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Telemonitoring: An opportunity in cystic fibrosis lung transplant recipients

Letizia Corinna Morlacchi [a,1], Emilia Privitera [b,*,1], Valeria Rossetti [a], Martina Santambrogio [a], Angela Bellofiore [a,b], Lorenzo Rosso [c,d], Alessandro Palleschi [c,d], Mario Nosotti [c,d], Francesco Blasi [a,d]

[a] Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Internal Medicine Department, Respiratory Unit and Cystic Fibrosis, Milan, Italy
[b] Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Healthcare Professions Department, Milan, Italy
[c] Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Thoracic Surgery and Lung Transplant Unit, Milan, Italy
[d] Department of Pathophysiology and Transplantation, University of Milan, Italy

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ABSTRACT

Introduction: Telemedicine has been successfully employed in a wide range of conditions, such as such as chronic lung disease and COVID-19. This study evaluate the role of telemonitoring for the early diagnosis of acute lung allograft dysfunction in cystic fibrosis adults who underwent lung transplant (LuTx). Quality of life and functional level achieved during a 12 months follow up were assessed.

Methods: Patients were randomized into two groups; control group received traditional hospital-based follow-up, whereas patients in the intervention group received, on top of standard care, a telemonitoring device, with a pulse oximeter and a spirometer integrated. Telemonitoring data were digitally transmitted to our centre.

Results: Sixteen patients were enrolled in each group. No statistically significant difference was found between the two groups in terms of incidence of allograft dysfunction, time from onset of symptoms to diagnosis and time of occurrence from LuTx. Moreover, both groups achieved similar quality of life and functional level. With reference to the telemonitoring group: 1) hospital reported data were consistent with those being remotely registered; 2) adherence to telemonitoring decreased during the follow up; 3) the majority of patients reported a high degree of satisfaction.

Conclusion: The COVID19 pandemic highlighted the necessity to investigate alternative practices to treat chronically ill individuals. Telemonitoring is a valuable tool to improve quality care to LuTx recipients.

* Corresponding author. Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Health and Care Professions Department, Milan, Italy.
E-mail address: emilia.privitera@policlinico.mi.it (E. Privitera).
[1] Shared first authorship.

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Abbreviations

ALAD	acute lung allograft dysfunction
CF	cystic fibrosis
CLAD	chronic lung allograft dysfunction
EBV	Eipstein-Barr Virus
FEV1	forced expiratory volume in the 1st second
FVC	forced vital capacity
HMA	home medical assistant
IQR	interquartile ranges
LuTx	lung transplant
6mWT	6-min walking test
NRS	numeric rating scale
PFTs	pulmonary function tests
PTLD	post transplant lymphoproliferative disease
RCT	randomized controlled trial
SGRQ	Saint George Respiratory Questionnaire

1. Introduction

Improved outcome after lung transplantation (LuTx) in the last 20 years was partly determined by the close monitoring of the postoperative clinical status with the early identification of possible respiratory complications and their timely treatment [1–3]. The outcome after lung transplantation has certainly improved but the morbidity and mortality rates are still high, especially in the first year [4].

To date, there is no defined element for the clinical, or rather preclinical, diagnosis of acute graft dysfunction, but the occurrence of "sentinel" events remains a cornerstone for early identification of allograft malfunction [5–7]. These events may include decreased body weight, a rapid decrease in FEV1 (forced expiratory volume in the 1st second) on spirometry and symptoms of respiratory exacerbation (increased cough and expectoration, hyporexia, decreased tolerance to fatigue, reduction of normal physical activity, rise in body temperature, disturbed sleep, increase in respiratory fatigue and/or reduction of SpO_2 at rest and/or during exercise) [8]. Hence, the need for close monitoring, careful surveillance programs and targeted and immediate actions by all the health personnel involved in the management of this kind of patients. Several evidences regarding the usefulness of telemedicine are currently available in a wide range of conditions, such as chronic lung disease and COVID-19 [9–12]. This precious tool may allow the remote and independent recording of some non-invasive diagnostic tests (global spirometry, oximetry and capillary glycaemia) at home on a regular basis, in order to early detect significant clinical problems, promptly diagnosing the possible complications and intensifying the frequency of these registrations even in the immediate follow-up phase once the acute event has been resolved. In our LuTx program, recipients coming from other Italian regions are requested to move nearby Milan for about 12 months after surgery. This requires an important effort both economical and emotional for patients and their families. Indeed, patients and their caregiver need to find a proper place to live, change their habits, sometimes leave temporary or permanently their job, being far away from their families and friends and in one of the most expensive cities of the country. In this scenario, telemonitoring could possibly reduce the time LuTx recipients have to spend in the Milan region and, in the same time, allow close and specific follow up of patients. Furthermore, telemonitoring could guarantee individual patients a constant control of their clinical condition without the need to increase the frequency of hospital-based evaluations. In this sense, it could represent a particularly useful tool for patients living in areas far away from the transplant centre [13] and could avoid infections, limiting the access to hospital facilities.

In LuTx recipients, home spirometry monitoring has already been advocated for the early detection of loss of function, suggesting acute infection and/or rejection [14–18]. However, experience with telehealth in this setting is limited. In the specific case of the cystic fibrosis (CF) recipients, this tool could be very useful seen the young age of patients and their need to return towards a more normal life [19,20].

The purpose of our study is to evaluate the possibility of using telemonitoring in the surveillance program of the first year after lung transplantation of CF patients. In particular, the ability to detect the onset of so-called acute lung allograft dysfunction (ALAD – an umbrella term including acute rejection, infections and any other cause that could determine an acute dysfunction of the allograft) [21] and the patients' adherence to this program. At the same time, we intend to investigate the impact of telemonitoring on the quality of life of transplanted patients and on the level of function achieved.

2. Methods

2.1. Study design, ethics and consent

This was a randomized controlled trial. Researchers received randomly generated treatment allocations within sealed opaque envelopes and, once a patient has consented to enter the trial, an envelope was opened and the patient was enrolled in the allocated

group. Patients were randomized into two groups; patients assigned to the intervention arm received telemonitoring on top of usual care. The patients enrolled in the control group received standard care.

This study was performed with the approval of the ethics committee (No. 312_2017).

Written informed consent was obtained from all the enrolled subjects.

2.2. Study population

Consecutive adult CF patients who underwent LuTx from September 2017 to August 2019 at Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico Milan, Italy, were included.

Inclusion criteria were: 1) age $\geq$18 years; 2) bilateral lung transplantation; 3) being affected by cystic fibrosis.

Exclusion criteria were: 1) re-transplantation; 2) combined transplantation; 3) extracorporeal membrane oxygenation bridge to transplantation; 4) lack of patient consent.

2.3. Standard care and telemonitoring procedures

Our post-LuTx standard program uses in-person clinic visits, including blood examination tests, spirometry, evaluation of gas exchanges at rest and on effort, imaging and surveillance transbronchial biopsies. See supplementary methods for standard of care at our centre for the first 12 months after LuTx. In this study, we intended to assess usefulness and feasibility of telemonitoring that can possibly reduce the time LuTx recipients have to spend in Milan, but, as data of efficacy and safety of this type of monitoring are still lacking for this patient population, we decided to assess the use of telemonitoring on top of usual care. Thus, both the groups received traditional hospital-based follow-up, including a visit with pulmonary function tests and blood examinations at least once a month and graft surveillance with CT scan and transbronchial biopsies at 3, 6 and 12 months from transplantation.

Whenever patients experienced any respiratory symptom (cough, purulent sputum production, dyspnoea) and/or any form of decline in home spirometry value and/or fever, they marked the onset of symptoms on the tablet, and therefore were called by the centre for an urgent visit at the hospital.

Patients randomized into the intervention group received a home medical assistant (HMA) system device, consisting of a tablet to which a pulse oximeter and a spirometer (Mir Spirobank II Smart®) with reusable turbine were integrated; the Comarch HomeHealth® app was installed on each tablet.

Patients were asked to perform a spirometry and register their SpO_2 overnight and on effort on a twice-weekly basis. After lung transplantation, CF patients can deal with uncontrolled diabetes and weight variations due to medical regimen, hence this group of patients was also required to fill in a diary with glucose level at fasting, weight (Kg) and temperature (°C) twice a week through the tablet. If measurements were not completed as scheduled, a remind alarm appeared on the app.

In case of altered fasting glycaemia and/or changed weight, the patient was contacted by telephone to discuss their diet, the possible use of insulin therapy, the possible referral to the diabetologist, as well as the daily water intake and diuresis.

Proper use of the devices was taught to each patient and practiced in presence of a trained respiratory physiotherapist [22]. Each individual was also given a brochure, with detailed instructions to use the HMA.

For spirometry, individuals were asked to perform at least 3 efforts and could see real-time flows on the tablet. Spirometry data were considered reliable when the difference among the three efforts was <15%. In order to test for consistency between data being collected with HMA device and hospital reported values, patients were instructed to perform a pulmonary function test (PFT) also the day before the routine-scheduled visit [22].

For effort pulse oximetry, SpO_2 and heart rate were registered during a standard workout session that consisted on endurance training with cycle ergometer or treadmill. At the beginning and at the end of the session, patients were asked to report perceived muscular fatigue and dyspnoea using Borg CR10 scale [23].

With regard to nocturnal pulse oximetry, registrations were taken into consideration only if they lasted more than 6 h.

Patients using HMA device were instructed to fill an alert on the app if they had any questions about the test results and/or symptoms. All the data were digitally transmitted to the cloud Comarch e-Care® platform. Measurements were analyzed weekly via a password-secured web portal by physiotherapists or real-time, when patients reported symptoms or decrease in their measured performances, as an alert was set in order to promptly detect any worsening.

At the end of the study, data on patients' satisfaction with this program were collected using numeric rating scale (NRS), where 0 represented "not satisfied at all" and 10 "fully satisfied". Moreover, information about the main difficulties identified during the study period were recorded.

3. Outcomes

Acute lung allograft dysfunction was defined as any event leading to an acute decline in FEV1 (with or without forced vital capacity (FVC) decline), which may be due to various conditions that affect the graft, including acute infection and acute rejection, among others. For the purpose of this study, we did not register respiratory infections, which did not lead to pulmonary function decline and/or were treated with oral antibiotics at home.

At different time periods (3, 6, 9 and 12 months post LuTx), exercise capacity was measured by the 6-min walking test (6mWT) [24] and Saint George Respiratory Questionnaire (SGRQ) [25] was administered to patients.

Adherence to telemonitoring was defined for each clinical variable as the ratio between the actual sessions being registered and

those who were expected, meaning that we excluded from the expected sessions all those that would have been performed during hospitalizations or those that were not carried out due to specific clinical conditions (e.g., temporary stop of exercise for specific musculoskeletal injuries or acute cardiac symptoms).

3.1. Statistical analyses

Descriptive analysis was performed with calculation of median and interquartile ranges (IQR) for continuous variables and proportion for categorical variables. Bivariate analyses were conducted using Mann Whitney's *U* test for continuous variables and chi-square or Fisher's exact tests for categorical variables. Statistical significance was defined as a 2-tailed $\alpha < 0.05$. All statistical analyses were performed using IBM SPSS 22 (SPSS, Inc., Chicago, IL, USA).

4. Results

A total of thirty-two patients was enrolled (Fig. 1); of those, sixteen were randomized for the telemonitoring group. One patient in the control group withdrew her consent to participate because of severe depression one month after enrolment; her data were not included in the analysis. One patient in the telemonitoring arm died 9 months after transplantation; his data are included, although he was not able to perform many sessions due to the long hospitalizations he experienced (he was affected by EBV-related post-transplant lymphoproliferative disease).

Baseline patient characteristics and relevant respiratory complications during the study period are presented in Table 1; no significant difference was found between the two groups.

Groups were compared in terms of acute allograft dysfunction. No statistically significant difference was found in terms of incidence ($p = 0.137$), time from onset of symptoms to diagnosis (Fig. 2A) and time of occurrence from LuTx (Fig. 2B).

Six patients (2 in the control group and 4 in the intervention group) were requested to anticipate their hospital routine based (details can be found in Table 2), in order to rule out possible acute lung allograft dysfunction.

Particularly, 4 of them (2 cases and 2 controls) contacted attending physicians by phone call because they were experiencing respiratory symptoms (e.g., cough, sputum, dyspnoea): these individuals were all later hospitalized for a respiratory infection. Among the two patients experiencing symptoms which were in the telemonitoring group, one did not show FEV1 decrease, whereas for the other no PFTs were recorded before the symptoms occurred, as the patient was not adherent to telemonitoring.

Among the 6 patients who anticipated their hospital visit, 2 were instead contacted by our centre, because the physiotherapists detected a significant FEV1 decrease at HMA measurement. The patients were immediately admitted to our ward with evidence of pulmonary infection, and therefore underwent the necessary treatment with no further delay; at discharge, patients exhibited a complete recovery of their graft function and no fatality occurred.

On the other hand, three patients received a "grade 1 acute rejection" diagnosis on their surveillance transbronchial biopsies; they were all completely asymptomatic and did not show any sign of decline in their PFTs (both the hospital-based and, for two individuals, the ones performed with HMA device).

Table 3 summarizes functional data that were registered at 3, 6, 9 and 12 months to evaluate allograft function and patients' quality

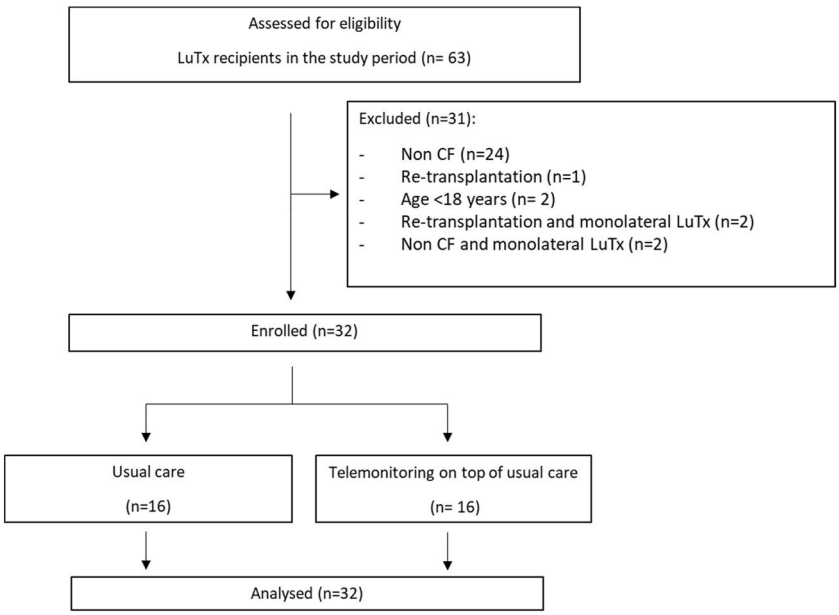

Fig. 1. Study flow diagram. Abbreviations: CF, cystic fibrosis; LuTx, lung transplant.

Table 1
Baseline characteristics.

	Total	Cases	Controls	p
	32	16	16	
Baseline characteristics				
Age at time of lung transplant (years)	32 (24; 36)	28 (23; 36)	33 (25; 38)	0.289
Sex, males (no, %)	18 (56)	10 (63)	8 (50)	0.479
Occurrence of acute rejection (no, %)	5 (16)	3 (19)	2 (13)	0.437
Hospitalizations for respiratory infection (no, %)	9 (28)	6 (38)	3 (19)	0.197

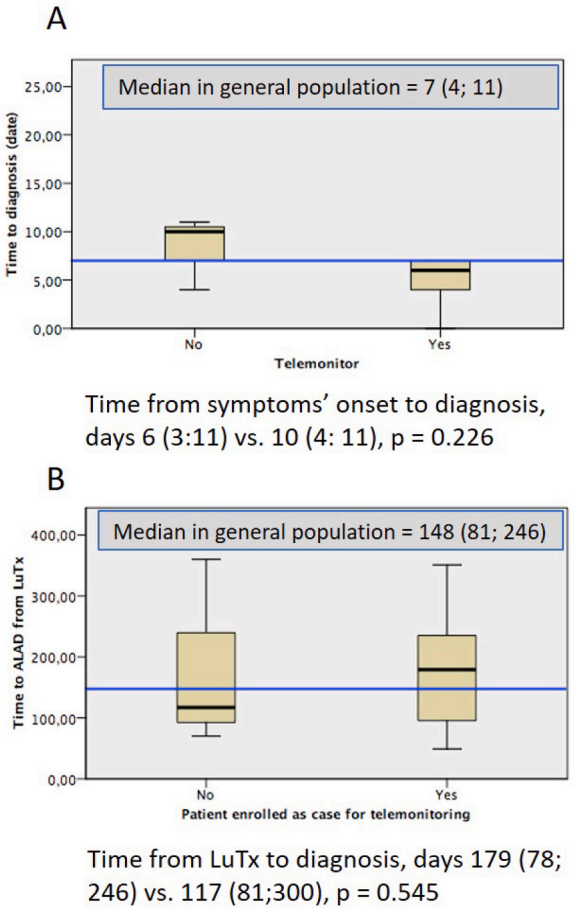

Fig. 2. ALAD, comparison between cases and controls in terms of (A) time from symptoms onset to diagnosis and (B) time from LuTx to diagnosis. Abbreviations: ALAD, acute lung allograft dysfunction; LuTx, lung transplant.

of life during traditional hospital visits. Again, no statistically significant difference was found between the two groups, even in terms of survival at 12 months, with just one death being registered among the cases (details above) and none in the controls group. As stated above, we observed only one death, in the cases group. All the patients showed an excellent graft recovery, with a median FEV1 $>$ 85% of predicted and a median 6mWT distance of 600 m at 12 months follow up. SGRQ results at the same timepoint suggested a high quality of life.

A total of 2470 events was registered with the telemonitoring devices. At the beginning of the study, several technical problems were registered with the equipment: we report a total of 55 events, meaning the number of registrations not obtained due to technical problems. We also report one change of equipment (1 oximeter because of improper working) without loss of weekly records.

With reference to the telemonitoring group.

Table 2
Acute lung allograft dysfunction.

Pt ID	Sex	Age at LuTx (yrs)	Case/ control	ALAD event	Symtom date	Symptom_type	PFTs on HMA	Diagnosis date	Type of event
Pt 1	M	33	Case	Yes	22/04/19	⚑ Cough, sputum	Normal	15/05/19	Hospitalized for infection; later evolved to CLAD BOS.
Pt 2	F	18	Control	No	NA		NA	NA	NA
Pt 3	F	24	Control	Yes	16/03/18	⚑ Cough, dyspnea on exertion	NA	26/03/18	Hospitalized for infection; then RA1 on TBB » steroid taper
Pt 4	F	42	Case	Yes	10/05/18	⚑ Cough, sputum	Not available	14/05/18	Hospitalized for multilobar pneumonia
Pt 5	M	28	Case	No	NA		NA	NA	NA
Pt 6	F	21	Control	No	NA		NA	NA	NA
Pt 7	F	25	Case	No	NA		NA	NA	NA
Pt 8	M	29	Control	Yes	No symptom		NA	20/06/18	RA1 on surveillance TBB » steroid taper
Pt 9	M	21	Case	Yes	No symptom		Normal	10/07/18	Hospitalized for pneumonia; September 2018: PTLD (nodules on surveillance CT scan)
Pt 10	M	38	Control	Yes	No symptom		NA	15/07/18	Hospitalized for CMV pneumonia
Pt 11	M	24	Case	Yes	No symptom		Normal	22/05/19	RA1 on surveillance TBB » steroid taper
Pt 12	M	35	Control	No	NA		NA	NA	NA
Pt 13	M	38	Control	No	NA		NA	NA	NA
Pt 14	M	35	Control	No	NA		NA	NA	NA
Pt 15	M	22	Case	Yes	21/01/19	Cough	⚑ FEV1 drop (−10%)	24/01/19	Hospitalized for infection
Pt 16	F	26	Case	No	NA		NA	NA	NA
Pt 17	M	31	Case	No	NA		NA	NA	NA
Pt 18	M	45	Case	No	NA		NA	NA	NA
Pt 19	M	27	Control	No	NA		NA	NA	NA
Pt 20	M	34	Case	Yes	No symptom		⚑ FEV1 drop (−10%)	21/11/18	Hospitalized for pulmonary mycosis
Pt 21	F	23	Control	*** withdrew her consent ***					
Pt 22	F	23	Case	No	NA		NA	NA	NA
Pt 23	F	38	Control	No	NA		NA	NA	NA
Pt 24	M	32	Control	Yes	01/04/19	⚑ Cough, sputum, dyspnea on exertion	NA	12/04/19	Hospitalized for multilobar pneumonia
Pt 25	F	36	Case	No	NA		NA	NA	NA
Pt 26	F	36	Control	No	NA		NA	NA	NA
Pt 27	F	18	Case	Yes	No symptom		Normal	16/10/19	RA1 on surveillance TBB » steroid taper
Pt 28	F	33	Control	No	NA		NA	NA	NA
Pt 29	M	28	Case	Yes	06/09/19		Normal	11/09/19	Hospitalized for pneumonia; later ACR (RA3) » pulse steroids
Pt 30	F	45	Control	No	NA		NA	NA	NA
Pt 31	M	43	Case	No	NA		NA	NA	NA
Pt 32	M	33	Control	No	NA		NA	NA	NA

⚑ For this reason, patients were called for urgent evaluation at the clinic.
Abbreviations: Pt, patient; M, male; F, female; yrs, years; ALAD, acute lung allograft dysfunction; FEV1, forced expiratory volume in the first second; NA, not applicable; CLAD, chronic lung allograft dysfunction; BOS, bronchiolitis obliterans syndrome; TBB, transbronchial biopsies; RA1: rejection, acute, grade 1–3 [26]; PTLD, post-transplant lymphoproliferative disease; CT, computed tomography; CMV, cytomegalovirus.

1. Hospital reported data were consistent with the last being registered with the HMA device; median difference between the devices was 54 (33; 102) mL;
2. Adherence to telemonitoring significantly decreased during the 12 months period of follow up (Fig. 3);
3. Patients were more likely to show a worse adherence to work out than spirometry assessments and, partly, overnight pulse oximetry (Fig. 3);
4. Twelve out of sixteen patients reported a high degree (NRS score >7/10) of satisfaction with the telemonitoring experience. Complaints mainly concerned the required frequency of measurements, which the patients considered excessive, and the malfunction of the equipment.

Further details on telemonitoring assessment can be found in Annex 1: the tables describe each measured obtained during the study period with the HMA device.

Table 3
Allograft function and patients' quality of life over time.

	Total	Cases	Controls	p	Missing
	32	16	16		
Walking test (in terms of distance, expressed in meters)					
At discharge	479 (426; 534)	492 (455; 532)	460 (412; 569)	0,289	0
At 3 months from LuTx	610 (550; 640)	615 (540; 652)	583 (555; 636)	0,715	3
At 6 months from LuTx	600 (542; 622)	590 (529; 636)	600 (555; 625)	0,756	5
At 9 months from LuTx	598 (549; 650)	585 (520; 636)	600 (581; 655)	0,434	7
At 12 months from LuTx	620 (576; 661)	611 (570; 665)	620 (576; 662)	0,999	4
SGRQ (expressed as no./100)		⚑			
At discharge	24 (9; 45)	24 (5; 42)	24 (13; 57)	0,724	0
At 3 months from LuTx	5 (2,15)	3 (1,18)	7 (4,11)	0,428	6
At 6 months from LuTx	5 (3,9)	4 (3,11)	6 (4,9)	0,65	6
At 9 months from LuTx	5 (1,7)	4 (1,7)	6 (3,7)	0,695	6
At 12 months from LuTx	3 (3,7)	3 (2,6)	4 (3,8)	0,435	7
PFTs, expressed as % of predicted		⚑			
FVC, at 3 months from LuTx	78 (68; 93)	80 (68; 95)	73 (70; 91)	0,586	1
FEV1, at 3 months from LuTx	81 (69; 90)	83 (70; 93)	76 (62; 83)	0,586	1
FVC, at 6 months from LuTx	87 (74; 96)	90 (75; 100)	82 (74; 92)	0,565	1
FEV1, at 6 months from LuTx	83 (72; 94)	87 (73; 98)	82 (68; 91)	0,357	1
FVC, at 9 months from LuTx	87 (77; 102)	92 (82; 104)	84 (75; 101)	0,466	2
FEV1, at 9 months from LuTx	84 (73; 96)	91 (74; 96)	78 (67; 97)	0,486	2
FVC, at 12 months from LuTx	91 (78; 103)	97 (83; 103)	85 (76; 107)	0,653	2
FEV1, at 12 months from LuTx	87 (74; 97)	92 (77; 98)	78 (72; 97)	0,285	2

⚑ For these patients, data were registered both with the HMA device and during the in-person visit.
Abbreviations: FEV1, forced expiratory volume in the 1st second; FVC, forced vital capacity; LuTx, lung transplant; PFTs, pulmonary function tests; SGRQ, Saint George Respiratory Questionnaire.

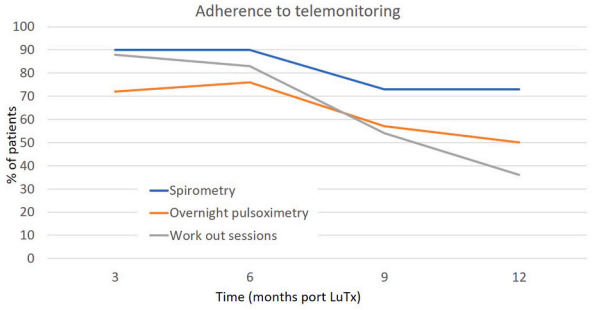

Fig. 3. Adherence to spirometry (blu line), ovenigth pulsoximetry (orange line) and oximetry during effort (grey line), measured at 3, 6, 9 and 12 month follow up after lung transplant. Abbreviations: LuTx, lung transplant.

5. Discussion

Telemedicine and telemonitoring have been defined as "remote delivery of healthcare services over the telecommunication infrastructure"; patients can be examined, symptoms evaluated, diagnosed and treated via remote consultations with personal technology [27,28]; given this definition, telemonitoring has the potential to dramatically transform health care after transplantation. Because transplant centers have a long catchment area resulting in long travel distances for patients, the possibility to use telemedicine tools is well suited for recipients' follow up. Several evidences exist for solid organ transplant, like in liver [29], kidney [30] and also lung [13,30] transplant recipients. However, the added benefit of this kind of new integrated approach should be demonstrated in order to justify the use of additional costs.

Our study promotes the use of telemonitoring in the setting of LuTx recipients follow up.

A previous study describes the importance of good training for both patients and hospital staff in order to collect the most reliable data from a home spirometry [31]. Despite some initial difficulties, which were certainly to be expected given the newness of equipment and the necessity of both the staff and the patients to gain experience, we achieved a reasonably high number of registrations, especially in the first part of follow up.

There was no significant difference in terms of baseline characteristics and short- and medium-term outcome between the two

groups. Excellent graft function was reported for both the groups, as expected from the latest evidences on lung transplantation for cystic fibrosis [32,33].

One of the most important results of our study is that telemonitoring may lead to an earlier diagnosis of graft dysfunction, as previously reported [14,34]. While four patients called our centre because they were experiencing respiratory symptoms, two individuals were given an anticipated in-person evaluation due to a FEV1 decline being detected with home spirometry. This means that, thanks to telemonitoring, we may have increased our diagnostic ability, triggering a virtuous cycle: the sooner we detect loss of graft function the sooner we can perform diagnostic tests. We can also speculate that the sooner we provide our patients with due treatment, the highest is the possibility to obtain complete recovery and favorable outcome. However, we are currently unable to assess if telemonitoring could, at least partially, replace in-person hospital visit, given our prudential choice to apply standard of care diagnostic approach to both the groups. We can speculate that applying a telemonitoring protocol to LuTx recipients can allow earlier return of patients to home region, around 6 months post LuTx with less hospital follow-up.

Pulmonary function data recorded with the HMA spirometer were compared with those obtained from the traditional hospital-based machine, showing an excellent correlation, which was even better that the data presented by previous studies (114 mL in the paper from Morlion and colleagues [15] and 120 mL in Lindgren's study [16]. This portable spirometer proved to be effective and reliable to monitor graft function even from home.

We are perfectly aware that, although telemonitoring of vital signs and functional parameters (spirometry, pulse oximetry, etc.) can be very useful to improve patient care, this form of care is not meant as a substitute for traditional hospital evaluation. On the contrary, it may enable prompter evaluation of those who prove unstable at their home monitoring. We should also be prepared for the fact that not every patient might want to—or be able to—perform telemedicine.

It has already been reported that adherence might be a difficult variable to assess. For instance, in a cohort of liver transplant recipients, adherence varied based on the task being requested: it was excellent (86%) for basic health sessions (vital signs recording), but only 45% for messaging and videoconferencing, because both patients and staff preferred regular phone calls [28].

In a previous RCT on LuTx recipients using an app to promote self-monitoring [26], adherence and use decreased over time. Similar data on adherence were reported even earlier: in 2013, Fadaizadeh L. et al. Described a falling adherence and compliance to home spirometry over time [14].

Our patients kept good level of adherence in terms of spirometries being performed even in the final phase of the study; however, we registered a significant fall in adherence to work out sessions and overnight pulse oximetry. This may be due to several reasons: firstly, this was a cohort of CF patients, who are historically very keen on their PFTs results since before transplant. We acknowledge an excessive expectation in terms monitoring schedule, mostly due to the double monitoring (hospital and telemonitoring) required to the patients in the intervention group; moreover, technical equipment was not optimal, especially at the beginning of the study.

For the future, we should probably improve the way we motivate patients to perform and register their work out sessions; a good option is also to change the way this variable is registered, offering, for instance, the possibility to perform work out session outdoor.

Daily check of telemonitoring data can provide hospital staff (both physiotherapists and physicians) with a close observation of their patients, offering the possibility to contact them whenever a registration is missing and an unexpected event occurs.

The majority of our patients were highly satisfied with the telemonitoring experience, similarly to what has already been shown by other studies [13,35]. Reported quality of life was not different between the two groups: we believe that this is because patients could not yet appreciate the potential benefits of the telemonitoring (given the high engament due to both hospital evaluations and home tasks) and, on the other hand, they did not consider this device very stressful; in the future, whenever this device could be integrated in a more extensive clinical approach with the aim to decrease hospital-based evaluations, we could also expect an increase of perceived QoL.

The COVID19 pandemic highlighted the necessity to investigate alternative practices to treat chronically ill individuals and many transplant centers have changed their regular practice and promoted telemedicine solutions [36,37].

Telemonitoring may represent an opportunity to reduce financial and travel burdens and simultaneously allowing multidisciplinary specialized care at the lung transplant centre [13,38]. On the other hand, this kind of approach has the potential to significantly reduce healthcare costs on facilities as well, giving the possibility to invest in other fields. Finally, high prevalence of contagious diseases in the hospital environment should always be considered and each visit could increase the risk of such infections in these highly susceptible patients.

In person follow up will still be essential for specific tests and procedures, but might be performed less often.

Another strength of our study was the use of several tools to analyze the telemonitoring performance, including spirometry, pulsoxymetry, 6mWT and SGRQ; details could be found in Annex 1. Moreover, user satisfaction when using m-Health applications as a tool to support self-management is of particular importance [39]. Because satisfaction reduces the barriers to successful implementation [40]. Our patients referred a high degree of satisfaction, and their feedbacks provided helpful suggestions on how we could improve our telemonitoring protocol.

Finally, it is important to remember that interprofessional cooperation is the foundation of any treatment plan after lung transplantation, including telemedicine. Physicians, surgeons, respiratory physiotherapists and nurses should work closely together to emphasize the importance of adherence to diagnostic and therapeutic prescriptions, to ensure timely implementation of treatment and to design a patient-specific rehabilitation program. This study promotes an interprofessional team approach as a key to achieve optimal outcomes in these patients.

Our study has several limitations; firstly, we have to acknowledge that blinding to the treatment of patients and hospital staff was not possible due to the nature of the study and to the type of intervention performed. Second, we took into consideration a very selected population, but we sincerely believe telemonitoring can be extended to any other LuTx recipient, provided that every patient should

receive tailored education. Generalization of our results is limited by the single centre nature of our study and the small sample size. Moreover, staff and patients might be more aware of the issue of adherence which can produce a performance bias and automatic remind alarm were not included in the HMA system. Finally, other potentially relevant variables, which were not taken into consideration and could be interesting fields in the hypothesis of future studies on every kind of recipient (not just cystic fibrosis), are age, education, ability to use apps and technology in general, as well as socioeconomic status.

Several studies have already observed significant benefits through telemedicine strategies in children [41], but it may be very interesting to investigate feedbacks among elderly patients.

Future challenges for developing this new area include concerns regarding data protection: patient information ought to be protected with security measures and standards for technical quality to be in place.

We should also find how to integrate this new "telemedicine" approach into healthcare processes to create efficiency gains and avoid clinically irrelevant time-consuming tasks.

Adequate staff training will be essential, with investment of resources for the education of personnel dedicated to telemonitoring procedures.

In conclusion, our study proves that telemonitoring could be a valuable and reliable tool to improve quality health care to LuTx recipients.

Our results indicate that patients are willing to adopt HMA device, showing a good adherence to registrations; home spirometry has proven again to be a reliable device for measuring pulmonary function, with results that were equivalent to those obtained with hospital – based instruments.

This RCT lends empirical support for the potential benefit of home spirometry, enabling the identification of cases warranting urgent evaluation for functional decline.

We are now implementing this approach scheduling online video consultations, in order to ease the transition from hospital to home and as a complement to traditional in person visits. Further research should be focused to standardize quality of telemedicine services.

Author contribution statement

Letizia Corinna Morlacchi: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper. Emilia Privitera: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper. Valeria Rossetti: Performed the experiments; Analyzed and interpreted the data; Wrote the paper. Angela Bellofiore: Performed the experiments; Analyzed and interpreted the data; Wrote the paper. Martina Santambrogio: Performed the experiments; Analyzed and interpreted the data; Wrote the paper. Francesco Blasi: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper. Mario Nosotti: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Data availability statement

Data will be made available on request.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.heliyon.2023.e19931.

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