(RESEARCH ARTICLE)

# The profile of cervical dysplasia and cervical cancer of patients at MRCCC siloam Hospital Semanggi

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## Abstract

Cervical cancer is one of the most common cancers found in Indonesia however it has not yet been properly resolved. Anatomical pathology archive data of histopathological features from cervical dysplasia and cancer lesions of 108 patients, who met the inclusion criteria, at MRCCC Siloam Hospital Semanggi in 2018 to 2020 are collected. This study is using retrospective design. Techniques were used to get the specimens are 66.7% cervical biopsy and 33.3% hysterectomy. There were 21.3%, 40.7% and 38% patients who were diagnosed with cervical dysplasia or cancer respectively in 2018, 2019 and 2020. Most of them who were diagnosed with cervical dyplasia lesions at the age of 20-29 and those with cervical cancer were at the age of 40-49. HPV DNA examination results show 21.3% were positive for High-Risk HPV types and 1.9% had positive results for a combination of High-Risk and Low-Risk types, which HPV type 16 was found the most. Histopathological examination intepretations of patients with dyplasia shows 61.9% had LSIL and 38.1% had HSIL. Those with cervical cancer shows 65.2% had squamous cell carcinoma and 34.8% had adenocarcinoma. Risk factors have important role in cervical dysplasia that can develop into cervical cancer, especially HPV infection. Routine test and histopathological examination are the only way to find out the possibility of cervical dysplasia/precancerous lesion or cancer so patients could receive prompt and appropriate management sooner.

Keywords: Histopathology; Cervical cancer; Cervical dysplasia; HPV

## 1. Introduction

Cervical cancer is one of the most common causes of death due to malignancy in women and occupies the 4th position in the worlds as most frequently diagnosed malignant tumors [1]. In 2018, there were around 570,000 cases of cervical cancer with 311,000 cases caused death. [2]. The Global Cancer Observatory (Globocan) through the International Agency for Research on Cancer (IARC), noted that in 2020 cervical cancer cases increased by 604,127 new cases and is ranked number 4 as most new cases of cancer in the world. Meanwhile, the death rate from cervical cancer increased by 341,831 new cases and is ranked number 4 as death caused by cancer. The 5-year prevalence of cervical cancer is 1,495,211 cases [3; 4]. Cervical cancer was ranked 19th most new cancer cases in Europe. The death rate of cervical cancer was ranked number 19 for the most deaths due to cancer [5]. In Germany, Netherlands and USA cervical cancer are ranked respectively number 21, 22 and 21 as cancer cases and number 21, 21 and 19 as cancer that causing death [6;7;8]. Cervical cancer cases increased by 351,720 new cases and were ranked 9th most new cancer cases in Asia while the death rate due to cervical cancer increased by 199,902 cases and was ranked 9th in the most cancer-related deaths. [9]. Cervical cancer in Singapore, Mayalsia and Indonesia are respectively ranked number 17, 11 and 2 for the newest cancer cases and as cause of cancer death are ranked number 16, 12 and 3 [10;11;12]. In 2018, a study at Cipto Mangunkusumo Hospital noted that in 2013 cervical cancer was ranked as the 2nd most common cancer case [13].

Cervical cancer has always been associated with HPV infection. Around 99.7% of cervical cancer cases are caused by persistent infection of HPV, which is classified as the High-Risk type [14]. HPV as double-stranded DNA virus have more than 150 known types and about 50 types can infect human mucosa. They are classified into 2 groups, namely High-Risk and Low-Risk type. High-Risk types are type 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. Some studies say that types 16 and 18 are the most frequently found that cause cervical cancer. HPV type 18 is reported to have a greater role in cervical cancer than type 16. In Indonesia, HPV type 52 has the highest prevalence, followed by type 16 and 18. [15]. HPV infection is a sexually transmitted disease, so it is most often found in women who sexually active, with the highest prevalence around the age of 25, and cervical cancer peaks at the age of 40 to 50 years, leading to death [16].

Other risk factor that can increase the incidence of cervical cancer in women is infection of human immunodeficiency virus (HIV). This could significantly increase risk of infection of high-risk types of HPV[2; 17]. In addition, interestingly women who have many sexual partners, whether infected or not infected with HPV, can increase the risk of cervical cancer [18]. The use of oral contraceptives, especially in the long term, also increases the risk of developing cervical cancer, especially adenocarcinoma [19].

The research aims to determine the histopathological feature in patients with cervical dyplasia and cancer also to confirm risk factor(s) the patients had. The data from year 2018 to 2020 was collected from MRCCC Siloam Hospital Semanggi.

## 2. Literature Review

In 1976 Prof. Herald zur Hausen, a virologist from Germany, is the first who made hypothesis about HPV as a cause of cervical cancer. In 1980, zur Hausen discovered HPV type 6 and 11 in female genital warts but he had lack of DNA in the samples. In 1984, he found type 16 and type 18 in cervical cancer samples. After further research he stated that HPV type 6 and 11 have more frequent prevalence in female genital warts meanwhile type 16 and 18 have more frequent prevalence in cases of cervical cancer. This discovery won the Nobel Prize in Physiology or Medicine in 2008 [20].

HPV is a member of the papovaviridae family that is round with diameter of 55 nm and not sheathed. [14] It has a tight cutaneous and mucosal epithelium tropism, especially in the oropharynx and anogenital tract [21]. It is categorized as a sexually transmitted infection (STI) [22]. Some studies also state that HPV can be transmitted only by direct skin-skin or skin-mucosa contact, and even transmission of HPV is also found vertically from mother to her child through amniotic fluid, placenta, or contact with maternal genital mucosa at birth [23].

The classification of HPV is used primarily for genital mucosa based on its level of oncogenicity. Low-Risk category induces hyperproliferative lesions but rarely develop into cancer and High-Risk category induces dysplasia that will develop into invasive cancer [21]. In infected cells, the HPV genome exists as an extrachromosomal element (episome) consisting of about 8 kilobase pairs encoding 6-8 open reading frames (ORF). With limited coding capabilities, virus can manipulate DNA replication capabilities and host cell repair mechanisms to aid their replication [24]. The virus life cycle is closely related to the differentiation of the mucosal epithelium from the host which are keratinocytes, and therefore the replication phase of the HPV life cycle is confined to the differentiation of the basal cells of epithelium [21]. After the virus enters body through micro-lesions in basal cells, there will be a temporary amplification of cell replication up to 50-100 copies per cell, and the genome of HPV is maintained at a stable copy number in undifferentiated basal cells and continues to replicate with DNA in cells [24].

HPV has two promoters known as early and late ones, to regulate gene expression that are activated at different life cycle phases. The early promoters, p97 for type 16 & 31 and p105 for type 18, are located at the top of ORF E6. They regulate early gene expression in undifferentiated cells but remain active during cell differentiation. The late promoters, p742 for type 31, p670 for type 16 and p811 for type 18, are located at ORF E7. They are activated during epithelial differentiation to induce the expression of delayed genes, including capsid genes L1 and L2 [21]. Expression of E6 and E7 allows virus life cycle to repeat after cell differentiation, whereas expression of L1 and L2 promotes capsid formation in the newly replicated genome and release of the virus from the overlying epithelium [24]. The long control region (LCR) or also known as the upstream regulatory region (URR), is a regulatory region that contains the keratinocyte strengthening region, the origin of replication, and the initial promoter. In LCR region can also be found a variety of binding sites for transcription factors and viral helicase E1 and E2 viral proteins contribute to the replication and regulation of gene expression [21].

During basal cell division, viral DNA partitions into daughter cells which migrate away from the basal cell layer and initiate terminal differentiation. Epithelial differentiation induces the reproductive phase of the virus life cycle and will activate the slow promoter and slow expression of viral genes (E4, E5, L1, and L2), as well as high levels of E1 and E2,

which encourage amplification of viral genome replication to thousands of copies per cell. Virus assembly and release can only occur in the uppermost layer of the epithelium because the immunogenic capsid proteins L1 and L2 will only be expressed in highly differentiated suprabasal cells. After epithelial cells complete their differentiation, the E6 and E7 proteins will deregulate cell proliferation and apoptotic mechanisms by targeting the p53 and pRb proteins. E7 promotes degradation of pRb, resulting in aberration of transcription factor activity, and promotes re-entry of the cell differentiation phase to provide a competent site of viral replication. This unscheduled event causes p53 to induce cell cycle arrest or apoptosis of infected cells, but E6 aborts the action of p53 by targeting it for degradation [21].

HPV DNA examination is more effective in screening cervical cancer cases than cytological examination [25]. In April 2014, the Roche cobas HPV test, the primary screening test for cervical cancer, in women aged 25 years and over, was made and it was the first time an HPV screening test was approved by the Food and Drug Administration (FDA) to replace the Pap test as the main screening for cervical cancer. The test can screen 12 High-Risk HPV genotypes in a direct reaction and is based on Real-Time PCR amplification targets [26].

A cervical biopsy is performed to establish the diagnosis of precancer or cancer. A biopsy usually takes a small piece of tissue suspected of having a change [27]. Before a biopsy is performed, Visual Inspection of Acetic Acid (VIA) test is conducted. The entire surface of the cervix will be smeared with 5% acetic acid, and if discoloration appears on the surface of the cervix into acetowhite lesions, a biopsy will be performed in that area. Usually, bright white lesions indicate low-grade lesions, and pale grey lesions indicate high-grade lesions [28].

Hysterectomy is an operation to remove part or all uterus and is often performed on patients with cervical dysplasia or cancer who no longer wish to have children. After hysterectomy, patients can usually carry out normal daily activities after 3-6 weeks [29]. Cervical dysplasia/precancerous lesions are characterized by manifestations of dysplasia in cervical epithelial cells, which normally consist of stratified squamous epithelial cells, simple ciliated columnar epithelium, and the transition area between the two epithelia which is known as the transformation zone or squamocolumnar junction (SCJ). WHO classifies cervical dysplasia into three categories, named cervical intraepithelial neoplasia 1 (CIN1), CIN2 and CIN3. This CIN category shows the degree of development and progression of dysplasia in cervical epithelial cells. In normal cervical tissue, squamous epithelial tissue will be well arranged and as it moves toward the surface, the epithelial cells will develop to maturity. In CIN1, mild dysplasia can be found, especially in the lower 1/3 of the squamous epithelium, and there are koilocytosis in the superficial part. In CIN2, moderate dysplasia can be found that has reached 2/3 of the epithelial tissue and begins to show variations in cell size, heterogeneity of chromatin and the presence of mitosis with some atypical cells. Superficial part of the epithelium shows differentiation and koilocytosis changes. CIN 3 is characterized by almost complete loss of differentiation with greater cell variety and size, chromatin heterogeneity, irregular cell orientation, abnormal mitosis, changes affecting the entire epithelial layer, and usually absent koilocytosis changes. In 2014, Bethesda system has made category system for reporting the level or degree of cervical dysplasia by classifying cervical dyplasia into two categories that relate to the existing WHO categories that are low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL). [27;31].

Cervical cancer has several definitions. According to various studies cervical cancer originates from tissue of cervix that is infected with HPV and grow uncontrollably slowly that in the beginning shows no symptoms [32;33]. According to the Indonesian Ministry of Health, cervical cancer is a malignancy that can be found in cervical tissue, which is in the lowest part of the cervix. It is one of the most common types of cancer in Indonesia both for inpatients and outpatients [34]. Cervical cancer is most often caused by persistent oncogenic or High-Risk HPV infection. HPV infection most often occurs during puberty and pregnancy for first time, after which it will slowly decrease after the menopause phase [14]. A study in 2008 in Indonesia reported that HPV type 52, 166 and 28 had the highest prevalence in Jakarta and Bali [15].

Approximately 5.5-11% of all cervical cancer cases are reported as not infected with HPV. This could happen because of unclear etiology or sometimes because of false negative HPV. HPV-negative cervical cancer is often diagnosed as advanced stage and has a poor prognosis. [35] Several studies state that the pathomechanism of cervical cancer with negative HPV is suspected to be due to mutations in tumor-related genes such as TP53, PIK3CA, and CDKN2A [36].

The risk factors for cervical cancer are age, HIV infection, sexual behaviour, oral contraceptives, vaginal microbiota, smoking habits, multiparity, and socioeconomic status [38; 39]. Almost everyone can be infected with HPV, especially sexually active men and women. However, infection from HPV can be overcome by immune system, and finally, there will be cleaning of the infection [40]. High-Risk HPV infection can occur due to virus entry through microlesions in keratinocytes in the basal layer that has not yet differentiated and is actively proliferating [21]. In most cases, the infection will be resolved by the body's immune system response and the role of the normal flora in the cervix, but in some cases, there can be persistent infection for years or even decades. This persistent infection will cause the

progression of epithelial cells into dysplasia known as CIN or LSIL, but regression can occur so that the epithelia can return to normal if the HPV infection can be resolved. If the infection persists and HPV can integrate with the host cell genome, clonal expansion will occur and can result in invasive cancer [41],

**Table 1** Mucosal HPV Types and Associated Major Diseases [37]

| HPV type | | Disease (% Cases) |
|---|---|---|
| Mucosa High-Risk Type | 16 | Cervical squamous cell carcinoma (50) Cervical adenocarcinoma (35) Oropharyngeal cancer (25) |
| | 18 | Cervical squamous cell carcinoma (20) Cervical adenocarcinoma (35) Oropharyngeal cancer (1-3) |
| Low-Risk Type Mucosa | 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 | Squamous cell carcinoma (30) Minority of oropharyngeal cancer |
| | 6, 11 | Benign lesions of the genitals Respiratory papillomatosis |
| | 13, 32 | Oral focal epithelial hyperplasia |

Squamous cell carcinoma develops from HSIL due to the expression of the oncogenes E6 and E7 on replicating epithelial cells and requires a 20–30 year process. Hypermethylation of CpG islands in the promoter region of tumor suppressor genes has been identified as a molecular alteration. In addition, more than 70% of cervical squamous cell carcinoma cases found genomic alterations in one or both of the PI3K/MAPK and TGF-B pathways. ERBB3 (HER3), CASP8, HLA-A, SHKBP1, and TGFBR2 were also reported as significant gene mutations, and in almost all cases, there was strong and diffuse overexpression of p16 in the nucleus and cytoplasm [42].

Adenocarcinoma is characterized by atypical glandular cells exhibiting nuclear changes such as enlargement, hyperchromatic, coarse chromatin granulation, and having many irregular nuclei [27]. This cancer is found in almost all cases associated with infection with HPV type 16 and 18. Oncoproteins E6 and E7 inactivate p53 and RB1, respectively, and this inactivation is associated with the integration of HPV into the host's genome, genomic instability, and somatic mutation accumulation. Hypermethylation of CpG islands is rare or only mild, but mutations of KRAS are common [42].

## 3. Research Method

This research uses a descriptive research method with a retrospective study. This study used secondary data from the archives of the Anatomical Pathology Laboratory of MRCCC Siloam Hospital Semanggi from January 2018 to December 2020. This research was conducted from April 2021 until November 2021. The specified study population was all patients diagnosed with cervical dyplasia or cancer. The research sample was selected using the total sampling method in which all subjects who met the inclusion criteria were included in the study. Data processing was carried out through several stages, namely the stages of editing, tabulation, and data analysis. The statistical analysis used is descriptive statistics using frequency analysis. The identities of patients are confidential and are not included in research reports and publications.

## 4. Results and discussion

In this study, as many as 108 patients who were included in the inclusion criteria. The variables used in this study were obtained from these patients: age data, HPV DNA examination, specimen collection techniques for histopathological examination, and histopathological diagnosis.

The table shows distribution of patients diagnosed with cervical dysplasia and cancer during the pre-pandemic and the pandemic, it was found that the frequency numbers obtained did not change. Meanwhile, in 2018, the frequency obtained was 23; this might be due to unspecified factors. According to data provided by the Global Cancer Observatory

or Globocan through the International Agency for Research on Cancer (IARC), cervical cancer rates in pandemic era have not experienced a significant increase or decrease [4].

**Table 2** Frequency Distribution of Patients with Cervical Dysplasia and Cervical Cancer in 2018-2020

| Year | Frequency | Percentage (%) |
|------|-----------|----------------|
| 2018 | 23 | 21.3 |
| 2019 | 44 | 40.7 |
| 2020 | 41 | 38 |
| Total | 108 | 100 |

**Table 3** Frequency Distribution of Histopathological Diagnosis of Patients with Cervical Dysplasia and Cervical Cancer in 2018

| Year | Frequency | Percentage (%) |
|------|-----------|----------------|
| LSIL | 6 | 26.1 |
| HSIL | 4 | 17.4 |
| Adenocarcinoma | 6 | 26.1 |
| Cell Carcinoma Squamous | 7 | 30.4 |
| Total | 23 | 100 |

**Table 4** Frequency Distribution of Histopathological Diagnosis of Patients with Cervical Dysplasia and Cervical Cancer in 2019

| Year | Frequency | Percentage (%) |
|------|-----------|----------------|
| LSIL | 5 | 11.4 |
| HSIL | 9 | 20.4 |
| Adenocarcinoma | 14 | 31.8 |
| Cell Carcinoma Squamous | 16 | 36.4 |
| Total | 44 | 100 |

**Table 5** Frequency Distribution of Histopathological Diagnoses in Patients with Cervical Dysplasia and Cervical Cancer in 2020

| Year | Frequency | Percentage (%) |
|------|-----------|----------------|
| LSIL | 15 | 36.6 |
| HSIL | 3 | 7.3 |
| Adenocarcinoma | 3 | 7.3 |
| Cell Carcinoma Squamous | 20 | 48.8 |
| Total | 41 | 100 |

**Table 6** Age Group Frequency Distribution of Patients with Cervical Dysplasia

| Age | Frequency | Percentage (%) |
|---|---|---|
| ≤ 20 | 0 | 0.0 |
| 20-29 | 20 | 47.6 |
| 30-39 | 13 | 31.0 |
| 40-49 | 5 | 11.9 |
| 50-59 | 3 | 7.1 |
| 60-69 | 1 | 2.4 |
| ≥ 70 | 0 | 0.0 |
| Total | 42 | 100 |

**Table 7** Age Group Frequency Distribution of Patients with Cervical Cancer

| Age | Frequency | Percentage (%) |
|---|---|---|
| ≤ 20 | 0 | 0.0 |
| 20-29 | 1 | 1.5 |
| 30-39 | 19 | 28.8 |
| 40-49 | 21 | 31.8 |
| 50-59 | 14 | 21.2 |
| 60-69 | 9 | 13.6 |
| ≥ 70 | 2 | 3.0 |
| Total | 66 | 100 |

**Table 8** Frequency Distribution of Patients with Cervical Dysplasia Undergoing HPV DNA Examination

| HPV DNA testing | Frequency | Percentage (%) |
|---|---|---|
| (+) High-Risk | 20 | 47.6 |
| (+) High-Risk  & Low-Risk | 3 | 7.1 |
| No test | 19 | 45.2 |
| Total | 42 | 100 |

**Table 9** Description of the Results of HPV DNA Examination in Patients with Cervical Dysplasia

| HPV DNA testing | Frequency | Percentage (%) |
|---|---|---|
| (+) 1 type | 13 | 56.5 |
| (+)Multiple | 9 | 39.1 |
| (+) No Description | 1 | 4.3 |
| Total | 23 | 100 |

The highest cases of cervical dysplasia at the hospital is at age 20-29. namely 20 patients (47.6%). followed by age 30-39 as many as 13 patients (31%). Meanwhile. age group for the highest cases of cervical cancer was at age 40-49 which are total of 21 patients (31.8%) and followed by the age group of 30-39 years as many as 19 patients (28.8%). The results in accordance with a study by Fowler JR et al. that noted the highest prevalence of High-Risk HPV infection was at the age of 25. and cases of cervical cancer peaked at the age of 40-50. [17] This kind of study was also conducted by Quinn BA et al. who stated that cervical cancer is most often diagnosed in women aged 35-44 [38].

The International Agency for Research on Cancer (IARC) records reproduction related activities of women in Indonesia aged 15-44. Based on data. the average number of women having sexual intercourse for the first time is between the ages of 19-22. Multiparity as another risk is also common in Indonesia because average number of children that women giving birth to is 2 (more than 1) [44]. In addition. having multiple sexual partners is also an important factor because it can cause microlesions in the cervix that can increase the risk of infection with HPV [45]. Persistent HPV infection that can progress to cervical cancer takes about 5-10 years [39]. If the age of a woman having sexual intercourse for the first time is at the age of 20 and we add 10 years as HPV duration to cause both dysplasia or cancer than it could be detected at the age of 30. It is in accordance with the available data obtained from the hospital.

**Table 10** Frequency Distribution of Patients with Cervical Cancer Conducting HPV DNA Examination

| HPV DNA testing | Frequency | Percentage (%) |
|---|---|---|
| (+) *High-Risk* | 2 | 3 |
| No test | 64 | 97 |
| Total | 66 | 100 |

**Table 11** Information on Results of HPV DNA Examination in Patients with Cervical Cancer

| HPV DNA testing | Frequency | Percentage (%) |
|---|---|---|
| (+) No Description | 2 | 100 |
| Total | 2 | 100 |

The results of HPV DNA examination were obtained in patients diagnosed with precancerous lesions and cervical cancer at the hospital. Twenty-three patients (21.3%) found positive for High-Risk HPV types and 2 patients (1.9 %) were positive for the combination of High-Risk and Low-Risk HPV types. In comparison. 83 patients (76.9%) did not take a test out of a total of 108 patients. The large number of patients who do not take the test is caused by the patients have already been diagnosed with cervical cancer. and a biopsy or hysterectomy is the only thing important to perform to confirm the diagnosis. That is why HPV DNA examination is deemed unnecessary or some patients are referral.

Persistent High-Risk HPV infection causes almost all cervical dysplasia and cancer [40]. In patients infected with the High-Risk type of HPV. multiple-types infections are often found and can increase the occurrence of persistent infections and lead to cervical cancer [46]. Infection with High-Risk and Low-Risk types of HPV is also frequently found. and research. according to Sundstrom K et al.. states that co-infection of the two types can reduce the risk of progression to invasive cancer and takes longer to develop diagnosis compared with women infected only with the High-Risk strain [47]. In a study conducted by Hasanzadeh M et al.. it was found that patients infected with both types of HPV have an increased risk of developing genital warts and persistent HPV infection. which are important precursors in the occurrence of dysplasia of the cervix [48]. The results of these two studies seem contradictory. but keep in mind that our body has an immunological response that can rid our body of HPV infection. so if the result of co-infection can occur a prolongation of the progestative period for cervical cancer. the body's immune system will have a longer time to respond trying to overcome the infection from the HPV [40].

Examination of HPV DNA is important because it is stated to be the most effective test for early detection. [25] Good early detection tests are performed on women aged 21 years or after having sexual intercourse for the first time. [45] However. HPV DNA testing is still not a standard for early detection in Indonesia that relies more on VIA and pap smear tests that might be because they are more available and have lower price [43].

**Table 12** Description of HPV DNA Examination Based on Type in Patients with Cervical Dysplasia

| Type | | Frequency | Percentage (%) |
|---|---|---|---|
| *High-Risk* | 16 | 10 | 27.8 |
| | 18 | 1 | 2.8 |
| | 31 | 1 | 2.8 |
| | 33 | 1 | 2.8 |
| | 39 | 2 | 5.5 |
| | 40 | 1 | 2.8 |
| | 42 | 1 | 2.8 |
| | 45 | 1 | 2.8 |
| | 51 | 1 | 2.8 |
| | 52 | 2 | 5.5 |
| | 53 | 4 | 11.1 |
| | 58 | 1 | 2.8 |
| | 59 | 1 | 2.8 |
| | 61 | 1 | 2.8 |
| | 66 | 1 | 2.8 |
| | 68 | 1 | 2.8 |
| | 82 | 1 | 2.8 |
| *Low-Risk* | 11 | 2 | 5.5 |
| | 43 | 2 | 5.5 |
| | 44 | 1 | 2.8 |
| Total | | 36 | 100 |

The results of the HPV DNA examination that HPV Type 16 was the most. with ten incidents (27.8%). followed by HPV Type 53. with four incidents (11.1%) out of a total of 36 incidents. The results of a meta-analysis of several studies state that HPV Types 16. 18. 31. 33. and 45 are the cause of invasive cervical cancer cases worldwide [49]. In a study conducted by Vet JNI et al. in Indonesia. HPV type 52 had the highest prevalence. followed by HPV types 16 and 18. [15] HPV type 16 was found more often in cervical squamous cell carcinoma patients. [39] Meanwhile. in a study conducted at Cipto Mangunkusumo Hospital and Dharmais Cancer Hospital. patients with cervical adenocarcinoma were found most often HPV type 18. followed by HPV type 45 [50]. A study conducted at Dr. Kariadi Semarang and Salatiga Hospital found that HPV type 52 was the most dominant in patients infected with HIV [51].

The results obtained in this study are different from the results of existing studies because not all patients undergo HPV DNA testing.

**Table 13** Frequency Distribution of Specimen Collection Techniques for Histopathological Examination

| Retrieval Technique | Frequency | Percentage (%) |
|---|---|---|
| Cervical Biopsy | 72 | 66.7 |
| Hysterectomy | 36 | 33.3 |
| Total | 108 | 100 |

Cervical biopsy and hysterectomy are specimen collection techniques used for histopathological examination of dysplasia and cervical cancer. It was found that most cervical biopsies were performed. namely 72 cases (66.7%) of a total of 108 cases. Cervical biopsies are most often performed with positive VIA and/or pap smear test indications. while hysterectomy is performed in patients who have experienced HSIL malignancy or precancerous lesions. as well as in patients who are not planning to give birth with the aim of a better patient prognosis.

**Table 14** Frequency Distribution of Histopathological Diagnoses with Cervical Dysplasia

| Histopathological Diagnosis | Frequency | Percentage (%) |
|---|---|---|
| LSIL | 26 | 61.9 |
| HSIL | 16 | 38.1 |
| Total | 42 | 100 |

It was found that the most common dysplasia were found at the LSIL level in 26 patients (61.9%) of a total of 42 patients with a pathological diagnosis of cervical dysplasia. The American Society for Colposcopy and Cervical Pathology (ASCPP) noted in 2019 that from the overall results of Pap smear tests conducted from 2003-2017 in women aged 25-65 years. LSIL results were 1.7% and HSIL were 0. 3%. [52] In a study by Liu Y et al.. it was found that the onset of LSIL was most commonly found at the age of 20-34 years. while the onset of HSIL was most often found at the age of 35-49 years. [53]

LSIL is caused by a transient HPV infection that is self-limiting and usually lasts for approximately two years and may regress so that the cervical epithelium may return to normal. or the HPV infection may become persistent and increase the risk of progression to HSIL or even invasive cancer. [30] In a study by Bruno MT et al.. it was found that 82.1% of women with LSIL regressed within two years. while 1.5% of women experienced progression to HSIL within three years. [54]

The results obtained can be adjusted to the results of existing studies because the majority of patients included in the inclusion data were aged 20-49 years. and most patients had cervical biopsies/hysterectomies due to patients experiencing cervical complaints. so they did an examination and found histopathological results in the form of LSIL.

**Table 15** Frequency Distribution of Histopathological Diagnoses with Cervical Cancer

| Histopathological Diagnosis | Frequency | Percentage (%) |
|---|---|---|
| Adenocarcinoma | 23 | 34.8 |
| Squamous cell carcinoma | 43 | 65.2 |
| Total | 66 | 100 |

In the table above. squamous cell carcinoma was the most common pathological diagnosis. namely 43 out of 66 patients (65.2%) with a pathological diagnosis of cervical cancer. Overall. adenocarcinoma of the cervix is more frequently began with infection of HPV types 18. 45. and 52 [50; 51]. Meanwhile. cervical squamous cell carcinoma is more often caused by infection with HPV type 16 [39]. In Indonesia. HPV type 52 has the highest prevalence. but the ability to become a persistent infection is low. After that. the highest prevalence was followed by HPV types 16 and 18. which have been declared to be the main cause of cervical cancer [2; 16].

In a study conducted at Cipto Mangunkusumo Hospital. cervical cancer ranked as the 2nd most common cancer case (12%) with a mean patient age of 49.5 and was most often found in patients with an age range of 45-49 years. Based on histopathological results. it was found that cervical squamous cell carcinoma was the most frequently found (74.2%). followed by cervical adenocarcinoma (14%) [13]. The results of the study followed existing studies. where cervical squamous cell carcinoma was more commonly found. and the results of the HPV DNA examination also found that HPV type 16 was the most commonly found.

## 5. Conclusion

There are some highlights found in this study. The number of patients diagnosed with cervical dysplasia or cancer before and during the COVID-19 pandemic did not experience significant changes. The technique for collecting specimens for

histopathological examination is most performed using a cervical biopsy. The most common histopathological diagnosis for cervical dysplasia is LSI and histopathological diagnosis for cervical cancer is mostly cervical squamous cell carcinoma. The most age group diagnosed with cervical dysplasia is at the age of 20-29 and the one diagnosed with cervical cancer is age of 40-49. In DNA examination HPV type 16 is the most high-risk type found. This findings are very important that can be used as addition recommendation for counselling women especially with risk factor(s) to start seeing local obstetrician for cervical health checkup periodically.

## Compliance with ethical standards

### Disclosure of conflict of interest

The authors (Ani Oranda Panjaitan. Jason Daniel Susanto . Fajar Lamhot Gultom and Batara Imanuel Sirait) declare no conflict of interest.

### Statement of informed consent

All necessary information provided and voluntarily signed consent form.

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