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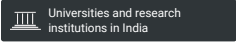
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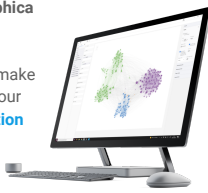
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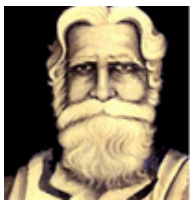
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## Risk Factors Recurrent Respiratory Papilloma (RRP) on Juvenile and Adult Type in Tertiary Hospital, Indonesia

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### Abstract

**Introduction:** Recurrent respiratory papillomatosis (RRP) is the most common benign neoplasm of the larynx among children as a result of HPV infection mainly type 6 and 11. RRP is still a serious problem in which papillomas in the airway cause hoarseness and obstruction as then described as an aggressive form and less aggressive form. Patients undergo multiple surgeries to keep the airway patent and in order to communicate vocally. There are several risk factor that affect on disease aggressivity. That factors include sex, age at diagnosis, papilloma implantation, tracheostomy, number of surgery, and histopathology. **Aim:** to determine the relationship between risk factors for RRP with the level of aggressiveness in juvenile type and adult type. **Method:** This research used analytic retrospectively, the data obtained from the medical record of outpatient unit of the otorlaryngology-head and neck surgery department. The data obtained in the study are displayed in tables and analyzed statistically using the Chi-Square test. The research sample was taken according total sampling. **Result:** The statistic test result was indicating the statistical test using Chi-Square results ( $p < 0.05$ ), showed there is a significant relationship between the aggressiveness of the disease based on the age  $< 12$  years (juvenile type), history of tracheotomy, and the frequency of MLS operations  $\geq 10$  times. **Conclusion:** the risk factors in patients with RRP were found at the age, history of tracheotomy, and the frequency of microscopic laryngeal surgery (MLS) with the type of RRP.

**Keywords:** *Risk factors, Recurrent respiratory papilloma, Juvenile type, Adult type.*

### Introduction

Recurrent respiratory papilloma (RRP) is a benign airway tumor caused by type 6 and type 11 human papilloma viruses (HPV) infection. The disease can occur in children and adults and can give manifestations of papilloma growth in the airway that is residif. The onset of RRP is divided into juvenile and adult types, based on age at diagnosis before or after 12 years of age. Juvenile types are often found at the age of fewer than 12 years while the adult type occurs at the peak age of 20-40 years. The juvenile type has an aggressive disease course [1, 2, 3].

The incidence and prevalence of RRP are still unknown, estimated between 80-1500 new cases each year in the US's pediatric population. The incidence of RRP in the United States is estimated at 4.3 per 100,000

in children and 1.8 per 100,000 in adults. Dr. Soetomo hospital, Surabaya in 1997 reported 57 new patients, 82% of patients under the age of 10 years. A tracheotomy was performed in 36 of 51 patients (70.59%). Patients with juvenile RRP (21.62%) have a history of microscopic laryngeal surgery (MLS) three or more times a year [4]. Research from the period January 2006 to December 2010 at Dr. Soetomo Teaching Hospital, Surabaya found 51 patients with RRP, 39 cases of juvenile type (76%), and 12 cases of adult type (24%).

The location of the spread that is found is to the trachea and bronchi. A tracheotomy was performed on 36 patients (71%) and juvenile RRP was more frequently performed microscopic laryngeal surgery (MLS) compared to the adult type which reached 6

operations in one year [5]. This disease can be non-aggressive so it experiences remission, but it can also grow more aggressively so it needs to be surgically performed repeatedly [1, 6, 7]. Aggressive disease is characterized by recurrent recurrence or growth of papillomas in a distal location, namely the trachea and bronchi [2,7-9]. The criterion for aggressiveness is the number of operations needed to achieve disease-free.

Other criteria according to Derkay, et al., include the overall number and frequency of operations, the location of the growth of more distal papillomas, and the history of tracheotomy [2,3,7]. Recurrent respiratory papillomas rarely undergo transformation into malignancy. Several studies have reported cases of changes related to HPV type 11 and the presence of other factors such as smoking, a history of previous radiation [6, 8].

The purpose of this study was to determine the relationship between risk factors for RRP with the degree of aggressiveness in juvenile type and adult type in the outpatient unit of the otolaryngology-head and neck surgery department at Dr. Soetomo Academic Hospital, Surabaya. The degree of aggressiveness covering gender, location of RRP, history of tracheotomy, the total number of MLS operations, histopathological features, and post-operative final evaluation.

## Method

**Table 1: Distribution by age diagnosed**

Age	Number	Percentage (%)
< 12 years	28	82
≥ 12 years	6	18
Total	34	100

Patients with RRP based on sex. Statistical test results using Chi-Square obtained 0.050 results ( $p < 0.005$ ), this shows there is no

**Table 2: Distribution by sex**

Sex	Group				Number	P value
	Juvenile Type		Adult Type			
	n	%	n	%		
Male	17	61	1	17	18	0.050
Female	11	39	5	83	16	( $P < 0.05$ )
Amount	28	100	6	100	34	

The spread of papillomas to the distal respiratory area was found in 4 patients (14%) juvenile type with extension to the

This research was conducted analytically retrospectively, the data obtained from the medical record of outpatient unit of the otolaryngology-head and neck surgery department at Dr. Soetomo Academic Hospital, Surabaya from January 2016 to December 2018. The study sample was old patients with RRP children and adults who had undergone at least three MLS surgery procedures times a year and meet the inclusion and exclusion criteria.

The inclusion criteria were all patients treated with RRP who had complete data and the exclusion criteria of patients with MLS surgery procedures <3 times per year. The data obtained in the study are displayed in tables and analyzed statistically using the Chi-Square test with the significance used  $\alpha = 0.05$ . This ethical clearance research was taken from ethical committee in Dr. Soetomo Academic Hospital, Surabaya, Indonesia with number 1992/KEPK/V/2020.

## Results

Data of RRP patients have found 43 patients. 9 patients were not included in the study population, because the examination data were incomplete. The sample size of RRP patients was 34 patients.

### Distribution of Characteristics Respondents

Types of RRP are based on diagnosed age. The youngest age diagnosed with RRP is 2 years and the oldest is 48 years.

relationship between the aggressiveness of the disease based on sex with the type of RRP.

trachea including stoma in 2 patients and to the bronchi in 1 patient.



Extralararyng papilloma that is to the tongue and uvula found 1 patient. Juvenile type was found in 24 patients (86%) with papilloma in the larynx region, namely supraglottis, glottis and subglottis. The adult type found papillomas in the laryngeal region in 6 patients (100%) and no distribution in the

distal area was obtained. Statistical test results using Chi-Square obtained 0.324 results ( $p < 0.005$ ), this shows that there is no relationship between disease aggressiveness based on the location of the distal papilloma of the respiratory tract with the type of RRP.

**Table 3: Distribution based on the location of the distal papilloma of the respiratory tract**

Papilloma location	Group				Number	P value
	Juvenile Type		Adult Type			
	n	%	n	%		
Distal papilloma	4	14	0	0	4	0.324
Laryngeal papilloma	24	86	6	100	30	( $p < 0,05$ )
Amount	28	100	6	100	34	

Statistical test using Chi-Square obtained 0.002 results ( $p < 0.05$ ), this shows there is a significant relationship between the

aggressiveness of the disease based on the history of tracheotomy with the type of RRP.

**Table 4: Distribution based on tracheotomy history**

Tracheotomy History	Group				Number	P value
	Juvenile Type		Adult Type			
	n	%	n	%		
Tracheotomy	28	100	4	67	32	0.002
Non-tracheotomy	0	0	2	33	2	( $p < 0,05$ )
Amount	28	100	6	100	34	

Statistical test using Chi-Square obtained 0.004 results ( $p < 0.05$ ), this indicates that there is a significant relationship between

the aggressiveness of the disease based on the overall amount of MLS with the type of RRP.

**Table 5: Distribution based on the total number of MLS operations**

Number of MLS Procedure	Group				Number	P value
	Juvenile Type		Adult Type			
	n	%	n	%		
$\geq 10$ times	18	64	0	0	18	0.004
$< 10$ times	10	36	6	100	16	( $p < 0,05$ )
Amount	28	100	6	100	34	

Statistical analysis using the Spearman correlation test with the significance level used  $\alpha = 0.05$ . Spearman correlation test between the degree of dysplasia with the type of RRP obtained  $p = 0.406$  with the strength

of the relationship between the two obtained  $R_s = -0.147$ . These results indicate no significant relationship between disease aggressiveness based on histopathology in the RRP type.

**Table 6: Distribution by histopathological data**

Level of Dysplasia	Group				Number	Correlation
	Juvenile Type		Adult Type			
	n	%	n	%		
Light level	18	64	5	83	23	$R_s = -0,147$ $P = 0,406$
Medium level	8	28	1	17	9	
Weight level	1	4	0	0	1	
Ferocious transformation	1	4	0	0	1	
Amount	28	100	6	100	34	

Spearman's correlation between the results of the post-operative final evaluation with the type of RRP obtained  $p = 0.784$ , indicating no significant relationship between risk factors for aggressiveness based

on post-operative evaluation with the type of RRP. The strength of the relationship analyzed by the Spearman test obtained  $R_s = 0.049$ , indicating a moderate positive correlation.

Table 7: Distribution based on the final postoperative evaluation

Outcome	Group				Number	Correlation
	Juvenile Type		Adult Type			
	n	%	n	%	n	
Remission	16	57	3	50	19	Rs = 0.049 P = 0,784
Recurrences	6	22	2	33	8	
Complications	2	7	1	17	3	
Died	4	14	0	0	4	
Amount	28	100	6	100	34	

## Discussion

RRP can affect all age groups [2]. The age distribution of the emergence of the disease forms a bimodal chart that manifests in children with the majority appearing at 5 years of age (75%). The second peak was found in adults in the fourth decade [6, 12]. The youngest age ever reported was 1 day and the oldest was 84 years [10]. Age limits for these two types according to Derkay and Larson, et al., is before or after the age of 12 years [2, 3, 7, 10].

Age at diagnosis is an important predictor of the severity of the disease. Adults who experience aggressive RRP are considered to have had the disease since they were children. Patients with RRP in children with non-aggressive diseases will still be called juvenile types [7, 10]. Juvenile types are generally diagnosed at 2-4 years of age, more aggressive with chief hoarseness complaints. 14 Children diagnosed at a younger age have a more aggressive disease risk [10]. The peak incidence in the adult type is found between the ages of 20-40 years and less aggressive so it does not require much surgery [3, 7, 9, 10].

The results of this study are consistent with research by Sonia *et al.*, RRP is more aggressive in the juvenile type than the adult type and often occurs in children with an average age of 6 years to 10 years. RRP sufferers based on sex found 18 males and 16 females. Gender is not a predictor of disease aggressiveness in juvenile and adult types [17].

Research by Ozgursoy, et al., Sex comparison in RRP of adult types found in males and females is 3:1.8 Predictions of certain sexes are not found in juvenile types whereas types mild adult tendencies in men. This might be due to smoking habits in men more often than women [10]. The results of statistical tests using Chi-Square obtained 0.050 results ( $p < 0.05$ ). The results of this study are in accordance with the study of Vankestan, et al., There were no significant differences based on sex in the RRP type.

Indirect or direct laryngoscopic examination shows a condyloma that protrudes and grows in the transitional mucosa between the squamous epithelium and the ciliated columnar epithelium in the airway. These transitional sites include the inferior surface of the vocal cords, the rice vestibulum, the nasopharyngeal palate, the trachea, carina and bronchi, and the area around the tracheotomy stoma. 76.4% with distal papilloma implantation, about 21.57% have extended to the trachea and bronchi [5].

Donne *et al.*, Showed involvement of the lower airway including the trachea (11%), bronchi (2-3%) and lung (3%). The most commonly affected laryngeal area is the glottis followed by supraglottis and subglottis in the juvenile and adult types [1]. Expansion of papilloma to the trachea was found in 5 patients (4%) of 106 patients and all had a tracheotomy [1]. The most frequent location was the oral cavity, trachea, bronchus, and esophagus [2, 11].

Statistical tests using Chi-Square obtained 0.324 results ( $p < 0.05$ ), this shows there is no relationship between disease aggressiveness based on the location of the distal papilloma of the respiratory tract with the type of RRP. The aggressive disease is characterized by recurrent recurrence or growth of papillomas in the distal location of the trachea and bronchi. The study found that 4 patients with juvenile type had distal papilloma expansion, 2 patients with trachea, bronchus, and extra larynx, namely uvula, and tongue.

Spread mainly around the stoma is caused due to injury of the tracheal mucosa and occurs in about 50% in young people. Papillomas of the bronchi are characterized by non-calcification and peripheral nodules. Enlarged lesions form a central cavity and necrosis. Patients can experience recurrent bronchiectasis, pneumonia, and decreased lung function. Papillomas in the lungs can cause respiratory failure due to extensive lung parenchymal damage [2].

Tracheotomy is needed if there is a risk of airway obstruction. RRP sufferers who require tracheotomy around 50% experience spread to the trachea. Clinical evaluation of whether or not a tracheotomy is subjective and there are some experts suggesting recurrent MLS as an alternative to tracheotomy [10, 15]. The percentage of tracheotomy varies around 13% - 21% in juvenile type RRP and about 4% - 6% in adult type RRP. Patients who require tracheotomy are considered as a group with more aggressive disease [2, 15].

The results of this study found that more patients with a history of tracheotomy, this shows that the disease is more aggressive and more often causes upper airway obstruction. Statistical test results using Chi-Square obtained 0.002 results ( $p < 0.05$ ), indicating there is a significant relationship. Tracheotomy performed on RRP sufferers will lead to the more aggressive and widespread growth of papilloma in the lower airway [2, 3, 15]. The tracheotomy is better avoided and if tracheotomy is recommended it is recommended to deannulate immediately after the RRP can be controlled operatively [2, 3, 7].

The development of papillomas into the trachea in RRP sufferers with tracheotomy compared with patients without tracheotomy is 56% and 8%. The number and frequency of operations is one indicator of the evaluation of the degree of aggressiveness of the disease [12, 15]. Statistical tests using Chi-Square obtained 0.004 results ( $p < 0.05$ ), this shows there is a significant relationship between the aggressiveness of the disease based on the overall amount of MLS with the type of RRP juvenile type was found to be more aggressive than the adult type. This study is in accordance with a research by Papaioannou, et al.

The juvenile type has a more frequent operating frequency than the adult type, indicating a high level of aggressiveness in the disease. Dysplasia is a premalignant condition that can change into a malignancy [17]. Dysplasia in the juvenile type is a predictor of disease aggressiveness. Dysplasia in the adult type is not a predictor of disease aggressiveness [17].

Dysplasia in RRP sufferers occurs in about 20% in decades 3 and 4. Changes in papilloma lesions to become malignant are

rare, mostly associated with HPV 11. Some studies report that HPV 11 in RRP is more aggressive in the long-term compared to HPV 6 and very vulnerable to development into malignancy (66.7%). The higher the degree of dysplasia, the higher the risk of malignancy. These changes rarely occur without the expansion of papillomas into the distal area, in studies found 1% in the juvenile type and 3-7% in the adult type. Statistical analysis using the Spearman correlation test between the level of dysplasia with the RRP type obtained  $p=0.406$  with the strength of the relationship between the two obtained  $RS= -0.147$ .

These results indicate no relationship between disease aggressiveness based on histopathology in the RRP type. The course of RRP disease varies between individuals, some sufferers can experience spontaneous remission after getting several operations, whereas in other conditions it can continue to grow and spread along the airway, thus requiring repeated operations for years [3]. Healing in RRP does not have a universal definition and there is still little research on this matter [19]. Patients who require 4 operations a year have better remission rates compared to more than 4 times each year. Factors that do not affect remission such as adjunctive therapy in the first year of diagnosis, race and sex [15].

High recurrence rates or recurrence may be due to multiple and solitary lesions [1]. Risk factors that are thought to cause recurrence of RRP (recurrence) are a tendency to channel disease breathing, living with smokers, low endurance, submandibular enlargement, reflux disease and dental caries [8]. Spearman's correlation between the results of the post-operative final evaluation with the RRP type obtained  $p = 0.784$ , indicating there was no significant relationship between risk factors for aggressiveness based on post-operative evaluation with the type of RRP.

The strength of the relationship analyzed by the Spearman test obtained  $RS = 0.049$ , indicating a moderate positive correlation. Curative treatment is not carried out in patients with RRP, and management is needed for repeated micro laryngoscopic examination with papilloma removal until the disease has remission.

## Conclusion

Patients with respiratory tract papillomas are found more at age <12 years (juvenile type). Distal respiratory papillomas (trachea and bronchi) show more aggressive disease. A

history of tracheotomy and the frequency of MLS operations  $\geq 10$  times overall, showed a risk factor for high disease aggressiveness. Histopathological features of papilloma squam with light level dysplasia are found in RRP.

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