed: 8 (27.6%), 17 (58.6%), and 4 (13.8%) with models 1, 2, and 3, respectively. The progression of the lesions was reported in ~50% for models 2 and 3. ASCUS was the main cytological finding that indicated biopsies, and for all models, the mean progression and regression time was 4 and 3.1 months, respectively.

**Conclusions:** The follow-up of cytological alterations in three models showed progression of lesions in half of the cases analyzed with a time of four months of evolution; ASCUS was the main finding that indicated histopathological study.

**Keywords:** atypical squamous cells of the cervix, follow-up studies, squamous intraepithelial lesions, cytology, Peru

## INTRODUCTION

In 1928, as part of the Third Breed Improvement Conference, disruptive Papanicolaou staining showing changes in cellular structures and infectious/inflammatory processes was presented for the first time on black and white slides [1]. Since then, the Papanicolaou (PAP) test has been successful in preventing cervical cancer, reducing its immeasurable incidence and mortality rates worldwide, especially in high-income countries that ensured the organized and sustainable implementation of cervical cancer (CC) screening programs [2,3].

This successful goal has been achieved despite the inherent limitations of PAP [4]. These limitations have prevented equivalent reductions in CC in low- and middle-income countries where only small proportions of reductions

in cervical cancer rates have been achieved [5]. Limitations in specimen collection, smear fixation, staining, reading, and interpretation of cytological findings are just a few of the interconnected issues that affect test performance. This reluctance to reduce mortality is associated with its low sensitivity, between 50-85%. However, previous studies have shown that diagnostic sensitivity can be improved with repeated testing and can increase diagnostic certainty and agreement between diagnostic categories in cytology and histology [6-9]. This approach to enhancing PAP quality allows for the comparison of cytological and histological data [10, 11]. Therefore, follow-up can indicate the progression or regression of initial cytological alterations [12].

In the context of assessing the quality of the cytological diagnosis, follow-up allows the progression and regression of squamous intraepithelial lesions (SIL) to be monitored. However, squamous cell atypia (ASC) can generate confusing

follow-up results as most of these regresses to benignity [13,14]. Follow-up of ASC generally results in remission of cervical lesions, which requires needless histological examinations and adds to the cost of their elucidation [10].

In Lima-Peru, there are two national hospitals specialized in mother-child care that have a PAP-based diagnosis and follow-up program for patients with cervical cancer. The Hospital Nacional Madre Niño San Bartolomé (HONADOMANI SB), the largest teaching women's hospital, performs more than 78 thousand PAP tests annually, examining 35% of the female population of Lima [8], but the proportion of progressive and regressive cytological findings in their subsequent cytology or the analysis of their cervical biopsies has not yet been assessed. Therefore, there is a need for follow-up studies to estimate subsequent cytological results characterized by previous findings.

In this study, we describe the evolution of ASC and SIL during cyto-histopathological follow-up at HONADOMANI SB during 2016. We describe the follow-up of one continued PAP with biopsies and several continued PAPs with a biopsy.

## MATERIALS AND METHODS

### Design and Study Site

We designed a retrospective analysis during 2016. The goal of this project was to optimize the processing of PAP by using an automated slide staining method. Improvements in the post-analytical step were implemented in 2016 when it started [7,8]. The diagnosis of CC is dependent on PAP because molecular testing for the identification of Human Papillomavirus (HPV) has not yet been introduced in the institution. HONADOMANI SB has seven medical technologists and five pathologists who make up the cytology team.

### Cytological and Histopathological Results

All cytological samples were processed on the Leica ST5010 autostainer XL (Leica Biosystems, Germany). As HONADOMANI SB receives a large number of samples from health networks, PAP results were selected only from hospitals that had two continuous tests or if the PAPs then had a histopathological cervical result within three months. The cytological interpretation suggestions of the Bethesda 2014 guidelines were taken into account when reporting findings [15].

The ASC results, including atypical cells of undetermined significance (ASCUS), atypical cells suggestive of high-grade (ASC-H), and atypical glandular cells (AGUS), were included. For SIL or higher categories, low-grade SIL (LSIL), LSIL with changes corresponding to HPV infection, and high-grade SIL (HSIL), squamous carcinomas and adenocarcinomas were considered. All of these data were gathered from the hospital's Cytology Department's clinical-cytological data storage system. The FIGO 2015 nomenclature was used to document cervical abnormalities such as cervical intraepithelial neoplasia grade 1 (CIN 1), grade 2 (CIN 2), and grade 3 (CIN 3), carcinomas, and other tissue findings for histological results [16]. The results were collected from histopathological reports from the Surgical Pathology area of the Anatomical Pathology Department of the hospital. Both results were corroborated by the Hospital Management System (SIGHOS v2.2).

### Inclusion of Patients and Variables

Patients with results of cytological alteration or monitored precancerous lesions were included in the study. Patients who underwent complete excisional surgeries were omitted since this might skew the results of actual precancerous lesion regression or progression [17]. Data included the date and type of diagnosis, the age of the patients, and subsequent test results within three months.

The primary outcomes measured from the PAP results were (1) the expected time-to-progression test showing (a) ASCUS to LSIL or higher; (b) the expected time to progress from LSIL to HSIL or higher; and (2) the time-to-regression test showing (a) HSIL to LSIL or lower; and (b) LSIL to ASCUS or lower. We looked at complementary biopsy findings followed by >1 PAP and subsequent PAP results accompanied by one or two biopsies as secondary outcomes. The ASC-H results were analyzed separately, considering their (1) progression from ASC-H to HSIL or higher and (2) regression from HSIL to ASC-H or lower.

### Data Analysis

Data analysis was performed on IBM SPSS v24.0 (Armonk, USA) for Chrome. The Kolmogorov-Smirnov test was initially employed to determine the data's normality. Then, using absolute frequency measures, we performed a descriptive analysis of both cytological and histological data. For each participant, the analysis periods and diagnoses for PAP and histopathology studies were determined. The Hazard ratios, as well as prediction and regression times, were calculated using the Markov model [18]. Analysis of simultaneity of cytology and histology results was determined based on the availability of the paired results based on cervical specimen collection and analysis data, with 0.05 and a 95% confidence interval (CI) considered significant for all analyses.

### Ethical Aspects

The ethical principles for human-based medical research established in the Declaration of Helsinki have been adhered to in all phases of the study phases [19]. Furthermore, this research has the approval of the Hospital's Ethics and Research Committee (OID-HONADOMANI-SB-N° 17013-16).

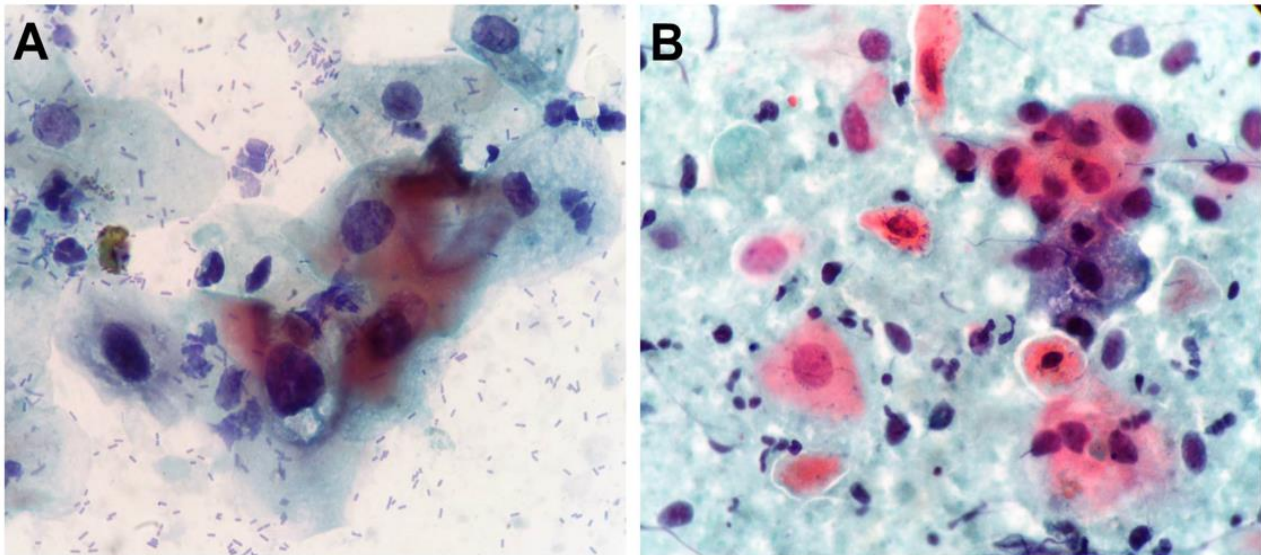
## RESULTS

In 2016, 10,385 PAP tests were performed and 486 (4.7%) had any result with cytological alteration, and only 156 (1.5%) cases had histo-cytopathological paired reports. The mean age of the patients was 41.1±12.6 years (95% CI 39.1 to 43.1) with an upper age limit of 80 years.

**Table 1.** Summary of cytology results from the Hospital Nacional Docente Madre Niño San Bartolomé, 2016

Result	N	%
NLIM	3	1.9
Undetermined	57	36.5
HPV**	13	8.3
LSIL	24	15.4
LSIL + HPV	10	6.4
HSIL	35	22.4
HSIL + HPV	7	4.5
Carcinoma	7	4.5
<b>Total</b>	<b>156</b>	<b>100</b>

\*\*Cellular or tissue changes consistent with Human Papillomavirus (HPV) infection



**Figure 1.** Cytological findings in the follow-up of Peruvian patients during 2016. **A:** Squamous cell atypia of undetermined significance, with the presence of koilocytes (100X). **B:** Squamous cell carcinoma (100X)

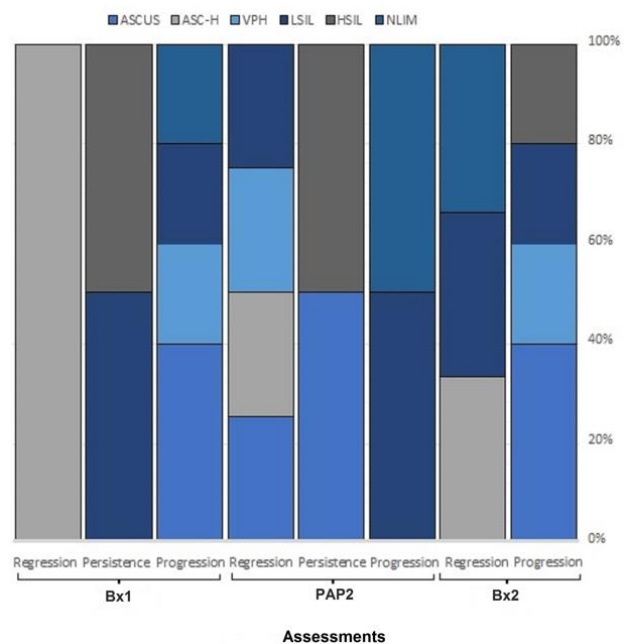
**Table 2.** Summary of histopathology results from the Hospital Nacional Docente Madre Niño San Bartolomé, 2016

Result	N	%
Unsatisfactory	2	0.6
NLIM	9	5.8
Other*	14	9.5
VPH**	15	9.6
NIC 1	11	7.3
NIC 1 + VPH	45	28.8
NIC 2	13	8.3
NIC 2 + VPH	10	6.4
NIC 3	17	10.9
NIC 3 + VPH	6	3.8
Carcinoma <i>in situ</i>	6	3.8
Squamous Carcinoma	7	4.5
Adenocarcinoma	1	0.6
<b>Total</b>	<b>156</b>	<b>100</b>

\*They include chronic cervicitis, endocervical hyperplasia, exocervicitis, orthokeratosis, etc. \*\*Cellular or tissue changes compatible with Human Papilloma Virus infection

The cytological results are shown in **Table 1**, where NLMI is negative for epithelial lesion or malignancy, HPV is human papillomavirus, LSIL is low-grade squamous intraepithelial lesions, and HSIL is high-grade squamous intraepithelial lesions. 36.5% (57 cases) were indeterminate alterations such as ASCUS 22.4% (35 cases), ASC-H 12.2% (19 cases), and AGUS 1.9% (3 cases). There were 21.8% (34 cases) LSIL and 26.9% (42 cases) HSIL findings. Carcinomas accounted for 4.5% (7 cases) of carcinoma findings. HPV-associated cytological changes were present in 4.5% (7 cases) of HSIL and 6.4% (10 cases) of LSIL (**Figure 1**).

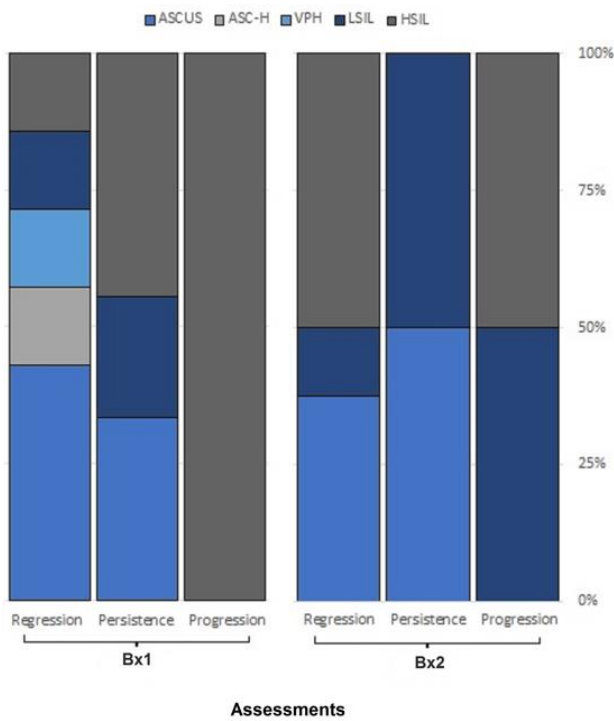
Histopathological findings are shown in **Table 2**, where CIN is 1 cervical intraepithelial neoplasia grade 1, CIN 2 is cervical intraepithelial neoplasia grade 2, and CIN 3 is cervical intraepithelial neoplasia grade 3. HPV koilocytosis was present in the results of 9.6% (15 cases). The number of findings with CIN1, CIN 2, and CIN 3 were 39.9% (56 cases) and 14.7% (23 cases each), respectively. Squamous carcinomas represented 4.5% (7 cases) and only 0.6% of the cases were cervical adenocarcinoma. HPV-associated tissue changes were present



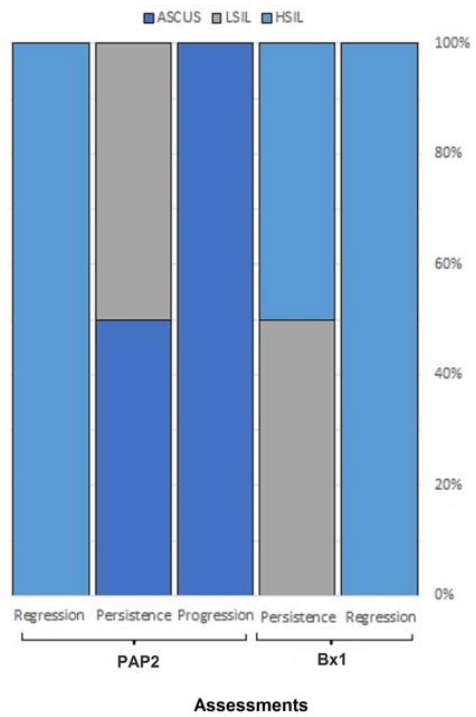
**Figure 2.** Follow-up model 1 of paired PAP and biopsy results. Cytology result with more than two PAPs and biopsies

in 4.5% (45 cases) of CIN1, 10 (6.4%) of CIN2 and 6 (3.8%) cases of CIN3.

The results of the follow-up and evolution of the tests are shown in **Figure 2**, **Figure 3**, and **Figure 4**, where SCUS is squamous cell atypia of undetermined significance and ASC-H is atypical cells suggestive of high grade or malignancy. Data are in %. Only 18.6% (29/156) of the matched results were followed. Of these, 8 (27.6%) cases had more than two PAPs and biopsies (**Figure 2**, model 1), 17 (58.6%) cases had one cytology and more than two biopsies (**Figure 3**, model 2), and 4 (13.8%) cases had two PAPs and one biopsy (**Figure 4**, model 3). Although we reported a high proportion of indeterminate and HSIL results in PAP, histological findings had a high proportion of CIN 1. For all models, differences between the evaluation groups were evident ( $p < 0.05$ ).



**Figure 3.** Follow-up model 2 of paired PAP and biopsy results. Cytology result with one PAP and more than one biopsy



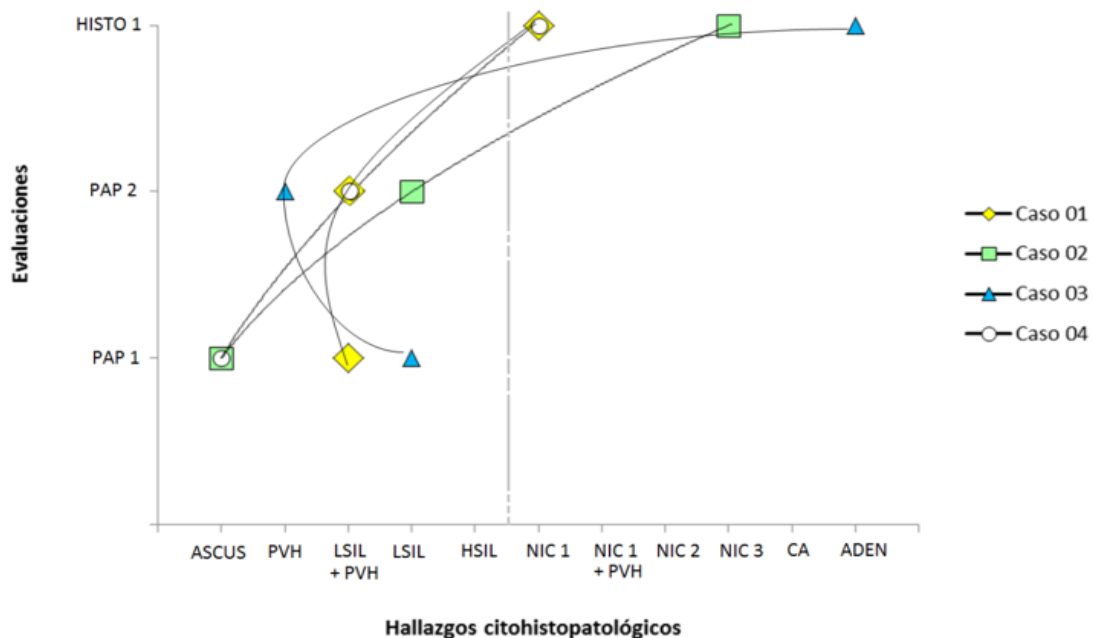
**Figure 4.** Follow-up model 3 of paired PAP and biopsy results. Cytology result with one PAP and one subsequent biopsy

For model 1 (as shown in **Figure 2**), there were more cases of ASCUS and LSIL that required subsequent follow-up, where 62.5% (5/8) had progression at the first biopsy (meantime, 3 months). For the second cytology, there were more cases of regression (time 3.2 months) and for the second biopsy, there were more cases of progression of the alterations (time 2.7 months), both with 5 (62.5%) cases.

For model 2 (as shown in **Figure 3**), the initial cytological findings leading to subsequent biopsies were ASCUS and HSIL, both with 6 (35.3%) cases. Subsequently, the first biopsy had persistence of the lesion for HSIL and LSIL (n=3, 17.6%), and for

ASCUS the results corresponded to CIN1. The time to progression and persistence averaged 3 and 1.5 months, respectively. In the second biopsy, progression was evident in 8 (47.1%) cases with a progression time of 6.5 months. In only two (11.7%) cases, regression was reported with an average time of 3 months.

In model 3 (as shown in **Figure 4**), there were cases of persistence of cytological alteration at 3 months, while in the control biopsy 2 (50%) cases showed progression. The main cytological alterations leading to follow-up and inclusion in the biopsy were HSIL (50%). 3/4 of the cytological follow-up



**Figure 5.** Follow-up of cytological results with two PAPs and later confirmed by histology (biopsy)

findings confirmed or revealed a large cervical lesion at biopsy in all patients (Figure 5). In Figure 5, CA is squamous carcinoma, ADEN is adenocarcinoma, PAP is Papanicolaou test, and HISTO is histopathological analysis. Only one instance had high-grade lesions at first (HSIL), then regression (NLIM with koilocytosis) at the second cytology and remarkable progress at the final histopathological control (infiltrating adenocarcinoma).

## DISCUSSION

In this follow-up study of cytological alterations, three models were evaluated, which showed the progression of lesions by ~50% for model 2 (one PAP and  $\geq 1$  biopsy) and 3 (2 PAPs and 1 biopsy) and a heterogeneous regression and progression pattern for model 1. ASCUS was also the most common cytological result that required biopsies, and the average time to progression and regression for all models was 4 and 3.1 months, respectively.

Although there have been numerous previous national cohort study follow-ups on lesion of approximately 12 years [14-17], there have also been follow-up studies that have only looked at a limited fraction of accessible cytologies due to a lack of comprehensive data for a proper progression analysis [9,10]. Our analyses in a largest tertiary-care women's hospital in Peru have also focused on a group of cases (156/10,385 patients) with follow-up, similar to previous reports in Nepal (75/1,922 patients) and Italy (24/264 patients) [9, 10].

A five-year Colombian follow-up study of 2,771 ASCUS results identified 69.8% and 84.6% regression and 10.8% and 6.6% progression to the first and second cytological control, respectively [12]. Our results are consistent as we had a high proportion of biopsy-confirmed ASCUS progression in 47% of the cases. Additionally, our ASCUS results, in particular, showed a slow progression to LSIL in subsequent controls; this progression time could be affected by ethnicity, as Hispanic patients have shown a slower progression from ASCUS to LSIL than Asian, African-American and Caucasian patients [17].

However, Hispanics also demonstrated a faster progression rate from LSIL to HSIL compared to all other racial categories. The lowest regression rate from LSIL to ASCUS was also reported for Hispanics [17]. In the Latin American population, a 1% progression rate for HSIL has been reported [12], with a higher risk of CIN 3 in those over 60 years of age (42.8%) [20]. As HSIL has a high proportion of CIN 2 and CIN 3, it is necessary to perform combined tests (including HPV genotyping and co-testing) to increase the possibility of detection in all age groups [21].

On the other hand, another study in China has shown progression to CIN 1 in 16%, CIN 2 in 19.4%, and CIN 3+ (or carcinoma in situ) in 11.8% at 3-year of histopathological follow-up of ASCUS [20]. Our Model 2 results have allowed the detection of larger lesions in 47% of cases, in agreement with this previous study. However, in Model 1 we report a different proportion of results with progression (Figure 2). Therefore, although these results have allowed us to identify larger lesions, more prospective-cohort studies with longer follow-up times are required [20].

Exfoliative cytology is subject to a set of interdependent factors that grade its final quality. These factors range from specimen collection to results delivery and sample storage [4-

8,22,23]. Additionally, the performance of PAP can vary between populations and its success depends on its organization, and in the same way, PAP represents a sensitive tool for the detection of cervical lesions through follow-up [24,25]. It has been shown that sensitivity in the detection of CIN 1 of 93% and the specificity of 73% have been detailed, and the sensitivity and specificity of cytology for women with CIN 2+ were 64% and 84%, respectively [26]. Although its performance may vary during follow-up, progression (24%) and regression (31%) of cervical lesions in women with Human Immunodeficiency Virus infection were identified at two years [27]. Therefore, postpartum follow-up in women with LSIL and HSIL showed persistence in 69% and 50% of cases, respectively [28].

According to our findings, the formation of two cervical PAPs allowed the confirmation or discovery of a large cervical lesion in histopathological research, primarily in ASCUS. There are still ambiguous follow-up results for ASCUS and LSIL, where negative cytology has been reported in 64.8% and 47.8%, respectively [29]. Another study did not find any difference at one-year follow-up between ASCUS and LSIL, with an association of HPV with ASCUS [19]. National and regional follow-up studies of ASCUS are needed including molecular testing and surveillance for the detection of major lesions, as there are differences in performance frequency [30,31].

Of the analyzed models, the most frequent involves the repeated use of PAP as it has an optimal diagnostic yield that improves with repetition [4, 5, 32]. Under this approach (with  $\geq 1$  PAP) it has been shown in a 22-year follow-up cohort in Sweden that women with a first cytological diagnosis of ASCUS/LSIL up to 27 years of age can be safely followed with PAP in six months [14]. Follow-up to rule out false-positive results has been estimated at three months, although to correctly demonstrate regression of lesions in ASCUS/LSIL has been estimated at one year of follow-up [13, 20]. Our results have shown evidence of progression of the lesion with three-month follow-up and subsequent biopsy-confirmed PAP controls.

This study had the following limitations.

1. Progression, regression, and frequency of cytological alterations can vary between populations according to age group, ethnicity, parity, abortion rate, and incidence of cervical infections [17-20].
2. Follow-up results were estimated in one hospital in Peru, and progression and regression results in other hospitals are needed to understand national differences. It is necessary to carry out extensive studies that include different hospitals in the Andes, jungle, and coast, since Peru is a multicultural country.

In conclusion, in this study, progression was observed in half of the samples in the three models analyzed, with a time of four months of evolution. Furthermore, ASCUS was the main finding, leading to a further histopathological study and the regression time was estimated at three months.

**Author contributions:** **JMS:** provided the study concept and design, statistical analysis, data management, and wrote the manuscript. **JH:** provided the design, data acquisition, formal analysis, and performed data management. **VRZ:** provided the design, data acquisition, and formal analysis. **DLV:** provided the design, and data acquisition. **HCP:** provided the study concept, statistical analysis, data analysis and interpretation, and wrote the article. All authors have sufficiently contributed to the study, and agreed with the results and conclusions. All authors have approved the final version to be published.

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**Declaration of interest:** No conflict of interest is declared by authors.

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