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Original Article

Implementation of standardized cystic fibrosis care algorithm to improve the center data-quality improvement project international collaboration

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ABSTRACT

Background: A collaboration between the University of Michigan (U of M) Cystic Fibrosis Center (CFC) and Marmara University (MU) CFC was initiated to improve the health status of people with cystic fibrosis (pwCF) at MU through implementing Quality Improvement (QI) initiatives. The main aim was to improve lung function in children with FEV1pp <80. The secondary aim was to assess the changes in health related quality of life.

Methods: Included in the project were pwCF who received cystic fibrosis (CF) care at the MU CFC and were 6–18 years of age with an FEV1pp <80. Flow charts were created and a standardized CF care algorithm was implemented. Weekly case review were done to develop individualized treatment plans. Appropriate intervention was applied and patient data were assessed at baseline, 3, 6, 9 and 12 months. The Cystic Fibrosis Revised Questionnaire (CFQ-R) was completed.

Results: 55 pwCF were included (mean age:11.8 ± 3.3 years). Mean FEV1pp (SD) at baseline, 6 and 12 month was 63.7 (14.6), 66.9 (16.6), 70.4 (19.2), respectively, with a relative increase of 5.0% in 6 months (p:0.002) and 10.5% in 12 months compared to baseline ($p<0.001$). Physical functioning, eating problems and respiratory symptoms domains of the CFQ-R questionnaire were improved at the end of the one year for 6–13 ($p = 0.024$, $p = 0.009$, $p = 0.002$) and 13–18 year olds ($p = 0.013$, $p = 0.002$, $p = 0.038$).

Conclusion: There was significant improvement in pwCF with FEV1<80%pp after implementing this QI project. The processes and assessments used can be adopted by other low-middle income countries to improve similar measures.

1. Background

Better lung function in people with cystic fibrosis (pwCF) is strongly associated with improved quality of life and survival. The most often used pulmonary function measurement parameter is forced expiratory volume in one second percent predicted (FEV1pp), and this is also one of the indicators of cystic fibrosis (CF) care quality [1,2]. Patient registries allow for comparison of different CF outcomes across care programs. FEV1pp in pwCF has been used as a benchmark for comparison between CF centers (CFCs). The FEV1pp is affected by age of diagnosis, changes in CF care, and the possibility of receiving modulator therapy [3,4]. International collaborations focused on identifying barriers to CF care

Abbreviations: pwCF, people with cystic fibrosis; FEV1pp, forced expiratory volume at 1 second percent predicted; CFC, Cystic fibrosis center; QI, quality improvement; HRQoL, health-related quality of life; MU, Marmara University; U of M, University of Michigan; CFF, CF Foundation; MECFA, Middle East CF Association; KIFDER, CF Patient organization; BMI, body mass index; Pex, pulmonary exacerbation; BMIp, body mass index percentile; CFQ-R, Cystic Fibrosis Questionnaire-Revised; IQR, interquartile range; PA, Pseudomonas aeruginosa; CFRD, cystic fibrosis related diabetes; ABPA, allergic bronchopulmonary aspergillosis.

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across different regions globally and improving the care of patients with CF have grown considerably in recent years [5].

In comparison with their European peers, Turkish pwCF are more likely to have a low FEV1pp [6]. We believe that late diagnosis is one of the most important reasons for the low FEV1pp values in pwCF who were born before 2015 in Turkey, when a countrywide newborn screening program for CF was launched [7]. The majority of these children were diagnosed after experiencing symptoms related to CF, which meant they missed the chance to start airway clearance and other treatments earlier.

The adoption of appropriate standardized algorithm in CF clinic has helped patients with FEV1pp <80 improve their pulmonary function[5]. We hypothesized that by using the same standardized care algorithm reported by Filbrun and colleagues (2020), children's FEV1pp would improve over the course of 12 months [8]. The main aim was to use University of Michigan (U of M) CFC QI procedures to improve FEV1pp in pwCF with FEV1pp <80. The secondary aim was to assess changes in health-related quality of life (HRQoL).

2. Methods

This prospective cohort QI project was conducted at MU as a result of a collaboration between U of M CFC and MU Selim Çöremen CFC, which was launched in 2019 with the support of the United States CF Foundation (CFF) and Middle East CF Association (MECFA). MU CFC is one of the largest in Turkey; with 399 CF patients, including 88 adult patients[6]. The MU CF team includes five pediatric pulmonologists, six pediatric pulmonology fellows, one physical therapy and rehabilitation specialist, two nurses, one dietitian, one physical therapist and a represantative of CF Patient organization of Turkey (KIFDER). A social worker, respiratory therapist and psychologist are not part of the CF team.

2.1. Study population

2.1.1. Inclusion criteria

PwCF 6–18 years old with FEV1pp <80 were included in this QI project. Patients had a confirmed diagnosis of CF through sweat chloride ≥60 meq/L and/or two CF disease causing mutations[9].

2.1.2. Exclusion criteria

Patients that did not come routinely (four times in the previous year) to clinic visits and/or those who did not agree to participate were excluded.

2.2. Project timeline

Initiation began in June 2019 and data was collected every three months between 6/2019–10/2020. Data were assessed at baseline, 3, 6, 9 and 12 months after enrollment. This QI project was approved by the Marmara University Institutional Ethical Committee.

2.3. Study protocol

All MU CFC team members were involved in the project. Two fishbone diagrams were created; the first was to identify potential barriers for low lung function, and the second was to create potential solutions for those barriers (Supplement 1). Based on these fishbones, team members from each discipline developed a flowchart to help address issues that fell under their area of expertise. Flowchart 1 shows the outpatient clinic protocol for the patients with FEV1pp <80. The team started doing weekly case review of these patients to develop an individualized treatment plan for each patient and to assess for barriers that may have resulted in FEV1pp <80. During the pre-clinic huddles, treatment plans for each patient were evaluated and appropriate changes were made with goals being set for the next visit.

Table 1
Interventions used to increase lung function.

- Check medications and implement changes if needed
- Evaluation of nutritional status and provide appropriate diet intervention according to the BMI status
- Evaluation of depression and anxiety level of children and implement intervention if needed
- Close monitoring of the patients by physiotherapist team and assess the need for airway clearence method change
- Provide required educational materials
- Evaluate if the patients have appropriate nebulizer compressors and supplies for their inhaled medications. Order new equipment if needed.
- Nebulizer cleaning and disinfection training
- In-clinic training and family trainings

The nursing flowchart focused on assessing adherence to medications, explaining the mechanism of action of current treatments to the patient, providing educational resources about equipment and inhaled medications, and evaluating the nebulizers and airway clearence devices which included ordering new ones if they are not working well (Supplement 2). The CF nurses also focused on assessing family dynamics and depression/anxiety in patients and families by using standardized questionnaires (PHQ-9 and GAD-7) recommended by CFF/ECFS[10]. Patients/parents with moderate-to-severe anxiety and depressive symptoms were referred for psychological/psychopharmacological interventions[11].

As a higher body mass index (BMI) is one of the most important predictors of higher FEV1pp, U of M nutritional algorithm was implemented to our routine CF and dietitian flowchart focused on the nutritional status of patients and identified those with significant malnutrition, initiating a stepwise approach to management[12]. The MU CFC dietitian evaluated the caloric intake, weight, height, and BMI at each clinic visit and high-calorie diet information was provided (Supplement 3). A high calorie diet (120–150% of the recommended dietary allowance (RDA) per day) was recommended for all pwCF. Oral supplements were recommended for the patients with BMIp<50. An appetite stimulant (cyproheptadine) was recommended for pwCF with poor appetite. The physical therapy and rehabilitation specialist and physical therapist emphasized the importance of regular airway clearance and exercise at each clinic visit (Supplement 4).

The following data was collected: demographics, genetics, hospitalization and oral antibiotic usage rate due to a pulmonary exacerbation (PEx), PEx rate, BMI percentile (BMIp). Pseudomonas aeruginosa (Pa) and Methicillin Resistant Staphylococcus Aureus (MRSA) colonization rates were calculated for both the previous year and the project period.

PEx was defined as the need for antibiotic treatment as indicated by an increase in at least two of the following: sputum volume or color; cough; malaise, fatigue or lethargy; anorexia or weight loss; decrease in pulmonary function by 10% or radiographic changes; dyspnea [13].

Pa and MRSA colonization is defined as the microorganism growth in more than half of the sputum/deep pharyngeal aspirate cultures taken in at least 4 samples in a year [14]. Interventions are reported in table 1.

2.4. Outcome measures

The primary outcome was a change in FEV1pp. Lung function was measured using a spirometer (WinspiroPRO 2.8 MIR, Rome, Italy) in accordance with international standards at baseline and every three months by the same device and technician. Only re-

Table 2
Characteristics of patients with FEV1pp <80.

Patient characteristics	Total $n = 55$
Age at CF diagnosis, years, median (25th-75thp)	0.3 (0.2–0.7)
Age, years, mean±SD	11.8 ± 3.3
Gender, n (%)	
Female	28 (50.9)
Height percentile, median (25th-75thp)	10.0 (3.3–31.6)
Weight percentile, median (25th-75thp)	4.5 (0.8–26.3)
BMI percercentile, median (25th-75thp)	9.4 (1.0–38.2)
FEV1pp (mean ±SD)	62.6 ± 15.3
Chronic Pa infection, n (%)	28 (50.9)
Chronic MRSA infection, n (%)	10 (18.2)
Pancreatic insufficiency, n (%)	48 (87.3)
Genetic Category, n (%)	
Homozygous dF508	10 (18.2)
Heterozygous dF508	12 (21.8)
Other	33 (60.0)
CFRD, n (%)	3 (5.5)
ABPA, n (%)	3 (5.5)
CF-related liver disease, n (%)	15 (27.3)

Abbreviations: FEV1pp, forced expiratory volume in 1 second percent predicted; Pa, Pseudomonas aeruginosa; MRSA, Methicillin-resistant Staphylococcus aureus; CFRD, cystic fibrosis related diabetes; ABPA, allergic bronchopulmonary Aspergillosis.

sults which met ERS/ATS criteria for interpretation were included in the project for analysis [15].

The secondary outcome was the HRQoL, which was measured by validated Cystic Fibrosis Questionnaire-Revised (CFQ-R) questionnaires[16]. The questionnaires used were in Turkish, which was applied twice; at baseline; before the initiation of the QI project and at the end of the 12th month. Older children self-completed the form, while younger children were interviewed by the CF nurses.

2.5. Statistical analysis

Statistical analysis was carried out with SPSS for Windows version 23.0. Continuous variables were described through means and standard deviation or medians and interquartile range (IQR), whereas categorical variables were presented as proportions. Categorical variables were compared with chi-square or with Fisher's exact test when 20% of the expected frequencies were less than five. Parameters with normal distribution were compared by independent groups (independent samples) *t*-test. Wilcoxon test was performed for comparing two dependent variables with nonnormal distribution. ANOVA repeated measures were performed for normal distributed three or more repeated measures. Friedman test was performed for three or more repeated measures without normal distribution. Results were evaluated in 95% confidence interval and significance level was set at p-value of 0.05. Comparisons of FEV1pp and BMI at different time points used paired t tests.

3. Results

There were 73 subjects with FEV1pp<80. 18 of them was not eligible. The program included 55 pwCF. Demographic features are shown in Table 2. Baseline, 6 and 12 month mean (SD) FEV1pp was 63.7 (14.6), 66.9 (16.6), 70.4 (19.2), respectively ($p = 0.004$), with relative increase of 5.0% in 6 months (p:0.002) and 10.5% in 12 months compared to baseline ($p<0.001$) (Fig. 1). This increase was sustained 1 year after the project, ended with mean (SD) FEV1pp value of 71.8 (19.1).

The baseline mean FEV1pp value of patients colonized with Pa [58.3 (15.6)] and on inhaled antibiotics [58.8 (16.3)] was significantly lower than the overall population, ($p = 0.021$, $p = 0.022$).

Table 3
Comparison of the treatment modalities, PEx rate, reversibility rate and nutrition status at baseline and at the end of the project.

	Baseline	12th month	p value
7% Hypertonic saline, n (%)	10 (18.2)	42 (76.4)	**<0.001**
Mannitol, n (%)	6 (10.9)	1 (1.8)	0.06
Inhaled antibiotic, n (%)	26 (47.3)	29 (52.7)	0.21
Bronchodilator, n (%)	52 (94.5)	53 (96.4)	0.50
Dornase alpha, n (%)	52 (94.5)	54 (98.2)	0.25
Inhaled steroid, n (%)	28 (50.9)	30 (54.5)	0.54
Oral steroid, n (%)	2 (3.6)	0	0.50
Azitromycin, n (%)	4 (7.3)	22 (40)	**<0.001**
Number of hospitalization due to PEx, median (25th-75thp)	1 (0–2)	0 (0–2)	0.33
Number of oral antibiotics due to PEx, median (25th-75thp)	2 (1–3)	2 (1–4)	0.40
Bronchodilator reversibility n (%)	2 (3.6)	6 (10.9)	0.11
Weight percentile, median (25th-75thp)	4.5(0.8–26.3)	16.2 (1.2–44.1)	**<0.001**
Height percentile, median (25th-75thp)	10 (3.3–31.6)	13.1 (3.6–33.4)	0.22
BMI percentile, median (25th-75thp)	9.4 (1.0–38.2)	22.6 (4.3–49.0)	**0.001**

Pa and MRSA colonization rate at baseline and at 12 months was 28%–28% ($p = 0.990$) and 18.2%–27.3% ($p = 0.261$) respectively.

7% hypertonic saline adjunct to dornase alpha and azithromycin usage was increased significantly at 12 months (p: <0.001). Table 3 shows the treatment modalities, PEx rate, broncodilator reversibility rate and nutritional status at baseline and at the end of the project. Although nebulizers of 29 (53.7%) patients were changed to a proper device and airway clearance method was changed in 33 (62.3%) patients during the project, there was no change in FEV1, whether or not the nebulizer device or airway clearing method was modified (p=0.300, $p = 0.940$).

The BMIp positively correlated with FEV1 value for the patients at 12 months of the project ($r = 0.418$, $p = 0.004$). Regarding the HRQoL, scores of physical functionning, eating problems and respiratory symptoms domains of the CFQ-R questionnaire were significantly improved at the end of the one year for 6–13 ($p = 0.024$, $p = 0.009$, $p = 0.002$) and 13–18 year olds ($p = 0.013$, $p = 0.002$, $p = 0.038$). Supplement 5 demonstrates the overall CFQ-R changes.

4. Discussion

This QI project resulted in a significant improvement in 12 months of FEV1pp for pwCF who were 6 to 18 years old. In terms of HRQoL, while many domains improved, the improvement in physical functioning, eating problems and respiratory symptoms domains of the CFQ-R was statistically significant.

Although continued care of pwCF at a CF center by a standardized multidisciplinary approach is known to increase the FEV1pp value, BMI and improve the quality of life; individualized management and close monitoring for any needed adjustment of the plan are required to improve outcomes further and prolong survival [17]. Improvement of FEV1pp in our pwCF in one year seems to be multifactorial. Close monitoring of each patient by the team and discussion of all issues regarding patients' therapy, airway clearance procedures, and concomitant psychosocial issues at the weekly preclinic huddles were critical milestones in the success of the project. These regular huddles resulted in significant collaboration between the team members and modifications of the treatment modality, such as an increase in 7% hypertonic saline and azithromycin usage rates. Another factor for the quick rise in the usage of hypertonic saline from 18.2% to 76.4% was the commercial availability of the 7% hypertonic saline in Turkey in 2019. Although we did not evaluate the compliance to the inhaler or oral treat-

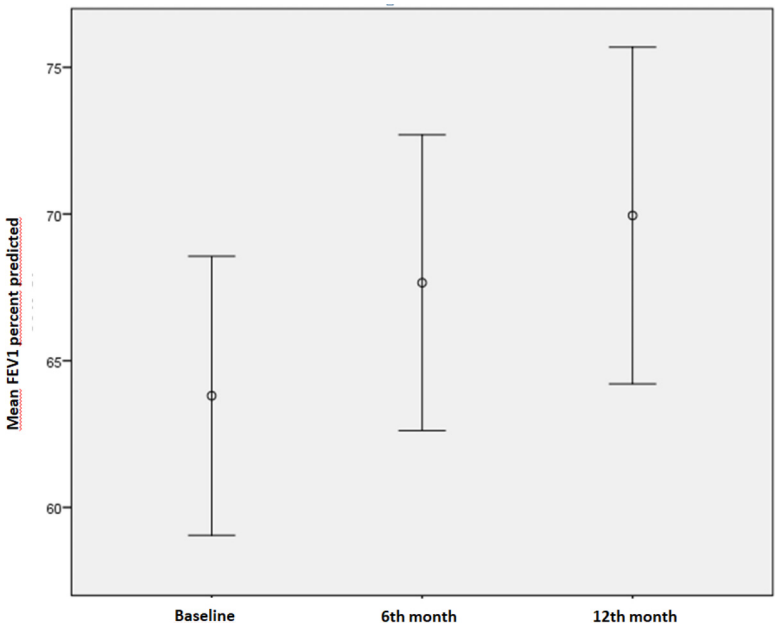

Fig. 1. The comparison of FEV1pp at baseline, 6th and 12th month. Mean values are shown;the error bars indicate the standard deviation.

ments, we assume that our patients' compliance was high during the COVID-19 pandemic.

The current study revealed that mean BMIp increased considerably in our patients following implementation of a standardized nutritional program which was consistent with the previous studies showing the association of higher lung function outcomes with improved nutrition [18,19]. Although changing the nebulizer device or airway clearance method did not appear to have a substantial effect on its own, cumulative effect of all interventions seems to lead to the significant improvement in FEV1pp. Throughout the year, team members collaborated with patients and families to overcome any barriers to treatment. During the project period, patients who did not respond well to standard protocols were also confidentially consulted with the U of M CFC team for a second opinion. We shared the progress of the project with them at the joint online meetings at the 3, 6 and 12 months and received their feedback and input. Our family advisory board (KIFDER) played an important role in informing pwCF and caregivers about the project, and also created and managed a social media group to facilitate communication.

The most important aspect of this project is that it was carried out in a low-middle income country. Although a comparable protocol was used at U of M CFC, MU CFC structure and resources are different including having less allied health care staff than U of M CFC [8]. Also, social workers, respiratory therapists, and psychologists are not available for the MU CFC settings. Patients who required psychosocial help were referred to psychologists working at MU. However, due to the long waiting duration for their appointments, several of the patients decided not to visit the psychologist or sought care from another private psychologist. As a result, it was impossible to standardize the patients' psychological support.

U of M CFC used this standardized algorithm and after 6 months of implementation, patients had an improvement in mean FEV1pp by 6.4%. At 12 months, mean FEV1pp had improved by 14% [8]. FEV1pp rise was better in U of M CFC, however 25% of their patients were on modulator therapy that may also contributed to FEV1 increase. At the time of the project, although 31 (56%) of the pwCF were eligible, none of our patients were using modulators because they were not available in Turkey [20,21] .

Patient-reported outcomes, such as HRQoL, are crucial markers for evaluating the patient's subjective benefits. The CFQ-R is often used as a pre- and post-intervention tool to assess HRQoL[22–23]. However, no study has been conducted to compare HRQoL before and after the implementation of a standardized CF care program. Physical functioning, eating problems and respiratory symptoms domains of the CF-QoL questionnaire improved after one year. Although FEV1pp and BMI of the project patients increased significantly, CF-QoL improvement was detected only in a few domains. This may be related with the COVID-19 pandemic. A few months after applying the baseline CFQ-R to the participants, the COVID-19 pandemic emmerged in Turkey with much of this project being conducted during the pandemic. Although we did not evaluate the anxiety level in this particular group during the project, generally pwCF with moderate to severe lung disease may have more stress and anxiety that could impact the CF-QoL.

There are some limitations of the study. The COVID-19 pandemic prevented in-person clinical appointments. In order to overcome this problem, virtual clinic visits or phone calls with pwCF and caregivers were used. Furthermore, due to the small sample size and, asymetric distribution of the data multiple linear regression analysis to determine the most significant predictor of the changes in FEV1pp was not conducted. Despite these limitations, to our knowledge this is the first QI study in low-middle income countries showing improvement in FEV1pp and BMIp after using a CF care algorithm from a CF center in the USA, through an international collaboration. Despite the lack of social worker and physcologist, the efforts of team members enabled us to successfully accomplish this project.

We think that by adding a psychologist and a social worker to the CF team, such QI studies will be more successful. Centers in developing countries might be able to implement such quality-improvement programs to help CF patients enhance their pulmonary function and nutrition. Similar programs could help improve the care and life expentency of CF patients in these countries. These results provide evidence for benefits of international collaborations to improve the care of pwCF globally.

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Declarations of Competing İnterest

The authors have indicated they have no potential conflicts of interest to disclose.

None

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CRediT authorship contribution statement

Yasemin Gokdemir: Conceptualization, Methodology, Software, Formal analysis, Writing – original draft. **Ela Erdem Eralp:** Conceptualization, Methodology, Software, Formal analysis, Writing – review & editing. **Almala Pinar Ergenekon:** Resources, Formal analysis, Data curation. **Cansu Yilmaz Yegit:** Data curation, Software, Visualization. **Muruvvet Yanaz:** Data curation, Software. **Hakan Mursaloğlu:** Visualization, Data curation, Resources. **Burcu Uzunoglu:** Resources, Project administration. **Damla Kocamaz:** Resources, Project administration. **Gamze Tastan:** Resources, Project administration. **Ozge Kenis Coskun:** Project administration, Resources. **Amy Filbrun:** Conceptualization, Resources, Supervision. **Catherine Enochs:** Conceptualization, Resources, Supervision. **Sandra Bouma:** Conceptualization, Resources, Supervision. **Courtney Iwanicki:** Conceptualization, Resources, Supervision. **Fazilet Karakoc:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration. **Samya Z Nasr:** Conceptualization, Methodology, Writing – review & editing, Project administration. **Bulent Karadag:** Conceptualization, Methodology, Writing – review & editing, Project administration.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2023.03.016.

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