Original Research

COVID-19 Lockdown Impacts Among Patients with Cystic Fibrosis: An Italian Regional Reference Centre Experience

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Academic Editors: Massimo Conese and Lorenzo Guerra
Submitted: 4 December 2021   Revised: 26 February 2022   Accepted: 4 March 2022   Published: 2 June 2022

Abstract

Background: Coronavirus pandemic has influenced our society with social distancing and management of chronic disease such as cystic fibrosis (CF). During the Italian lockdown from March to May 2020, CF patients reduced the number of outpatient visits, limited social interactions and spent more time at home. The aim of this study is to evaluate the impact of the lockdown on body mass index (BMI) and lung function tests on CF patients. **Methods**: We retrospectively reviewed clinical data about 111 CF patients followed in our Regional Cystic Fibrosis Reference Centre (Policlinico Umberto I, Rome) according to two periods: pre-lockdown (from October 2019–March 2020) and post-lockdown (from May 2020–October 2020). We collected data on nutritional (BMI and body weight) and lung function status; we chose the best values of the 'pre-lockdown' and 'post-lockdown' period for each patient. Patients were divided into 3 groups according to FEV1 value (Forced Expiratory Volume in the 1st second): group 1 (FEV1 <40%), group 2 (FEV1 40–70%), group 3 (FEV1 >70%). All patients received a telephone interview asking for the number of hours per week devoted to physical activity, number of pulmonary acute exacerbations and subjective evaluation of adherence to medical therapy, respiratory physiotherapy and diet, during the two periods. **Results**: Comparing weight, BMI and respiratory function between pre and post lockdown periods, we noticed an increase in weight during among overall patients. Male patients improved weight, BMI, FEF 25–75% (Forced Expiratory flow between 25% and 75% of vital capacity) and Tiffenau index more than female patients. The most severely compromised patients (group 1), showed a significant loss of both weight and BMI. Instead, patients with moderate respiratory function (group 2) showed a significant increase of both weight and BMI and a slightly reduced CVF (Forced Vital capacity). We found no differences among patients with good respiratory function (group 3). Comparing each clinical sub-groups, we noticed a significative improvement of weight (p = 0.018) and BMI (p = 0.030) among patients with moderate respiratory function compared to patients with compromised respiratory function. During lockdown, patients reported less physical activity, no variation in food amount and composition, more adherence to therapy (43%) and more consistent daily respiratory physiotherapy (47.6%). **Conclusions**: Lockdown period had benefit among CF patients in terms of weight in particular in male patient. The greatest benefit on nutritional state was observed in patients with moderate reduction of respiratory function. In addition, we noted a stabilization and sometimes a slight improvement of lung function, instead of a continuous and steady decline that is normally observed in CF patients. These beneficial effects are slight but significative, bearing in mind the general worsening that CF patients experience annually.

Keywords: cystic fibrosis; lockdown; SARS-CoV-2; COVID-19; nutritional status; lung function tests; lung function status

1. Introduction

Cystic fibrosis (CF) is a genetic condition with multi-organ involvement, which requires a multi-specialist approach that involve physicians, nurses, dieticians, psychologists and physiotherapists [1]. As a result, CF patients undergo periodical medical check-ups in an outpatient setting or a regular telemedicine reviews. In December 2019 a new severe acute respiratory syndrome caused by SARS-CoV-2 was identified in China and in March 2020 World Health Organization declared a pandemic state with more

than 381000 infected people around the world and more than 16000 deaths (WHO) [2]. On 10 March 2020, Italy was an endemic area with more than 10000 cases of SARS-CoV-2 infections, second only to China. For the control of SARS-CoV-2 diffusion, the Italian government decide to start a strict national lockdown, that has greatly influenced our society consequences on management of chronic disease such as CF. In the Regional CF Centre in Rome, outpatient visits have been drastically reduced with only transplanted and severely ill patients followed in the outpatient

clinic. On the other hand, there was an implementation of telemedicine, with the use of telephone or video devices. The lockdown has interrupted all work and study activities, reducing social interactions as well as the risk of infection but probably increasing their free time for home physical activities and physiotherapy. Moreover, increased free time may have improved a better adherence to therapy that is pivotal in management of chronic diseases. On the contrary, many patients may have reduced their physical activities due to the closure of gyms and parks and may have suffered a negative psychological impact with poor adherence to therapy. The aim of this study was to evaluate the impact of restrictions following the strict lockdown on respiratory function and body mass index (BMI) on CF patients.

2. Materials and Methods

We conducted a retrospective cohort study from October 2019 to October 2020 enrolling 111 CF patients older than 18 years followed at the Lazio Regional CF center (Hospital Policlinico Umberto I, Sapienza University of Rome). To eliminates bias, we have excluded patients who undergone lung transplantation and patients who have started, in the same period, any CFTR modulator therapies, (i.e., ivacaftor, lumacaftor, elexcaftor, tezacaftor or their combinations). We divided the studied follow-up period into 2 parts: pre-lockdown and post-lockdown. The pre-lockdown period considered was from October 2019 to March 2020 while the post-lockdown period considered was from May 2020 to October 2020. Italian strict lockdown period, also called Phase 1, ran from 11 March to 4 May 2020.

The following data was extracted from medical records of the patients: age, gender, type of bacterial colonization and type of mutations.

For each studied period (i.e., pre and post-lockdown) we have evaluated pulmonary function tests and nutritional state by body weight, BMI (WHO) from all patients enrolled. Lung function was assessed following the American Thoracic Society/Europena Respiratory Society (ATS/ERS) minimum requirements and using relative reference values [3].

Patients have been also stratified in subgroups by gender (males and females) and FEV1% (Forced Expiratory Volume in the 1st second) values. In particular, patients with FEV1 <40% were considered with a severely impaired respiratory function, patients with a FEV1 between 40–70% with a moderately impaired respiratory function and patients with a FEV1 >70% with a normal respiratory function. BMI <16 is severe underweight, BMI 16–18.5 is considered underweight, BMI 18.5–24.9 is normal weight, BMI 25–29.9 is overweight and BMI >30 is obesity.

In November 2020, all patients received a telephone interview with a structured questionnaire in which we asked information on the number of hours per week devoted to physical activity and the number of acute pulmonary exacerbations in the pre-lockdown and post-lockdown periods. We also asked to our patients for a subjective evaluation of adherence to therapy, respiratory physiotherapy and diet, comparing the two periods. The telephone interview was provided by resident medical doctors who had been attending the centre for several months.

Statistical Analysis

We describe the demographic characteristics of the study population by absolute and relative frequencies. The Shapiro Wilk test, skewness and kurtosis indices, were applied to assess the normality of the distribution of each variable and we reported descriptive statistics by median with IQR (1st and 3rd quartile). We have evaluated the trend of each respiratory and nutritional parameters comparing the two studied periods using "delta value" that is the median of the differences between the same parameter. Comparisons among each group were performed using the Wilcoxon or Mann-Whitney rank-sum test as appropriate. Statistical significance was assumed as p-value < 0.05 for all tests. The data were collected in an Excel database (v 16.43, Microsoft, Washington, USA) and the statistical analysis was performed using IBM SPSS Statistics Version 27.0.1.0 software (SPSS Inc., Chicago, Illinois, USA).

3. Results

3.1 Demographic Data and Clinical Features

We enrolled 111 CF patients, 54 females (48.6%) and 57 males (51.4%), from 19 to 70 years old with a median age of 35 years (1–3 IQR: 24–44).

15 (13.5%) patients had a class 1 mutation, 50 (45%) class 2 mutation, 7 (6.3%) class 3 mutation, 3 (2.3%) class 4 mutation, 10 (9.9%) class 5 mutation and 26 (23%) patients had no mutations or undefined ones (Fig. 1a).

Regarding lung colonization, most patients were colonized by a single germ (49.6%), 31.5% with two germs and 9% with three germs, 8.1% of the population was not colonized and only 0.9% was colonized by 4 or 5 germs (Fig. 1b).

Stratifing the population according to Body Mass Index (BMI): 0.9% were severely under-weighted, 6.3% were underweighted, 67.5% had a normal weight, 20.7% were over-weighted and 4.5% were obese (Fig. 1c).

Furthermore, patients were stratified into 3 categories according to FEV1% values as follow (Fig. 1d):

FEV1 <40%: patients with severely impaired respiratory function (10 patients, 9%);

FEV1 between 40% and 70%: patients with moderate respiratory function (38 patients, 34.2%);

FEV1 >70%: patients with good respiratory function (63 patients, 56.8%).

During the study three patients had a SARS-CoV-2 infections. A 26 years old man with FEV1 between 40 and 70%; a 28 years old woman with FEV1 >70%; a 33 years old man with FEV1 >70% without major complications.
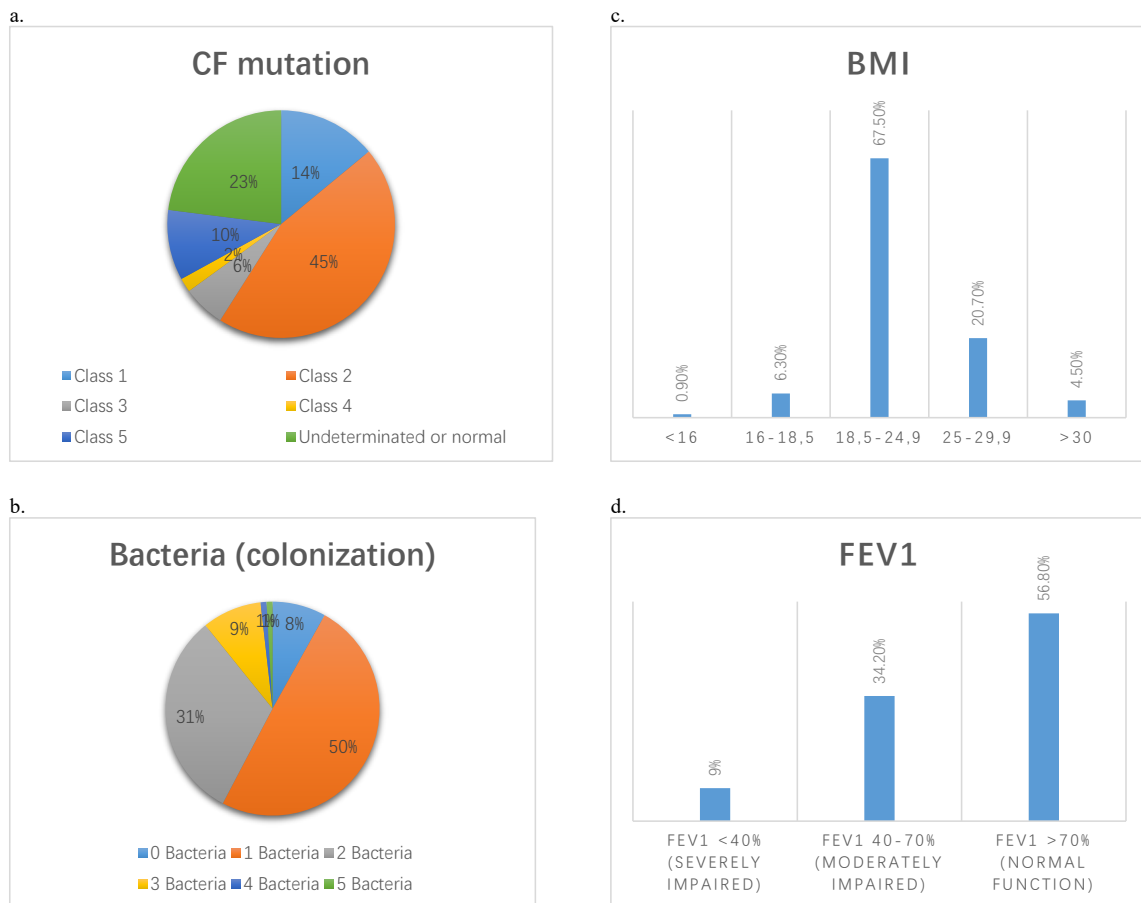
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Fig. 1. Patient characteristics. (a) CFTR type of mutations. (b) Number of bacteria of lung colonization. (c) BMI distribution of the population. (d) FEV1% distribution of the population.

All three patients had a disease with few minor symptoms without the need for hospitalization, followed by complete remission.

3.2 Answers to the Questionnaire

Out of a total of 111 patients, 82 (74%) answered to the telephone questionnaire (**Supplementary Fig. 1**); the other 29 (27%) patients did not answer the phone or did not give consent to the interview. Patients who did not respond to the telephone questionnaire were a homogeneous population, 1 with severely impaired respiratory function, 10 with moderate respiratory function and 18 with good respiratory function.

During the lockdown, the most of patients (70.7%) experienced a reduction in the number of hours per week dedicated to sport and physical activity: an average of 5.6 hours before the lockdown compared with an average of 3.7 hours during the lockdown with an average reduction of 34%. Regarding the type of diet consumed during the lockdown, patients subjectively reported in the majority (52.4%) the same diet in terms of composition and frequency. We did not observe differences in responses among patients with different impairment of respiratory function.

Almost half of the patients (43%) stated that they had greater adherence to daily therapy (both pharmacological and physiotherapy) because they had more free time; 47.6% of the patients stated that they performed respiratory physiotherapy more consistently and effectively on a daily basis.

3.3 Comparison between Pre and Post Lockdown Periods

Comparing nutritional state between pre and post lockdown period in the total population, we noticed a statistically significant increase in weight (+0.4%; p-value = 0.02) (Table 1) but not in BMI.

Considering only male patients, we report a benefit in terms of nutrition in the post-lockdown period, with improving of weight (+0.8%; p-value = 0.002) and BMI (+0.24%; p-value = 0.005) while, among female patients we did not notice any changes in weight and BMI. In the patients who were stratified according to FEV1 value we found that the most severely impaired patients (FEV1 <40%), showed a significant loss of both weight (–0.1%; p-value = 0.042) and BMI (–0.04%; p-value = 0.027). Instead, patients with moderate respiratory function (FEV1% between 40 and 70) have a significant increase in both weight (+0.8%; p-value = 0,021) and BMI (+0.23%; p-

Table 1. Comparison of the studied nutritional characteristics of the 111 patients recorded pre- and post-lockdown.

Population (111 patients)	Pre lockdown[m]	Post lockdown[m]	Delta[d]	p-value[w]
Weight (Kg)	63.50 (53.30–71.40)	63.00 (53.95–73.15)	+0.40	0.020
BMI (Kg/m^2)	22.41 (20.21–24.99)	22.21 (20.27–24.98)	0	0.081

[m]: Median (1st and 3rd quartile); [w]: Test of ranks with Wilcoxon sign to correlated samples; [d]: The median of the differences between the same parameter before and after lockdown.

value = 0,035). Comparing males versus female patients we found a significant increase only of BMI (respectively +1.07% and –0.12%; p-value < 0.045) (Table 2). We also compared the group of patients with a FEV1 <40% versus those with a FEV1 between 40 and 70%. We found a statistical significant increased trend of weight (respectively –0.14% and +1.09%; p-value = 0.018) and BMI (respectively –0.17% and +1.05%; p-value = 0.030) (Table 2). Regarding pulmonary function tests, we found no significant differences in the overall population. (Table 3). Male patients presented a significant increase not only of FEF 25–75% (+3%; p-value = 0.01); female patients showed a significant decreased of CVF (–2%; p-value = 0.05).

In the patients who were stratified according to FEV1 value we found that patients with moderate respiratory function (FEV1% between 40 and 70) have a significant, reduction of CVF (–0.12%; p-value = 0.043), but improvement of FEF 25–75% although not statistically significant (+1.5%; p-value = 0.065). Considering the spirometric respiratory parameters most commonly used in CF patient monitoring in clinical practice for the assessment of bronchial obstruction and small airway function (FEV1 and FEF 25–75%), we have a steady upward trend and stabilization in the median FEV1%. In particular, we noticed a slight upward trend in FEV1% (Median 32% vs 33%) in the group severely impaired and with moderate respiratory function (Median 56% vs 56.5%) and no variation in the group with FEV1 >70% (Median 88% vs 89%). Regarding FEF 25–75 %, surprisingly we have reported an increase of median only in patients with moderate and good respiratory function (Table 4).

4. Discussion

The aim of this study is to evaluate the impact of social restrictions following the lockdown on respiratory function and nutritional state of CF patients. We report benefits in terms of weight, in particular in male patient with an increase in both weight and BMI; as well as among patients with moderate reduction of respiratory function. In addition, we notice a stabilization and sometimes improvement of lung function, instead of a continuous decline that is normally observed in CF patients.

Although SARS-CoV-2 infection appears to be less transmitted among CF patients and less aggressive than previously assumed, the pandemic has greatly altered their social relationships, reducing time spent away from home and reducing their clinical management [4–6]. In fact, during the lockdown in March 2020–May 2020, Italian CF centers cancelled routine appointments to avoid unnecessary hospital visits; respiratory function tests were postponed and telephone and e-mail contacts were increased.

Our data show a statistically increase in weight among all population; this result represents one of the desirable goal in clinical management of CF patient; in fact, the energy balance of CF patients is altered by a number of factors such as increased energy expenditure at rest due to chronic lung inflammation and lung infection. On the other hand, body weight reduction secondary to psychogenic anorexia and increased number of lung exacerbations may greatly affect this delicate balance [7]. In CF population, the correlation between regular growth (weight and height) and good respiratory function has demonstrated [8–10] both in children and adults [11,12] and also confirmed by the North America and European guidelines [13,14].

We think that during lockdown, despite the fact that most of our population reported an unchanged diet, patients had greater adherence to therapy, assuming that they took their pancreatic enzymes more regularly and did not skip meals. In addition, although the population similarly stated reduced physical activity in another study, most patients reported better adherence to respiratory physical therapy [15].

Considering gender differences, our data show that males presented a more beneficial effect of lockdown on nutritional state and lung function comparing to female patients with a positive trend up on nutritional state and respiratory lung function (in terms of Tiffenau Index and FEF 25–75%). These data reflect the well-known gender difference in terms of outcomes between male and female patients probably linked to sociological, behavioral, hormonal and genetic factors [16]. It is known from the literature that female CF patients are diagnosed later, have a worse overall survival and a higher risk of diabetes mellitus probably related to a proinflammatory state related to female hormones [17–19].

Considering respiratory function, we noted that severely compromised patients (FEV1 <40%) presented loss of weight and BMI; this may probably be related to the fact that CF is a chronic disease with a genetically determined progression. Probably this group of patients are too compromised to recover despite more adherence to treatment and unfavorable genetic mutations.

On the other hand, improvement on BMI and lung function were observed in patients with moderate respiratory function (FEV1 40–70%).

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Table 2. Comparison of the changes in characteristics recorded before and after the lockdown between the various patient groups. The values represent the Delta that is the variation in percentage.

	Males	Females	FEV1 ≤40%	FEV1 40–70%	FEV1 ≥70%	Mann-Whitney U test		
						Males vs Females	FEV1 <40% vs FEV1 40–70%	FEV1 40–70% vs FEV1 >70%
	(N = 57)	(N = 54)	(N = 10)	(N = 38)	(N = 63)			
	Delta	Delta	Delta	Delta	Delta	*p*-value	*p*-value	*p*-value
Weight (Kg)	0.8 (p = 0.002)	0	0.04	0.8 (p = 0.021)	0.4	0.07	0.02	0.41
BMI (Kg/m^2)	0.24 (p = 0.005)	–0.02	0.03	0.23 (p = 0.035)	0.04	0.04	0.03	0.32
FEV1 (litres)	0.05	–0.06	0.51	–0.05	0.03	0.1	0.56	0.65
FEV1 (%)	2	–2	0.59	–1	0	0.08	0.59	0.33
CVF (litres)	0.01	–0.06	0.86	–0.12 (p = 0.043)	0.01	0.494	0.64	0.26
CVF (%)	0	–2 (p = 0.045)	1	–2.5	0	0.272	0.74	0.06
FEF 25–75 (litres)	0.12 (p = 0.027)	–0.01	–0.01	0.01	0.04	0.077	0.77	0.3
FEF 25–75 (%)	3 (p = 0.013)	0	0	1.5	2	0.084	0.77	0.39
Tiffenau	0.7 (p = 0.049)	0.66	–0.18	1.86	0.62	0.24	0.61	0.12

Table 3. Comparison of the studied lung functional tests of the 111 patients recorded pre- and post-lockdown.

Population (111 patients)	PRE Lock–down[m]	POST Lock–down[m]	Delta[d]	*p*-value[w]
FEV1 (litres)	2.43 (1.72–3.07)	2.43 (1.73–3.05)	0	0.877
FEV1 (%)	72 (55.50–90.50)	72 (55.50–90.50)	–0.19	0.972
CVF (litres)	3.53 (2.87–4.25)	3.41 (2.64–4.20)	–0.03	0.163
CVF (%)	88 (75.00–102.00)	89 (69.50–99.5)	–2.16	0.078
FEF 25–75 (litres)	1.38 (0.85–2.72)	1.56 (0.91–2.62)	0.08	0.085
FEF 25–75 (%)	39 (23.00–72.00)	41 (24.50–68.00)	2.22	0.055
Tiffenau Index	67.79 (61.90–78.39)	69.17 (63.00–78.59)	0.67	0.097

[m]: Median (1st and 3rd quartile); [w]: Test of ranks with Wilcoxon sign to correlated samples; [d]: The median of the differences between the same parameter before and after lockdown.

Other authors have also shown a stability/improvement in respiratory function of CF patients during/after lockdown in line with our data. In support of this result, a reduction in the number of hospitalisations and exacerbations has also been described in literature [20,21]. On the other hand, however, Greek Authors showed that in their CF patients there were no changes in BMI while in our population we described this increase only in the male population when compared with the female population [20].

After lockdown period, we have noticed a substantial stabilization and sometimes a slight increase in FEV1% in all population supporting the hypotheses that chronic diseases such as CF, whose decline is genetically determined

Table 4. Comparison of medians (interquartile range) pre and post lockdown of total population.

	FEV1 ≤40% (N = 10)		FEV1 40–70% (N = 38)		FEV1 ≥70% (N = 63)	
	Pre	Post	Pre	Post	Pre	Post
	Median (Q1–Q3)	Median (Q1–Q3)	Median (Q1–Q3)	Median (Q1–Q3)	Median (Q1–Q3)	Median (Q1–Q3)
Peso (Kg)	60.75 (49.58–67.55)	60.75 (49.58–63.38)	62.25 (53.83–73.38)	63 (54.20–74.00)	65 (53.90–70.60)	65.5 (54.55–71.75)
BMI (Kg/m^2)	20.81 (18.58–24.02)	20.78 (18.58–23.49)	21.42 (20.06–25.04)	22.18 (20.68–25.38)	22.64 (20.46–25.44)	22.86 (20.01–24.97)
FEV1 (litres)	1.1 (0.95–1.39)	1.09 (0.90–1.64)	1.78 (1.62–2.33)	1.77 (1.49–2.35)	2.85 (2.44–3.59)	2.97 (2.42–3.46)
FEV1 (%)	32 (30.25–36.75)	33 (29.00–42.50)	56 (49.00–61.75)	56.5 (46.50–61.75)	88 (75.50–97.50)	89 (77.00–98.00)
CVF (litres)	2.16 (1.66–2.91)	2.07 (1.61–3.03)	3.08 (2.40–3.76)	2.8 (2.32–3.80)	3.97 (3.21–4.79)	3.92 (3.31–4.63)
CVF (%)	53 (45.00–64.75)	54 (44.00–66.25)	77 (71.00–82.00)	72.5 (65.00–80.50)	101 (92.50–111.00)	99 (92.00–111.00)
FEF 25–75 (litres)	0.5 (0.38–0.56)	0.52 (0.36–0.69)	0.87 (0.66–1.27)	0.99 (0.66–1.33)	2.61 (1.59–3.33)	2.34 (1.59–3.55)
FEF 25–75 (%)	11.5 (11.00–13.75)	13 (10.25–17.75)	24.5 (19.00–31.50)	28.5 (19.00–33.00)	67 (42.50–85.50)	63 (42.50–94.50)
Tiffenau	49.8 (45.93–60.86)	49.63 (48.25–56.88)	62.21 (57.89–66.24)	64.72 (57.80–69.31)	76.45 (68.23–80.07)	75.19 (68.52–81.39)

and constant [22], can be strongly influenced by external factors such as good nutrition, adherence to therapy and reduction of pulmonary exacerbations.

The strengths of our study are that selected sample is large, well balanced about sex and age and well representative of the adult FC population. The lack of comparison of the number of exacerbations between pre- and post-lockdown and the patient's subjective assessment of adherence to therapy and improvement in dietary quality are limitations of our study. A bias of the study could be that it compared different seasonal periods with different probabilities of pulmonary exacerbations and consequent declines in respiratory function.

5. Conclusions

Controlling respiratory exacerbations and increasing quality of life are integral to the management of chronic disease such as CF. The suspension of most of the work activities and the empowering of work from home resulted in the availability of more time for a greater therapeutic adherence. All these factors led to a stable clinical and respiratory picture of all classes of patients, nullifying the well-known annual decline among CF patients. Male patients showed more marked improvement than females. The most critically ill patients have less capacity for improvement than those with moderate respiratory impairment. The lower incidence of pulmonary exacerbations has probably made much of the periodic check-ups superfluous, but a less rigorous follow-up would not be desirable with the return to previous living conditions. Despite the tragic consequences of the pandemic and the measures applied to contain it, such as the limitations of personal freedoms, these have also had positive side effects, as demonstrated in this study. In the future, it is also desirable to use telemedicine to better monitor CF patients, outside of the usual outpatient visits. In this way, telemedicine can be a tool to improve the therapeutic alliance with patients by making them understand how important it is to devote time to medical and physiotherapy therapy, adhere to daily therapy and eat properly.

Abbreviations

CF, Cystic fibrosis; BMI, Body Mass Index; FEV1, Forced Expiratory Volume in the first second; CVF, Forced Vital Capacity; FEF 25-75, Forced expiratory flow between 25% and 75%; IQR, Interquartile.

Author Contributions

BA and MM designed the research study. BA, RV, DLF performed the research. CC, DAV, TP provided help and advice on the design of the study. CG, NR, MF conceived and directed the work thanks to their knowledge of the subject matter. MM analyzed the data. BA, MM wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

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Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.fbl2706178.

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