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Prevalence of Cervical Dysplasia and Cervicitis in South India Comparing Standard Cytology and Mobile Colposcopy

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ABSTRACT

Aim: To compare visual screening for cervical cancer using a mobile connected colposcope to standard of care cytology.

Methodology: This was a multicentric cross sectional study where 597 patients were recruited at six centers in southern India. Each patient first underwent screening through standard of care cytology, followed by visual screening using a mobile colposcope (Enhanced visual assessment (EVA) system). Patients testing positive in either of these tests underwent colposcopy with biopsy, following the standard of care approach. Clinical decisions made by the provider were recorded on a decision support job aid integrated into the mobile colposcope application. Information on patient socioeconomic status was also recorded.

Results: In five of six sites, the rates of dysplasia detected visually (10.3%) was higher than using cytology (3.3%). However, cervicitis was found to be much more common, detected in 33% of the patients using EVA system and 37% using cytology. Dysplasia was more common among low income patients and less among middle income patients, whereas cervicitis was common among middle income patients, and less common in low and high income patients.

Conclusion: Cervicitis is much more common in southern India than dysplasia among women who access private healthcare. Socioeconomically, dysplasia is much more prevalent in low income patients, while cervicitis is prevalent in middle income patients. Because cervicitis make it difficult to visually identify dysplasia, methods should be devised to call back patients for rescreening to ensure dysplasia cases are not missed.

Keywords: Cervical cancer, cervicitis, cytology, dysplasia, screening, low resource settings, colposcopy, digital health.

INTRODUCTION

There were 528,000 newly diagnosed cases of cervical cancer in the year 2012 globally, resulting in 266,000 deaths.[1] Approximately 85% of cervical cancer deaths occur in low and middle income countries (LMICs).[2]

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India alone is home to one fourth of all cervical cancer deaths worldwide,[3] with 67,477 death each year.[4] However, only 3.1% of women aged 25-64 years are screened every 3 years in India.[3]

Despite gradual improvement, challenges still prevail in implementing effective cervical cancer screening programs, especially in low socioeconomic backgrounds.[5] Today, three screening methods are deployed in India: human papillomavirus (HPV) testing, conventional cytology, and visual inspection with acetic acid (VIA). Most providers in the private sector rely on conventional cytology as the primary screening method as per recommendations by the Indian government and WHO at the district level.[6] However, cytology faces several challenges, including high false-negative rates, low-sensitivity, and low predictive values.[7] Loss-to-follow-up from cytology (and HPV programs) are also high, given the needed lab infrastructure.[8]

Recently, a low-cost, connected mobile colposcope was developed on a smartphone platform. The device captures colposcopy-quality images, but at a fraction of the size of a traditional colposcope. The device has been successfully piloted in several LMICs, including Kenya,[9,10] Haiti,[11] Mexico,[12] and Cambodia.[13] As a connected medical device, it contains workflow management features, including a decision support job aid to record the provider's clinical decisions, and an image portal that is Health Insurance Portability and Accountability Act (HIPAA) compliant to store images and patient information entered in the smartphone app controlling the device. With these new capabilities overcoming many challenges associated with VIA, there is renewed interest in visual screenings as a potential low cost screening alternative for India.

The objective of the current study was to compare visual screening on a mobile colposcope to standard of care cytology in six health clinics in South India.

METHODOLOGY

This was a cross-sectional study. The duration of the study was 6 months. All sites were a part of a private sector hospital network, where cytology efforts were already in place. The six centers included four centers in Tamil Nadu (serving different geographic and socioeconomic groups), one urban center in Telangana, one semi-urban center in Madurai, and rural villages in Andhra Pradesh (Table 1). The study was approved by Institutional ethical committee of all the centers involved in the trial and by Clinical Trials Registry India (CTRI) registration number: CTRI/2017/08/009335.

Table 1

Summary of clinical sites and the socioeconomic status of patients they serve

Site no.	*Socioeconomic status of patient population*
1.	Middle to upper income patients, and also in part to the lower income group. Located in the center of a big city.
2.	Rural population from remote villages. Located in a village.
3.	Lower to middle income group, located in the peripheries of a big city.
4.	Middle income group. Located in the peripheries of a big city.
5.	Lower income group. Though located in the center of a big city, it is public hospital catering to the need of general public.
6.	Middle to high income group of patients. Located in a big town.

The study team comprised of 29 health care providers including primary investigators, gynecologists, study coordinators, and nurse-midwives. The study was conducted by a Lead Investigator with a responsibility to review and monitor the conduct of all the sites. Each site appointed a primary investigator and a lead nurse already conducting cervical cancer screening, who attended a one-day training on the use of the mobile colposcope that included modules on the use of the software, job aid, and instructions of operation to capture clinically useful images of the cervix. After the training was completed, primary investigators provided further training to junior gynecologists in their respective centers on use and operation of the EVA System.

Outreach and Patient Enrollment

Outreach to increase patient enrollment was conducted by one of the rural centers to rural women with very low rates of awareness through Accredited Social Health Activists (ASHAs) on the importance of screening, and dates of screening camps. Transportation was provided at no cost to interested women from their villages to the health center for screening camp days. Other centers placed informational flyers at the hospital, but did not

have active outreach for patient enrollment outside their normal patient load in the outpatient department (OPD) clinic.

All the women in study were sensitized about both screening methods of the study (cytology and visual screening). All women were counseled on the next steps following an examination. All patients received instructions prior to the exam, and providers explain data usage and risk before an informed consent was signed in the local language.

Outreach and enrollment efforts were focused on recruiting women who came to the OPD clinic, or for screening camps, within a predefined limited time frame outlined in the IRB-approved protocol. As such, the sample size was not calculated prior to study commencement. Within the time frame allocated for the study, 597 women between the ages of 18-65 years, attending routine screening at the OPD clinic consented to participate in the study. Exclusion criteria consisted of menstruating women, pregnancy and hysterectomized women. In addition, patients who declined cytological screening after enrollment were also excluded.

Clinical Protocol

At the time of screening, patients first underwent routine cytology testing. Patient information was collected, including age, marital and socioeconomic status directly into the EVA System mobile application that is integrated into the device.

Following collection of cytology specimen, providers applied diluted 5% acetic acid, with a 1-2 minute waiting period prior to visualization. Providers visualized the cervix through the mobile colposcope, conducting a standard visual screening with the dedicated device. The EVA System (Fig. 1A) was then used to capture white light and green filter images of the cervix. Women with a visual assessment that included inflammation were prescribed antibiotics at the primary screening. Follow-up procedures, including counseling on when to schedule a secondary visit for women with inflammation varied by protocol at each site, following the local clinic's standard of care.

All Pap smears were sent to the pathologist for review. Pathologists reviewed the samples according to their own training, and documented adequacy of the sample, glandular cell abnormalities, squamous cell abnormalities, and inflammation (cervicitis). All abnormal smear results with indication of dysplasia were communicated to patients through standard process of each clinic in the study, and women were called back for secondary colposcopy and confirmatory biopsy, and their return for biopsy was tracked. Histopathological analysis of biopsies collected followed the same procedure.

Documentation and Data Analysis

A decision support job aid integrated into the device was used to document visual impression at the time of screening according to the tree in Figure 1B and C. Providers recorded any abnormalities, including dysplasia and cervicitis. Patient details, images, annotations, and colposcopic impression by provider were automatically uploaded to the HIPAA-compliant image portal through an integrated SIM card.

At the end of the study, all cytology and histopathology results were collected and compared to visual impressions from the primary screening recorded in the mobile colposcope app. Job aid decisions were compared to cytology results and biopsy, as well as to socioeconomic status (low, middle, high, N/A). While histopathology analysis was originally planned, a high loss-to-follow-up occurred. As such the inability to meaningfully conduct an analysis using histopathology is a limitation of the study results.

RESULTS

Figure 2 shows how patients enrolled in the trial are distributed by site (A), age (B), and socioeconomic level (C).

Rates of suspected cervical dysplasia and suspected cervicitis as recorded visually and determined through mobile colposcopy (on the EVA app) and by cytology are shown in Figure 3. It can be seen that overall, there was much more cervicitis than dysplasia. In comparing suspected dysplasia to suspected cervicitis rates as measured, the data showed that suspected cervicitis rates were more than twice as high as suspected dysplasia rates in five of six sites. In three sites, visual cervicitis rates reached over 40%, while suspected dysplasia rates did not reach 20% in any site. Only in one site (site 2), rates of suspected cervicitis and suspected dysplasia were identical. In comparing inflammatory smears to visually detected cervicitis, our results showed roughly the same average (37%, compared to 33% detected visually), but with very large variations

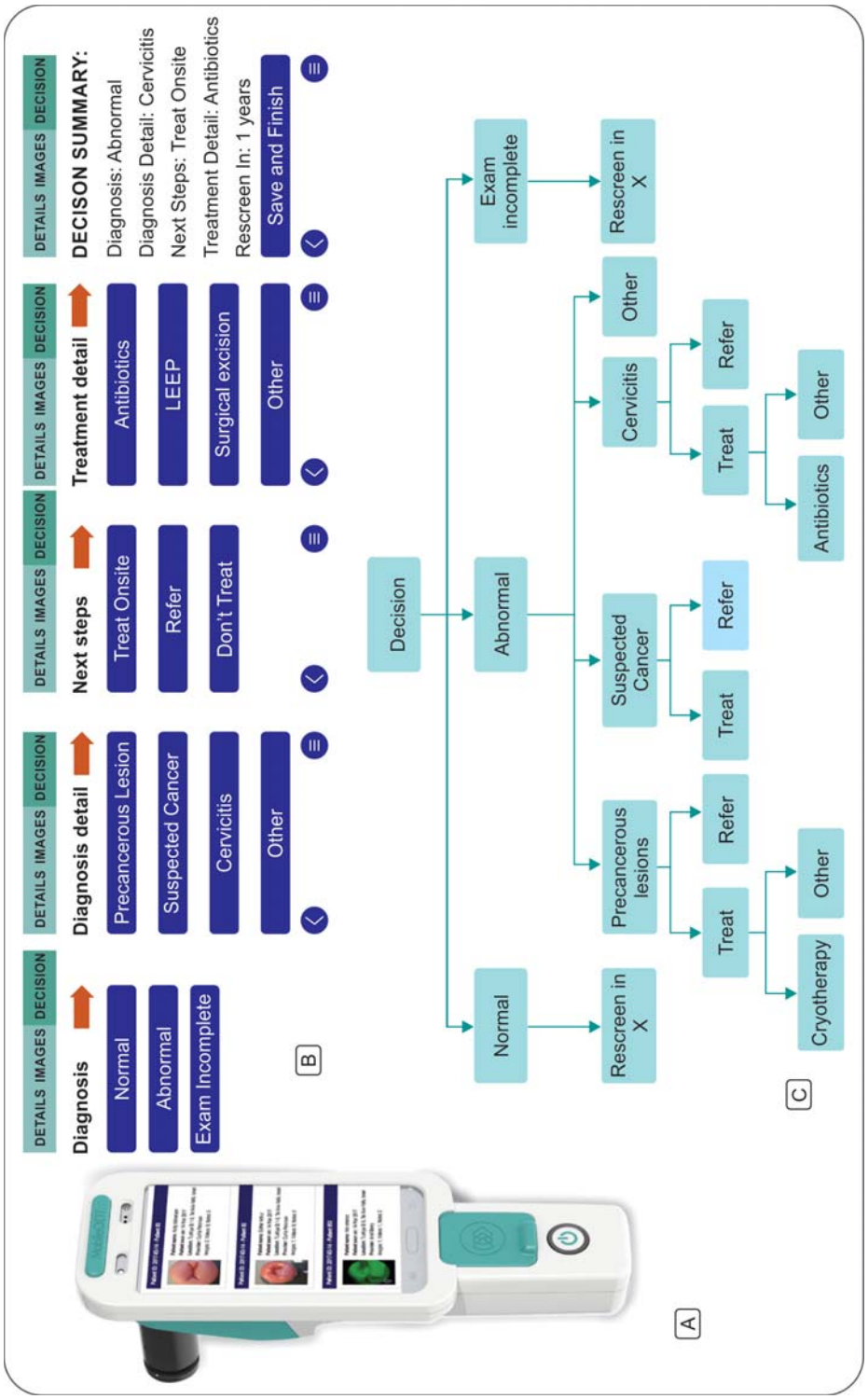

Fig. 1: (A) EVA system, (B) Screenshots of decision support job aid on the EVA system app., (C) Full decision tree of job aid

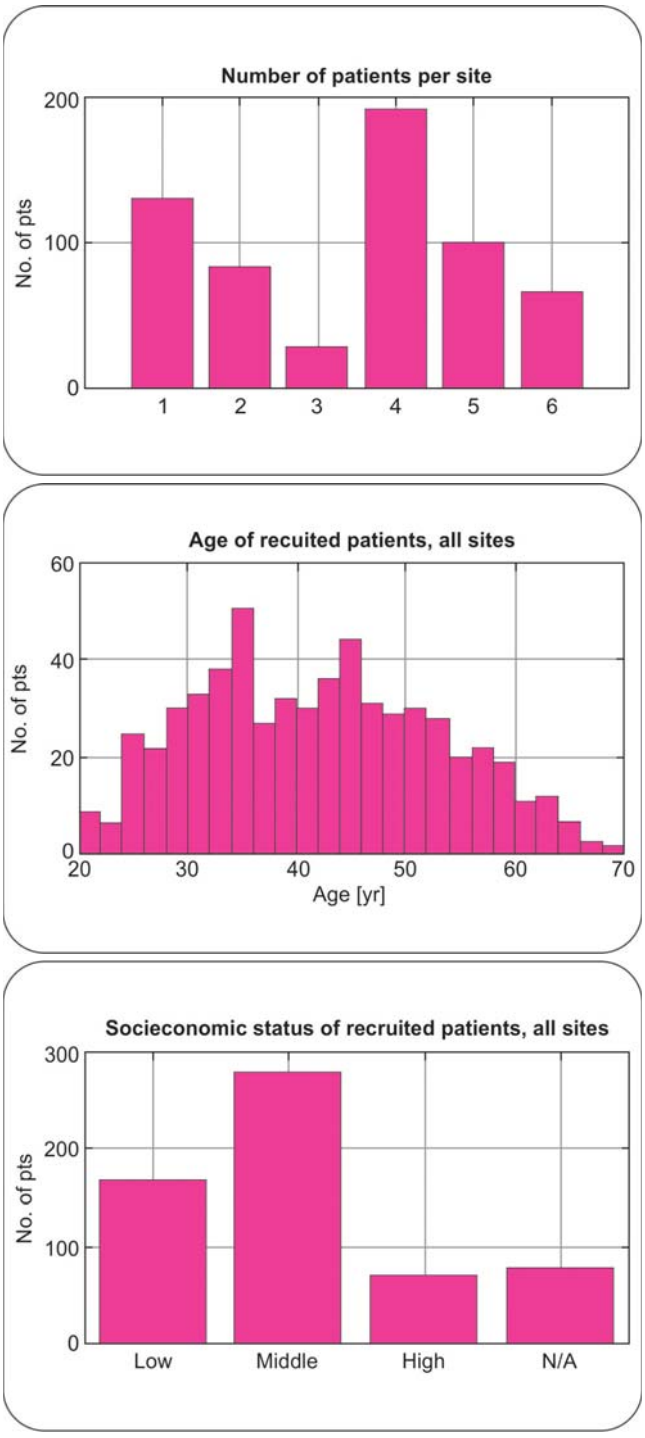

Fig. 2: Distribution of patients by (A) site, (B) age group, (C) socioeconomic status

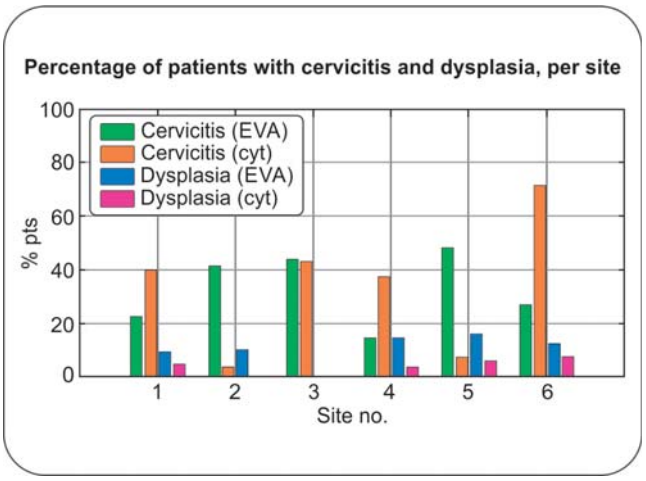

Fig. 3: Distribution of patients with cervicitis and dysplasia (measured visually or by cytology) across clinical sites. The left-most sites are all from a large city in South India

between sites, with rates reaching as low as 1% and as high as 71% were observed.

In terms of suspected dysplasia, the number of patients who visually screened positive (vis+ patients) through mobile colposcopy was larger than those who cytologically screened positive (Pap+ patients) in five sites, and in the sixth site (3) no suspected dysplasia was recorded using either method. In the five sites with suspected dysplasia patients, the vis+ rate was 12.4% ± 2.79%, but the cytology rate was only 4.37% ± 2.86%. The differences between the vis+ rate and the Pap+ rate is striking; the Pap+ rate in particular appears to be lower than expected for a country like India, which has the largest number of deaths from cervical cancer in the world.[16]

To better understand how cervicitis and dysplasia are related to socioeconomic level, we compared the socioeconomic breakdown of patients with either cervicitis or dysplasia (Fig. 4A). Here, our results showed that most (~60%) of the patients with dysplasia were from low income households, and the rest were middle income or did not provide an answer. However, cervicitis patients had a representation of all three socioeconomic levels, with middle income patients being the largest group (~50%). For comparison, the breakdown of dysplasia and cervicitis patients by age is shown in Figure 4B, though there are no obvious trends in the data. Of note, in the 10-15% of cases, the patients did not have a socioeconomic level recorded in the app. Further inquiry revealed that this was most likely because of cultural sensitivities - either the patient declined to answer, or the provider did not find the question appropriate given the circumstances of that particular patient. As the results do not distinguish one group from another, but rather assess different clinical

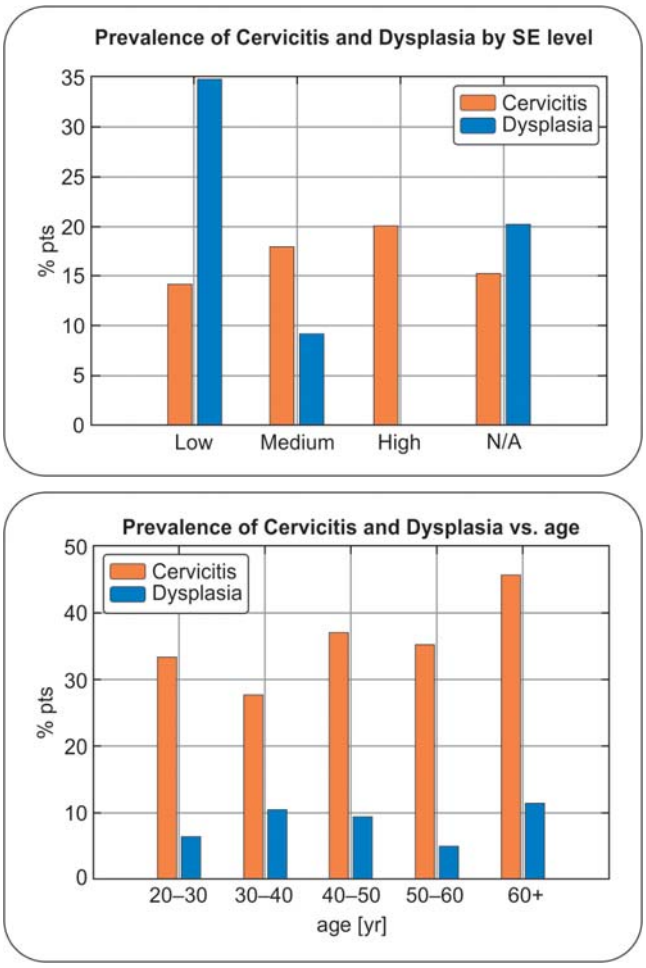

Fig. 4: Prevalence of cervicitis and dysplasia patients by (A) socioeconomic level and (B) age group

outcomes within a single patient cohort, as such, it was not meaningful to calculate statistical significance in this specific study

DISCUSSION

In this study, we compared visual screening for cervical cancer using a cloud-connected mobile colposcope to standard of care conventional cytology, at six sites in southern India. Results of the data aim to assess different clinical outcomes from a single patient cohort. The mobile application in the colposcope was used to record both a clinical decision and socioeconomic information about each patient. Our results showed that approximately 40% of the vis+ positive patients were Pap-, while no Pap+ patients were vis- (Fig. 3). Interestingly, approximately four times as many patients were identified to have cervicitis as with dysplasia, as recorded both on the job aid. The ratio in the cytology results was even higher. Patients identified with dysplasia were more likely to be from lower socioeconomic status, while cervicitis had a higher prevalence among middle income patients (Fig. 4). This is in line with older other studies showing dysplasia rates higher among women from low-socioeconomic groups in India.[19,20]

The most important and striking result in our study was the high observed rates of cervicitis through both visualization and cytology, which averaged across the six sites at 33.8% and 36.7%, respectively (Fig. 3). In contrast, other India studies have shown rates at 5.5% of smears resulting in an inflammatory finding.[17] Notable variations were also observed across the six sites, with cervicitis rates ranging visually from 14-48%, and cytologically from 1-71%. In contrast, dysplasia rates detected visually did not exceed 16%, and were relatively stable in the five sites (9.3%-16%). This finding is particularly intriguing because India has the highest mortality from cervical cancer worldwide[18] and even here cervicitis levels are still substantially higher. For a developing health system like India this information is pertinent to properly planning resource allocation, as cervicitis requires re-screening to ensure it did not mask dysplasia. The additional patient visits further requires a patient tracking system to ensure loss-to-follow-up is minimal, since rates can be as high as 80%.[23] Our data shows that cervicitis is prevalent across all levels of Indian society, and that the antibiotics to treat it should be readily available at gynecology clinics.

In assessing whether there was a relationship between a patient's socioeconomic status and their likelihood of disease, our findings showed a higher prevalence of dysplasia among low income women, and higher prevalence of cervicitis among middle income women (Fig. 4). No high income women had recorded dysplasia, further underscoring this point. These findings are consistent with what has been reported previously in the literature for LMICs broadly, and India in particular.[21,22]

The comparison between different methods of diagnosing cervical dysplasia (visually versus cytology) showed that the rate of Pap+ patients was much lower than vis+ patients at five of six sites (Fig. 3). The cytology results were particularly surprising, as there were only 20 Pap+ patients out of 597 enrolled in the study altogether, for a total rate of 3.3%. A higher positivity

rate was expected given recent studies,[15] even if there are disparities in care in India.

In analyzing the results, we closely examined the data from two urban sites (3 and 4) which had low rates of dysplasia. At site 4, no dysplasia was recorded at all with either method. This clinic generally services higher income women, which could explain the low dysplasia rates, at least in part. At site 3, all the cytology results were negative, while the vis+ rate was 10.3%. What was unexpected here is that site 3 serves a lower and middle income urban population, and have a sliding scale pay system, and so one would expect a higher rates of positive cytology among this patient population.

In addition, findings from visual screening were verified on the EVA System's quality assurance (QA), with expert colposcopists monitoring decisions made by clinicians at various sites. QA was performed periodically throughout the pilot. However, the QA results (not shown) highlighted significant variations between providers, with agreement rates between the reviewer and the point of care clinician ranging between 20-85%. More than anything, the variability in QA agreement rates across sites appears to demonstrate differences in clinical practice, specifically in terms of diagnosis, treatment, and referral. The cytopathology image assessments did not have a QA review, as the images were captured on separate software that did not (yet) integrate with EVA software. Standardization of clinical practices throughout the health system - from screening to diagnosis to treatment to prognosis - will likely further improve outcomes.

In trying to assess how accurate visual and cytological screening were at detecting dysplasia, the protocol called for all patients positive with either screening method to return for a follow up colposcopy with biopsy, as a standard method of histopathology ground-truth. However, only six of the positive patients did return to undergo the follow up colposcopy and confirmatory biopsy at the sites during the study period. The histopathology results that were obtained showed four cases of historically confirmed cervicitis and 2 cases of metaplasia. As such, histopathology data is excluded from this analysis, which is a key limitation of this study. The low rates of histopathology also made it impossible to assess statistically significant differences between the groups. Another limitation is the lack of HPV testing, which would have allowed for better assessing the two methods' negative predictive values.

Although on its face the low return rate for colposcopy and biopsy appears to be loss-to-follow-up, we cannot rule out that the positive patients chose to undergo the procedure at a free government clinic, or alternatively, that the patients needed more time to save for the procedure and by then the study had already concluded. The fact that most of the dysplasia patients were from a low socioeconomic status (Fig. 4) lends credence to this assertion.

Another limitation had to do with care for cervicitis patients, who did not always undergo a follow up visit, as the standard of care varied across the sites; in most cases patients returned after the study concluded. All this suggests that further research into patient health seeking behaviors is needed in order to better understand the decision making process and its implications.

CONCLUSION

Two cervical cancer screening methods were compared in a six-site multi-center trial: standard of care conventional cytology, and visual screening using a mobile colposcope. Overall, many more patients tested positive for suspected cervicitis (33.8% visually and 36.7% cytologically). Cervicitis infections make it difficult to visually identify dysplasia, and affected patients should return to the clinic to ensure dysplasia is not missed. These results suggest that cervicitis should play a major role in planning or resource allocation for many LMIC clinics, but that dysplasia is still critical for very low-income patient populations, that requires additional screening and procedures to minimize loss-to-follow-up.

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Conflict of Interest Statement

CS, CP, and DL were employees of Mobile ODT at the time of the study, and all three owned stock in the company. DL also sits on Mobile ODT's Board of Directors.

Financial Disclosure

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Disclosure Statement

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