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Recommended shielding against COVID-19 impacts physical activity levels in adults with cystic fibrosis

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ABSTRACT

Background: Severe acute respiratory syndrome – coronavirus-2 (SARS-CoV-2) has caused a pandemic threatening the life of people with chronic respiratory diseases including cystic fibrosis (CF). This study was designed to investigate health-related aspects of individuals with CF, with and without lung transplantation (LTX), their communication with their specialist healthcare providers during the pandemic, potential changes in peoples' individual therapy regimes and daily physical activity levels.

Methods: A web-based survey was conducted among Swiss adults with CF with and without LTX, study period from March 16th, 2020 – the day the “extraordinary situation” was officially declared in Switzerland introducing stringent measures protecting the public – until May 16th, 2020.

Results: 327 individuals (25% LTX recipients) were included, 45 individuals reported coronavirus-2019 disease (COVID-19) like symptoms. Of 28 subjects tested, only three subjects were tested positive, all with mild symptoms, no hospitalization required. Almost half of the survey respondents (45%) reported undertaking less physical activity during the lockdown, while 79% and 91% of participants reported no change in traditional airway clearance and inhalation therapies, respectively. Distress regarding a potential SARS-CoV-2 infection or worsening of lung disease were no major concerns for subjects.

Conclusions: Our study reveals that the direct impact of SARS-CoV-2 on clinical outcomes of individuals with CF was mild although people with chronic lung diseases like CF are considered a high-risk population; overall, this is reassuring. However, strict lockdown measures substantially affected peoples' physical activity levels, a vital cornerstone of CF therapy; and this is worrisome.

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1. Introduction

Severe acute respiratory syndrome – coronavirus-2 (SARS-CoV-2), has caused a pandemic of unknown example to date [1]. The World Health Organization described the disease caused by SARS-CoV-2 coronavirus disease 2019 (COVID-19) [2]. The COVID-19 pandemic impacted in health care systems worldwide, its long-term consequences are still to be seen. To date, predictors for the development of severe COVID-19 have not been well established; however, patients with chronic lung diseases among other risk factors are more likely to suffer [3]. When COVID-19 expanded from China to Europe and North America, it was unknown how COVID-

19 affects people with cystic fibrosis (CF) lung disease given the much higher prevalence of CF as an inherited disease in the Caucasian population within Europe and North America [4]. According to the latest European Cystic Fibrosis Society (ECFS) Patient Registry Report, almost 50'000 individuals with CF live in 35 European countries [5]. Further, CF is nowadays the second most common primary indication for bilateral lung transplantation (LTX) in adults and the third most common overall indication based on figures of a International Society for Heart and Lung Transplantation (ISHLT) Thoracic Transplant Registry Report [6,7]. To date, there is a paucity of data on predilection, presentation, and prognosis of COVID-19 after organ transplantation [8]. It is unknown, if post-transplant immunosuppression modifies the vulnerability of solid organ transplant (SOT) recipients of acquiring SARS-CoV-2 or impacts considerably on the clinical course of COVID-19 [8].

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Switzerland is one of the countries with the highest number of COVID-19 cases per capita [9]. However, the COVID-19 pandemic developed with regional differences, severely affecting French-speaking parts of Switzerland bordering with France, and the Italian-speaking Canton of Ticino bordering with Italy. In the French-speaking Canton of Geneva, there were more than 100 confirmed cases per 10'000 inhabitants, in the Canton of Ticino more than 90 cases per 10'000 inhabitants [10]. Tschopp and co-workers have reported on the Swiss experience of SARS-CoV-2 infections in SOT recipients, describing 21 patients, predominately after abdominal organ transplantation but only one LTX recipient [11]. Overall, the clinical course of COVID-19 in SOT recipients seemed comparable to the general population; however, there was a selection bias towards symptomatic patients as SOT recipients with fewer or no symptoms were more likely not to report to a health care professional for testing [11].

As there is a lack of data on the impact of SARS-CoV-2 on individuals with CF with and without LTX during the COVID-19 pandemic, we surveyed over 500 adults with CF living in Switzerland according to the ECFS Patient Registry, investigating medical and non-medical aspects related to the COVID-19 pandemic. We also aimed to capture the influence of SARS-CoV-2 on patients' individual therapy regimes, perceived health status and daily physical activity levels. We hypothesized that the effect on the health of people with CF with and without LTX is rather limited, with a larger burden on individuals' overall health status and physical activity behaviour.

2. Methods

The Study Team, composed of a pulmonologist with special interest in CF and lung transplantation, an occupational medicine physician and an exercise scientist, developed a self-administered questionnaire with support of four individuals with CF. The questionnaire (see supplementary material) contained questions on demographics and medical characteristics, current therapies, and individuals' perceptions towards various medical and non-medical aspects related to the SARS-CoV-2 crisis. In addition, the Study Team implemented a so-called "feeling thermometer", a visual analogue scale (VAS) with marked intervals from 0 (worst imaginable health state) to 100 (best imaginable health state), part of the EuroQoL quality of life questionnaire (EQ-5D-5L) [12]. The EuroQoL is a valid health outcome instrument in CF [13], previously applied in various LTX populations including people with CF [14,15].

Prior to starting the survey, the online questionnaire was pilot tested by four individuals with CF (two females) including one LTX recipient. The pilot was done to evaluate the comprehensibility of questions and instrument as a whole, and to estimate the time for completion the online survey. The individuals provided important feedback implemented into the survey. The final version of the questionnaire was made available in three national languages in Switzerland: French, German, and Italian.

Severity of COVID-19 was classified using the following stages: Stage I – mild symptoms (e.g. dry cough, fatigue, headache); Stage II – moderate to severe symptoms (e.g., dyspnoea, hypoxia); Stage III – critical symptoms (e.g., acute respiratory distress syndrome, cardiac failure); Stage IV – death [16].

On April 27th, 2020, one day after the first phase of easing the nationwide six-week complete lockdown during the pandemic in Switzerland, the online link to the questionnaire was distributed via email to all current members of the Swiss Cystic Fibrosis Society, it was additionally also made available on the CFCH' official Facebook page. A second survey invitation was sent as a reminder on May 7th, 2020. The Study Team additionally shared the link with the two Swiss LTX Centers, Centre Universitaire Romand de Transplantation and the University Hospital Zurich, two

Shared Care Centers in Basel and Berne caring for LTX patients, and the largest adult CF center in Switzerland, the Quartier Bleu in Berne. The questionnaire comprised the study period from March 16th, 2020 – the day the Swiss Federal Office of Public Health declared the nationwide "extraordinary situation" introducing stringent measures to protect the public – until May 16th, 2020.

The original study questionnaire was also translated into English (see online supplements).

This study does not fall under the scope of the Human Research Act. Research projects with anonymously collected or anonymous health-related personal data are exempt from requirement for approval. The study investigators paid special attention to the anonymity by using age categories and time of LTX (i.e., < 1 year, 1–5 years, >5–10 years, > 10 years).

2.1. Statistical methods

Data were summarized as *n* (%) or median (interquartile range). Continuous outcomes were compared using the Wilcoxon-Mann-Whitney test (for two groups), or the Kruskal-Wallis test (for more than two groups), and categorical outcomes were compared using the chi-square test. Data cleaning and analysis was performed using R (version 4.0), and graphs constructed using ggplot2 (version 3.3) [17,18].

3. Results

During the 3-week study period from 27th, April 2020, 345 survey responses were captured. Double-data entries were noted for three individuals, two respondents did not provide consent, nine responses were empty, and a further four were incomplete (only answered demographic questions), leaving 327 individual responses for final analyses (270 questionnaires were completed in German, 47 in French and 10 in Italian). According to the latest report of the ECFS Patient Registry [5], 517 adults with CF live in Switzerland, indicating that well over 50% of the Swiss adult CF population responded to the survey.

3.1. Participant population

Participants' clinical and socioeconomic characteristics are shown in **Table 1** and **Table S1**, respectively. Among 327 respondents, 83 (25.4%) were LTX recipients, of which 14.6% reported to have chronic lung allograft dysfunction. In the LTX cohort, hypertension and diabetes were the most frequent co-morbidities. In the non-transplant cohort (*n*=244, 48.4% females), about 85% of subjects reported to have known mild-to moderate CF lung disease, CF-related diabetes was the most frequent co-morbidity (**Table 1**). Self-reported health status (EQ-5D VAS) of people with and without LTX is provided in **Figure S1**. People without LTX reported a lower health status compared to those with LTX (*p*=0.002) (**Figure S1**).

3.2. COVID-19 related symptoms, diagnostic testing and disease stages

Between March 16th to May 16th 2020, 45 individuals (13.8%) conveyed to experience COVID-19 like symptoms (**Table 2**). Among symptomatic subjects, 28 individuals underwent SARS-CoV-2 testing, three individuals (10.7%) were tested positive, all suffered with mild symptoms only - corresponding to COVID-19 Stage I, [16] individuals self-quarantined, no hospitalization required.

Table 1.
Participants' characteristics.

Variables	All (n = 327)	Non-LTX (n = 244)	LTX (n = 83)
Sex			
Male	171 (52.3)	125 (51.2)	46 (55.4)
Female	155 (47.4)	118 (48.4)	37 (44.6)
Other	1 (0.3)	1 (0.4)	–
Age categories			
< 40 years	237 (72.5)	192 (78.7)	45 (54.2)
≥ 40 years	90 (27.5)	52 (21.3)	38 (45.8)
Lung function (FEV₁)^a			
> 80 % pred	64 (26.2)	64 (26.2)	–
40 – 80 % pred	143 (58.6)	143 (58.6)	–
< 40 % pred	37 (15.2)	37 (15.2)	–
Years post LTX			
< 1 year	2 (2.4)	–	2 (2.4)
1–5 years	17 (20.5)	–	17 (20.5)
> 5 – 10 years	30 (36.1)	–	30 (36.1)
> 10 years	34 (41.0)	–	34 (41.0)
Comorbidities			
Heart disease	3 (0.9)	2 (0.8)	1 (1.2)
Hypertension	48 (14.7)	10 (4.1)	38 (45.8)
Diabetes	135 (41.3)	69 (28.3)	66 (79.5)
Kidney disease/-transplant	21 (6.4)	2 (0.8)	19 (22.9)
Cancer [#]	7 (2.1)	3 (1.2)	4 (4.8)

Data are presented as numbers (percent). FEV₁, forced expiratory volume in 1s; LTX, lung transplantation.

^a Lung function was only surveyed in non-transplant patients.

[#] Other than skin cancer.

Table 2

COVID-19 like symptoms, diagnostic testing and disease stages.

Variables	All (n = 327)	Non-LTX (n = 244)	LTX (n = 83)
COVID-19 like symptoms	45 (13.8)	38 (15.6)	7 (8.4)
Symptomatic tested	28 (62.2)	21 (55.3)	7 (100)
SARS-CoV-2 positive	3 (10.7)	2 (9.5)	1 (14.3)
COVID-19 Stage I ^a	3 (100)	2 (100)	1 (100)
COVID-19 Stage II ^a	–	–	–
COVID-19 Stage III ^a	–	–	–
Asymptomatic tested	43 (13.1)	13 (5.3)	30 (36.1)

Data are presented as numbers (percent). COVID-19, coronavirus disease 2019; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2.

^a COVID-19 stages were adapted from Sidiqqi & Mehra.¹⁸

Table 3

Impact of the SARS-CoV-2 pandemic on patients' daily maintenance therapy.

Variables	All (n = 327)	Non-LTX (n = 244)
Daily physical activity^a		
Change in therapy	222 (67.8)	172 (70.5)
Less frequently	146 (65.8)	110 (45.1)
More frequently	75 (33.8)	62 (25.4)
Daily airway clearance		
Change in therapy	53 (16.2)	52 (21.3)
Less frequently	22 (41.5)	22 (42.3)
More frequently	31 (58.5)	30 (57.7)
N/A	72 (22.0)	21 (8.6)
Daily inhalation therapy		
Change in therapy	27 (8.2)	26 (10.6)
Less frequently	6 (22.2)	5 (19.2)
More frequently	21 (77.8)	21 (80.8)
N/A	29 (8.9)	3 (1.2)

Data are presented as numbers (percent).

N/A, not applicable.

^a 326 responses

3.3. Impact of the SARS-CoV-2 pandemic on patients' daily maintenance therapy

Table 3 provides an overview on changes in people's daily maintenance therapy, i.e., physical activity, airway clearance, and inhalation therapy, a cornerstone of CF care. During lockdown, about 45%, 9%, and 2% of individuals undertook less daily PA, airway clearance, and inhalation therapy, respectively (**Table 3**).

3.4. Physical activity

Among those who reported to do less physical activity during the pandemic, reasons provided were closed training facilities (66%), lack of motivation (32%) or everyday structure (30%), and cancelled supervised training (27%), such as professional training therapy. Some survey respondents reported on self-organized informal virtual exercise groups via the video communication tool Zoom®, meeting twice daily for exercises such as Pilates®, gymnastics, or yoga.

3.5. Airway clearance and inhalation therapy

Among non-transplant individuals 12% and 7% reported to perform airway clearance and inhalation therapy more frequently during the pandemic (**Table 3**). Among those carrying out less therapy during lockdown, the most frequently reported single reason (55%) was canceled supervised therapy (i.e., physiotherapy, **Table 3**) and lack of motivation and nonexistent daily structure.

3.6. Impact of COVID-19 lock-down on routine outpatient clinic appointments

During the lockdown, 214 (66%) of subjects reported planned routine outpatient clinic appointments at their CF or transplant centers. Around half of appointments were either postponed or cancelled (**Table S2**). Overall, routine clinic appointments were equally cancelled by either the specialist health care teams or the patients (51% vs. 49%). Among subgroups, patient-initiated cancellations of routine appointments were more frequently in LTX recipients compared to non-transplant individuals (64% vs. 44%). Alternatives for cancelled or postponed appointments were provided by 53% of specialist health care teams, telephone consultations were used most frequently (38%, see **Table S2**). During the study period, 173 (53%) individuals reported that their specialist health care team informed them directly about COVID-19 rules of conduct. In this regard, significant differences were noted between LTX recipients and non-transplant patients (83% vs. 43%, $p < 0.0001$). Information were most commonly provided by e-mail (40%), less frequently by phone (16%) or other platforms (9%). Overall, 87% of survey respondents felt sufficiently well informed by their specialist health care team.

3.7. Impact of COVID-19 lockdown on patient's health status

Subjects reported not being concerned of an infection with coronavirus; however – among non-transplant individuals – people with advanced CF lung disease expressed the highest level of concern/fear of worsening lung disease (**Figure S2**).

4. Discussion

This survey was designed to capture medical and non-medical aspects related to the COVID-19 pandemic in Swiss people with CF with and without LTX. In addition, we wanted to learn how individuals with CF communicate with their specialist health care providers during the pandemic. Further, we aimed to explore the

impact of SARS-CoV-2 on subjects' individual therapy regimes and daily physical activity levels, as well as the socioeconomic impact of the pandemic on individuals with CF.

Our study reveals that the impact of SARS-CoV-2 on Swiss individuals with CF with and without LTX was interestingly only mild despite the fact that people with chronic lung diseases are considered a high-risk population. This is all the more surprising knowing that Switzerland is one of the countries worldwide with the highest number of COVID-19 cases per capita [9]. Further, one-quarter of our study population were LTX recipients. So far, there is no robust data on the incidence of SARS-CoV-2/COVID-19 in LTX recipients, and their clinical presentation, clinical course, and overall clinical outcome [8]. It remains to be seen, if immunosuppression alters the likelihood of LTX recipients to capture a SARS-CoV-2 infection or how immunosuppression changes the clinical course of COVID-19 in LTX recipients [8]. In our cohort, only 15% of patients reported COVID-19 like symptoms with 28 individuals undergoing diagnostic testing to exclude SARS-CoV-2. In total, only three subjects tested positive, all with mild symptoms - corresponding to COVID-19 Stage I [16]. No patient required hospital admission, all self-quarantined at home and recovered without sequelae. One of the three SARS-CoV-2 positive was a LTX patients. Our data complement the results of a very recently published multinational report from national CF registries in eight countries including a heterogeneous patient group (n=40), including eleven LTX recipients. However, the method of case capture used in the study by Cosgriff et al. [19] was not exhaustive, thus, not identifying all cases.

It is important to note that well less than 20% of the LTX subjects in our study cohort suffered with chronic lung allograft dysfunction even though 77% of these individuals were over five years post-transplant. According to ISHLT Registry figures, over 50% of alive patients experience chronic lung allograft dysfunction five years post-transplant [7]. A low incidence of SARS-CoV-2 infections comparable to the general population was also reported in a large cohort of SOT recipients in Switzerland; however, the study cohort comprised almost exclusively abdominal transplant recipients [11].

Insufficient physical activity is a growing public health issue [20], and a known major risk factor for cardiovascular disease and mortality [21]. In CF, physical activity is associated with aerobic exercise capacity [22], an independent predictor of mortality [23]. The pandemic and officially recommended protective measures (i.e. social distancing and isolation policies for risk groups) impacted profoundly on survey respondents' physical activity behavior with almost half of the subjects reporting less physical activity during lockdown. Similar numbers were recently reported in a large population-based French survey, indicating that about 52% of survey respondents performed less physical activity during lockdown [24]. Regular physical activity is a well-established cornerstone of maintenance CF care [25,26], and lack of physical activity and increased sedentary behaviors potentially lead to deleterious consequences regarding individuals' overall health status. This is supported by a recent international survey showing that individuals who reported a negative change in physical activity during early COVID-19-related restrictions stated lower mental and physical health compared to their more active counterparts [27]. It is well described that many individuals with CF value physical activity as important for their (lung) health, overall well-being, and daily life [28]. Moreover, many people with CF incorporate physical activity and exercise into their airway clearance regimen and - according to recent surveys among individuals within the CF community - almost half of individuals have used exercise as substitute for traditional airway clearance techniques [29,30]. Given the fact that gym facilities and physiotherapy centers were closed during lockdown, it appears that some individuals "replaced" their physical activity by increased airway clearance therapy. Further, some

people with CF self-organised daily virtual exercise sessions among peers during the pandemic.

Interestingly, the strict lockdown measures did not appear to impact on LTX recipients perceived health status [i.e., feeling thermometer (EQ-5D VAS, **Figure S1**)]. The reported health status of LTX recipients during lockdown is perfectly comparable to a previously conducted survey in Swiss LTX recipients [28]. The study including 111 adult LTX recipients with comparable clinical profile (i.e., 18% chronic lung allograft dysfunction) and gender distribution showed a similar perceived health status as assessed with the EQ-5D VAS [28]. This is supported by the fact that - on a population level - LTX recipients with CF do not fear SARS-CoV-2 infection or worsening of their lung disease (**Figure S2**).

A strength of our study is the high response rate in comparison to previously published web-based surveys in people with CF [31]. According to the latest ECFS Patient Registry Report [5], 517 adults with CF live in Switzerland, 327 individuals from various regions across Switzerland participated in our study.

This study has limitations due to its nature of a questionnaire-based survey; the accuracy of individual responses cannot be verified possibly introducing self-reporting bias. However, as our survey focused on a relatively short time period, i.e., from May 16th, 2020, the start of lockdown, until May 16th, 2020, the ease of the lockdown, recall bias is unlikely to be a key problem in our survey. Moreover, our self-designed survey covered general demographics and CF-related specific data (i.e., co-morbidities, lung function) and focused on participants' perceptions and (potential) changes in therapy during the pandemic rather than sensitive information on health behaviors (i.e., drug use), all well known to be affected by social desirability bias. In this survey, physical activity was only assessed with a categorical variable (i.e., less, more, or unchanged) and not with a validated instrument. The study team was primarily interested in the subject's overall perception of changes in physical activity during lockdown restrictions rather than providing estimates of the time spent in different physical activity intensity domains and/or activity-related metabolic equivalents. Finally, Switzerland has four official languages (German, French, Italian, and Romansh) ; however, our survey was not provided in Romansh as it is spoken by less than 1% of the total Swiss population, and most of those individuals also speak one of the other official languages.

In summary, this study reveals that the direct impact of SARS-CoV-2 on clinical outcomes of individuals with CF was mild although people with chronic lung diseases such as CF are considered a high-risk population, in particular, following LTX; overall, this is reassuring and a central message for CF and transplant communities alike. However, it warrants further research to evaluate if self-implementation of strict lockdown rules plays a key role here or if the subpopulation of individuals with CF with and without LTX is less vulnerable as thought earlier. This is even more so important as individuals with CF in our study were more distressed by strict lockdown measures impacting on their daily lives, in particular, their physical activity levels, a vital cornerstone of CF therapy; and this is worrisome.

Declaration of Competing Interest

The authors have no conflicts of interest to disclose.

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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.2020.08.013.

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