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Quality of Life in Recurrent Respiratory Papillomatosis Patients after Vocal Fold Surgery: An In-Depth Exploration

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Keywords
Recurrent respiratory papillomatosis · Quality of life · Dysphonia · Vocal fold surgery · Voice Handicap Index

Abstract
Introduction: This study explores the quality of life among patients with recurrent respiratory papillomatosis (RRP) after vocal fold surgery as measured by the outcome scores of the Voice Handicap Index (VHI) and the Distress Thermometer and Problem List in Patients with Recurrent Respiratory Papillomatosis (DT&PL). Differences in quality of life were explored within the independent variables age, surgical frequency, weeks since last vocal fold operation, gender, HPV type, surgical location, vaccination with Gardasil©, and a patient's request to speak with a speech-language pathologist. ***Methods:*** A single-center, observational cohort study was conducted using VHI and DT&PL scores and demographic and clinical data obtained from patient files. Inclusion criteria were a confirmed HPV type, age 18 years or older, the ability to fill in both questionnaires in Dutch, and having undergone at least one surgical procedure to remove laryngeal papilloma. Relationships of the independent variables with VHI and Distress Thermometer (DT) scores were explored using univariable and multivariable regressions and linear regression models. ***Results:*** Of 271 RRP patients, 100 met the inclusion criteria and responded to requests to fill in both questionnaires with a minimum of 12 weeks after their last operation. Our study showed a statistically significant negative relationship between age and VHI scores ($p = 0.02$) in the univariable, and multiple linear regressions ($p = 0.01$), indicating that patients experienced fewer self-perceived functional voice disabilities with each increase in age. A parallel negative relationship is seen between the variables age ($p = 0.03$) and DT scores. Our results showed a statistically significant positive relationship between the number of vocal fold surgeries and DT scores ($p = 0.03$). ***Conclusion:*** The results of this study show a significant relationship between age, surgical frequency, and quality of life in patients with RRP. Older patients have lower Voice Handicap Index (VHI) and Distress Thermometer (DT) scores, indicating fewer self-perceived voice and disease-related quality of life problems. Conversely, a rise in surgical frequency is significantly associated with higher DT scores, reflecting greater disease-related distress.

Plain Language Summary
This study looked at the difficulties patients with recurrent respiratory papilloma (RRP) face after having vocal fold surgery. RRP is a rare disease that can cause voice and

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breathing problems, impacting a person's daily life. One hundred patients filled in 2 questionnaires to measure difficulties caused by RRP: the Voice Handicap Index (VHI) and the Distress Thermometer and Problem List in Patients with Recurrent Respiratory Papillomatosis (DT&PL). Characteristics such as gender, age, and the number of surgeries a patient needed to control the disease were also looked at in this study. Our study found that age and the number of surgeries a patient had can affect the quality of life. Older patients report fewer difficulties, while younger patients experience more struggles related to RRP.

Introduction

Recurrent respiratory papillomatosis (RRP) is a rare, benign chronic disease caused by the human papillomaviruses HPV-6 and HPV-11 [1]. RRP affects children and adults and is characterized by exophytic neoplasms of the aerodigestive tract for which there is no cure [2]. The USA's Recurrent Respiratory Papillomatosis Task Force measured an estimated incidence rate in adults of about 1.8 per 100,000 [3]. RRP can appear as papillomatous growths in the respiratory and upper digestive tract, causing problems in the voice and airway [4]. RRP is frequently referred to as "laryngeal" or "glottal" papillomatosis because of its propensity for appearing in the larynx [5]. Due to the growth of the papilloma in the larynx, many patients struggle with dysphonia and, in severe cases, stridor [6]. Current clinical management options to reduce the impact of RRP include the excision of papilloma, the use of HPV vaccines, and adjuvant medical treatments such as bevacizumab [2, 7].

Multiple studies show that RRP patients experience voice-related quality of life problems [7–11]. Health state preferences refer to the quality of life or level of "subjective satisfaction, distress, or desirability that patients associate with their health state" [12]. The impact of dysphonia on the quality of life measured by health state preferences concluded that "dysphonia had a significant effect on quality of life, with moderate dysphonia ranking equivalently with monocular blindness" [7]. An international qualitative study showed that 69 out of 73 RRP patients reported feeling restricted in their career and social activities due to experiencing functional voice problems [8]. A Swedish study showed that 78% of RRP patients experienced quality of life problems as measured with Voice Handicap Index (VHI) [13] and SF-36 [14] scores with the variables frequency of operation, age at onset, gender, and HPV type [9]. In 2009, our center conducted a cross-sectional study of 34 RRP patients measuring the relationship between quality of life and patient-reported voice outcomes with the variables age, gender, coping style, lifestyle, type of surgery, surgical frequency, and time since the last surgery with standardized questionnaires [11]. This study showed higher VHI scores were related to a shorter time between surgical procedures and younger patients.

Age and gender may be associated with the experienced voice-related quality of life. Laryngeal function changes as part of the aging process, with an increase in voice disorders among people over 65 [15, 16]. Literature suggests that females, in general, may have a higher risk of voice problems than males at a rate of about 2:1 [17–19].

Previous research among 91 RRP patients showed that females experience a lower disease-related quality of life than their male counterparts, possibly motivating them to seek care from a speech-language pathologist (SLP) for their voice problems due to RRP [20]. This same study indicated that RRP patients who experience depression and anxiety were more likely to seek help from an SLP for their voice problems.

There are more than 90 subtypes of HPV that are classified either as high or low risk based on their potential for malignant transformation of the epithelial cells [1]. While both HPV-6 and 11 are considered low risk, HPV-11 is associated with a more aggressive clinical course and a higher rate of developing cancer [21]. Previous research shows that HPV-11 can cause a more aggressive spread of papilloma in the larynx than HPV-6 [22, 23]. Up to now, it is unclear if HPV-11 has a greater impact on the quality of life and experienced voice function than HPV-6.

Regardless of the surgical method, there is a risk of injury with each vocal fold surgical intervention [24]. Multiple vocal fold surgeries may cause vocal fold scarring, an inefficient closure of the cords, and poor mucosal wave, which could reduce voice quality [25]. In contrast, a study of 23 adults with RRP who underwent multiple CO_2 laser surgeries to remove laryngeal papillomatosis showed no statistically significant difference in voice quality, measured with acoustic measurements, between patients with less than or more than five surgical procedures [11]. The number of vocal fold surgeries needed to contain the effect of papilloma in the larynx can vary per patient. A previous study indicated 12 as the mean number of adult surgeries, with a range from 1 to 100 [7]. There may be a difference in voice quality between unilateral and bilateral surgical removal of laryngeal papilloma, as bilateral removal of papilloma from the vocal folds may cause the

formation of a glottal web [26]. Glottal webs can cause dysphonia and difficulty breathing by obstructing a portion of the airway [27].

Research regarding the influence of HPV vaccines among RRP patients on the quality of life is still in its early stages. The recombinant quadrivalent human papillomavirus vaccine Gardasil© (Merck) is an intramuscular, 3-dose vaccine administered at 0-, 2-, and 6-month intervals and contains strains for HPV types 6, 11, 16, and 18 [28]. Vaccinating RRP patients with Gardasil aims to reduce the frequency of RRP complications and increase the time between surgical procedures [29, 30]. A systematic review of HPV vaccination as a treatment for active RRP found that 75% of studies (9 out of 12) reported a decrease in the recurrence of laryngeal papilloma, therefore reducing the surgical frequency and decreasing disease burden [31].

The objective of this study was to explore the quality of life among patients with RRP as measured with the scores of 2 patient-reported outcome measurements – the Voice Handicap Index (VHI) and the Distress Thermometer and Problem List in Patients with Recurrent Respiratory Papillomatosis (DT&PL) [32] – with the variables age, surgical frequency, weeks after last vocal fold surgery, gender, HPV type, surgical location, vaccination with Gardasil, and a patient's request to speak with an SLP – after vocal fold surgery.

Methods

Study Design

A single-center, observational retrospective cohort survey study was conducted in the Department of Otolaryngology–Head and Neck Surgery at the Amsterdam University Medical Centers in 2023.

Setting and Population

Research participants were drawn from the database of 271 RRP patients treated at the Amsterdam University Medical Centers, with both the VHI and DT&PL completed between August 20, 2020, and October 30, 2023.

Participants

RRP patient files were screened for eligibility by the researchers. Eligibility criteria were: alive at the time of inclusion, confirmed HPV type by the hospital's pathology laboratory, age of 18 years or older when filling in the questionnaires, independent completion of both questionnaires in Dutch at 12 weeks or more since last vocal fold operation for removal of papilloma, and at least one operation to remove laryngeal papilloma. The threshold of 12 weeks after a vocal fold operation was to exclude patients still in the acute phase of recovery. This threshold is based on the researchers' clinical experience.

Variables

The following variables were chosen for our study based on published scientific literature [7–11]: age at the time of filling in the questionnaires, surgical frequency, time since last vocal fold operation as measured in weeks, gender, HPV type, surgical location (all locations where papilloma has been removed from the larynx), vaccination with the Gardasil, and the request to speak with an SLP. We define the variable surgical frequency as the total amount of surgical procedures to remove laryngeal papilloma since disease onset.

Voice Handicap Index

The Voice Handicap Index (VHI) is a validated, self-administered 30-item instrument measuring the patients' perception of the impact of their voice disorder on daily activities [13]. Questions are categorized into three subscales: physical, functional, and emotional. Each item contains five response levels (0–4) with a sum score range of 0–120 [33]. A higher score corresponds to more experienced quality of life restrictions due to the voice. The sum score remains the best interpretation of the VHI, as the subdomains have a high correlation [34]. This study used sum scores to measure the experienced voice-related quality of life. In developing the VHI, patients with a score of 33 reported their voice severity as mild, with scores of 44 reported for moderate and 61 for severe self-perceived voice disability [13]. The validated Dutch translation was used in our study [35] (see online suppl. material 1; for all online suppl. material, see https://doi.org/10.1159/000540310).

Distress Thermometer and Problem List in Patients with Recurrent Respiratory Papillomatosis

The Distress Thermometer and Problem List in Patients with Recurrent Respiratory Papillomatosis (DT&PL) [32] is a validated 51-item screening instrument that collects information regarding the quality of life problems experienced by patients with RRP. The Dutch language questionnaire is divided into two sections. The Distress Thermometer (DT) is a single-item scale ranging from 0 (no distress) to 10 (extreme distress), with a threshold score of ≥4 indicating experienced distress due to RRP. The patient indicates their score on the thermometer as an answer to the following question: "How much do you suffer from problems, complaints, distress?" The Problem List (PL) collects dichotomous (yes/no) information regarding the experienced quality of life, ranging from practical, family, social, emotional, spiritual, to physical problems. The PL concludes with two questions: would the patient like to speak with a medical professional about their RRP-related problems (yes/maybe/no), and, if so, to indicate the preferred medical professional. One of the options in this self-reporting list is an SLP. The PL used in the validation study of the DT&PL included the ability to score PL answers. Developers later introduced an unscored clinical version of the PL. As the unscored PL version was already in use in our clinical practice, we only analyzed DT scores to measure distress. The validated Dutch version was used in this study (see online suppl. material 2), and the outcome of the DT was used as a measurement for the experienced quality of life.

Data Collection and Analysis

Quantitative demographic, clinical data, VHI, and DT scores were collected from patient medical files from consenting participants meeting the eligibility requirements. Eligible patients with incomplete or missing questionnaires were sent new questionnaires by mail to fill in before the start of our study. To preserve data integrity, only complete observations were used in the

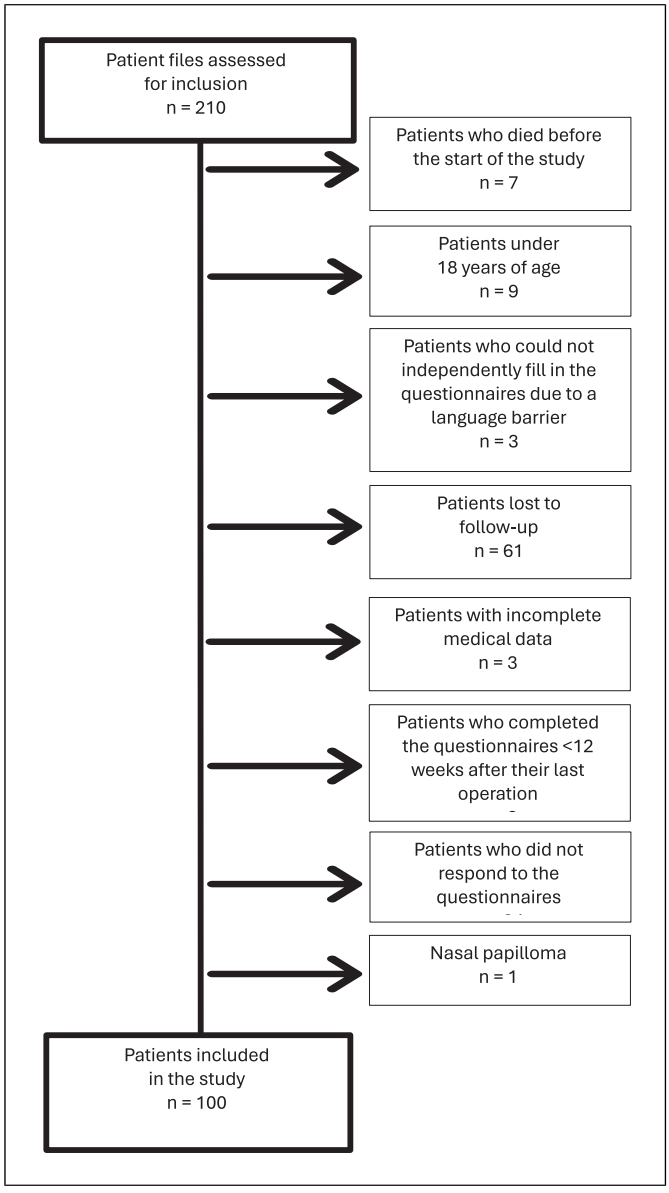

Fig. 1. Flowchart study population selection.

analyses. Relevant statistics were used to describe the characteristics of the study population. Univariable and multiple linear regression models were used to describe the relationships between the independent variables with the VHI and DT scores. All analyses were performed using R (RStudio, PBC).

A three-step statistical analysis was performed to describe the relationships between variables and VHI and DT scores while reducing the risk of confounding factors. Univariable linear regressions were used to describe the relationship between each independent variable and the experienced voice-related quality of life and distress. The second step of the analysis was fitting a multiple linear regression with the independent variables for a full model analysis of the VHI and DT scores to describe the combined effect of multiple variables on both dependent variable scores. The third step describes the relationship between each independent variable with both VHI and DT scores with unstandardized betas while controlling for the effects of other variables included in the linear regression model. Relationships in both the univariable and multiple linear models were described with betas(β), 95% confidence intervals, p values (with a value of < 0.05 being significant), and the explained variance (R^2) for VHI and DT scores. Unstandardized betas from the linear regression models are reported in estimated values of the dependent variable (VHI or DT) when all independent variables have a value of zero. Multicollinearity was described with the variance inflation factor [36], with a factor of 1 indicating no correlation between variables, 1–5 a moderate correlation, and >5 a strong correlation.

Table 1. Patient characteristics

Characteristic	Value, *N* (%)
N	100
Age (mean [SD])	53.2 (15.6)
Surgical frequency (median [range])	5 (1–127)
Time since last operation and quality of life measurements	
Weeks (median [range])	92 (12–1,092)
Gender	
Male	71 (71.0)
Female	29 (29.0)
HPV Type	
HPV-6	90 (90.0)
HPV-11	8 (8.0)
HPV-6 and 11	1 (1.0)
HPV-6 and 33	1 (1.0)
Surgical location	
Unilateral	26 (26.0)
Bilateral	69 (69.0)
Gardasil© treatment	
No	80 (80.0)
Yes	20 (20.0)
Request to speak with an SLP	
No	92 (92.0)
Yes	4 (4.0)
Maybe	4 (4.0)

Results

Participant Characteristics

The selection process of patients from the RRP database of the Amsterdam University Medical Centers for our study can be found in Figure 1. Of 271 patients in the database, 100 met the inclusion criteria and completed both the VHI and DT 12 weeks or more after their last vocal fold surgery. The median timeframe from inclusion in the RRP database to

Table 2. Distribution of Voice Handicap Index and Distress Thermometer scores within the categorical variables

	Median (IQR) VHI		Median (IQR) DT
Total median VHI (range)	26 (0–82)	Total median DT (range)	3 (0–8)
Male	24 (36.5)		3 (5)
Female	31 (27)		3 (5)
HPV-6	24 (36)		3 (5)
HPV-11	29.5 (12.8)		4.5 (4.5)
Surgical location			
Unilateral	16.5 (30)		1.5 (3)
Bilateral	27 (31.2)		3 (5)
No Gardasil	26.5 (33.25)		3 (5)
Yes Gardasil	37 (34)		3 (6.25)
Request to speak with an SLP			
No	25 (35)		3 (5)
Yes	48 (24.8)		5.5 (1.5)
Maybe	31.5 (7)		3 (2.5)

completing both questionnaires for the 100 study participants at the Amsterdam University Medical Centers is 27.8 years, with a range of 0.7–54.9 years. At the time of questionnaire submission, the population's mean age (SD) was 53.2 (15.6) years, ranging from 19 to 89. There was an overrepresentation of groups within the categorical variables as shown in Table 1. Males comprised 71% (n = 71) of the study population. The most dominant groups were HPV-6 (90.0%, n = 90) and no treatment with Gardasil (80%, n = 80). Due to the extreme overrepresentation in the variable request to speak with an SLP (92% answered "no"), this variable was left out of all statistical analyses. As shown in Table 2, median and interquartile ranges of VHI and DT scores were used to describe the data dispersion within the categorical variables gender and HPV type. There was a high response rate, with only 24 out of the 210 patients not responding to requests to fill in the questionnaires. The nonresponders in our database have comparable characteristics to those patients who did respond. The average age of the nonresponders is 41 years, comprised 7 females, 17 males, 4 patients with HPV-11, one with HPV-6 and 11, and 19 with HPV-6. Three nonresponders were vaccinated with Gardasil. Our regressions did not violate the assumption of multicollinearity, with variance inflation factors ranging from 1.05 to 1.78.

Self-Perceived Functional Voice Health State: Voice Handicap Index Scores

The median VHI score in our study population was 26 (range of 0–82). The univariable and multiple linear regressions showed a significant relationship between age and VHI scores. Our study population experienced fewer functional voice health disabilities with each increase in age. The univariable linear regression (β = −0.33 [95% CI −0.60, −0.06]) and the multiple linear regression (β = −0.29 [95% CI −0.58, −0.01]) both yielded significant p values <0.05. Unstandardized betas showed that the predicted VHI score decreased by approximately 0.29 units for each additional year increase in age, supporting the outcomes of both the univariable and multiple linear regressions. A linear model was used to test if the relationship between the variable age and VHI scores follows the U-shaped curve, referring to the theory which argues that men and women in the Netherlands experience better well-being after the age of 46.9 (with both genders pooled and controlled for other demographic factors) [37]. Analyses yielded a negative and significant coefficient (β = −2.07, p < 0.05), resulting in an inverted U-shape curve, with the lowest VHI scores (best self-perceived voice-related quality of life) reported by patients around 60 years of age. The ages of the participants with the highest VHI and DT scores in our population were 19 (VHI 82; DT 8), 40 (VHI 78; DT 8), 56 (VHI 76; DT 3), and 81 (VHI 76; DT 5). None of the other variables had statistically significant relationships with VHI scores.

Disease-Related Quality of Life Assessment: Distress Thermometer Scores

The median DT score in our study population is 3 with a range of 0–8. Among the 32 patients with a DT score of 5 and higher, the average age was 47.8 (range 19–89)

years, and an average VHI score of 49.4 (range 6–82). The negative relationship between DT scores and age (univariable regression: β = −0.04, 95% CI: [−0.07, −0.00], p = 0.03, multiple linear regression: β = −0.04, 95% CI: [−0.07, −0.00], p = 0.03) was comparable to that with the VHI scores, and statistically significant. The multivariable linear regression showed a significant positive relationship with DT scores with surgical frequency (β = 0.03, 95% CI: [0.00, 0.06], p = 0.03), indicating increased DT scores (distress) with each additional vocal fold operation. Univariable and multiple linear regressions showed an insignificant difference in VHI and DT scores between males and females, with median VHI scores among females 7 points higher than by males. With median DT scores identical for males and females, our findings do not concur with previous studies stating females with RRP experience a significantly lower disease-related quality of life than males [9, 20]. Unstandardized betas again supported the outcomes of both the univariable and multiple linear regressions, showing that for each additional year increase in age, the predicted DT score decreases by approximately 0.04 units. The unstandardized beta for surgical frequency showed that the predicted DT score increases by approximately 0.033 units for each additional surgical operation. Although the linear regression analysis of the quadratic relationship between DT scores and age yielded insignificant results, the average age of 47.8 years for experiencing distress due to RRP aligns with the U-shaped curve observed in quality of life studies in the Netherlands, where the lowest experienced quality of life occurs at around 46.9 years.

Discussion

Our study aimed to explore the quality of life among patients with RRP as measured by the VHI and DT outcome scores after vocal fold surgery. With RRP being such a rare disease, our population size of 100 allowed us to look further in-depth than previous studies into the experienced quality of life of patients using the VHI and the Distress Thermometer of the DT&PL for RRP. Both questionnaires were used in this study to encompass the wide range of voice-related quality of life and distress experienced by patients with RRP. While examining possible correlations between the outcomes of both questionnaires may be of clinical interest, our study explicitly refrained from performing this clinometric analysis as it would overextend the boundaries of this exploratory study. The most notable relationships in our study are between the self-perceived functional voice health state, as measured with the VHI, and the amount of disease-related stress, as measured with the DT, with the variables age and surgical frequency. All other variables in this study had statistically insignificant relationships with VHI and DT scores.

Our population has, on average, mild self-perceived voice disabilities. Except for the patients with HPV-11, most median scores were under the threshold of 4 points regarding experiencing distress due to RRP. The median VHI score of our study is comparable to previous studies measuring self-perceived voice problems among RRP patients after vocal fold surgery [9, 10]. In contrast to previous studies [15, 16], where an increase in age is generally associated with a subjective self-perceived reduction in voice quality, our population reports fewer experienced voice disabilities with each increase in age. In comparison, a study measuring the relationship between age and VHI scores among patients undergoing thyroplasty showed no relationship between both variables [38]. Our results are congruent with one previous study, where younger RRP patients have higher VHI scores (more experienced voice problems), with the study's outcome implying that older patients cope better with their disease-related voice problems [10]. With RRP being a chronic disease, it is possible that our study population has developed coping mechanisms to accommodate the burden of the disease. A previous study of emotion regulation and aging indicates that, as people age, they focus on more satisfying events and experiences in life, helping them maintain and even increase their self-reported well-being [39]. In the validation of the DT&PL questionnaire, DT scores were significantly correlated with factors such as pain, shortness of breath, depression, problems with daily activities, and feelings of anxiety, which may be due to the unpredictable course of RRP. When comparing the impact of RRP on the quality of life to that of multiple sclerosis, both patient populations struggle with the uncertainties of future relapses and the burden of disease management, which may force some patients to adapt their lives to accommodate the disease [40].

Our multiple linear regression results regarding surgical frequency relationships with both DT and VHI scores concur and contrast with previous studies. Our study population's relationship between DT scores and surgical frequency contrasts with a comparable study, which showed no significant difference in the quality of life between RRP patients who had 2 surgeries and patients receiving more than 2 surgeries, as measured with the Hospital Anxiety and Depression Scale (HADS) questionnaire [20]. The relationship with the DT scores in our population was expected to correlate with the

HADS, but this was not the case. Our results concur with a study among 27 patients with RRP which found no difference in the VHI sum scores and subscale scores when comparing patients who have only 1 operation per year to those who need multiple operations in a year [9]. It is plausible that the lack of a significant relationship between surgical frequency and VHI scores is due to the varied recurrence of the laryngeal papilloma after the initial surgical removal. Some of our study patients were operated on frequently at disease onset, with no need for an operation years later when filling in the questionnaires. These patients may have developed coping mechanisms for maintaining a stable voice-related quality of life by accepting the burden of multiple vocal fold operations to limit the impact of the disease. The incorporation of chronic disease management as part of maintaining a stable quality of life with RRP is comparable to studies among patients with multiple sclerosis [41]. Acoustic and perceptual measurements by RRP patients after multiple vocal fold surgeries also show no significant relationship between the number of vocal fold surgeries and voice quality, concurring with our analyses with VHI scores [11].

Our results showed no significant relationships between gender and VHI scores, which concur and contrast with previous RRP and quality of life studies. Our study contrasts the outcomes of a Swedish study, which had a significantly smaller population of 27 RRP patients, all non-smokers, with females reporting more quality of life problems than males [9]. The exclusion of smokers may have influenced both VHI and SF-36 scores, as smoking can have a negative influence on larynx histology, causing changes in voice quality [42]. A large study of 509 participants (272 controls and 273 with initial voice complaints and 92 patients who underwent vocal fold surgery) used the VHI sum scores and subscales to determine if there were differences in self-perceived voice quality between males and females [43]. Their outcomes show no significant influence of gender on VHI scores, with the exception that male patients scored significantly higher on the VHI functional subscale than female patients. Our results are supported by a study of 86 patients with voice problems, showing that there is no significant relationship between voice-related quality of life measurements and gender, where women scored worse than men, but not at significant levels [44]. While none of these studies included patients with RRP, the findings are comparable in that all of them measured the self-perceived voice quality among patients with an organic vocal fold disorder. There are currently no large-scale studies comparing VHI sum scores and subscales between genders among RRP patients.

The 4 patients requesting an appointment with an SLP had a median VHI score of 48 (range 7–76), indicating a moderate self-perceived voice disability and distress due to RRP with an average DT score of 5.5 (range 3–6). It is possible that patients in our study were satisfied with the voice improvements after surgery and, therefore, did not express a need for voice therapy. In a previous study analyzing changes in VHI score before and after vocal fold surgery, 194/237 patients had a lower VHI score (better voice-related quality of life), and 221/237 reported improvements in the voice after vocal fold surgery [43]. It is also possible that RRP patients do not know the possible role of voice therapy in managing their disease. In a study among 90 RRP patients, 37 people received voice therapy, giving a satisfaction score of 6.9 (range 1–10), indicating only a fair amount of satisfaction from the therapy [20]. Patients within our study were seen by the department SLP for a voice evaluation before and after surgery. Referrals for further voice therapy outside of the hospital were only given if they were requested by the patient.

Among the 4 patients who requested to see an SLP, 2 (patients 22 and 91) had previously received voice therapy from an SLP outside of the hospital and were, respectively, 37 and 32 years of age. Both participants reported physical issues on the PL, including intelligibility, voice problems, and a fear that their voice quality would worsen. The other 2 patients (numbers 6 and 26) were, respectively, 81 and 65 years of age and described different problems on the PL due to RRP. Patient 6 experienced more family and social problems as well as physical problems and fear due to the disease, while patient 26 only experienced physical problems (coughing, phlegm in the throat) and sleeping problems. The similarities between these 4 patients are too few to indicate that a certain disease profile may or may not be more inclined to ask for voice therapy.

Limitations

While acquiring patient-reported outcomes is valuable for clinicians, our study acknowledges potential biases in the data collection [45]. Specifically, nonresponse bias was identified, wherein 24 patients could not be included in the study due to a lack of one or both questionnaires. Noteworthy is the financial aspect of Gardasil vaccinations, which are not covered by Dutch health insurance, potentially introducing selection bias. Patients able to afford the vaccine may have been more likely to receive it, influencing the demographic of those benefiting from Gardasil. Additionally, there is a potential bias in the administration of Gardasil, as it might have been more frequently offered to younger patients with more severe RRP.

Effect modifiers most likely influenced our outcomes. Although our study did not measure personal habits such as alcohol consumption and smoking, previous research indicates that these habits can influence both VHI and DT scores [22, 42]. We also did not factor in gastroesophageal and laryngopharyngeal reflux and the herpes simplex virus type 2, which may increase papilloma growth in the larynx, possibly impacting the self-perceived functional voice health state [46, 47]. The severity of laryngeal papilloma can be assessed by the number of subsites affected. We did not measure the severity in our research, which may have influenced our outcomes. Objective voice data were not collected, which could have provided clinical measurements of the voice quality. Our data did not include information about current or previous voice therapy, which may have influenced VHI scores, as voice therapy may help relieve voice-related quality of life problems. Other demographic variables such as relationship status, economic situation, comorbidities, depression, and anxiety were also not measured in our study and could have better described the self-reported quality of life. Despite our study having a larger population than any other RRP observational study, using only complete cases reduced our population size, possibly affecting our study's statistical power and generalizability.

Recommendations

Along with medical interventions, healthcare options to relieve the psychological and social burden of RRP, especially for younger patients, should be included in patient treatment plans. To investigate further improvements in RRP patient care, a large prospective study is recommended to investigate the efficacy of voice therapy on the voice-related quality of life among patients. Additionally, further research is recommended to create a clinical prediction model to help better identify patients who may significantly suffer from a lower quality of life due to RRP.

Conclusion

Our study highlights the quality of life in RRP patients after vocal fold surgery, measured by the Distress Thermometer of the DT&PL and Voice Handicap Index scores. Analyses show a significant relationship between increased age and reduced VHI and DT scores, while a rise in surgical frequency and younger age correlates with higher DT scores. Median scores indicate mild self-perceived voice disabilities and distress below the Distress Thermometer threshold. No significant relationships were found between recovery time (post 12 weeks), gender, surgical location, and Gardasil treatment with quality of life and self-perceived voice quality in our cohort.

Statement of Ethics

This study protocol was reviewed and approved by the METC of the Amsterdam University Medical Centers and given the non-WMO Approval No. 2023-0362. Our study was conducted according to the principles of the Declaration of Helsinki [48], the Dutch Code of Conduct for Research Integrity [49], and the Amsterdam University Medical Centers Research Code (2023). Study participants were assigned a random case number to ensure privacy. Written informed consent was obtained from all participants according to the requirements of the METC of the Amsterdam University Medical Centers.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

M.M. initiated the research, made substantial contributions to the study design, obtained the METC waiver and participants, performed all data analysis and initial interpretations independently, and drafted the work, obtaining final approval for the study. L.W. contributed to acquiring study participants and data, reviewed the study's progress, interpreted the data analysis, and assisted in drafting and approving the final study. B.S. provided substantial input into the study's concept and design, including the selection of analysis techniques, critically reviewed the work, and approved the final draft. R.R., as a research initiator, made significant contributions to the study design, participated in participant acquisition, and contributed to the interpretation of data analysis, critically reviewed the work, and approved the final published version. M.M., L.W., B.S., and R.R. are all accountable for all aspects of the work and can ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement

Data supporting the findings of this study are available from the corresponding author upon reasonable request. Due to privacy concerns, the data are not publicly available, but access can be granted after obtaining appropriate permissions from the Amsterdam University Medical Centers. Requests for access to the data should be directed to M.M.

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