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Clinical Characteristics of Pediatric Chronic Rhinosinusitis: A Nationwide Retrospective Multicenter Study

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Background and Objectives: Pediatric chronic rhinosinusitis (CRS) significantly affects children's quality of life and learning abilities. This study aimed to evaluate the postoperative outcomes in pediatric patients who underwent functional endoscopic sinus surgery (FESS) for CRS.

Methods: A retrospective review was conducted on pediatric patients who underwent FESS for CRS at 11 university hospitals. The inclusion criteria were patients under 20 years old with bilateral disease who were operated on between January 2005 and December 2021. The data collected included demographics, clinical history, blood tests, preoperative computed tomography, and preoperative and postoperative symptom control. The Kruskal-Wallis and Fisher exact tests were used to compare the quantitative and qualitative data, respectively.

Results: In total, 213 patients were enrolled. The mean age was 13.4±3.0 years, and 145 (68.1%) were male. One hundred sixty-four patients (77.0%) had nasal polyps and 33 patients (15.5%) underwent revision FESS. The preoperative symptoms, in order of prevalence, included nasal obstruction (87.8%), rhinorrhea (71.8%), a sense of postnasal drip (58.2%), hyposmia (44.6%), cough (24.4%), and facial fullness (18.3%). These symptoms were significantly alleviated for up to 3 years after surgery ($p<0.001$). At the time of the last follow-up, 121 patients (56.8%) were controlled, 80 (37.6%) were partly controlled, and 12 (5.6%) were uncontrolled. Patients in the uncontrolled group had higher Lund-Mackay scores, longer follow-up durations, and more instances of revision surgery compared to those in the controlled and partly controlled groups. When age was categorized into three groups, those aged 16 years or older tended to have lower Lund-Mackay scores and better control.

Conclusion: FESS significantly improves both the postoperative symptoms and the long-term quality of life in pediatric CRS patients. Better symptom control is associated with older age and a lower disease burden.

Keywords: Rhinosinusitis; Child; Functional endoscopic sinus surgery; Postoperative outcomes.

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INTRODUCTION

Chronic rhinosinusitis (CRS) is a prevalent condition in pediatric clinical practice, significantly affecting children's quality of life and learning abilities. It is estimated that CRS affects about 2.1%–4% of the pediatric population [1]. CRS has a significant negative impact on children's lives, particularly in terms of absenteeism, classroom concentration, sleep patterns, and mental and physical well-being [2,3]. Pediatric CRS is characterized by the presence of two or more symptoms, such as nasal obstruction, rhinorrhea, facial pain, and cough, persisting for over 12 weeks. Notably, either nasal obstruction or rhinorrhea must be one of the symptoms [1]. Initial treatment typically involves medical management strategies, including the use of intranasal corticosteroid sprays, saline irrigation, and antibiotics, aimed at reducing inflammation and clearing the infection [1]. Despite these efforts, some patients do not respond to medical treatment and may require surgical intervention [4].

The most common surgical treatments for pediatric CRS are adenoidectomy and functional endoscopic sinus surgery (FESS) [1]. Adenoidectomy often serves as the first-line surgical approach in cases of CRS with adenoid hypertrophy, with approximately 50% of patients experiencing improvement from this procedure alone [1,5]. FESS has gained recognition for its effectiveness in treating refractory pediatric CRS, significantly enhancing quality of life and providing symptom relief [6]. Research underscores the favorable outcomes associated with FESS, establishing it as a suitable option not only for adults but also for pediatric patients who do not respond to adequate medical therapy [7]. However, the surgical process and postoperative care in children are considered more challenging due to the narrow nasal cavity and smaller paranasal sinuses compared to adults [8].

Postoperative outcomes for children with chronic rhinosinusitis, either with nasal polyps (CRSwNP) or without, have shown that FESS can significantly improve quality of life and alleviate nasal symptoms [9,10]. Success rates for adenoidectomy, balloon sinuplasty, and FESS in treating pediatric CRS range from 47%–61%, 80%–200%, and 62%–87%, respectively [11]. However, surgeons often hesitate to perform FESS on children due to concerns about poor prognoses after surgery, especially in younger patients [12].

This study conducted a retrospective analysis of data from pediatric patients with CRS who underwent FESS at university hospitals. The aim was to explore the clinical characteristics and course of CRS in pediatric patients, with a particular focus on the effectiveness of the surgery, postoperative outcomes, and improvements in quality of life.

METHODS

Patient selection

This study retrospectively enrolled pediatric patients who underwent surgical treatment for CRS at eleven university hospitals associated with the Korea Chronic Rhinosinusitis and Nasal Polyp Study Group under the auspices of the Korean Rhinologic Society. The inclusion criteria were patients under 20 years of age with bilateral disease who underwent surgery between January 2005 and December 2021. The exclusion criteria ruled out patients with unilateral disease, those aged 19 years or older, those with a follow-up period of less than 1 year post-surgery, and those diagnosed with nasal or paranasal sinus tumors. The study protocol received approval from the Institutional Review Board of Samsung Medical Center (IRB NO. 2021-08-141-001), and the requirement for informed consent was waived.

Data collection and clinical outcome measures

The collected data included demographic details such as age at surgery, sex, past medical history, and social history. It also included laboratory results, specifically blood eosinophil count and serum immunoglobulin E levels, as well as preoperative computed tomography (CT) findings. These findings comprised the Lund-Mackay score, the presence of a conchal cell, septal deviation, infraorbital cell, and paradoxical middle turbinate. Additionally, the Lund-Kennedy score and the severity of symptoms before and after surgery were recorded. At the final follow-up, patients were categorized based on their response to treatment according to the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020 guidelines. The categories were controlled, partially controlled, and uncontrolled [1]. A controlled response is characterized by the absence or minimal presence of symptoms such as nasal blockage, rhinorrhea or postnasal drip, facial pain or pressure, impaired smell, and sleep disturbances or fatigue, coupled with healthy mucosa and no need for rescue medication in the last six months. Partially controlled is defined by the presence of at least one significant symptom or the need for one course of rescue medication. Lastly, uncontrolled status is defined by the persistence of three or more symptoms despite treatment, accompanied by diseased mucosa.

Statistical analyses

Data were presented as mean values with standard deviations or frequencies. The Shapiro–Wilk test was used to assess the normality of distribution. Qualitative data were compared using Kruskal–Wallis test to compare differences of continuous variables among three disease groups or three age groups and the Fisher exact test for categorical variables. A p-value of <0.05

was considered statistically significant for all analyses. All statistical analyses were conducted using Stata software version 18.0 (StataCorp LLC).

RESULTS

Demographics

A total of 213 patients were included, with a mean age of 13.4±3.0 years and 68.1% being males (Table 1). Additionally, 22.1% of the patients tested positive for atopy in various allergy tests, and 5.2% had comorbid asthma. The majority of patients (77.0%) had nasal polyps, and 15.5% were revision cases with a history of previous FESS. The mean preoperative Lund-Kennedy score was 7.9±2.7. Furthermore, 22.5% of the patients had undergone or were undergoing adenoidectomy concomitant with FESS. The mean follow-up period was 25.2±24.1 months. Preoperatively, the most common symptom was nasal obstruction (87.8%), followed by rhinorrhea (71.8%), postnasal drip (58.2%), hyposmia (44.6%), cough (24.4%), and facial pressure (18.3%) (Fig. 1). All these symptoms showed significant improvement up to 3 years post-surgery.

Table 1. Demographics of pediatric patients with chronic rhinosinusitis

Variables	Value	Total number
Age (yr)	13.4±3.0	213
Male sex	145 (68.1)	213
Nasal polyp	164 (77.0)	213
Previous FESS history	33 (15.5)	213
Adenoidectomy	48 (22.5)	213
Tonsillectomy	23 (10.8)	213
Atopy	47 (22.1)	213
Asthma	11 (5.2)	213
Blood eosinophil (%)	2.8±2.4	186
Blood eosinophil (cells/μL)	159.5±188.8	184
Total IgE (kU/L)	239.9±456.3	127
Lund-Mackay score	15.4±6.0	209
Lund-Kennedy score	7.9±2.7	167
Mean follow-up duration (mon)	25.2±24.1	213
Computed tomographic findings		
Conchal cell	24 (14.3)	168
Septal deviation	80 (47.6)	168
Infraorbital cell	21 (12.5)	168
Paradoxical middle turbinate	7 (4.2)	168
Social history		
Passive smoking	4 (6.1)	66
Breastfeeding	30 (62.5)	48
Pet ownership	4 (8.0)	50
No sibling	48 (29.3)	164
Past medical history		
Otitis media	20 (9.5)	210
Pneumonia	21 (10.0)	210
Primary ciliary dyskinesia	2 (1.0)	210

Values are presented as mean±standard deviation or number (%).
FESS, functional endoscopic sinus surgery; IgE, immunoglobulin E

Postoperative symptom control

Based on the EPOS 2020 guidelines [1], 56.8% of the subjects were classified as controlled, 37.6% as partly controlled, and 5.6% as uncontrolled (Table 2). A subgroup analysis was conducted to assess the degree of treatment response at the final follow-up. The controlled group had a significantly higher proportion of males compared to the other groups (75.2% vs. 58.8% vs. 58.3%, p=0.038). The uncontrolled group had more revision cases than the controlled and partly controlled groups (14.9% vs. 11.3% vs. 50.0%, p=0.002), longer mean follow-up periods (22.4±20.3 vs. 23.6±19.8 vs. 64.5±46.2, p=0.002), and a higher incidence of otitis media (8.5% vs. 7.5% vs. 33.3%, p=0.038). The controlled group was slightly older than the other groups and exhibited lower rates of adenoidectomy (16.5% vs. 31.3% vs. 25.0%, p=0.039) and tonsillectomy (7.4% vs. 11.3% vs. 41.7%, p=0.006). There was no significant effect of previous or concurrent adenoidectomy on control status (p=0.500). Although the preoperative Lund-Mackay score was higher in the uncontrolled group (14.9±6.0 vs. 15.6±6.0 vs. 18.2±6.2, p=0.175), this difference was not statistically significant. This may be more pronounced in younger patients due to the underdevelopment of the frontal or sphenoid sinuses. CT scans revealed other anatomical findings in 78.9% of all subjects, with no significant differences between the groups. Other factors, such as passive smoking, breastfeeding history, pet ownership, and having no siblings, showed no significant differences among the three groups, likely due to a low response rate.

Differences in surgical outcomes by age group

Patients were categorized into three age groups for the analysis: under 12 years (n=57, 26.8%), 12–15 years (n=101, 47.4%), and over 16 years (n=55, 25.8%) (Table 3). The rate of adenoidectomy was lowest in the oldest group, with 33.3% in the youngest, 23.8% in the middle, and only 9.1% in those aged 16 years or older (p=0.006). The prevalence of atopy was also lower in the middle age group (33.3% vs. 12.9% vs. 27.3%, p=0.007). Additionally, the oldest group exhibited a significantly lower Lund-Mackay score compared to the other groups (16.9±5.6 vs. 15.3±6.3 vs. 13.9±5.7, p=0.027). No other factors showed significant differences among the groups.

Disease control status among the three age groups

An analysis was conducted to assess disease control status

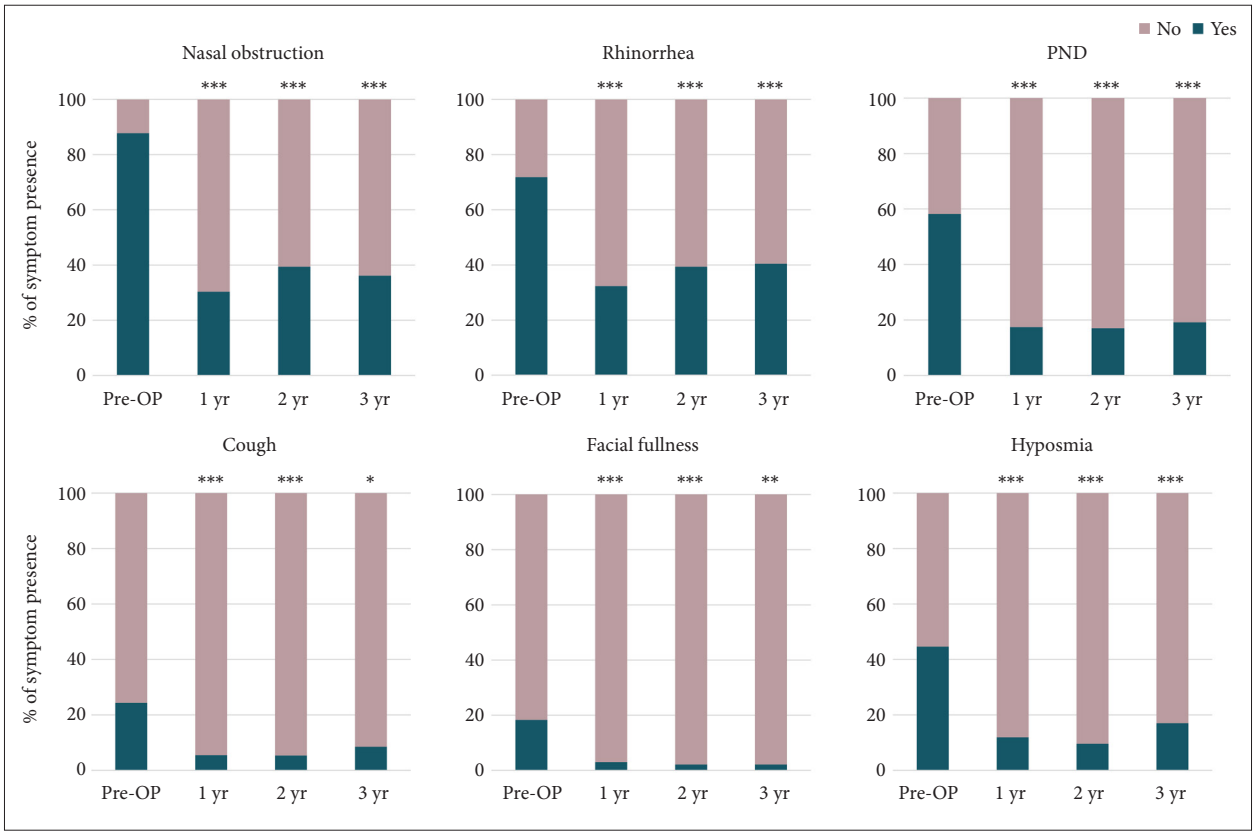

Fig. 1. Symptom improvement after functional endoscopic sinus surgery in pediatric chronic rhinosinusitis patients. Statistical significance was assessed through a comparison to the preoperative score. *p<0.05; **p<0.01; ***p<0.001. PND, postnasal drip.

across different age groups (Table 4). Although the results did not reach statistical significance (p=0.233), the highest control rate was observed in the over-16 age group (69.1%), compared to 54.4% and 51.5% in the younger groups. Conversely, the 12–15 age group exhibited the highest rate of uncontrolled disease (7.9%), which was more than double that of the other groups (3.5% and 3.6%). In cases requiring revision (n=33), the average age was lowest in the uncontrolled group (11.2±3.1 years), in contrast to the partly controlled (13.7±3.1 years) and controlled groups (14.4±2.7 years). However, this difference was not statistically significant (p=0.105). No significant differences were found in age (p=0.703) or preoperative Lund-Mackay scores (p=0.183) between primary and revision cases. The retrospective nature of the study limited our ability to determine the age or Lund-Mackay scores prior to the initial surgery.

DISCUSSION

This study is the first nationwide retrospective analysis to explore the postoperative outcomes of FESS for CRS in pediatric patients. We evaluated surgical outcomes based on the clinical control criteria for CRS from the EPOS 2020 guidelines: 56.8% of cases were controlled, 37.6% were partly controlled, and 5.6% were uncontrolled. In this study, nasal obstruction was the most prevalent symptom at 87.8%, followed by rhinorrhea at 71.8%, postnasal drip at 58.2%, hyposmia at 44.6%, cough at 24.4%, and facial pressure at 18.3%. All symptoms showed significant improvement following FESS, persisting up to three years post-surgery. However, approximately 30% of patients continued to report symptoms after surgery, a rate that remained unchanged from one to three years postoperatively. A previous study indicated that 76% of children showed improvement 5.4 years after surgery [13]. In patients with CRSwNP, 86% of 44 patients experienced a positive outcome four years post-FESS without requiring revision surgery [10]. Well-known risk factors for pediatric CRS include cystic fibrosis, primary ciliary dyskinesia, immunodeficiency, allergic rhinitis, and asthma [14]. In our cohort, a history of previous surgery and otitis media were identified as risk factors for uncontrolled symptoms. Other factors, such as nasal polyps, atopy status, and asthma, did not influence disease control. None of the patients had cystic fibrosis, only two were diagnosed with primary ciliary dyskinesia, and 5.2% had asthma.

These differences in prevalence may explain the discrepancies with previous reports. Wu et al. [15] identified nasal allergy and a higher Lund-Mackay score as risk factors for revision surgery in pediatric CRS patients. However, our study found no significant differences between the primary and revision surgery groups. Notably, the uncontrolled group was young-

Table 2. Subgroup analysis of disease control status

Variable	Controlled (n=121, 56.8%)	Partly controlled (n=80, 37.6%)	Uncontrolled (n=12, 5.6%)	p-value
Age (yr)	13.7±3.2	13.1±2.7	12.8±2.8	0.182
Age at last follow-up (yr)	15.5±3.2	15.1±3.2	18.2±3.0	0.010
Male sex	91 (75.2)	47 (58.8)	7 (58.3)	0.038
Nasal polyp	94 (77.7)	60 (75.0)	10 (83.3)	0.828
Previous FESS history	18 (14.9)	9 (11.3)	6 (50.0)	0.002
Adenoidectomy	20 (16.5)	25 (31.3)	3 (25.0)	0.039
Tonsillectomy	9 (7.4)	9 (11.3)	5 (41.7)	0.006
Atopy	28 (23.1)	17 (21.3)	2 (16.7)	0.963
Asthma	3 (2.5)	7 (8.8)	1 (8.3)	0.095
Blood eosinophil (%)	2.7±2.1	2.8±2.7	3.1±2.6	0.905
Total IgE (kU/L)	246.3±390.1	248.9±566.9	128.4±70.9	0.980
Lund-Mackay score	14.9±6.0	15.6±6.0	18.2±6.2	0.175
Lund-Kennedy score	8.2±2.7	7.4±2.8	8.5±2.4	0.297
Mean follow-up duration (mon)	22.4±20.3	23.6±19.8	64.5±46.2	0.002
Computed tomographic findings				
Conchal cell	11 (11.6)	12 (19.4)	1 (9.1)	0.386
Septal deviation	51 (55.7)	24 (38.7)	5 (45.5)	0.175
Infraorbital cell	8 (8.4)	12 (19.4)	1 (9.1)	0.107
Paradoxical middle turbinate	4 (4.2)	2 (3.2)	1 (9.1)	0.535
Social history				
Passive smoking	1 (2.9)	3 (12.0)	0	0.401
Breastfeeding	15 (57.7)	11 (61.1)	4 (100)	0.394
Pet ownership	3 (10.7)	1 (5.6)	0	>0.999
No sibling	26 (28.3)	18 (29.0)	4 (40.0)	0.697
Past medical history				
Otitis media	10 (8.5)	6 (7.5)	4 (33.3)	0.038
Pneumonia	11 (9.3)	7 (8.8)	3 (25.0)	0.216

Values are presented as mean±standard deviation or number (%). FESS, functional endoscopic sinus surgery; IgE, immunoglobulin E

Table 3. Subgroup analysis of age groups

Variable	<12 years (n=57)	12–15 years (n=101)	≥16 years (n=55)	p-value
Age at last follow-up (yr)	12.0±2.7	15.8±2.2	18.7±1.5	<0.001
Male sex	38 (66.7)	66 (65.4)	41 (74.5)	0.483
Nasal polyp	45 (79.0)	77 (76.2)	42 (76.4)	0.920
Previous FESS history	9 (15.8)	14 (13.9)	10 (18.2)	0.774
Adenoidectomy	19 (33.3)	24 (23.8)	5 (9.1)	0.006
Tonsillectomy	8 (14.0)	12 (11.9)	3 (5.5)	0.307
Atopy	19 (33.3)	13 (12.9)	15 (27.3)	0.007
Asthma	5 (8.8)	2 (2.0)	4 (7.3)	0.129
Blood eosinophil (%)	2.9±2.3	2.5±2.0	3.1±2.9	0.733
Total IgE (kU/L)	192.8±353.0	263.9±555.0	237.0±322.1	0.264
Lund-Mackay score	16.9±5.6	15.3±6.3	13.9±5.7	0.027
Lund-Kennedy score	8.3±2.7	8.1±2.7	7.0±2.8	0.062
Mean follow-up duration (mon)	29.4±29.4	25.7±23.9	20.0±16.9	0.243

Values are presented as mean±standard deviation or number (%). FESS, functional endoscopic sinus surgery; IgE, immunoglobulin E

Table 4. Disease control according to age group

Age (yr)	Controlled	Partly controlled	Uncontrolled	Total
<12	31 (54.4)	24 (42.1)	2 (3.5)	57
12–15	52 (51.5)	41 (40.6)	8 (7.9)	101
≥16	38 (69.1)	15 (27.3)	2 (3.6)	55
	121 (56.8)	80 (37.6)	12 (5.6)	213

Values are presented as number (%)

er at the time of revision surgery, suggesting a higher incidence of refractory cases in this group. The most common reasons for revision surgery in children were adhesions (57%) and stenosis of the maxillary sinus ostium (52%) [16]. Additionally, the revision surgery rate was higher in patients with asthma (19% vs. 8% in non-asthmatics) and in children under 6 years of age (20% vs. 9% in those older than 6 years). Thus, preventing adhesions and scars during surgery could potentially reduce the need for reoperation. Our findings indicate that the presence of atopy or asthma did not significantly impact symptom control or the rate of revision surgery. Previous studies have highlighted these factors as significant in patients undergoing revision surgery [15,16]. Further research is necessary to determine whether atopy and asthma also influence symptom control. Anatomical considerations, such as septal deviation and turbinate hypertrophy, should be taken into account during FESS in children. Ramadan [16] reported that four of the 23 revision cases (17%) underwent septoplasty in conjunction with FESS. According to the consensus statement, procedures such as inferior turbinoplasty and reduction or removal of the middle turbinate conchal cell can be beneficial in reducing symptoms [17].

This study highlights important demographic and clinical factors that influence postoperative outcomes in pediatric CRS, offering insights into the patient characteristics linked to disease control status. A key observation was the higher proportion of males in the controlled group, who were also slightly older than those in other groups. Additionally, the controlled group exhibited lower rates of adenoidectomy, possibly reflecting the older age of these patients. Tsukidate et al. [18] noted that symptoms often worsened or remained unchanged post-surgery in patients younger than 12 years. The clinical consensus statement on pediatric CRS advocates for distinct treatment approaches for children under 12 years compared to those over 13 years [17]. The underdevelopment of sinus cavities and frequent respiratory infections are primary contributors to poor postoperative outcomes. In this study, patients over 16 years of age demonstrated the highest rate of controlled outcomes, suggesting that older age may be linked to better recovery and symptom management, potentially due to anatomical maturity, immunological development, or greater adherence to postoperative care protocols [19]. The paranasal sinuses reach full development between the ages of 12 and 14. Performing FESS on underdeveloped or poorly pneumatized paranasal sinuses in children can result in unfavorable outcomes, such as synechia, ostium stenosis, and fibrosis [20]. Moreover, the humoral immune system may play a role in the history of recurrent upper respiratory tract infections. The prevalence of immunoglobulin deficiency was found to be 13% and 23% in patients with recurrent and difficult-to-treat CRS, respectively [21]. In some instances of immunoglobulin subclass deficiency, serum immunoglobulin levels returned to normal ranges for up to 6 years [22]. The prevalence of humoral immunodeficiency was 21.8%, with no significant difference observed between adults and children with refractory CRS [23]. In summary, the failure to control symptoms in some pediatric patients may indeed stem from immunodeficiency, and variations in symptom control across different ages may be influenced by factors related to anatomical development.

Adenoidectomy is considered a first-line surgical option for pediatric CRS when adenoid hypertrophy is present, as the adenoids can serve as a bacterial reservoir [11,24]. The EPOS 2020 guidelines recommend adenoidectomy as an adjunct to FESS in children with persistent CRS symptoms, especially in cases of adenoid hypertrophy or when previous adenoidectomy alone has not fully resolved the symptoms [1]. Research indicates that combining adenoidectomy with FESS can enhance postoperative outcomes by reducing the inflammatory load and improving sinus ventilation, thus increasing the effectiveness of FESS. This strategy may be particularly advantageous for younger children up to six years of age or those with significant adenoid tissue contributing to sinus obstruction [17,25]. Our study examined pediatric patients with CRS undergoing FESS, many of whom had previously or concurrently undergone adenoidectomy. Additionally, the study included only seven patients aged 6 years or younger. These factors underscore the challenges in comparing the effectiveness of adenoidectomy across different studies.

Similarly, in adult CRS cases, the preoperative disease severity, as indicated by the Lund-Mackay score, was significantly higher in the uncontrolled group. Interestingly, older patients exhibited notably lower preoperative Lund-Mackay scores, suggesting that they may present with milder forms of the disease at the time of surgery. This could potentially lead to better-controlled outcomes after surgery. The development of paranasal sinuses progresses gradually from infancy through adolescence, achieving full maturity only in the late teenage years [26,27]. Our analysis, which examined age groups in greater detail than the previously suggested 12-year cutoff [17], showed favorable results for individuals aged 16 and older. Once the growth of the paranasal sinuses is complete,

treatment outcomes similar to those observed in adults are expected.

This study has several limitations stemming from its retrospective design. Key issues include missing data points, particularly in follow-up data, inconsistencies in hospital record-keeping, and variations in documentation practices, all of which could compromise the reliability of certain outcomes. Additionally, we were unable to gather information on postoperative management, and treatment approaches varied across institutions. To reduce biases in our study, we implemented standardized data collection protocols at all centers and used uniform criteria to assess disease control. However, variations in the duration of follow-up could introduce bias, as longer follow-up periods might skew the outcomes to appear worse. Future studies should consider using standardized follow-up durations or conducting multicenter randomized controlled trials. Our analysis did not include the pediatric CRS group that underwent only adenoidectomy. Further research could explore a broader age range and include patients who had only adenoidectomy. Although balloon sinuplasty is a potential surgical option [28], it was not considered in this study due to its infrequent use in South Korea.

In conclusion, this study provides valuable insights into the postoperative outcomes of FESS in pediatric patients with CRS, identifying factors linked to successful symptom management. Controlled outcomes were positively associated with older age, male sex, and lower disease severity. Conversely, patients who required revision surgery, those with higher preoperative Lund-Mackay scores, or those with a history of otitis media were more likely to experience persistent symptoms after surgery. These findings underscore the importance of careful patient selection and thorough preoperative evaluation, particularly concerning age and disease severity, to optimize surgical results in pediatric CRS. Although this retrospective, multicenter study provides a comprehensive overview of the efficacy of FESS, further prospective research employing standardized protocols is essential to refine treatment strategies and improve outcomes for this patient group.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

Gwanghui Ryu, Shin Hyuk Yoo, and Min-Seok Rha who are on the editorial board of the *Journal of Rhinology* were not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

Author Contributions

Conceptualization: Gwanghui Ryu, Ji-Hun Mo. **Data curation:** all authors. **Formal analysis:** Donghyeok Kim, Gwanghui Ryu. **Funding acquisition:** Ji-Hun Mo. **Methodology:** Gwanghui Ryu, Ji-Hun Mo. **Supervision:** Ji-Hun Mo. **Validation:** all authors. **Visualization:** Donghyeok Kim, Gwanghui Ryu. **Writing—original draft:** Donghyeok Kim, Gwanghui Ryu. **Writing—review & editing:** Gwanghui Ryu, Ji-Hun Mo.

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