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Quality of Life and Impact of Endoscopic Sinus Surgery in Adult Patients With Cystic Fibrosis

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Abstract

Background: Cystic fibrosis (CF) is the most common autosomal recessive disease in Caucasian population. Due to its pathological mechanism, chronic rhino sinusitis (CRS) associated or not with nasal polyposis usually occurs in adults and affects close to one-half of all CF patients. The goal of our work was to evaluate the impact of endoscopic sinus surgery (ESS) in the quality of life (QoL) of the CF patients and demonstrate an improvement of the functional outcomes in the patients undergoing the surgical procedure rather than in the not treated ones.

Methodology: We studied 54 adult patients affected by CF. Lund–Kennedy, Lund–Mackay scores, and Sino-Nasal Outcome Test-22 (SNOT-22) were analyzed.

Results: Twenty-two (40.7%) of the 54 CF patients underwent ESS. This group presented more likely complaints consistent with CRS. Lund–Kennedy and Lund–Mackay scores appeared higher in the ESS group: 10 (range of 6–12) and 16 (range of 12–20), respectively. SNOT-22 showed median values for non-ESS and ESS group of 17.5 (range of 3–68) and 44 (range of 10–73), respectively.

Conclusions: ESS represents the best option to improve clinical QoL of CF patients who do not response to conventional medical therapy.

Keywords

cystic fibrosis, endoscopic sinus surgery, chronic rhino sinusitis, Sino-Nasal Outcome Test-22, quality of life

Introduction

Cystic fibrosis (CF) is the most common autosomal recessive disease in Caucasian population, with a reported incidence of 1 in 2500 to 3000 healthy newborns.[1,2] It is caused by mutations in the CF transmembrane conductance regulator (CFTR) gene, encoded on the q31 region of the chromosome 7. The resulting dysfunction of chloride and sodium channels causes the improvement of the visco-elastic properties of the mucus and an impairment of the mucus-ciliary clearance, which contribute to the mechanical obstruction of the nasal and paranasal sinuses[3–5] Due to the pathological mechanism, chronic rhino sinusitis (CRS) usually occurs in adults and affects close to one-half of all CF patients.[6] In specific, the patients with homozygosity for F508del and other severe mutations appear to have an elevated risk to develop CRS associated with nasal polyposis (NP).[7,8]

Sinonasal symptoms such as nasal obstruction, sneezing, runny nose, thick nasal discharge, and reduced sense of smell and taste are reported from about 50% to 63% of CF patients.[9–11] These symptoms are often associated with a relevantly impairment of quality of life (QoL) and are

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refractive to conventional medical therapy. Endoscopic sinus surgery (ESS) is widely accepted as the standard of care for CRS that do not respond to conventional medical treatment.[12,13] The goal of the surgical procedure in CF patients is to achieve the drainage of the paranasal sinuses and therefore mitigate the inflammatory cascade. It should be noted that ESS procedure, in this disease, finds the same indications than in non-CF patients.[14–16] Furthermore, CF patients undergo a high amount of regular checkups that could worsen the QoL and the daily routine of these patients. In order to quantify the subjective sinonasal symptoms and to assess the health-related QoL, the American Sino-Nasal Outcome Test-22 (SNOT-22) is usually used as a well-validated test.[17]

The primary aim of our work was to evaluate the impact of ESS procedure on the QoL of CF patients in terms of functional outcomes. The second purpose was to demonstrate the improvement of the abovementioned outcomes in patients who underwent the surgical procedure rather than in the not treated ones. Finally, we wanted to suggest indications and timing for the surgical treatment in CF adult patients affected by CRS.

Materials and Methods

Between January 2012 and December 2017, 54 adult patients affected by CF were referred to the ENT outpatient clinic of our institution and received a clinical and instrumental examinations of the head and neck district.

In order to accomplish our overmentioned purposes, we enrolled in our study only patients presenting the following criteria: $\geq$18 years old patients affected by CF who did not receive any previous sinus surgical treatment. Patients were given extensive information about the surgical procedures they were about to undergo, and all the participants signed an informed consent agreement. On the other hand, pediatric patients (<18 years), patients with incomplete medical records, or who had previous sinus surgical treatment were excluded. This study was conducted in agreement with the institutional review board of the University of Florence, and the Helsinki Declaration guidelines were followed.

Clinical, radiological, and surgical characteristics were extracted from each patient chart. The following characteristics of patients and disease-status were recorded: gender, age, body mass index, type of genetic mutations (G542X, 2789 + 5G->A, F508del), diabetes mellitus (if present), hepatic alterations (if present), nasal obstruction, rhinorrhea, headache, smell dysfunction, and NP. The distribution of genotypes and mutation classes is reported in Table 1. Homozygous patients or compound heterozygous for class I–III mutations were allocated to the class I–III mutation and patients who carried at least 1 class IV–V mutation were addressed to the class IV–V.[18] The endoscopic evaluation was summarized following the Lund–Kennedy score, which evaluates the endoscopic aspects of the nasal cavities by giving a score ranging from 0 to 12 on the base of the following characteristics: presence of polyps, nasal discharge, edema, adhesions, or crust.[19] The radiological aspects were evaluated accordingly to the Lund–MacKay staging system that is a score based on the numerical sum of abnormal findings on sinus computed tomography (CT) scans.[19]

Table 1. Distribution of Genotypes and Class Mutation.

Genotype	Frequency; N (%)	Class of Mutation
F508del/F508del	23 (42.6)	I–III
F508del/N1303K	4 (7.4)	I–III
F508del/G542X	2 (3.7)	I–III
F508del/R553X	2 (3.7)	I–III
F508del/G1244E	1 (1.8)	I–III
F508del/C276X	1 (1.8)	I–III
F508del/E585X	2 (3.7)	I–III
F508del/1717-1G N A	2 (3.7)	I–III
F508del/R1066H	1 (1.8)	IV–V
F508del/UNK	3 (5.5)	I–III
G542X/2789 + 5G->A	1 (1.8)	IV–V
G542X/R347P	1 (1.8)	IV–V
R347P	1 (1.8)	IV–V
N1303K/N1303K	3 (5.5)	I–III
R553X/N1303K	1 (1.8)	I–III
R347P/711 + 3A->G	1 (1.8)	IV–V
2789 + 5G->A/2183AA->G	1 (1.8)	IV–V
G542X/E585X	1 (1.8)	I–III
G542X/G542X	1 (1.8)	I–III
W1282X/2183AA->G	1 (1.8)	I–III
G542X/N1303K	1 (1.8)	I–III

Laboratory and functional respiratory parameters were collected at the Cystic Fibrosis Centre at the Meyer Children University Hospital in Florence, where these patients are routinely followed. The examinations included: spirometry [forced expiratory volume in the 1st second (FEV1) and forced vital capacity (FVC)] and sputum bacteriology.

SNOT-22 questionnaire was administered to all of the 54 patients. It is a self-administered questionnaire consisting of 22 items, each one counting of 6 possible answers ranging from 0 to 5 points. The higher the scores the worse rhino sinusitis problems are associated, and it is divided into different subscores to evaluate firstly nasal symptoms, secondly rhinogenous symptoms, and then functional limitation and emotional consequences.

Twenty-two (40.7%) of the 54 CF patients presented important nasal symptoms refractive to conservative medical measures, and they underwent endoscopic sinus surgical procedure performed by the senior author (G. M.). In these patients, the principles of minimal invasively of functional ESS (FESS) were modified to a more extensive approach due to their systemic

disability to clear the viscous mucus and to the need to create larger apertures of the paranasal sinuses to achieve a better drainage. These procedures included a combination of medial maxillectomy, partial or total ethmoidectomy, frontal sinusotomy (extended from type IIb to III according to Draf, if necessary), and sphenoid sinusotomy. Nasal septoplasty and inferior turbinate reduction were also performed if important signs and symptoms of nasal obstruction were reported.

The 22 patients who underwent the ESS procedure were hospitalized in the infectious diseases ward 1 week before surgery in order to receive a complete systemic intravenous antibiotic prophylaxis before undergoing the operation based on sputum bacteriology. Medical therapy consisted of saline irrigation associated with serial antimicrobial lavage when required. Then, a postoperative systemic antibiotic prophylaxis due to the large mucosa defects, to reduce the risk of superinfection, was given as well. Antihistamine therapy could be suggested to avoid tearing and sneezing due to the nasal packs. We are used to administer steroid irrigations when CRS was associated with nasal polypoid. Otherwise systemic corticosteroids and antibiotics administrations were evaluated case by case from the Infectious Disease Department.

Postoperative results were gathered and represented in accordance with the Lund–Kennedy postoperative score and the postoperative SNOT-22 results. Clinical and functional characteristics registered were evaluated before surgery and 6 months after the surgical treatment.

The remaining 32 patients who did not undergo ESS represented the control study group. In both groups, there were patients who undergone lung transplantation, in specific: 14 patients in the non-ESS group and 9 in the ESS group.

Statistical analysis was realized with GraphPad Prism version 7.00. Descriptive statistics including the median, mean, and standard deviation (SD) were calculated for the continuous clinical data. Clinical and functional characteristics of the non-ESS and ESS groups were determined with Mann–Whitney (MW) test or by the χ^2 test with Yates's correction when required. A P value $< .05$ was taken as statistically significant.

To verify the significance between the 2 groups, the MW test was performed for quantitative variables (Lund–Kennedy, Lund–Mackay, and SNOT scores). The statistical analysis performed to estimate the probability to undergo surgical treatment as a function of our variables and their values, exploited the logistic model (LOGIT). The elaborations were carried out with the statistical software R.

Results

The study population counted 34 (63%) males and 20 (37%) females. The median age was of 33 years (range 18–55), and the mean follow-up was about 44 months $\pm$ 23.51 SD (range 8–70 months). Twenty-two (40.7%) of the 54 patients underwent the ESS procedure and represented the study group. Study and control group characteristics were summarized in Table 2.

Compared to the non-ESS group, study group patients presented more likely complaints consistent with chronic rhinitis preoperatively, in specific percentage of presentation were reported in brackets as follow: nasal obstruction (60.7%) ($P = .004$), rhinorrhea (86.4%) ($P = .02$), headache (68.2%) ($P < .001$), NP (77.3%) ($P < .001$) and mild or severe smell dysfunction (68.2%) ($P = .004$), and rhino sinusitis (86.4%) ($P < .001$). The endoscopic and radiologic aspects evaluated in accordance with the Lund–Kennedy and the Lund–MacKay scores, respectively, presented median values higher in the ESS group before surgery than in the control group at their first presentation: 10 (range of 6–12) and 16 (range of 12–20) for the study group, against 2 (range of 0–10) and 1 (range of 0–6) values for the control group, with a final statistical significant difference for both the score systems ($P < .001$).

Table 2. Demographics and Clinical Characteristics of Both Study and Control Groups.

Variables	Non-ESS	ESS	*P*
Patients, n	32	22	–
Males, n (%)	18 (56.3)	16 (72.7)	.34
BMI (median)	21.2	22.5	.47
Age (median)	33	34	.84
Diabetes, n (%)	17 (53.1)	12 (54.5)	.86
Liver dysfunction, n (%)	12 (54.5)	6 (42.9)	.73
F508 heterozygous, n (%)	10 (44.4)	8 (38.9)	.92
Staphylococcus aureus, n (%)	9 (28.1)	6 (27.3)	.81
Pseudomonas aeruginosa, n (%)	12 (37.5)	7 (31.8)	.89
Preoperative FEV1 (median)	66	73	.72
FEV1 after 6 months (median)	63.5	76	.51
FEV1 after 12 months (median)	68.5	73	.68
FEV1 after 24 months (median)	71	79	.83
Preoperative FVC pre-op. (median)	83	82	.84
FVC after 6 months (median)	73	81	.76
FVC after 12 months (median)	87	76.5	.32
FVC after 24 months (median)	81.5	84	.98
Nasal obstruction, n (%)	11 (39.3)	17 (60.7)	.004
Rhinorrhea, n (%)	17 (53.1)	19 (86.4)	.02
Headache, n (%)	3 (9.4)	15 (68.2)	<.001
Smell dysfunction, n (%)	8 (25.0)	15 (68.2)	.004
Lund–Kennedy tot (median)	2	10	<.001
Lund–Mackay (median)	1	16	<.001
SNOT (median)	17.5	44	<.001
Nasal polyposis, n (%)	3 (10.0)	17 (77.3)	<.001
Rhinosinusitis, n (%)	6 (20.0)	19 (86.4)	<.001

Abbreviations: BMI: body mass index; ESS: endoscopic sinus surgery; FEV1: forced expiratory volume in the 1st second; FVC: forced vital capacity; SNOT: Sino-Nasal Outcome Test.

Table 3. Clinical and Functional Characteristics of the ESS Patient Group Before Surgery.

No.	Persistent Sinonasal Symptoms	Preoperative Lund–Kennedy	Preoperative SNOT-22	Preoperative Lund–Mackay
1	+	12	17	12
2	+	12	73	18
3	+	12	18	14
4	+	10	18	16
5	+	6	58	16
6	+	12	46	16
7	+	10	10	16
8	+	12	67	18
9	+	10	55	16
10	+	6	24	16
11	+	12	41	20
12	+	10	24	12
13	+	10	42	13
14	+	12	69	14
15	+	8	55	15
16	+	12	54	16
17	+	12	73	14
18	+	6	25	12
19	+	10	30	12
20	+	8	53	16
21	+	12	55	16
22	+	10	22	16

Abbreviation: SNOT-22: Sino-Nasal Outcome Test-22.

QoL, reflected by the SNOT-22 questionnaire scores, showed median values for non-ESS and ESS groups of 17.5 (range of 3–68) and 44 (range of 10–73), respectively, with a P value lower than .001. The clinical and radiological findings in association with QoL of the ESS group were reported in Table 3. Based on the class mutation, we analyzed the postoperative values of SNOT-22, FEV1 and FVC in Table 4.

Furthermore, clinical and radiological parameters of the ESS group were recorded 6 months after surgery, as reported in Table 5. In specific, improvements in nasal obstruction (4.34%), rhinorrhea (4.55%), headache (0%), and mild or severe smell loss (30.4%) were found to be statistically significant postoperatively ($P < .001$). In addition, the median value of the Lund–Kennedy score decreased from 10 (range of 6–12) preoperatively to 2 (range of 0–10) 6 months after the surgical procedure ($P < .001$). And, the SNOT-22 median value 6 months after the ESS was reduced of more than 10 values (median 7; range of 0–44) ($P < .001$).

On the other hand, although the comparison between the laboratory and functional characteristics of both groups did not show any statistically significant differences, there was a trend in pulmonary function improvement in the ESS group, represented by Figures 1 and 2 in terms of rising in FEV1 and FVC postoperatively in the study population.

Table 4. Postoperative Outcomes According to Class Mutation.

No.	Class of Mutation	SNOT-22	FVC	FEV1
1	I–III	0	94	107
2	I–III	6	78	83
3	I–III	7	85	77
4	I–III	0	91	80
5	I–III	16	95	85
6	I–III	14	97	82
7	IV–V	0	111	119
8	I–III	4	96	90
9	IV–V	6	88	89
10	I–III	15	48	31
11	I–III	2	93	87
12	I–III	3	64	41
13	IV–V	3	103	100
14	I–III	18	113	110
15	I–III	12	81	56
16	I–III	9	75	53
17	I–III	44	70	35
18	I–III	12	42	44
19	I–III	7	78	85
20	I–III	27	71	76
21	I–III	5	68	48
22	I–III	14	38	30

Abbreviations: FEV1: forced expiratory volume in the 1st second; FVC: forced vital capacity; SNOT-22: Sino-Nasal Outcome Test-22.

Table 5. Clinical Characteristics in the ESS Patient Group Before and After Treatment.

Variables	Pre-ESS	Post-ESS	P
Nasal obstruction, n (%)	17 (60.7)	1 (4.34)	.001
Rhinorrhea, n (%)	19 (86.4)	1 (4.34)	.001
Headache, n (%)	15 (68.2)	0 (0.00)	.001
Smell dysfunction, n (%)	15 (68.2)	7 (30.4)	.001
Lund–Kennedy score (median)	10	2	.001
SNOT-22 (median)	44	7	.001

Abbreviations: ESS: endoscopic sinus surgery; SNOT-22: Sino-Nasal Outcome Test-22.

Discussion

Nowadays, the management of CF patients involves a multidisciplinary approach to prevent local and/or systemic infections and to reduce time of hospitalization. CRS is the chronic disease that occurs more frequently in adult patients affected by CF, whose identification is important for their QoL and their whole health condition. The prevalence of CRS in patients with classic CF approaches 100% even though patients with CF underreport CRS symptoms.[20] Dosanjh et al.[21] showed a

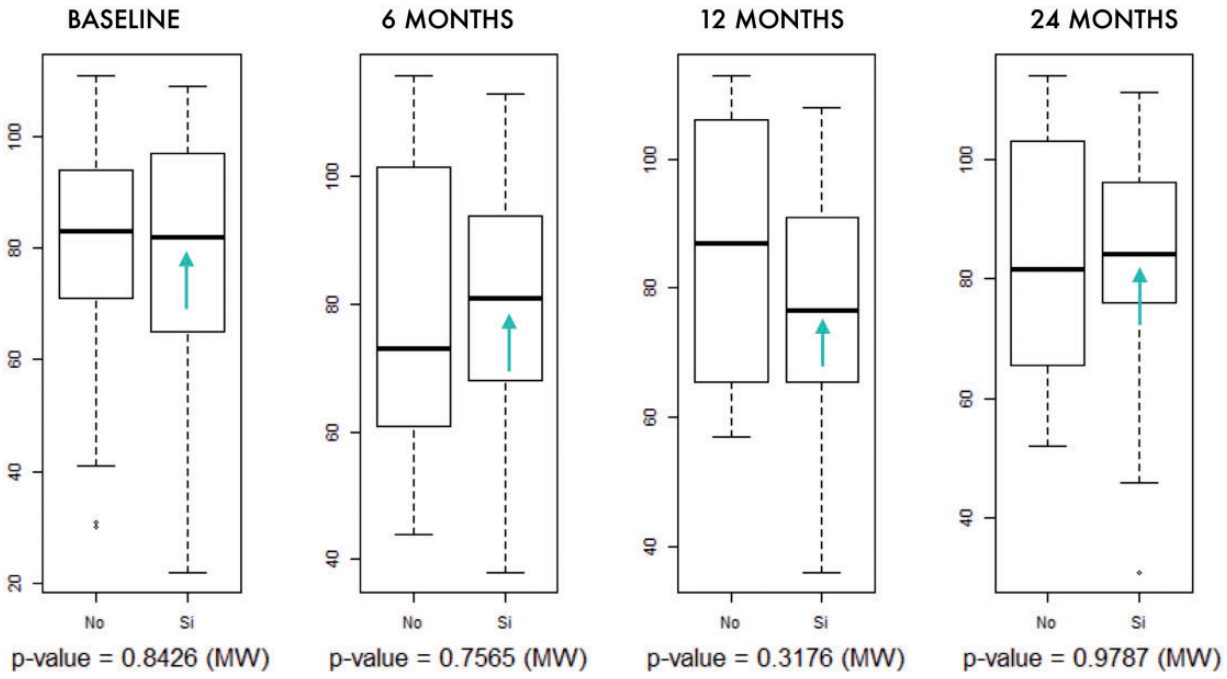

Figure 1. FVC before and after surgery. MW: Mann–Whitney.

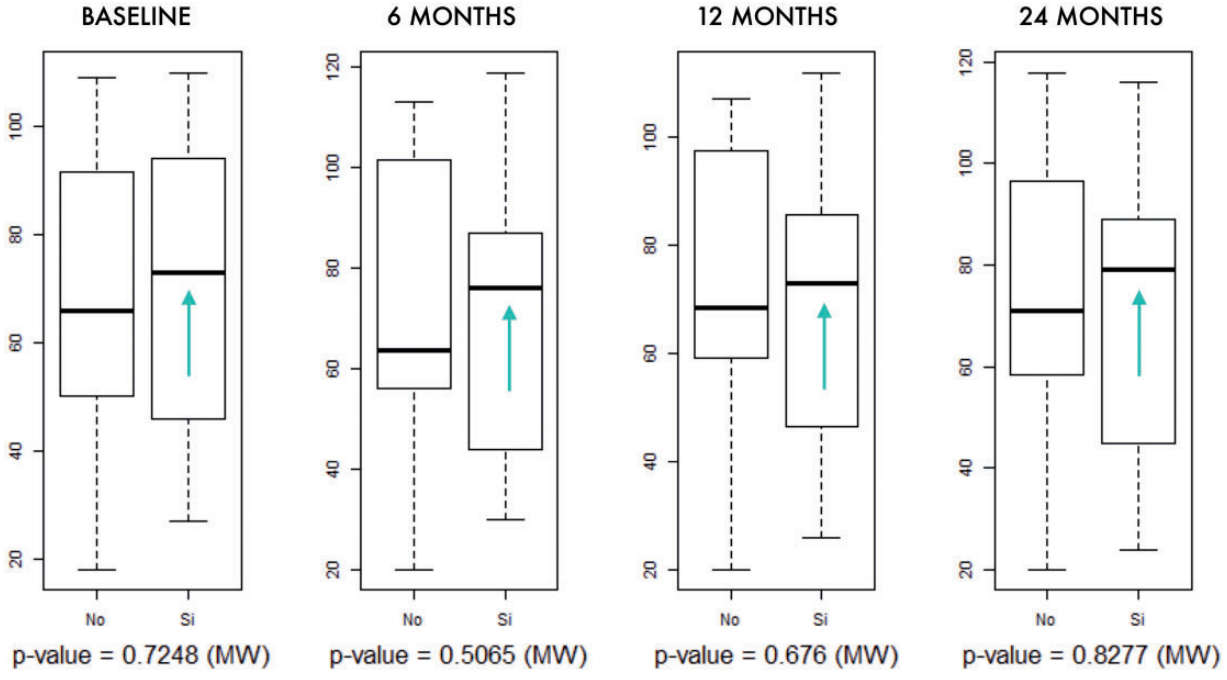

Figure 2. FEV1 before and after surgery. MW: Mann–Whitney.

correlation between the microbial flora in CF paranasal sinus cultures and those in cultures of the lower airway, thus suggesting a possible role of ESS procedure in influencing upper and lower airway conditions.[22]

Although there are few studies about sinonasal treatment of CF adult patients, it is well established that ESS can be safely performed.[23] Approximately 10%–20% of CF patients require surgical management of their sinonasal disease, several authors advocate aggressive sinus surgery to open all sinuses in order to avoid insufficient opening of the sinuses, thus requiring revision surgery and mucus retention. The endoscopic maxillary

mega-antrostomy and the complete removal of the medial maxillary wall[24,25] have been already described in the literature with reported good outcomes. In our study, patients who underwent endoscopic sinonasal surgery presented: worse baseline endoscopic and CT scores than the control group and severe sinonasal symptoms not responding to medical treatment. We have tailored surgical procedure on each patient's need, by performing endoscope surgical opening of the sinuses involved by the disease as widely as possible, preserving their functionality at the same time. In the literature, the percentage of surgical treatment failure requiring revision surgery ranges from 13% to 89%.[26,27] Despite these declarations, to date, none of our patients has needed revision surgery neither has claimed recurrent rhino sinusitis symptoms.

As shown, imaging and endoscopic findings associated with QoL in terms of sinonasal symptoms are *not* important and necessary to give indications for surgical treatment.

CT scan is now considered as a valuable tool for the diagnosis and follow-up of CF patients with CRS in which the main affections found are opacification, pseudomucocele, sinus agenesis, or hypoplasia. The lack of pneumatization variants of the sinus represents one of the most important and frequently sign in CF patients.[28] Furthermore, CT may also be useful for surgical planning by using the intraoperative neuronavigator in conjunction with an endoscopic view.[22]

Accordingly to Keck and Rozsasi,[23] we are able to demonstrate that patients who underwent sinus surgical treatment experienced significant improvements in all the disease features, not only in the endoscopic and radiological aspects but also in the SNOT-22 scores, thus confirming the necessity of surgical treatment to improve the global QoL of these patients affected by a chronic disease.

Another unresolved question is the relationship between sinus surgery and its possible influence on the pulmonary status in CF patients. Umetsu et al.,[24] reported an improvement in pulmonary symptoms in adult CF patients after sinus surgery, but they did not show any associated better lung function postoperatively. Although Rosbe et al.[20] failed to demonstrate a significant difference in respiratory function tests after ESS, they reported a reduced 6-month hospitalization rate. In accordance with the abovementioned data, we did not obtain any statistically significant difference in FEV1 and FVC values after surgery; however, these respiratory function tests showed a tendency to improve or remain stable during our follow-up. These results, if demonstrated by future studies with larger cohorts, might represent an interesting point of debate in the treatment of these patients.

Based on our results (Table 5), we would suggest the following values as threshold scores for sinus surgery indication in CF patients: Lund–Kennedy score > 7 and SNOT-22 values > 30, which both increased the possibility to undergo ESS of more than 50%, whereas a Lund–Kennedy score > 10, SNOT-22 > 70, and Lund–Mackay > 10 required surgical treatment in more than 95% of our cases. Our results confirmed the importance of these scores in order to suggest surgical procedure for CF patients as previously reported by Kang et al.[29]

Although the Cystic Fibrosis Centre of the Meyer Children University Hospital in Florence is a regional reference center where patients are sent from all over Italy, when an episode of pulmonary exacerbation occurs these patients could be admitted to the infectious diseases department of their city. This missing information associated with the retrospective nature of our work and small sample size could represent weaknesses within our study that should be taken into account. Nonetheless, it is one out of the few existing studies investigating adult CF population and the role of ESS in QoL and functional outcomes.

Conclusions

CF is a severe disease interesting upper and lower airways in which CRS represents one of the commonest clinical manifestations compromising the QoL of these patients. ESS represents the best option for the treatment of patients who do not respond to conventional medical therapy, and its success rate includes not only an improvement in sinonasal symptoms but also in patients' QoL as documented by SNOT-22 postoperative scores. In addition, further future analyses through larger cohort patients studies should be addressed toward the comprehension of the influence of ESS on respiratory function improvement.

Authors' Note

Giuditta Mannelli is currently affiliated with Head and Neck Oncology and Robotic Surgery, Department of Experimental and Clinical Medicine University of Florence.

Declaration of Conflicting Interests

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