Human Papilloma Virus (HPV) DNA Testing and HPV-16/-18 Genotyping Based Cervical Cancer Screening among Gynaecology Clinic Attendees in Two Selected Hospitals, Yangon

Mu Mu Shwe[1], Lynn Pa Pa Aye[1], Kham Mo Aung[1], Nu Nu Lwin[1], Htwe Htwe Nyunt[1], Saw Kler Ku[2], Khin May Thin[2] & Win Maw Tun[1]*

[1]Department of Medical Research
[2]University of Medicine (2), Yangon

Screening women for the presence of Human Papilloma Virus (HPV) is a critical aspect for secondary prevention and early treatment of cervical cancer. This study was aimed to conduct HPV-DNA testing and HPV-16/-18 genotyping based cervical cancer screening among married women and to identify the cervical cytological abnormalities among women who have HPV- infection. It was a prospective cross-sectional descriptive study. Total of 220 married women (median-age 40 years; range 30-60) who had no previous history of cervical cancer screening were studied in two selected-hospitals, Yangon in 2018-2019. Cervical cells were obtained from the cervix by sterile disposable cytobrush and collected in cell-collection-media. HPV-DNA testing and HPV-16/18 genotyping was performed using Cobas4800 system. It is an automated real-time polymerase chain reaction and nucleic acid hybridization test for detection of 14 HR-HPV genotypes. It specifically detects genotypes HPV-16 and HPV-18 while concurrently detecting other 12-HR-HPV types (-31, -33 ,-35, -39, -45, -51, -52, -56 ,-58, -59, -66 and -68) as pooled-12-HR-HPV types. Overall, HPV was determined in 10% (22/220) of screened women. Among HPV positive cases, 50% of cases were vaccine preventable HPV genotypes i.e., HPV-16 was 32% (7/22) and HPV-18 was 18% (4/22) while pooled-12-HR-HPV genotypes were 50% (11/22). Among HPV positive cases, 95.5% (21/22) had cervical cytological abnormalities comprising 27.3% (6/22) had high-grade squamous intraepithelial lesion (HSIL), 45.5% (10/22) had low-grade squamous intraepithelial lesion (LSIL) and 22.7% (5/22) had atypical squamous cells of undetermined significance (ASCUS). Only 4.5% (1/22) were negative for intraepithelial lesion or malignancy (NILM). All HPV-16/18 cases were cervical pre-cancers constituting HSIL 54.5% (6/11) and LSIL 45.5% (5/11). This study highlighted that using HPV-DNA testing followed by HPV-16/18 genotyping technology in cervical cancer screening is beneficial to determine the most high-risk women who may develop cervical cancer. Early detection and effective management can be performed as it is a very useful way to detect cervical pre-cancers and cervical cancers. Thus, it should be considered to apply in National Cervical Cancer Screening Program.

Keywords: HPV DNA testing, HPV 16/18 genotyping, LBC, Cervical cancer screening

INTRODUCTION

According to Global Cancer Statistics 2020, cervical cancer is the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in women worldwide in 2020. Cervical cancer is the most commonly diagnosed cancer in 23 countries and is the

*To whom correspondence should be addressed.
Tel: +95-95193958
E-mail: drmumushwe@gmail.com
DOI: https://doi.org//10.34299/mhsrj.009121

leading cause of cancer death in 36 countries with the vast majority of these countries found in sub-Saharan Africa, Melanesia, South America, and South-Eastern Asia.[1]

According to ICO/IARC Information Centre on HPV and Cancer report (2021), globally, cervical cancer is the second most common female cancer in the woman the women aged 15 to 44 years and the second most common female cancer deaths with an estimated 604,127 new cases and 341,831 deaths in 2020 (GLOBOCAN).[2] In Southeast Asia (SEA), incidence and mortality of cervical cancer are about 68,623 cases and 38,530 deaths respectively.[3] The global burden of cervical cancer is projected to continue to increase, rising nearly 700,000 cases and 400,000 deaths in 2030, with analogous increases anticipated in future years.[4]

This represents a 21% increase in the number of cases and a 27% increase in the number of deaths over the 12-year period. The vast majority of these increases will be in women from LMICs, reflecting the magnitude of the global split in cervical cancer morbidity and mortality. In Myanmar, women at risk for cervical cancer (Female population aged >=15 years) were 20.8 million. It is the second leading cause of female cancer in Myanmar (Kaung Myat Shwe, 2013-2017).[5] But, it is the first most common female cancer and the first leading cause of cancer deaths in women aged 15 to 44 years (IARC 2021). Age standardized incidence rate of cervical cancer were 22.6% in Myanmar, 17.8% in Southeast Asia and 13.3% in the world. Age standardized mortality rate of cervical cancer were 14.4% in Myanmar, 9.9% in Southeast Asia and 7.3% in the world.[6]

The primary cause of precancerous and cancerous cervical lesions is infection with a high-risk or oncogenic HPV type.[7] HPV is a group of viruses that are extremely common worldwide - there are more than 100 types, of which at least 14 cause cancer. A subset of HPV types is responsible for virtually all cases of cervical cancer. HPV 16 and 18, which together are responsible for approximately 70% of cervical cancer worldwide, are the most oncogenic types. Cervical HPV is the most common sexually transmitted infection. The pathogenesis of cervical cancer is the same worldwide. The higher rates of cervical cancer incidence and mortality in LMICs are not attributable to differences in cervical infection with oncogenic HPV types. Instead, they are mainly attributable to the relative lack in both high-quality cervical cancer screening and effective treatment of invasive cervical cancer in LMICs.[8]

In LMICs, cytology-based screening programs have been difficult to implement, and anywhere they have been implemented, the screening coverage is low. Visual inspection of the cervix with acetic acid (VIA), followed by treatment (screen and treat), is an alternative approach to secondary prevention in resource-constrained settings. While relatively easy to establish, the quality of VIA is mainly provider dependent and its sensitivity is quite variable. HPV testing offers superior specificity and its strong negative predictive value means women who test negative only need to be re-tested after a minimum interval of five years.

Providing women with the option of self-sampling contributes and facilitates the acceptability of cervical cancer screening. Existing technological platforms that are being used in countries to test for HIV, tuberculosis and other infections can also be used for HPV testing, enabling rapid scale up. Because of its high level of performance, countries should ideally transition to HPV testing as the primary method of screening for cervical cancer. Evidenced-based strategies for the evaluation and management of women who test HPV positive are available.[9]

In Myanmar, various opportunistic screening activities in recent years have covered less than 1% of the 7.6 million women aged 30-49 who should be screened. This study aimed to conduct Human papillomavirus (HPV) DNA testing and HPV-16/-18 genotyping based Cervical Cancer Screening among

Gynaecology Clinic attendees in two selected hospitals, Yangon and to identify the cervical abnormalities among women who have HPV infection.

MATERIALS AND METHODS

Study population and design

This study was a cross-sectional descriptive study. Total of 220 married women (median-age 40 years; Range 30-60) who had no previous history of cervical cancer screening were studied in OPD of North Okkalapa General and Teaching Hospital and Sanpya General Hospital (Thingangyun) in 2018-2019. After obtaining a written informed consent, a thorough history was taken using structured-proforma. Then, speculum examination was performed under good light source. Cervical cells were obtained from the cervix by sterile disposable cytobrush and collected in Cobas PCR-cell-collection-media.

Those samples were sent to the Technology Development Division, Department of Medical Research (DMR), Yangon at room temperature. Then, samples were stored in 4°C prior to testing Cobas HPV test and LBC.

Laboratory Testing

Human Papilloma Virus Testing

Cobas HPV Test is the clinically validated, US-FDA-approved cervical cancer screening test. It is an automated, polymerase chain reaction and nucleic acid hybridization test. It was performed on the Cobas® 4800 System. This HPV test simultaneously detects a total of 14-HR-HPV types: HPV-16 and HPV-18 individually, pooled-12-HR-HPV genotypes (-31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66- and -68).

All tests were performed according to the manufacturer's instructions. HPV positive and HPV negative control were tested in each run. Each sample was tested for the human ß globin gene. The system was completed by the soft-ware which integrates sample preparation, amplification and detection, and result management.[10]

Liquid Based Cytology (LBC)

One mililitre of the samples was taken and added in 5ml tube and then centrifuged at 8000rpm for 3 minutes. Cell deposits were placed over the glass slide and the cervical smear were made. Then, fixative spray was applied over the cervical Pap smear. Pap staining was done onto the cervical smear slides. Cytological screening was performed using Bethesda system.[11]

Data analysis

All study data were double-entered using Microsoft Excel. Statistical analysis of the data were performed by using Statistical Package for Social Sciences (SPSS-16.0).

Funding

This project was funded by DMR Grant.

Ethical consideration

This study was approved by Institutional Review Board (IRB), Department of Medical Research, Yangon Approval No: Ethics/DMR/2019/010.

RESULTS

A total of 220 married women who had no previous history of cervical cancer screening were studied in OPD of North Okkalapa General and Teaching Hospital and Sanpya General Hospital (Thingangyun) in 2018-2019.

Regarding the baseline characteristics of women who participated in this hospital-based cervical cancer screening, most of the women were 30-39 years (49.5%) (109/220) of age group, followed by 40-49 years (29.5%) (65/220), 50-60 years (20.9%) (46/220). The mean age was 42 years (±SD,8.6 years: range-30-60), mean age of menarche was 14 years (±SD, 1.6 years: range-11-19), and mean age of first marriage was 23 years (±SD, 5.5 years, range-14-46). Most of the screened women had single marriage (95.9%) but 4.1% had second marriage. In Parity, women who were less than parity three

was (58.6%) (128/220) and equal or more than parity three was (41.4%) (91/220). Regarding the education status, (27.7%) (61/220) were graduated, (19.5%) (43/220) were high-school level, (24.5%) (54/220) were middle-school level, (23.6%) (52/220) were primary-school level, and (4.5%) (10/220) were illiterate. Only 4.1% (9/220) women had history of HPV vaccination. According to their symptoms, 21.8% (48/220) had white discharge, (2.3%) had postcoital bleeding, (2.3%) had postmenopausal bleeding, (11.4%) had dyspareunia, (21.4%) had SPA pain, (21.4%) had back pain, and (6.8%) had dysuria respectively.

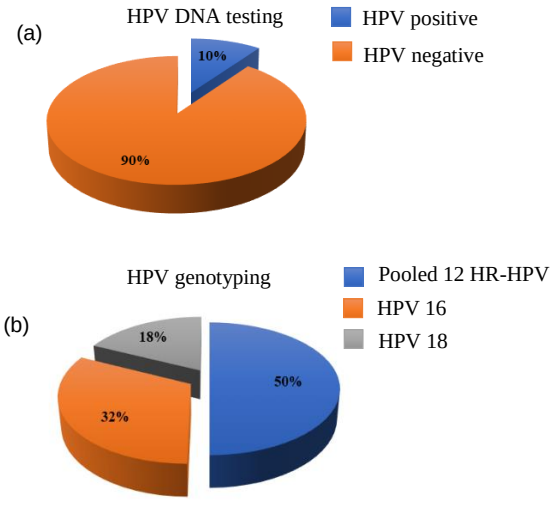

Fig.1. Proportion of (a) HPV infection and (b) HPV genotypes among Gynaecology Clinic attendees in two selected hospitals, Yangon

HPV DNA testing

In this study, HPV was determined in 10% (22/220) of screened women (Fig. 1a). According to percentage of HPV within the age-group, HPV was detected in 7.3% (8/109), 12.3% (8/65) and 13% (6/46) of screened women in the age group of 30-39 years, 40-49 years and 50-60 years respectively (Table1).

HPV genotyping

Among the screened women, detection of HPV-16 genotype was 3.2% (7/220), HPV-18 was 1.8% (4/220) and pooled-12-HR-HPV genotypes were 5% (11/220).

Table 1. Proportion of HPV infection among Gynaecology clinic attendees in two selected hospitals, Yangon according to age

HPV	Age group (Years)			Total
	30-40	40-49	50-60	
HPV positive				
Count	8	8	6	22
% within HPV DNA	36.4	36.4	27.3	100
% within age group	7.3	12.3	13	10
% of total	3.6	3.6	2.7	10
HPV negative				
Count	101	57	40	198
% within HPV DNA	51	28.8	20.2	100
% within age group	92.7	87.7	87	90
% of total	45.9	25.9	18.2	90
Total				
Count	109	65	46	220
% within HPV DNA	49.5	29.5	20.9	100
% within age group	100	100	100	100
% of total	49.5	29.5	20.9	100

Table 2. Proportion of HPV genotype among Gynaecology clinic attendees in two selected hospitals, Yangon according to age

HPV genotype	Age group (Years)			Total
	30-40	40-49	50-60	
HPV 16				
Count	0	4	3	7
% within HPV type	0	57.1	42.9	100
HPV 18				
Count	3	1	0	4
% within HPV type	75	25	0	100
Pooled-12-HR-HPV				
Count	5	3	3	11
% within HPV type	45.5	27.3	27.3	100
Count	8	8	6	22
% within HPV type	36.4	36.4	27.3	100

Among HPV positive cases, 50% of cases were vaccine preventable HPV genotypes i.e. HPV-16 was 32% (7/22) and HPV-18 was 18% (4/22) while pooled-12-HR-HPV genotypes were 50% (11/22) (Fig.1b). According to percentage of HPV genotypes within the age-group, HPV-16 was detected in 57.1% in 40-49 years of age

group and 42.9% in 50-60 years. HPV-18 was detected in 75% in 30-39 years of age group, 25% in 40-49 years. Pooled-12-HR-HPV was determined in 45.5% in 30-39 years of age group, 27.3% in 40-49 years and 27.3% in 50-60 years (Table 2).

Association of HPV infection and genotypes with LBC

Among HPV positive cases, 95.5% (21/22) had cervical cytological abnormalities comprising 27.3% (6/22) had high-grade squamous intraepithelial lesion (HSIL), 45.5% (10/22) had low-grade squamous intraepithelial lesion (LSIL) and 22.7% (5/22) had atypical squamous cells of undetermined significance (ASCUS). Only 4.5% (1/22) were negative for intraepithelial lesion or malignancy (NILM) (Fig. 2a).

Among HPV-16 positive women, 57.1% had HSIL and 42.9% had LSIL (Fig. 2b). In HPV-18 positive women, 50% each had HSIL and LSIL (Fig. 2c). Among pooled-12-HR-HPV positive cases, LSIL (45.5%), ASCUS (45.5%) and NILM (9.1%) were determined. (Fig. 2d). All HPV-16/-18 cases were cervical precancers constituting HSIL 54.5% (6/11) and LSIL 45.5% (5/11) (Fig. 2e).

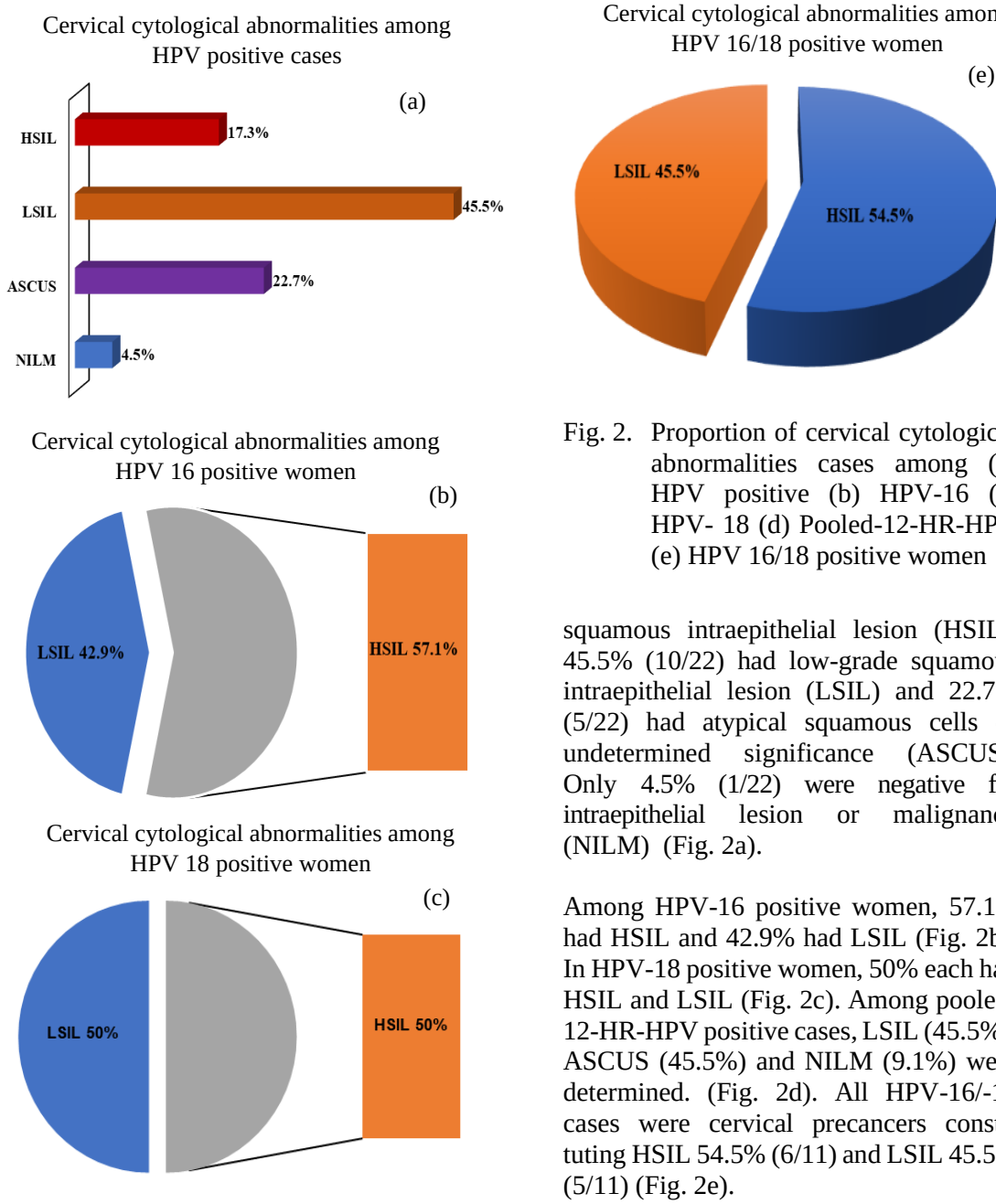

Fig. 2. Proportion of cervical cytological abnormalities cases among (a) HPV positive (b) HPV-16 (c) HPV- 18 (d) Pooled-12-HR-HPV (e) HPV 16/18 positive women

DISCUSSION

Recently in 2020, WHO announced the global strategy to eliminate cervical cancer: as follows (1) a vision of a world where cervical cancer is eliminated as a public health problem (2) a threshold of 4 per 100,000 women-year for elimination as a public health problem (3) the following 90–70–90 targets that need to be met by 2030 for countries to be on the path towards cervical cancer elimination: (a) 90% of girls were fully vaccinated with the HPV vaccine by age 15; (b) 70% of women are screened with a high-performance test by 35, and again by 45 years of age; (c) 90% of women identified with cervical disease receive treatment (4) a mathematical model that illustrates the following interim benefits of achieving the 90-70-90 targets by 2030 in low and lower middle-income countries; (a) median cervical cancer incidence rate is projected to fall 10% by 2030, 70% by 2045 and more than 90% by 2120, averting more than 70 million new cases of cervical cancer (b) cumulative number of cervical cancer deaths averted will be approximately 2 million by 2040, 4.5 million by 2050, 39 million by 2100 and 62 million by 2120.[9]

With the aim of WHO cervical cancer elimination in 2030, Myanmar needs the well-organized national cervical screening program to establish and achieve 70% coverage. Nowadays, various opportunistic screening activities in recent years have covered less than 1% of the 7.6 million women aged 30-49 who should be screened. In 2018, national cervical screening program guideline was introduced in Myanmar, in which, HPV-based cervical screening will be used in rural area but VIA or existing cytology will be used in urban due to limitation of HPV tests. To be optimally effective, cervical cancer screening measures must be scaled to national levels (all stated and divisions) and delivered using health service platforms that are sensitive to women's needs, their social circumstances, and the personal, cultural, social, structural and economic barriers hindering their access to health services. Health services that are integrated, people-centered, and that respect and uphold women's rights and dignity are vital.

Regarding the prevalence of HPV among women with normal cervical cytology in Asia varied: 1.7%-45.6% in China, 2.3%-36.9% in India, 7.6% in Bangladesh, 3.3%-40.6% in Thailand, 1.5%-10.2% in Vietnam, 3.1%-46.7% in Malaysia, 9.3% in Philippines, 8.8%-31% in Indonesia.[2] In ATHENA HPV study (USA), prevalence of HPV was 16.4%. Pooled-12-HR-HPV, HPV-16 and HPV-18 were detected in 12.6%, 2.8% and 1% of women respectively.[12] In Myanmar, Mu Mu Shwe, *et al* investigated the HPV-based cervical cancer screening in general population in which HPV was detected in 5.5% of women residing in North Okkalapa Township, Yangon in 2017[13] and 6.1% of women residing in Magway Region, Myanmar in 2019.[14] In present study,

HPV was determined in 10% of women attending gynaecology clinics in two selected-hospitals, Yangon. Prevalence of HPV in this study was relatively higher than the previous studies[13,14] because this study included symptomatic women who had no previous history of cervical cancer screening.

Regarding age-group, HPV was determined in 7.3% in age group of 30-39 years, 12.3% in age group of 40-49 years and 13% in age group of 50-60 years. Previous study (2011) revealed that most patient infected with HR-HPV were 40-49 years.[15] Annual number of new cases of cervical cancer by age group was the highest among 45-49 years in Myanmar and 50-54 years in SEA regions. Annual deaths number of cervical cancer by age group was mostly seen in 50-54 years in Myanmar and 55-59 years in SEA regions.[13] The present study pointed out that HPV was more detected in older age group. It may be due to persistence of HRHPV and lack of cervical cancer screening in their lives.

Regarding HPV genotypes among HPV-positive cases in general population, HPV-16, HPV-18 and pooled-12-HR-HPV types were 25%, 8.3% and 66.7%, respectively in North Okkalapa Township, Yangon (2017)[13] and 12.5%, 12.5% and 75% respectively in Magway (2019).[14] In the present study, HPV-16, HPV-18 and pooled-12-HR-HPV types were 32%, 18% and 50% respectively. Therefore, the prevalence of HPV16/18 among HPV-positive gynaecology clinic attendees was 50%. HPV-16 was detected in 57.1% in 40-49 years of age group and 42.9% in 50-60 years. This finding indicated that cervical cancer screening should also be added more in older age group if resources are available.

Worldwide, HPV-16/-18 genotypes contribute to over 70% of all cervical cancer cases, between 41%-67% of high-grade cervical lesions and 16-32% of low-grade cervical lesions.[2] In meta-analysis of SEA studies (2019), prevalence of HPV-16/-18 among women with normal cytology, low grade lesion, high grade lesion and cervical cancer were 1.0%, 30.4%, 49.3%, 88.7% respectively in Malaysia and 3.4%, 25.5%, 29.6%, 67.6% respectively in Thailand. The prevalence of HPV-16/-18 among women with normal cytology was 4% in Indonesia, 2.9% in Philippines and 2.1% in Vietnam.[15] In Myanmar (2016), Mu Mu Shwe, *et al* reported that HPV infection and genotypes among cervical cancer cases; HPV was identified in 85.8% of cervical cancer patients attending Central Women Hospital, Yangon. The most prevalent HPV genotype was HPV-16 (63.7%) and HPV-18/45 (17.6%).[17] In the present study, the prevalence of HPV16/18 among gynaecology clinic attendees was 5%. Detection of HPV16/18 was more prevalent in cervical cancer cases than general population. Those findings were similar with other worldwide studies, and previous Myanmar studies and, ATHENA HPV study.[2, 3, 12-14]

Among HPV positive cases, 95.5% had cervical cytological abnormalities, which were HSIL (27.3%), LSIL (45.5%) and ASCUS (22.7%) respectively. Only 4.5% were NILM. Among HPV-16 positive women, HSIL and LSIL were 57.1% and 42.9% respectively. In HPV-18 positive women, 50% were HSIL and 50% were LSIL. In pooled-12-HR-HPV-positive-cases, 45.5% were LSIL, 45.5% were ASCUS, and 9.1% were NILM. All HPV-16/-18 cases were cervical pre-cancers constituting HSIL (54.5%) and LSIL (45.5%). In previous study of community-based study in North Okkalapa Township[13], among HPV-16 positive women, all women had abnormal cytology comprising 33.3% of each had ASC/AGC, LSIL and HSIL. All HPV-18 positive cases were LSIL. Of the pooled-12-HR-HPV positive women, 62.5% had abnormal cytology comprising 50% LSIL and 12.5% ASCUS.

HPV-based cervical cancer screening in Myanmar indicated that less than 10% of HPV positive women were needed to attend regular follow up and further management. If there are resources for HPV genotyping, the number of cases for colposcopy and biopsy will be reduced. According to this study, only 5% of gynaecology clinic attendees i.e, HPV16/18 positive cases will be needed for colposcopy and biopsy. Therefore, the burden of health care providers for further management will also be reduced. In rural areas of Myanmar, there are low human resources for primary health care. It will be one of the major obstacles to achieving the success of National cervical cancer screening program in Myanmar.

To reduce the incidence and mortality of cervical cancer, successful implementation of well-organized National cervical screening program is necessary. This will require political commitment and greater international cooperation and support for equitable access, including strategies for resource mobilization. Primary HPV DNA testing followed by HPV genotyping takes very crucial role for the early detection of cervical cancer. Currently, HPV testing alone or with cytology triage is used as a primary screening approach for detection of cervical pre-cancer and cancer. HPV DNA testing has been shown to be efficacious in screening for precancerous cervical lesions. Primary HPV screening test is very useful which do not lead more

unnecessary referrals. Negative HPV test is more reassuring than a negative cytological test, as the cytological test has a greater chance of being falsely negative, which could lead to delays in receiving the appropriate treatment.

Conclusion

This study highlighted that using HPV-DNA testing followed by HPV-16/18 genotyping technology in cervical cancer screening is beneficial to determine the most high-risk women who may develop cervical cancer. By doing this, early detection and effective management can be performed. It is a very useful way to detect cervical pre-cancers and cervical cancers so that it should be applied in National Cervical Cancer Screening Program.

Competing interests

The authors declare that they have no competing interests.

ACKNOWLEDGEMENT

We would like to express their sincere gratitude to Director General, Department of Medical Research for allowing to conduct this study. We are much grateful to all Obstetric and Gynecologists, midwifes from Out Patient Departments of North Okkalapa General and Teaching Hospital and Sanpya General Hospital (Thingangyun) and all Research Assistants from Technology Development Division, Department of Medical Research and all the women participating in this research.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I & Ahmedin Jemal A Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of incidence and mortality world-wide for 36 Cancers in 185 Countries**.** *CA Cancer Journal for Clinicians. 2021; 71(3): 209*-249 https:// doi.org /10.3322/caac .21660.
2. Bruni L, Albero G, Serrano B, Mena M, Collado JJ, Gómez D, *et al*. ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and related diseases in the World. *Summary Report* 22 October 2021. [Internet] Available from: https://hpvcentre.net/ statistics/ reports /XWX.pdf
3. Bruni L, Albero G, Serrano B, Mena M, Collado JJ, Gómez D, *et al*. ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre). Human papillomavirus and related diseases in Asia. *Summary Report* 22 October 2021. [Internet] Available from: https:// hpvcentre .net /statistics/ reports /XSX.pdf
4. IARC. Global Cancer Observatory (GLOBO-CAN) Cancer Tomorrow 2018 Estimates. [Inter-net] Available from: https://gco.iarc.fr/tomorrow.
5. Kaung Myat Shwe, Soe Myat Win, Aye Nyein Thant, Aung Myo Sat Htay, Hlwan Moe Han & Naw Hsah Ka Paw. Cancer Incidence and Mortality in Central Myanmar: Report of Nay Pyi Taw Population-Based Cancer Registry. *Asian Pacific Journal Cancer Prevention*. 2022 Jan; 23(1): 311–318. doi: 10.31557 /APJCP .2022. 23.1. 311.
6. Bruni L, Albero G, Serrano B, Mena M, Collado JJ, Gómez D, *et al*. ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases in Myanmar. *Summary Report* 22 October 2021. [Internet] Available from: https:// hpvcentre. net /statistics /reports /MMR .pdf
7. Wardak S, Human Papillomavirus (HPV) and cervical cancer. *Medycyna Doswiadczalna i Mikrobiologia*. 2016; 68:73.
8. World Health Organization. HPV and cervical cancer (2020) [Internet]. Available from: http://www.who.int/
9. World Health Organization. WHO cervical cancer elimination strategy (2020). [Internat] Available from: http:// www.who.int/.
10. Roche Cobas 4800 Molecular System (http://hpv16 and 18.com/hcp/HPV-Test-FDA approval)
11. Nayar R, Wibur DC. The Pap test and Bethesda 2014. *Acta Cytologica* 2015; 59:121-132.

12. Wright TC, Stoler MH, Behrens CM, *et al.* The ATHENA human papillomavirus study: Design, methods, and baseline results. *American Journal Obstetrics Gynecology* 2012; 206: 46. e1-114

13. Mu Mu Shwe, Kyi Kyi Nyunt, Win Maw Tun, *et al*. Community-based Cervical Cancer Screening using Cobas HPV test and LBC in married women living in North Okkalapa Township, Yangon.*46th Myanmar Health Research Congress* 2018; Jan 8-12; Yangon, Myanmar. p.57.

14. Mu Mu Shwe, Khin May Thin, Win Maw Tun *et al*. Human Papillomavirus (HPV) DNA testing based Cervical Cancer Screening in Magway Region. *Myanmar Health Sciences Research Journal* 2021; 33(1-3): 74-82.

15. Mu Mu Shwe, Teruo Harano, Shigeru Okada, *et al.* Prevalence of HR-HPV infection among women with normal and abnormal cervical cytology in Myanmar. *Acta Medica Okayama* 2014; 68(2): 79-87.

16. Bruni L, Albero G, Serrano B, *et al.* ICO/IARC Information Centre on HPV and Cancer. Human Papillomavirus and related diseases in Myanmar, 2019.

17. Mu Mu Shwe, San San Myint, Yin Yin Soe, *et al.* Detection of high risk HPV genotypes using GeneXpert HPV assay among cervical cancer patients in Myanmar. *6th Annual Symposium on Global Cancer Research*, New York, USA 15th March 2018. (Poster)