gondo mastutik <gondomastutik@fk.unair.ac.id>

Distribution Genotype High Risk (HR) And Low Risk (LR) Human Papillomavirus (HPV) at Condyloma Acuminata

[BHSJ] Submission Acknowledgement

1 message

Muhammad Miftahussurur, MD, Ph.D <bhsj@journal.unair.ac.id> Wed, Apr 7, 2021 at 7:35 AM
To: "Gondo Mastutik, M.Sc., Ph.D" <gondomastutik@fk.unair.ac.id>

Gondo Mastutik, M.Sc., Ph.D:

Thank you for submitting the manuscript, "DISTRIBUTION GENOTYPE HIGH RISK (HR) AND LOW RISK (LR) HUMAN PAPILLOMAVIRUS (HPV) AT CONDYLOMA ACUMINATA" to Biomolecular and Health Science Journal. With the online journal management system that we are using, you will be able to track its progress through the editorial process by logging in to the journal web site:

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4 messages

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Fri, May 28, 2021 at 11:42 AM
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Yth. Gondo Mastutik,

Berikut kami lampirkan hasil review artikel dengan judul **"Distribution Genotype High Risk (HR) and Low Risk (LR) Human Papillomavirus (HPV) at Condyloma Acuminata"**. Kami mohon untuk direvisi sesuai dengan komentar reviewer.
Revisi dikembalikan paling lambat tanggal **4 Juni 2021.**
Atas perhatian dan kerjasamanya, kami sampaikan terima kasih.

--
Best Regards,

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2 attachments

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Yth Editor,

Bersama ini saya kirimkan file yg sudah kami revisi sesuai dengan komentar Reviewer beserta list perubahan before and after.
Terima kasih.

Salam,
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Regard,
GM
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To: gondo mastutik <gondomastutik@fk.unair.ac.id>

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We have the pleasure to inform you that your paper has been accepted for publication after peer-review process. Following that, please pay the APC as manuscript handling charges within 7 (seven) days (see invoice attachment). We might suspend all further process if the payment is due. The issue will be published by the end of June 2021.

--
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AUTHORSHIP FORM

I, the undersigned, hereby declare:

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NIP : 197306272002122001
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First Author : Gondo Mastutik
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1. Has been ensure the validity, originality, exempt from plagiarism and does not infringe any copyright or properties from third parties of the manuscript.
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All authors have given consent. All statements were made rightfully to be used as the matter of course.

Surabaya, 30 Maret 2021

Dr. Gondo Mastutik, drh., M.Kes.
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Menjawab comments reviewer

BHSJ Revision 29 May 2021 (Gondo Mastutik)

Before	After
Gondo Mastutik[1*], Alphania Rahniayu[1,2], Dwi Murtiastutik[3,4], Afria Arista[3], Trisni Artami Setyaningrum[3,4], Nabiha Missaoui[5,6], Suhartono Taat Putra[1]	Gondo Mastutik[1*], Alphania Rahniayu[1,2], Dwi Murtiastutik[3,4], Afria Arista[3], Trisniartami Setyaningrum[3,4], Nabiha Missaoui[5,6], Suhartono Taat Putra[1]
Abtract: **Results:** All patients were diagnosed as condyloma acuminata, some with focus dysplasia and koilocytosis. All patients were positive for HPV, including LR-HPV were HPV 6, 11, 42, 54, 61, 81,87,89 and HR-HPV were HPV 18, 26, 45, 51, 52, 66, 67, 68B, 69, 82. The single infection of LR-HPV was 44.4%, multiple infection LR/LR-HPV were 13,9% and the multiple infection of LR/HR-HPV was 41.7%. The LR-HPV infected 70,6% and HR-HPV infected 29,4%.	Abtract: **Results:** All patients were diagnosed as condyloma acuminata, some with focus dysplasia and koilocytosis. All patients were positive for HPV, including LR-HPV were HPV 6, 11, 42, 54, 61, 81,87,89 and HR-HPV were HPV 18, 26, 45, 51, 52, 66, 67, 68B, 69, 82. The single infection of LR-HPV was 44.4%, multiple infection LR/LR-HPV was 13,9% and the multiple infection of LR/HR-HPV was 41.7%. The LR-HPV infected 70,6% and HR-HPV infected 29,4%.
Introduction: Approximately 30-40 percent of cases of condyloma acuminata will undergo spontaneous regression with in the first month of infection and some will be persistent infection.[1, 2, 7] Persistent LR-HPV infection is a risk factor for epithelial lesions that manifest as benign hyperplasia, whereas HR-HPV infection increases the risk of developing premalignant lesions and is associated with cervical cancer in women.[1] Identification HPV genotype is very important to predict the progression of the diseases, to be benign lesion or malignant lesion in anogenital region. In addition, it can also provide a more complete management of the patient. Without knowing these types of HPV genotypes, the management of condyloma acuminata in patients is limited to removing the lesions. The objective of this study is to	Introduction: Approximately 30-40 percent of cases of condyloma acuminata will undergo spontaneous regression with in the first month of infection and some will be persistent infection.[1, 2, 7] Persistent LR-HPV infection is a risk factor for epithelial lesions that manifest as benign hyperplasia, whereas HR-HPV infection increases the risk of developing premalignant lesions and is associated with cervical cancer in women.[1] The objective of this study is to analyze distribution of the genotype HR-HPV and LR at condyloma acuminata in anogenital region. This study identified 40 genotypes of HPV, including HR-HPV and LR from condyloma acuminata lesions in men and women using a reverse line blot assay.

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Metode : DNA virus was extracted from specimen c condyloma acuminata by using QIAam DNA Mini Kit (Qiagen) and genotyping c HPV was using A*mpliquality* HPV *typ express* v 3.0 (AB Analitica) according to th manufacture's protocol. This assa identified 40 type of HPV. There were HP type 6, 11, 16, 18, 26, 31, 33,35, 39, 40, 4 43, 44, 45, 51, 52, 53, 54, 55, 56, 58, 59,6 62, 64, 66, 67, 68a, 68b, 69, 70, 71, 72, 7 81, 82, 83,84, 87, 89, and 90. [should be result section]	Metode : DNA virus was extracted from specimen of condylom acuminata by using QIAamp DNA Mini Kit (Qiagen) an genotyping of HPV was using A*mpliquality* HPV *typ express* v 3.0 (AB Analitica) according to th manufacture's protocol that identified 40 genotypes HPV.
Method: The inclusion criteria of sample were all c patients with diagnosed as condylom acuminata using visual inspection b Dermatologist and willing to participate i this study by sign the informed consent.	Method: The inclusion criteria of sample were all of patients diagnosed with condyloma acuminata using visual inspection by Dermatologist and willing to participate in this study by sign the informed consent.
Discussion: There are more than 40 genotype of HPV that can infect in anogenital region. In this study, from 36 specimen condyloma acuminata, including male and female, we found all of specimens was positive for HPV. There were a group of LR-HPV including HPV 6, 11, 42, 54, 61, 81,87, 89 and a group of HR-HPV including HPV 18, 26, 45, 51, 52, 66, 67, 68B, 69, 82. Other study showed that form 879 patients with genital warts, including 512 men and 367 women, showed LR-HPV were HPV6, 11, 42, 43 and 81 and HR-HPV were HPV16, 18,	Discussion: [This paper will be more benefit if there are explanation about the importance of genotyping, and what the impact if do not do the genotyping] This study identified 40 genotypes of HPV. There were HPV type 6, 11, 16, 18, 26, 31, 33,35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 55, 56, 58, 59,61, 62, 64, 66, 67, 68a, 68b, 69, 70, 71, 72, 73, 81, 82, 83,84, 87, 89, and 90. Identification HPV genotype is very important to predict the progression of the diseases, to be benign lesion or malignant lesion in anogenital region. In addition, it can also provide a more complete management of the patient. Without knowing these types of HPV genotypes, the management of

31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82 and 85).[22]	condyloma acuminata in patients is limited to removing the lesions. From 36 specimen condyloma acuminata, including male and female, we found all of specimens was positive for HPV. There were a group of LR-HPV including HPV 6, 11, 42, 54, 61, 81,87, 89 and a group of HR-HPV including HPV 18, 26, 45, 51, 52, 66, 67, 68B, 69, 82. Other study showed that form 879 patients with genital warts, including 512 men and 367 women, showed LR-HPV were HPV6, 11, 42, 43 and 81 and HR-HPV were HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82 and 85).[22]
Discussion: Condyloma acuminata is a benign tumor that the most often to be caused by infection of LR-HPV and some is co-infection with HR-HPV. The single infection of LR-HPV in this study was is 16/36 (44.4%), multiple infection of LR-HPV and LR-HPV is 5/36 (13,9%) and the multiple infection of LR-HPV and HR-HPV is 15/36 (41.7%). This study was in accordance with other study. Single infection in condyloma acuminata patients in Peking China showed that there was 1.453/3.288 (44.19%) of LR-HPV and HR-HPV were 945/3.288 (28.74%), multiple infection of HR-HPV/LR were 890/3.288 (27.07%).[14]	Discussion: Condyloma acuminata is a benign tumor that the most often to be caused by infection of LR-HPV and some is co-infection with HR-HPV. The single infection of LR-HPV in this study was 16/36 (44.4%), multiple infection of LR-HPV and LR-HPV was 5/36 (13,9%) and the multiple infection of LR-HPV and HR-HPV was 15/36 (41.7%). This study was in accordance with other study. Single infection in condyloma acuminata patients in Peking China showed that there was 1.453/3.288 (44.19%) of LR-HPV and HR-HPV was 945/3.288 (28.74%), multiple infection of HR-HPV/LR was 890/3.288 (27.07%).[14]
Discussion: The determination of HR-HPV can be used to predict the malignant transformation of condyloma acuminata into invasive cancer in the anogenital area and also to establish a preventive program by vaccination.	Discussion: The determination of genotype HPV, including HR-HPV can be used to predict the malignant transformation of condyloma acuminata into invasive cancer in the anogenital area and also to establish a preventive program by vaccination.
References: 9. Bouvard V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, Benbrahim-Tallaa L, Guha N, Freeman C, Galichet L, Cogliano V; WHO International Agency for Research on Cancer Monograph	References: 9. Bouvard V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, Benbrahim-Tallaa L, Guha N, Freeman C, Galichet L, Cogliano V; WHO International Agency for Research on Cancer Monograph Working Group. A review of human

Working Group (2009). A review of human carcinogens--Part B: biological agents. Lancet Oncol 10, 321-2	carcinogens--Part B: biological agents. Lancet Oncol. 2009; 10: 321-2

REVIEWER'S REPORT

Manuscript Number	247
Manuscript Title	DISTRIBUTION GENOTYPE HIGH RISK (HR) AND LOW RISK (LR) HUMAN PAPILLOMAVIRUS (HPV) AT CONDYLOMA ACUMINATA

REVIEWER'S RESPONSIBILITIES

1. Responsible for reviewing the content of manuscripts within the area of expertise.
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Indicate your level of acceptance by ticking (✓) the appropriate boxes with the following scales:
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Evaluation Criteria	1	2	3	4	5	Comments
TITLE, ABSTRACT AND INTRODUCTION						
The title is relevant, precise and reflects the overall contents of the study.					✓	
The abstract is clear and precise consist bacis information, which includes the purpose, issues, methodology, and significance of the study.				✓		Urgency to determine genotype of HPV doesn't stated clearly
The abstract reflect the overall content of the study.				✓		
Keywords are relevant and appropiate.					✓	
The introduction section has a clear statement demonstrating that the focus of the study. The problem definition is stated clearly. There is a brief, well-articulated summary of research literature that substantiates the study.				✓		Need to explain more about the HR HPV incidence in other country
The purposes, research question(s), and /or hypotheses appropiate to the topic and area of study are related clearly.				✓		The urgency about this research not stated clearly
The significance of the study is described in terms of: a) Knowledge generation b) Professional application c) Positive social change				✓		

Show appropriate preparation and knowledgfe through the background/ review of literature in the related area.				✓		
Comparison/ contrast of different viewpoints/ different research outcames is made.				✓		
The content of the reviews is drawn from acceptable peer-reviewed journals or sound academic journals and the literature is reasonably recent.				✓		

Evaluation Criteria	1	2	3	4	5	Comments
METHOD						
Clearly explain the research design, sampling procedure and instruments development.					✓	
The process by which the data were generated, gathered, and recorded is clearly described.					✓	
How the data will be analyzed is articulated. Clearly describe the software program used to analyze the data.					✓	

FINDINGS AND CONCLUSION						
Results are presented clearly and analyzed appropiately.				✓		
The conclusions adequately tie together the other elements of the paper.				✓		
The paper identifies clearly any implications for research, practice and/or society.				✓		
The findings are clear, well grounded and thought out.						

WRITING AND REFERENCING STYLE						
The paper clearly presents its case and is written with correct grammar, punctuation, spelling and sentence structure.				✓		
Does not have over-reliance on limited sources and in-text citations are found in the reference list.					✓	

FINAL RECOMMENDATION

Please (✓) in the selection box

	Accepted
v	Accepted with Minor Revision
	Accepted with Major Revision
	Reject

Comment:

This paper will be more benefit if there are explanation about the importance of genotyping, and what the impact if do not do the genotyping, and also the benefit to encourage the preventive program such as vaccination

Reviewer #1	Reviewer #2	Reviewer #3	Editor decision
Reject	Reject	Reject	**Reject**
Major	Reject	Reject	**Reject**
Major	Major	Reject	**Reject**
Major	Major	Major	**Major**
Major	Major	Minor	**Major**
Major	Minor	Minor	**Minor**
Minor	Minor	Minor	**Minor**

Menjawab comments reviewer

DISTRIBUTION GENOTYPE HIGH RISK (HR) AND LOW RISK (LR) HUMAN PAPILLOMAVIRUS (HPV) AT CONDYLOMA ACUMINATA

ABSTRACT

Introduction: Condyloma acuminata that is also known as genital warts are one of the most common sexually transmitted that caused by infection of Human papillomavirus (HPV). Persistent infection of Low Risk (LR) or High risk (HR) HPV is a risk factor for progress into benign or malignant cancer. The objective is to analyze distribution of genotype LR-HPV and HR-HPV at condyloma acuminata in anogenital region.

Methods: A cross sectional study using were 36 lesions from men and women of condyloma acuminata patients. All subject signed the informed consent and ethic obtained from our institution, number 382/Panke.KKE/V/2016. The specimen was used to histopathological examination and to identified 40 genotypes of HPV using a reverse line blot assay.

Results: All patients were diagnosed as condyloma acuminata, some with focus dysplasia and koilocytosis. All patients were positive for HPV, including LR-HPV were HPV 6, 11, 42, 54, 61, 81,87,89 and HR-HPV were HPV 18, 26, 45, 51, 52, 66, 67, 68B, 69, 82. The single infection of LR-HPV was 44.4%, multiple infection LR/LR-HPV were 13,9% and the multiple infection of LR/HR-HPV was 41.7%. The LR-HPV infected 70,6% and HR-HPV infected 29,4%.

Conclusion: LR-HPV is the major infection of condyloma acuminata, in single infection or multiple infection with HR-HPV. The most common infections were HPV 11, followed by HPV 6, HPV 18, HPV 51, and HPV 82. The determination of genotype of HPV can be used to predict the malignant transformation.

Keywords: Condyloma acuminata, Low risk HPV, High Risk HPV, focus dysplasia, koilocytosis.

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Introduction

Condyloma acuminata that is also known as genital warts are one of the most common sexually transmitted diseases in the world.[1, 2] In United States, there were 500,000 to one million new cases diagnosed.[2] In Valencian community, Spain, it was estimated 612 cases of genital warts with overall incidence rate was 75.8 per 100,000 people per year.[3] In the world base on systematic review study showed that the overall incidence of condyloma acuminata was 160-289 per 100,000 people per year. The new cases incidence of condyloma acuminata in males is 103-168 per 100.000 persons and in females is 76-191 per 100.000 persons. Incidence recurrent is 110 per 100.000 persons.[4] The incidence new cases of condyloma acuminata in Bali, Indonesia during period 2015-2017 was 260 of 4743 persons (5.47%)[5] and in Surabaya, Indonesia during 2009-2011 was 259 per 2960 persons (8.7 %) and 2012-2014 was 318 per 3674 persons (8.7%).[6]

Condyloma acuminata are usually found in warm and moist mucosal regions, that is characterized of skin in the region of anal and genital.[1, 4] It appears as flat lesion, dome-shaped,

Commented [U1]: Urgency to determine genotype of HPV doesn't stated clearly in abstract

Commented [L2]: was

Commented [L3]: need to explain more about the urgency of this research

keratotic, pedunculated, or cauliflower shaped, which are single or cluster lesion.[1,7] These are accompanied by anogenital pruritus, burning, itching, vaginal discharge and bleeding These lesions are visible on the peri genital and perianal region, including the penis, scrotum, vulva, pubic, perineal, perianal areas, cruralfolds.[1, 4, 7]

The most common causes of condyloma acuminata is an infection by Human papillomavirus (HPV).[8] There are more than 100 genotypes of HPV. Base on the ability to cause malignancy of HPV, the International Agency for Research on Cancer (IARC) have classified into high-risk (HR) (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59), possibly HR (HPV 26, 30, 34, 53, 66, 67, 68, 69, 70, 73, 82, 85, 97), and probably low-risk (LR) (HPV 6, 11).[9, 10] The LR-HPV such as HPV types 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, and 81 are associated with causes of condyloma acuminata and un-oncogenic,[11-13] but study in China in 2013 showed that HR-HPV (HPV16, 52, 58, 56, 18, 66, 33) and LR-HPV (HPV 6, 11, and 43) caused condyloma acuminata.[14] A prospective study to follow up 3.033 men with HPV infection during 12 months showed that infection with HPV 6 and HPV 11 developed to be condyloma acuminata and HPV 16 was to be penile intraepithelial neoplasia as precursor of penile cancer.[15] A retrospective study was also showed that invasive penile cancer associated with infection of HR-HPV.[16] These cases indicated that LR-HPV was co-infection with HR-HPV or single infection with HR-HPV that may lead to progression on malignancy on anogenital.

Approximately 30-40 percent of cases of condyloma acuminata will undergo spontaneous regression with in the first month of infection and some will be persistent infection.[1, 2, 7] Persistent LR-HPV infection is a risk factor for epithelial lesions that manifest as benign hyperplasia, whereas HR-HPV infection increases the risk of developing premalignant lesions and is associated with cervical cancer in women.[1] Identification HPV genotype is very important to predict the progression of the diseases, to be benign lesion or malignant lesion in anogenital region. In addition, it can also provide a more complete management of the patient. Without knowing these types of HPV genotypes, the management of condyloma acuminata in patients is limited to removing the lesions. The objective of this study is to analyze distribution of the genotype HR-HPV and LR at condyloma acuminata in anogenital region. This study identified 40 genotypes of HPV, including HR-HPV and LR from condyloma acuminata lesions in men and women using a reverse line blot assay.

Commented [U4]: Need to explain more about the HR HPV incidence in other country

Methods

This study was a cross sectional study conducted at Out clinic Patient of Department Dermatology and Venereology, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia during period January-December 2017. The specimens were taken from patient after they sign the informed consent. Those who were not willing to participate in this study were excluded. This study was approved by the Medical Ethic Research from Dr. Soetomo General Academic Hospital Surabaya, number 382/Panke.KKE/V/2016.

The inclusion criteria of sample were all of patients with diagnosed as condyloma acuminata using visual inspection by Dermatologist and willing to participate in this study by sign the informed consent. The exclusion criteria of patients were women in menstruation period or pregnant and cervicitis, women or men in infection HPV and AIDS.

Commented [L5]: all patients diagnosed with

There were 36 specimens of the biopsy tissues taken from lesion patient who diagnosed as condyloma acuminata. The specimen was separated become two sections; one section is for tissues processing in block paraffin as procedure for making histopathology diagnose. The

histopathology diagnosed of condyloma acuminata performed by Expert Pathologist. The other section is for genotyping HPV.

The genotyping of HPV was performed by Polymerase Chain Reaction (PCR) and followed by reverse line blot assay. DNA virus was extracted from specimen of condyloma acuminata by using QIAamp DNA Mini Kit (Qiagen) and genotyping of HPV was using A*mpliquality* HPV *type express* v 3.0 (AB Analitica) according to the manufacture's protocol. This assay identified 40 type of HPV. There were HPV type 6, 11, 16, 18, 26, 31, 33,35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 55, 56, 58, 59,61, 62, 64, 66, 67, 68a, 68b, 69, 70, 71, 72, 73, 81, 82, 83,84, 87, 89, and 90.

Commented [L6]: should be in result section

Results

Histopathology Diagnose

The results of histopathology diagnose showed that all patients were diagnosed as condyloma acuminata. Some specimens showed condyloma acuminata with focus dysplasia and koilocytosis which specific for HPV infected cells (Figure 1)

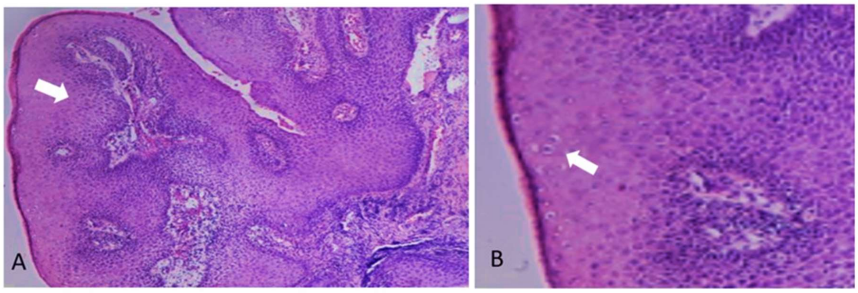

Figure 1 Histopathology of condyloma acuminata in anogenital with hematoxylin eosin (HE) staining. Arrow indicated the focus dysplasia (in figure A) and koilocytosis (in figure B)

Distribution Genotype of LR-HPV and HR-HPV at the condyloma acuminata patients.

A total of 36 the condyloma acuminata patients participated in this study, including 15/36 (41.67%) for male and 21 (58.33%) for female, aged 18-64 years old. In 15 males, showed that 6/36 (16.67 %) were positive infected by multiple type HR-HPV/LR and 9/36 (25%) were positive infected by single and multiple infection LR-HPV/LR. In female, 8/36 (22.22%) were positive infected by multiple type HR-HPV/LR and 13 (36.11%) were positive infected by single and multiple infection LR-HPV/LR. The most patients of aged was 15-24 years old that were 7/36 (19.44%) positive infected by HR-HPV and 10/36 (27.79%) by LR-HPV (Table 1).

Clinical characteristic of this patient consisted of the duration presence of each warts, type lesions, history of previous lesions, and location lesions. The most patients based on the duration presence of each warts was 1-3 months, type lesion was multiple lesions and the history of previous lesions was first time lesions (Table 1). The locations of condyloma acuminata in male were in penis and anus with the most frequent was in penis and in female

were in labia majora, labia minora, vulva, introitus vagina, anus, and perineum. The most location of lesion in male was in penis and in female was in labia majora (Table 1).

Table 1. Distribution of LR-HPV and HR-HPV in the anogenital condyloma acuminata

	N (%)	Multiple infection HR/LR-HPV N (%)	Single or multiple infection LR/LR-HPV N (%)
Sex			
Male	15 (41.67)	6 (16.67)	9 (25.00)
Female	21 (58.33)	8 (22.22)	13 (36.11)
Age			
15-24 years	17 (47.22)	7 (19.44)	10 (27.78)
25-34 years	6 (16.67)	3 (8.33)	3 (8.33)
35-44 years	8 (22.22)	2 (5.56)	6 (16.67)
45-54 years	4 (11.11)	2 (5.56)	2 (5.56)
55-64 years	1 (2.78)	0	1 (2.78)
Duration presence of each warts			
< 1 month	5 (13.89)	3 (8.33)	2 (5.56)
1-3 month	23 (63.89)	7 (19.44)	16 (44.44)
4-6 month	6 (16.67)	3 (8.33)	3 (8.33)
>6 month	2 (5.56)	1 (2.78)	1 (2.78)
Type lesion			
Solitary	2 (5.56)	1 (2.78)	1 (2.78)
Multiple	34 (94.44)	13 (36.11)	21 (58.33)
History of previous lesions			
First time lesions	29 (80.56)	11 (30.55)	18 (50.00)
Recurrence lesions	7 (19.44)	3 (8.33)	4 (11.11)
Location of lesions			
Penis	7 (19.44)	3 (8.33)	4 (11.11)
Anus	6 (16.67)	3 (8.33)	3 (8.33)
Penis and Anus	2 (5.56)	0 (0)	2 (5.56)
Labia Majora	10 (27.78)	3 (8.33)	7 (19.44)
Labia Minora	2 (5.56)	1 (2.78)	1 (2.78)
Labia Majora and Minora	3 (8.33)	2 (5.56)	1 (2.78)
Vulva	2 (5.56)	1 (2.78)	1 (2.78)
Labia Majora, Vulva	1 (2.78)	0 (0)	1 (2.78)
Vulva, Introitus Vagina, Anus	1 (2.78)	0 (0)	1 (2.78)
Introitus Vagina	1 (2.78)	0 (0)	1 (2.78)
Perineum	1 (2.78)	0 (0)	1 (2.78)

N: number, HR: high risk, LR: low risk

The genotype of HPV was HR-HPV and LR-HPV, in single infection of LR-HPV, multiple infection of LR/LR-HPV, or multiple infection of LR/HR-HPV. The genotypes of LR-HPV in this study were HPV 6, 11, 42, 54, 61, 81,87,89 and HR-HPV were HPV 18, 26, 45, 51, 52, 66, 67, 68B, 69, 82. The single infection of LR-HPV was 44.4%, multiple infection of LR/LR-HPV was 13,9% and the multiple infection of LR/HR-HPV is 41.7% (Table 2).

Table 2. Single and multiple infection of HPV in the condyloma acuminata patients

Genotype HPV	Type HR or LR	N (%)	
Single infection		**16**	**44.4%**
– HPV 6	LR	4	11.1%
– HPV 11	LR	12	33.3%
Multiple infection LR/LR-HPV		**5**	**13.9%**
– HPV 6, 11	LR/LR	2	5.5%
– HPV 6, 61	LR/LR	1	2.8%
– HPV 6,81,87,89	LR/LR/LR/LR	1	2.8%
– HPV 11,87	LR/LR	1	2.8%
Multiple infection LR/HR-HPV		**15**	**41.7%**
– HPV 6, 11,18,51,82	LR/LR/HR/LR/HR	1	2.8%
– HPV 6, 42,51,61	LR/LR/HR/LR	1	2.8%
– HPV 11, 18	LR/HR	2	5.5%
– HPV 11,18,45	LR/HR/HR	1	2.8%
– HPV 11, 26	LR/HR	1	2.8%
– HPV 11, 51	LR/HR	1	2.8%
– HPV 11, 51, 82	LR/HR/HR	1	2.8%
– HPV 11, 52, 54	LR/HR/LR	1	2.8%
– HPV 11, 52,69,90	LR/HR/HR/LR	1	2.8%
– HPV 11, 66	LR/HR	1	2.8%
– HPV 11, 67	LR/HR	1	2.8%
– HPV 11, 68B	LR/HR	1	2.8%
– HPV 11, 82	LR/HR	2	5.5%

The frequency of HPV 11 infected 28 per 68 times (41.18%), HPV 6 infected 11 per 68 times (16.18%), and HPV 18, 51 and 82 respectively infected 4 per 68 times (5.88%). The frequency of LR-HPV infected in 48/68 (70,6%) and HR-HPV infected in 20/68 (29,4%). The most common LR-HPV were HPV 11 and HPV 6, and HR-HPV were HPV 18, HPV 51, and HPV 82 (Table 3).

Table 3. The most often of HPV genotype found at the condyloma acuminata patients

Genotype HPV	N (%)	
HPV 11	28	41.18
HPV 6	11	16.18
HPV 18	4	5.88
HPV 51	4	5.88
HPV 82	4	5.88
HPV 52	2	2.94
HPV 61	2	2.94
HPV 87	2	2.94
Other type (HPV 26, 42, 45, 66, 67, 81, 54, 68B, 69, 89, 90)	11	16.18

DISCUSSION

Condyloma acuminata or anogenital warts are single or multiple lesions, soft or raised masses that appears as smooth, verrucous or lobulated, with flat, dome-shaped, cauliflower shaped, or pedunculated, filiform, fungating, plaque-like in anogenital regions.[2,17] Histopathology features can be observed by hematoxylin-eosin (HE) that showed papillomatosis, hyperkeratosis, parakeratosis, hypergranulosis, and koilocyte, as well as some showed focus dysplasia. The papillary dermis presented dilated capillaries.[17,18,19] These microscopic appearances were also seen on the HE slides in this study, where several slides showed papillomatosis, hyperkeratosis, with focus dysplasia and koilocytosis.

The age of people with condyloma acuminata in this study peaked at the age of 15-24 years, namely 47.2% and those were under 35 years of 23/36 (63.9%). This was in accordance with others studies showed that condyloma acuminata patients usually occurred at the sexually active age, namely 15-24 years.[2, 20] The highest prevalence of condyloma acuminata was around the age of 20-30 years, in female or male patients.[4, 21]

We found that there were 6 patients who showed histopathological results of condyloma acuminata with focus dysplasia. The presentation of dysplasia base on the histopathological finding was associated with increased infection of HPV 16 and HPV 18, while the rounded papillomatosis, hypergranulosis, and dilated vessels were associated with HPV 6 and HPV 11.[19] The ages of these patients were 20, 22, 26, 42, and 44 years old and infected with HR-HPV and LR-HPV were each 3 patients. Patients diagnosed as condyloma acuminata with a focus on dysplasia and infected by HR-HPV should be monitored to determine the progression of the disease to malignancy.

There are more than 40 genotype of HPV that can infect in anogenital region. In this study, from 36 specimen condyloma acuminata, including male and female, we found all of specimens was positive for HPV. There were a group of LR-HPV including HPV 6, 11, 42, 54, 61, 81,87, 89 and a group of HR-HPV including HPV 18, 26, 45, 51, 52, 66, 67, 68B, 69, 82. Other study showed that form 879 patients with genital warts, including 512 men and 367 women, showed LR-HPV were HPV6, 11, 42, 43 and 81 and HR-HPV were HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82 and 85).[22]

Condyloma acuminata is a benign tumor that the most often to be caused by infection of LR-HPV and some is co-infection with HR-HPV. The single infection of LR-HPV in this study was is 16/36 (44.4%), multiple infection of LR-HPV and LR-HPV is 5/36 (13,9%) and the multiple infection of LR-HPV and HR-HPV is 15/36 (41.7%). This study was in accordance with other study. Single infection in condyloma acuminata patients in Peking China showed that there was 1.453/3.288 (44.19%) of LR-HPV and HR-HPV were 945/3.288 (28.74%), multiple infection of HR-HPV/LR were 890/3.288 (27.07%).[14]

LR-HPV infection in the anogenital area was associated with benign tumors and HR-HPV infection was associated with a risk of malignancy. LR-HPV (HPV 6,11) were related to condyloma acuminata.[13] A prospective study to follow up 3.033 men with HPV infection during 12 months showed that infection with HPV 6 and HPV 11 developed to be condyloma acuminata.[15] The HR-HPV (HPV 16, and HPV 18), were the most related with cervical cancer and pre-cancer lesions in women such as cervical, vaginal, and vulvar intraepithelial neoplasias and high-grade squamous intraepithelial lesions.[19] In addition, HR-HPV was considered as causes of squamous cell carcinomas and associated precursor lesions in men as penile intraepithelial neoplasia, Bowenoid papulosis, Erythroplasia of Queyrat),[19] as well as related with invasive penile carcinomas.[13] Follow up infection HPV 16 in male was to be penile

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intraepithelial neoplasia as precursor of penile cancer.[15] Other study was also reported that condyloma acuminata was associated with the risk of cancer in anogenital. A cohort study involving 10,971 patients (1,685 men and 9,286 women) in Swedish population concluded that condyloma acuminata was strongly associated with increasing the risk of cancer in anogenital, such as vulva, penis, and anus.[23]

The most dominant infection in the condyloma acuminata was infection of HPV 6 and 11. Condyloma acuminatum (CA) or venereal/genital warts refered to benign proliferative epidermal or mucosal lesions attributed mostly to HPV type 6 or 11, but co-infections with HR-HPV types are frequent.[17] In this study, the most common LR-HPV in condyloma acuminata was HPV 11 (41.18%), HPV6 (16.18%) and HR-HPV was HPV 18 (5.88%), 51 (5.88%) and 82 (5.88%). Other study showed that the most common LR-HPV and HR-HPV in condyloma acuminata were in French LR-HPV was 6 (69%) and 11 (16%), followed by HR-HPV were 16 (9%), 51 (8%), 52 (7%), 66 (6%) 53 (5%), 31 (3%), and 18 (3%).[20] In Peking, China showed that LR-HPV were HPV 6 (16.98%,), 11 (11.09%) and 43 (6.75%,) and HR-HPV were 16, 52, 58, 56, 18, 66 and 33, and the incidence ratios were 6.31%, 5.06%, 4.04%, 2.60%, 2.41%, 2.40% and 2.28% in condyloma acuminata.[14] In Xi'an China HPVLR was HPV6 (24.9%), HPV11 (17.9%), HPV52 (9.9%) and HR-HPV was HPV16 (7.3%).[22] The estimated prevalence of HPV 6 and HPV 11 DNA in the US male population were 2.9%.[24] The common HR-HPV in men with condyloma acuminata was HPV 16 and followed by HPV 18.[25] Our previous study showed that the most common HPV infected in men with condyloma acuminata was LR-HPV were HPV 6, HPV 11 and HR-HPV were HPV 18, 51, 52, 82 [26] and in cervical precancerous lesion and squamous cell carcinoma were is HPV 16 (62.68%), then followed by HPV 18 (20.9%), HPV 45 (5.97%), 52 (5.97%), and 67 (4.48%).[27]

However, condyloma acuminata is usually caused by LR-HPV infection, this finding demonstrated that LR-HPV co-infection with HR-HPV. HR-HPV such as HPV 16, HPV 18, HPV 45, HPV 52, and 67 was HPV have been founded in cervical cancer and precancerous lesion.[27] Several other studies have also shown that HPV 16, as well as LR-HPV (HPV 6 and 11) were also found in penile intraepithelial neoplasia.[8] HPV 16 and HPV 18 were founded on vulval and vaginal cancel cell.[28] Persistent infection of HR-HPV is a risk factor for progression of cell transformation into malignant cells. The determination of HR-HPV can be used to predict the malignant transformation of condyloma acuminata into invasive cancer in the anogenital area and also to establish a preventive program by vaccination.

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Conclusion

This finding demonstrated that LR-HPV is the major infection of condyloma acuminata, in single infection or multiple infection with HR-HPV. The most common infections were HPV 11, followed by HPV 6, HPV 18, HPV 51, and HPV 82. The determination of HR-HPV can be used to predict the malignant transformation of condyloma acuminata into invasive cancer in the anogenital area and also to establish a preventive program by vaccination.

Acknowledgement: We would like to thank to the Government of the Republic of Indonesia, the Ministry of Research, Technology, and Higher Education, in particular the Faculty of Medicine, Airlangga University for financial support and all of the patients who are willing to participate in this study.

Conflict of interest: No conflict of interest.

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