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A novel web-based tool for lung transplant patients undergoing extracorporeal photopheresis

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BACKGROUND: Extracorporeal photopheresis (ECP) is considered an emerging rescue therapy for patients with chronic lung allograft dysfunction (CLAD). The aim of the study was to set up a web-based data collection tool for lung transplant patients with CLAD undergoing ECP.
METHODS: The web-based tool was developed using Oracle MySQL and coded in HyperText Markup Language, JavaScript and Cascading Style Sheets and was set up with pre- and post-transplant data of possible interest in CLAD.
RESULTS: The software consists of 7 major sections. The validation cohort consisted of 25 lung transplant patients (13 men and 12 women, median age at transplant 51 years). A significant improvement in the rate of decline of forced expiratory volumes in 1 second (FEV1), forced vital capacity (FVC) and FEV1/FVC after introduction of ECP was observed. Forty-four percent of patients showed a $< 10\%$ decline in FEV1 at 6 months. Patients with recurrent respiratory infections showed less probability of responding to ECP.
CONCLUSIONS: Today informatics is an integral part of medical science and an essential tool for clinical decision-making under many circumstances, reducing costs and improving patient outcomes. The "Siena ECP Database" allowed us to identify major functional trajectories after the introduction of ECP. It showed good data collection capacity, providing significant pre- and post-transplant information associated with ECP response. Although no clear clinical profile of responders has yet been defined, bronchiolitis obliterans syndrome phenotype and absence of recurrent respiratory infections seem to be associated with a positive response to ECP therapy.
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Background

Lung transplant (LTX) is a life-saving treatment option for selected patients with end-stage pulmonary disease, who are not or no longer responding to maximal medical therapy, or for whom no effective medical or surgical therapy exists.[1,2] Chronic lung allograft dysfunction (CLAD) remains the first cause of mortality in LTX patients; around 50% of transplanted patients develop CLAD within 5 years.[3,4] The most frequent forms are bronchiolitis obliterans syndrome (BOS) and restrictive allograft syndrome (RAS); however, mixed BOS/RAS and undefined phenotypes are possible.[4]

Different therapeutic approaches have been proposed for CLAD, but no effective treatment has yet been found.[5] Some clinical trials have shown a positive impact of azithromycin and montelukast; however among other rescue therapies proposed, the most promising appears to be extracorporeal photopheresis (ECP).[5–9] Based on ultraviolet (UV) irradiation of peripheral leukocytes, ECP has been shown to activate leukocytes and induce cell modifications, including apoptosis and an increase in peripheral T regulatory lymphocytes.[10–12] Certain clinical observations suggest that it may be effective in patients with CLAD.[13–23]

No specific registry for patients with CLAD has yet been described. The absence of such a registry hinders systematic data collection, holding back research, and management of this condition. Information technology plays a fundamental role in modern medicine, contributing significantly to clinical decision-making. It has proven decisive in many fields, such as clinical data management, clinical decision support, management/analysis of big data, telemedicine and e-health.[24–26]

In this study, our aim was to develop a web-based data collection tool for patients with CLAD treated with ECP. The tool is proposed for data collection and registry foundation.

Methods

Software design

We built a novel web-based tool named "Siena ECP Database," specifically designed for patients with CLAD treated with ECP. The software was developed using Oracle MySQL and coded in HyperText Markup Language, JavaSript, and Cascading Style Sheets. "Siena ECP Database" can be accessed by portable devices.

We reviewed the literature on treating patients with CLAD with ECP to identify variables associated with a positive response. We considered literature in the following databases: PubMed, Embase, Cochrane Library, clinical trial registers, and proceedings of conferences. The variables were incorporated into the software, together with pre- and post-transplant data.

Patient application

The functionality assessment of the software was performed by entering data, retrospectively collected, from a cohort of 25 LTX patients (13 men and 12 women, median age at transplant 51 years), who underwent ECP therapy at our center after being diagnosed with CLAD. Diagnosis of CLAD was made according to international guidelines.[4] All patients included were 18 years or older, diagnosed with CLAD more than 2 months previously, had been treated with ECP for at least 6 months, or were currently being treated with ECP. Data were collected and entered into the software by 2 pulmonary physicians.

At our center, ECP is offered to all capable patients with CLAD who have been treated with azithromycin for at least 8 weeks without achieving functional stability. ECP cannot be offered to patients with severe cardiac dysfunction or those with difficulties in peripheral and/or central venous access. Other issues that can limit access to therapy include patient preferences and travel distance. LTX patients with causes of graft dysfunction other than CLAD, or patients with CLAD who could not undergo ECP treatment were excluded from the study.

All patients gave informed consent to participation in the study which was approved by our local ethics committee (CEAVSE protocol number 18556 – Siena ECP, January 18, 2021).

Eight patients started ECP before 2016 using the Therakos UVAR XTS system and shifted to Therakos CELLEX since then; the rest of the patients were treated since then beginning with the latter system. Treatment consisted of an initial leukapheresis, centrifugation, addition of 8-methoxypsoralen (8-MOP) to the leukocyte fraction which is photoactivated with UV light before reinfusion into the patient. All these functions are performed by a single closed-circuit device, which adds 8-MOP directly to the leukocyte component, avoiding toxic complications linked to systemic administration of this agent.[5,20,27]

The ECP treatment protocol consisted of 2 consecutive days of ECP every 2 weeks for the first 3 months, followed by a monthly cycle. Our policy is not to interrupt ECP therapy unless contraindications develop.

Patients with a decrease in forced expiratory volume in 1 second (FEV1) < 10% after 6 months of ECP were considered responders. Survival and all new medical events occurring during ECP treatment were recorded and included in the final analysis.

Statistical analysis

Nonparametric statistics were used in this study. Values are reported as median with 25th (Q1) and 75th percentiles (Q3). Statistical significance was set at $p < 0.05$. Variance was studied by Kruskal-Wallis test and differences between 2 groups by the Mann-Whitney test. Prevalence analysis was done with the Fisher exact test. Kaplan-Meyer curves were used to study survival. Analyses were performed using GraphPad Prism 10.0.2 (San Diego, CA).

Results

Siena ECP Database

"Siena ECP Database" consists of 7 major sections: (1) transplant data, (2) CLAD diagnosis, (3) ECP treatment, (4)

graft complications, (5) other complications, (6) immunomodulatory therapy, (7) pulmonary function tests. The tool requires step-by-step compilation of the sections for new patients. All variables require specific information that the user must add to proceed to the next step. Sections 1 and 2 are completed once, while sections 3 to 7 can be updated at every visit. The user can save the data entered at every access, reopen a form later, and correct data.

1. Transplant data: information on patient history at the time of LTX (body mass index, height, weight, smoking history), Lung Diagnosis Code (with/without pulmonary hypertension), date/type (mono-/bilateral)/characteristics of transplant (donor/recipient cytomegalovirus (CMV) status, pre-emptive/prophylactic treatment, ganciclovir/valganciclovir treatment associated or not with anti-CMV immunoglobulin; bridge to LTX (mechanical ventilation/extracorporeal membrane oxygenation); primary graft dysfunction; need of extracorporeal membrane oxygenation post-LTX or mechanical ventilation > 96 hours; tracheostomy; acute renal failure; need of surgical revision; immunosuppressive therapy (induction and maintenance); stay in intensive care unit (days), patient and graft survival.
2. CLAD: date of onset, data regarding diagnosis—pulmonary function test (PFT), high-resolution computed tomography (HRCT), bronchialveolar lavage (BAL), and pathology; therapy of CLAD (other than ECP): azithromycin, montelukast, total lymphoid irradiation, other; CLAD phenotypes—BOS, RAS, mixed, undefined.
3. ECP data: starting data, indication, type of treatment (cell collection, 8-MOP, whole blood volume), related complications and side effects.
4. Graft complications: acute cellular rejection, antibody-mediated rejection, airway complications, acute lung allograft complications.
5. Other complications: thoracic complications, respiratory infection, medical complications, gastroesophageal reflux, malignancies, and others.
6. Immunomodulatory therapy: immunosuppressive induction therapy, maintenance therapy—prednisone/methylprednisolone, tacrolimus/cyclosporine, azathioprine/mycophenolate, mechanistic target of rapamycin inhibitors.
7. Pulmonary function tests: assessment of functional decline (FEV1, forced vital capacity [FVC], forced expiratory flow 25-75% (FEF25-75), intrathoracic gas volume (ITGV), total lung capacity, residual volume, diffusing capacity of the lung for carbon monoxide [DLCO]) at baseline and at every visit.

The software automatically produces a registry of patients with CLAD undergoing ECP with instant feedback on the cohort included (basic information: sex, age, type of LTX, underlying diagnosis, number of patients alive, etc.; lung function analysis with single parameter trends; number of patients responding to ECP at 6 months). It also produces a Comma Separated Values file for further statistical analysis.

Functionality assessment of the software

Twenty-five LTX patients (13 men and 12 women, median age at transplant 51 years), undergoing ECP therapy at our center after diagnosis of CLAD were included in this study. The underlying diseases that led to transplant were pulmonary fibrosis in 8 cases (32%), chronic obstructive pulmonary disease (COPD) in 7 (28%), cystic fibrosis (CF) in 7 (28%), and other diagnoses in 3 cases (12%), including a case of redo-transplant (Table 1).

The software compilation was performed by a single operator, with an average compilation time of 14 minutes and 32 seconds per patient.

According to the different phenotypes of CLAD, patients were diagnosed with BOS in 19 (76%) cases, RAS in 2 (8%), and mixed BOS/RAS in 4 (16%). CLAD stages at the start of ECP were stage 1: 12 (48.0%), stage 2: 5 (20.0%), stage 3: 5 (20.0%), and stage 4: 3 (12.0%) (Table 1).

Lung function tests before and after the start of ECP therapy (Table 2) showed a statistically significant improvement in rates of decline of FEV1 ($p = 0.0047$), FVC ($p = 0.0089$), and FEV1/FVC ($p = 0.0497$) (Figure 1). After 6 months of ECP, 11 (44%) patients were classified as responders and 14 (56%) patients as nonresponders.

Responders had a median age at transplant of 50 years (36.06, 62.00), 8 (72.7%) were men, 3 (27.3%) were women, and 5 (45.5%) were ex-smokers. Three (27.3%) patients were diagnosed with idiopathic pulmonary fibrosis (IPF), 3 (27.3%) with COPD, 3 (27.3%) with CF, and 2 (18.2%) with other diseases. Nonresponders were 5 men (35.7%) and 9 women (64.3%), median age at transplant 54 years (40.86, 61.60). Diagnoses leading to transplant were IPF in 5 (35.7%) patients, CF in 4 (28.6%), and other diagnoses in 1 (7.1%) patient (Table 1). No statistically significant differences in the preoperative characteristics of responders and nonresponders were detected.

Responders demonstrated a significantly slower decline in FEV1, FVC, and FEV1/VC after starting ECP (FEV1 before ECP −53.3 ml/month (−114.0, −29.6) and after 6 months of ECP 11.67 ml/month (3.3, 36.7), $p = 0.0019$) (Table 2, Figure 2). We also observed an increase in FEV1 and FVC in some patients ($n = 7/10$ at 3 months, $n = 9/11$ at 6 months, and $n = 5/9$ at 12 months) indicative of a gain in respiratory function with ECP. Responders with a > 5% improvement in FEV1 were arbitrarily defined as improved ($n = 6$, 54.5%).

The stage of CLAD at the start of ECP did not correlate with response to treatment; more nonresponders than responders were in stages 3 and 4 (18.2% responders vs 42.9% nonresponders), although the difference was not statistically significant. There were no nonresponders in stage 2, and this stage was the most frequent among responders (45.5% vs 0%, $p = 0.0087$) (Table 1). All patients with BOS/RAS phenotype ($n = 4$) were nonresponders (28.6% vs 0%); regarding the 2 patients with RAS, 1 responded to treatment, and 1 did not. The rate of PFT decline before ECP (fast decliners were defined when FEV1 drop was > 100 ml/month; slow decliners < 100 ml/month) did not show a significant correlation with response to

Table 1 Preoperative and Postoperative Data

Variable	All	Responders	Nonresponders	Significance
Number	25	11	14	
Age	51 (39.36, 61.65)	50 (36.06, 62.00)	54 (40.86, 61.60)	$p = 0.9893$
Male sex	13 (52.0%)	8 (72.7%)	5 (35.7%)	$p = 0.1107$
Smoke history	12 (48.0%)	5 (45.5%)	7 (50.0%)	$p > 0.9999$
BMI	23.00 (22.00, 28.5)	23.00 (17.75, 27.75)	25 (22.00, 30.00)	$p = 0.4907$
Diagnosis				
Pulmonary fibrosis	8 (32.0%)	3 (27.3%)	5 (35.7%)	$p > 0.9999$
COPD	7 (28.0%)	3 (27.3%)	4 (28.6%)	$p > 0.9999$
Cystic fibrosis	7 (28.0%)	3 (27.3%)	4 (28.6%)	$p > 0.9999$
Other diagnosis	3 (12.0%)	2 (18.2%)	1 (7.1%)	$p = 0.5648$
Comorbidities				
Diabetes mellitus	9 (36.0%)	5 (45.5%)	4 (28.6%)	$p = 0.4341$
Arterial hypertension	6 (24.0%)	2 (18.2%)	4 (28.6%)	$p = 0.6609$
Hypercholesterolemia	8 (32.0%)	5 (45.5%)	3 (21.4%)	$p = 0.3892$
Osteoporosis	18 (72.0%)	9 (81.2%)	9 (64.3%)	$p = 0.4065$
Time on waiting list (days)	292.00 (167.50, 556.00)	511 (186.00, 1,035.00)	221 (145.75, 487.00)	$p = 0.2022$
Pre-LTx ECMO (bridging)	3 (12.0%)	3 (27.3%)	0	$p = 0.0717$
LTx procedure				
Single LTx	7 (28.0%)	2 (18.2%)	5 (35.7%)	$p = 0.4065$
Bilateral LTx	18 (72.0%)	9 (81.2%)	9 (64.3%)	$p = 0.4065$
Ischemic time				
First lung (minutes)	240.00 (222.00, 320.00)	320.00 (240.00, 350.00)	235 (210.75, 250.50)	$p = 0.1179$
Second lung (if bilateral LTx) (minutes)	310.00 (240.00, 410.00)	393.00 (250.00, 450.00)	255 (228.75, 382.50)	$p = 0.1874$
Induction therapy (basiliximab or thymoglobulin)	16 (64.0%)	6 (54.5%)	10 (71.4%)	$p = 0.4341$
CNI therapy				
Cyclosporine	6 (24.0%)	2 (18.2%)	4 (28.6%)	$p = 0.6609$
Tacrolimus	19 (76.0%)	9 (81.2%)	10 (71.4%)	
Antimetabolite therapy				
Azathioprine/MMF	17 (68.0%)	7 (63.6%)	10 (71.4%)	$p = 0.4341$
Severe hypotension/hemodynamic decompensation	3 (12.0%)	2 (18.2%)	1 (7.1%)	$p = 0.5648$
Blood transfusion (yes/no)	11 (44.0%)	8 (72.7%)	3 (21.4%)	$p = 0.0172$[a]
IMV > 96 hours	12 (48.0%)	6 (54.5%)	6 (42.9%)	$p = 0.6951$
Tracheostomy	3 (12.0%)	1 (9.1%)	2 (14.3%)	$p > 0.9999$
Intraoperative ECMO	8 (32.0%)	6 (54.5%)	2 (14.3%)	$p = 0.0810$
Postoperative ECMO	1 (4.0%)	1 (9.1%)	0	$p = 0.4400$
PGD at 72 hours				
All grades	20 (80.0%)	9 (81.2%)	11 (78.6%)	$p > 0.9999$
Grade 1	9 (36.0%)	2 (18.2%)	7 (50.0%)	$p = 0.2077$
Grade 2	6 (24.0%)	5 (45.5%)	1 (7.1%)	$p = 0.0561$
Grade 3	5 (20.0%)	2 (18.2%)	3 (21.4%)	$p > 0.9999$
ICU stay (days)	8 (5.00, 13.50)	9 (8.00, 15.00)	6 (4.75, 12.00)	$p = 0.1765$
Total in-hospital stay (days)	31 (25.50, 49.50)	37 (28.00, 53.00)	29 (23.75, 41.50)	$p = 0.1450$
At least 1 episode of AR	15 (60.0%)	7 (63.6%)	8 (57.1%)	$p > 0.9999$
≥2 Episodes of AR	1 (4.0%)	1 (9.1%)	0	$p = 0.4400$
Highest AR grade				
A1	8 (32.0%)	5 (45.5%)	3 (21.4%)	$p = 0.3892$
A2	4 (16.0%)	1 (9.1%)	3 (21.4%)	$p = 0.6043$
A1/A2	3 (12.0%)	1 (9.1%)	2 (14.3%)	$p > 0.9999$
ALAD	7 (28.0%)	2 (18.2%)	5 (35.7%)	$p = 0.4065$
Recurrent respiratory infections	12 (48.0%)	2 (18.2%)	10 (71.4%)	$p = 0.0154$[a]
FEV_1 progression pattern				
Fast decliners	10 (40.0%)	3 (27.3%)	7 (50.0%)	$p = 0.4139$
Slow decliners	15 (60.0%)	8 (72.7%)	7 (50.0%)	
CLAD phenotype				
BOS	19 (76.0%)	10 (90.1%)	9 (64.3%)	$p = 0.1804$
RAS	2 (8.0%)	1 (9.1%)	1 (7.1%)	$p > 0.9999$
BOS/RAS	4 (16.0%)	0	4 (28.6%)	$p = 0.1052$
CLAD stages at ECP				
Stage 1	12 (48.0%)	4 (28.0%)	8 (28.6%)	$p = 0.8434$
Stage 2	5 (20.0%)	5 (45.5%)	0	$p = 0.0087$[a]
Stage 3	5 (20.0%)	1 (9.1%)	4 (28.6%)	$p = 0.3406$
Stage 4	3 (12.0%)	1 (9.1%)	2 (14.3%)	$p > 0.9999$
CLAD-free survival (days)	463 (265.5, 1,292.5)	561 (285.00, 1,308.00)	454 (246.75, 1,285.75)	$p = 0.6475$
LTx to CLAD diagnosis				
Within 1 year	9 (36.0%)	3 (27.3%)	6 (42.9%)	$p = 0.6766$

(*continued on next page*)

Table 1 (*Continued*)

Variable	All	Responders	Nonresponders	Significance
Within 2 years	6 (24.0%)	3 (27.3%)	3 (21.4%)	$p > 0.9999$
Within 3 years	2 (8.0%)	1 (9.1%)	1 (7.1%)	$p > 0.9999$
> 3 years	8 (32.0%)	4 (36.4%)	4 (28.6%)	$p > 0.9999$
CLAD diagnosis to ECP start (days)	72 (31.00, 206.00)	122 (53.00, 181.5)	46 (20.00, 61.00)	$p = 0.0038$[a]
Survival after CLAD diagnosis (days)	616	1,805	432	$p = 0.0014$[a]
Survival after ECP start (days)	450	1,685	361	$p = 0.0019$[a]

Abbreviations: ALAD, acute lung graft dysfunction; AR, acute rejection; BMI, body mass index; BOS, bronchiolitis obliterans syndrome; CLAD, chronic allograft dysfunction; CNI, calcineurin inhibitors; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation, ECP, extracorporeal photopheresis; FEV1, forced expiratory volume in 1 second; ICU, intensive care unit; IMV, invasive mechanical ventilation; LTx, lung transplant; MMF, mycophenolate mofetil; PGD, primary graft dysfunction; RAS, restrictive allograft syndrome.

[a]Statistically significant.

treatment. Patients with recurrent respiratory infections and episodes of acute lung allograft dysfunction before ECP introduction were more frequent in the nonresponder group (2/11, 18.2% vs 5/14, 35.7%; not significant). The incidence of acute rejection did not differ between the 2 groups.

The median time from LTX to the diagnosis of CLAD (CLAD-free survival) was 463 days (265.5, 1292.5); no difference between responder and nonresponder groups was observed. The time elapsing between diagnosis of CLAD and the start of ECP was greater for responders (median 122 vs 46 days, $p = 0.0038$).

Regarding prediction of response to ECP, lung function analysis at 3-month follow-up showed that all patients listed as responders at 6 months could already be classified as responders after 3 months of therapy. At 12-month follow-up, PFT data were available for 9 responders, that is, only 1 showed a > 10% decline in FEV1 (−15.79% at 12 months).

Patients in the nonresponder group also showed a slower, but not significant, rate of decline after ECP introduction of FEV1, FVC, and FEV1/FVC after 6 months of treatment (FEV1 before ECP −113.3 ml/month (−331.3, 29.17) than after 6 months of ECP −88.33 ml/month (−140.8, −73.3)) (Table 2, Figure 2). Lung function parameters after 12 months of ECP were only available for 3/14 nonresponders and showed a progressive decline in lung function (−49%, −35%, and −14% for each patient).

Regarding DLCO measurements, we observed a progressive and more marked decline in DLCO at 6 months in nonresponders than in responders, all of the latter remaining stable (−25.5% vs −2.4%, $p = 0.0485$).

Median survival of the whole population after diagnosis of CLAD was 616 days and median survival after starting ECP was 450 days (Table 1). Analysis of Kaplan-Meyer curves demonstrated that responders had a median survival of 1,685 days after starting ECP and this was significantly greater than that of nonresponders (316 days, 3 patients among responders vs 11 among nonresponders died during observation) ($p = 0.0019$) (Figure 3). Median survival after diagnosis of CLAD was also significantly longer for responders than nonresponders (1,805 vs 432, $p = 0.0014$).

Regarding safety, we only observed 1 case of nonsevere bloodstream infection by *Stenotrophomonas maltophilia* related to an indwelling catheter in a CF patient colonized by this micro-organism.

Discussion

The "Siena ECP Database" is a web-designed tool for patients with CLAD treated with ECP. It is based on clinical variables associated with the development of chronic rejection and response to ECP.[13–23] Information technology nowadays plays a fundamental role in modern medicine, contributing significantly to clinical decision-making. It has proven decisive in many fields, such as clinical data management, clinical decision support, management/analysis of big data, telemedicine and e-health.[24–26]

Several years ago, our group proposed a tool for instant accurate diagnosis of IPF by virtual means for patients suspected to have IPF with typical clinical features and demographics. The tool reduced the need for multidisciplinary discussions and the number of referrals to regional specialist centers for complex and atypical cases, saving time, costs, and physical burden on patients.[28] The basic idea of the IPF project was similar to the present one and is an absolute novelty in the field of LTX.

Our approach was to build a closed database where the user must enter all the necessary information step-by-step. This allows a homogeneous data collection that can enable more precise conclusions and considerations regarding ECP treatment, today considered an emerging treatment for CLAD which has aroused great expectations. Use of our tool also enables clinicians to be certain of doing a correct and exhaustive diagnosis of CLAD, of considering other factors associated with graft dysfunction and of evaluating the trends of lung function and other variables used to monitor grafts assessing patients treated with ECP. Diagnostic accuracy and monitoring during treatment are fundamental aspects in real-life studies, and in this way, our tool enables greater security and reliability of the collected sample.

The database was designed with 7 major sections to collect all significant information regarding transplant history, therapies, graft complications, diagnosis of CLAD, trends in lung function decline, and survival. All the variables included were chosen after meticulous review of the literature on ECP treatment of CLAD.[13–23]

The tool proves to be an excellent clinical information system, allowing easy access and management of clinical data and facilitating complete assessment of CLAD patients, for example by providing complete clinical history,

Table 2 Pulmonary Function Parameters in Relation to Response to ECP

LFT	*CLAD onset—ECP start*					*3-month follow-up since ECP start*				
	Responder n = 11		*Nonresponder n = 13*			*Responder n = 10*		*Nonresponder n = 9*		
	ml/month	*%*	*ml/month*	*%*	*p*	*ml/month*	*%*	*ml/month*	*%*	*p*
FEV_1	−53.3 (−114.0, −29.6)	−32.7 (−37.4, −12.9)	−113.3 (−331.3, 29.2)	−18.7 (−50.7, −6.7)	0.5309	38.3 (−8.3, 68.3)	8.3 (1.7, 11.7)	−60.0 (−83.3, −38.3)	−14.4 (−20.9, −4.5)	0.0007[a]
FVC	−50.0 (−87.0, −10.9)	−14.3 (−24.7, −4.7)	−72.0 (−180.4, 3.3)	−9.4 (−30.2, −1.4)	0.6789	43.34 (−0.0, 84.2)	5.3 (0.1, 11.0)	−56.7 (−150.0, 86.7)	−4.6 (−14.9, 2.6)	0.0368[a]
FEV_1/VC	−0.7 (−2.4, −0.2)	−24.7 (−27.3, −2.0)	−0.7 (−6.3, 2.7)	−6.7 (−28.7, −3.2)	0.8201	1.1 (−0.2, 1.9)	5.5 (−0.7, 11.5)	−1.2 (−2.9, 0.5)	−5.2 (−13.6, −0.3)	0.0057[a]
TLC	4.6 (−52.5, 14.4)	0.9 (−7.3, 4.1)	−70.0 (−110.7, 0.8)	0.7 (−6.34, 3.8)	0.8470	−31.7 (−81.7, 30.0)	−1.9 (−4.6, 1.5)	−13.3 (−114.2, 7.5)	−1.1 (−3.5, 1.2)	0.9790
RV	8.6 (0.9, 34.8)	2.8 (0.4, 28.2)	−28.0 (−76.7, 137.1)	6.7 (−4.3, 42.3)	0.8977	−33.3 (−92.5, 25.8)	−4.4 (−12.3, 3.8)	−63.3 (−150.8, 76.7)	1.6 (−13.3, 12.6)	> 0.9999
	mmol/min/kPa/ month	*%*	*mmol/min/kPa/ month*	*%*	*p*	*mmol/min/kPa/ month*	*%*	*mmol/min/kPa/ month*	*%*	*p*
DLCO	−0.1 (−0.1, −0.02)	−7.5 (−22.0, −2.4)	−0.1 (−0.5, 0.1)	−18.8 (−25.4, 8.0)	0.2809	0.0 (−0.3, 0.3)	−0.2 (−20.4, 12.2)	−0.3 (−0.4, 0.1)	−20.3 (−32.6, −11.8)	0.0530
	mmol/min/kPa/ va/month	*%*	*mmol/min/kPa /va/month*	*%*	*p*	*mmol/min/kPa/ va/month*	*%*	*mmol/min/kPa/ va/month*	*%*	*p*
KCO	0.0 (−0.1, 0.0)	2.0 (−10.9, 9.7)	−0.0 (−0.0, 0.1)	−7.0 (−15.6, 10.2)	0.2951	0.0 (−0.0, 0.0)	2.3 (−12.0, 4.0)	−0.1 (−0.1, 0.0)	−18.0 (−31.4, −9.2)	0.0286[a]
PFT	*6-month follow-up since ECP start*					*12-month follow-up since ECP start*				
	Responders n = 11		*Nonresponders n = 5*		*p*	*Responders n = 9*		*Nonresponders n = 3*		*p*
	ml/month	*%*	*ml/month*	*%*		*ml/month*	*%*	*ml/month*	*%*	
FEV_1	11.7 (3.3, 36.7)	8.1 (1.0, 9.0)	−88.3 (−140.8, −73.3)	−33.6 (−36.1, −22.5)	0.0055[a]	0.8 (−7.9, 11.7)	0.5 (−4.2, 7.8)	−85.4 (−116.7, −54.2)	−35.1 (−49.1, −14.8)	0.0182[a]
FVC	36.7 (1.7, 56.7)	7.8 (0.3, 15.5)	−90.0 (−140.0, −60.8)	−19.8 (−23.9, −13.6)	0.0007[a]	13.3 (−9.6, 2.9)	4.5 (−3.7, 10.8)	−87.1 (−127.5, −46.7)	−20.9 (−41.1, −10.7)	0.0136[a]
FEV_1/FVC	−0.1 (−0.6, 1.4)	−1.2 (−9.1, 15.3)	−2.3 (−3.76, −0.2)	−18.1 (−29.9, 3.7)	0.0275[a]	−0.1 (−0.4, 0, 4)	−3.2 (−6.1, 7.1)	−1.54 (−1.6, −1.4)	−2.4 (−24.6, −6.2)	0.0364[a]
TLC	16.7 (−53.3, 66.7)	−1.9 (−5.3, 6.6)	−41.7 (−205.8, 53.8)	−4.2 (−21.6, 6.5)	0.5714	10.0 (−49.9, 60.2)	1.9 (−9.9, 12.1)	−32.5 (−89.2, 24.2)	−5.8 (−16.8, 6.3)	0.4970
RV	11.7 (−48.3, 41.7)	3.6 (−9.8, 6.36)	56.7 (−64.2, 117.5)	10.6 (−17.4, 33.1)	0.4894	0.0 (−13.1, 50.6)	0.2 (−7.2, 23.8)	35.0 (12.5, 57.5)	5.7 (−5.1, 35.8)	0.8121

(*continued on next page*)

Table 2 (*Continued*)

	mmol/min/kPa/month	%	*mmol/min/kPa/month*	%	*p*	*mmol/min/kPa/month*	%	*mmol/min/kPa/month*	%	*p*
DLCO	0.0 (−0.1, 0.3)	−2.4 (−15.4, 44.3)	−0.2 (−0.3, −0.1)	−25.5 (−32.0, −9.1)	0.0485[a]	−0.0 (−0.0, 0.1)	−4.2 (−8.4, 11.3)	−0.1	−13.4	0.6071
	mmol/min/kPa/va/month	%	*mmol/min/kPa/va/month*	%	*p*	*mmol/min/kPa/va/month*	%	*mmol/min/kPa/va/month*	%	*p*
KCO	−0.0 (−0.0, 0.0)	−2.4 (−6.9, 7.8)	−0.0 (−0.0, 0.0)	−9.5 (−15.4, 1.0)	0.2485	0.0 (−0.0, 0.0)	3.7 (−30.3, 12.3)	−0.0	−7.8	0.2381

Abbreviations: CLAD, chronic lung allograft dysfunction; DLCO, diffusing capacity of the lung for carbon monoxide; ECP, extracorporeal photopheresis; FEV1, forced expiratory volume in 1 second; FEV1/VC, forced expiratory volume in 1 second/vital capacity; FVC, forced vital capacity; KCO, transfer coefficient of the lung for carbon monoxide; LFT, lung function test; PFT, pulmonary function test; RV, residual volume; TLC, total lung capacity.
[a]Statistically significant.

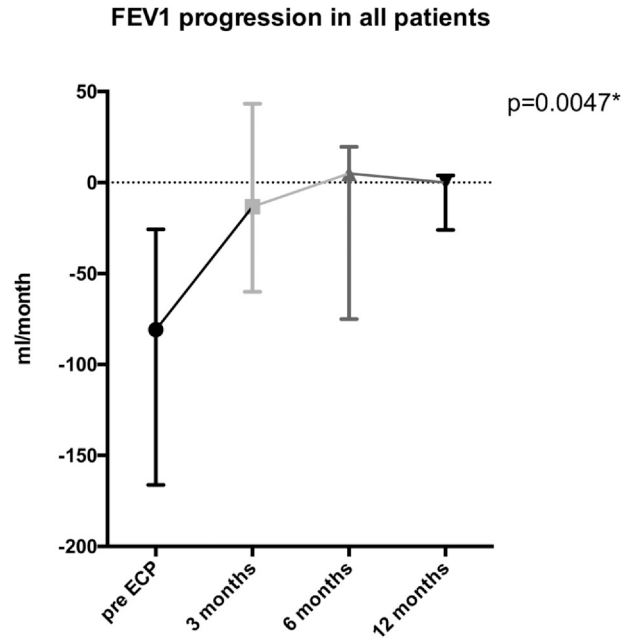

Figure 1 FEV1 progression over time of all included patients. ECP, extracorporeal photopheresis; FEV1, forced expiratory volume in 1 second.

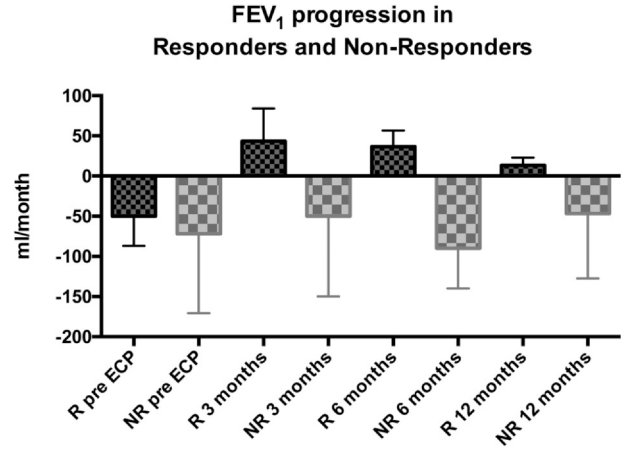

Figure 2 Responders demonstrated a significantly slower decline in FEV1, FVC, and FEV1/FVC after starting ECP (FEV1 before ECP −53.3 ml/month (−114.0, −29.6) and after 6 months of ECP 11.67 ml/month (3.3, 36.7), $p = 0.0019$). ECP, extracorporeal photopheresis; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity. NR, nonresponders; R, responders.

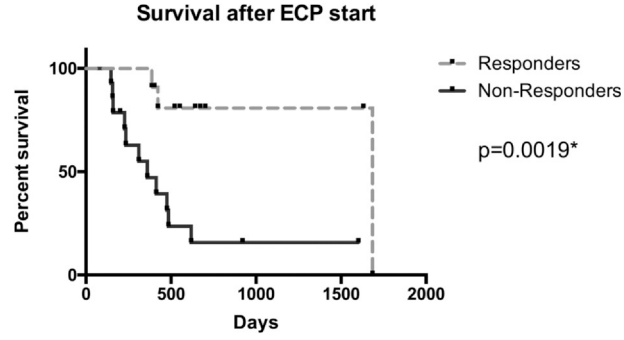

Figure 3 Survival after the start of ECP for responders and nonresponders patients. ECP, extracorporeal photopheresis.

test results, diagnostic imaging, pathology reports, and medical notes. It is a typical tool for the management and analysis of big data serving LTX. Indeed, it supports the collection and analysis of large quantities of clinical data from different sources on which to base in-depth analysis by different statistical approaches to reveal patterns and correlations, allowing a personalized approach based on specific patient features. This emerges clearly from the validation data of our study, which made it possible to confirm associations with response to ECP therapy, such as BOS phenotype and absence of recurrent respiratory infections before diagnosis of CLAD.

Our tool has proven to be fast in its usage and easy to implement. The compilation time averaged 14 minutes and 32 seconds per patient. The calculated time does not include the search for individual information in the electronic or paper patient records. There is a preworking time that we are unable to calculate and that may vary from center to center. In our case, the software compilation task was carried out by a single operator, and we observed a decrease in compilation times as the experiment progressed, suggesting increased compilation speed with software learning through preconditioning and anticipation of necessary information step-by-step.

Today ECP is considered an emerging and safe therapy for CLAD. It has an established safety profile and is known to be well-tolerated.[10] Many clinical studies sustain its use, especially in patients with BOS phenotype.[13–23] A positive impact of ECP in a consistent number of patients with CLAD (up to 60%) has been reported,[5,13–23] although no randomized trials have yet been performed. Almost free of side effects, ECP is considered a successful rescue therapy that may stabilize and, in some cases, even improve FEV1 in patients with CLAD.[5] In addition to the lack of clinical studies, one of the primary challenges associated with the utilization of ECP is its high cost, which serves as a barrier to accessing this treatment method. We are optimistic that the emergence of new clinical and laboratory data will delve deeper into understanding the mechanisms involved in CLAD and the pathobiological changes induced by ECP. This increased understanding has the potential to shed light on the effectiveness of ECP in these patients, ultimately paving the way for improved accessibility to this treatment modality in LTX centers.

In our study cohort ($n = 25$), ECP showed a positive impact on PFT trends with a significant reduction in FEV1 decline at 3-, 6-, and 12-month follow-up and significantly better survival in responders. The analysis of clinical characteristics revealed that patients with BOS phenotype and absence of recurrent respiratory infections before diagnosis of CLAD were associated with a positive response. Forty-four percent of our patients showed a reduction in FEV1 $< 10\%$ after 6 months of therapy, and more than half of these patients showed an improvement in FEV1 $> 5\%$ (54.5%). These findings are in line with the recent literature, even if response rates varied across study cohorts (31%-69%).[13–17]

Lung function trajectories showed that patients defined as responders at 6 months could already be classified as responders after 3 months of ECP, and except for a single patient, continued to be responders at 12 months. This suggests that a 3-month checkpoint could be sufficient to define responders to ECP, a result that however calls for confirmation in larger populations.

Regarding CLAD stages at the start of ECP, we did not observe any significant differences, although most responders had a CLAD stage ≤2 (81.8% vs 57.2% of nonresponders); however, the dimension of our cohort did not allow secure deductions. No significant differences in the time elapsing between transplant and diagnosis of CLAD were found between responders and nonresponders (median 561 vs 454 days). Different findings were reported by Jaksch et al[15] who found that patients who developed CLAD within 3 years of transplant and with lower CLAD stage showed the best response to ECP; however, the literature is not unanimous on this point.[13–23] Interestingly, we observed an inverse relation of response and the interval between CLAD diagnosis and the start of ECP treatment, as reported by Del Fante et al[17] who attributed this effect to better graft tolerance and consequently slower and less aggressive progression of CLAD. These same authors reported a better response in BOS than RAS patients[17]; we too observed a similar pattern in our patients; however, statistical significance was not reached because of the low number of included patients (10 out of 19 BOS patients, 1 out of 2 RAS, and 0/4 BOS/RAS phenotypes responded to treatment).

In our population, recurrent respiratory infections were found to be significantly more frequent in nonresponders to ECP. The role of respiratory infections in ECP response is not clear: airway colonization by *Aspergillus* was associated with a worse response to ECP,[17] but no association with *Pseudomonas aeruginosa* was demonstrated.[15,17]

Finally, ECP therapy had a positive impact on survival: responders had a median survival of 1,685 days after starting ECP compared to 361 days for nonresponders, confirming previous observations,[13–23] although Greer et al[16] found briefer survival than we did (stable patients 401 days vs 133 nonstabilized).[16]

Considering the data that our tool and the literature offer, it is impelling to learn more about the role played by ECP in patients with CLAD. CLAD remains the first cause of mortality in LTX patients; around 50% of transplanted patients develop it within 5 years.[3,4] In such a scenario, it is urgent to delve deeper into disease characterization and identify effective therapies; our tool can have a role in this and could be the backbone of a CLAD registry that could contribute to the management, research, and therapy of this pathology. The application of this software on a larger number of patients, thanks to the reliability and quality of the entered data, will allow the verification of new hypotheses for a better definition of the response profile to therapy. This will facilitate a more accurate personalization of treatments, enabling significant progress in understanding and optimizing medical strategies.

Besides all these aspects, our application can be integrated into telemedicine and e-health systems, to allow, for example, remote monitoring of patients, remote health

care, and improved access to care in remote areas or for patients with limited possibility of movement. The potential integration with other computer platforms is an important aspect of our work. In fact, it is our intention to make the software open source, thus providing the possibility of integration with other software upon request from other working groups. This could, for example, enable the automatic collection of respiratory functional data performed at patients' homes. Telemonitoring and e-health will increasingly become an integral part of clinical work, and precompiling our tool with an automatic flow of information generated by others could further reduce compilation times.

Finally, the Siena ECP Database can be an electronic registration system to replace conventional hard-copy records, simplifying access to data, reducing registration errors, and facilitating the safe sharing of information between members of the medical team and other international research groups.

Our study has some limitations. The software is based on variables proposed by prior published studies. Other factors and/or measurements not included in the present version could conceivably describe the response to ECP better. However, the ductility of information technologies makes this limit easy to correct through continuing updating of the software as new scientific data, recommendations, and guidelines are released. Though similar to other studies in the literature on ECP in LTX,[13–22] the cohort of patients we used for the functionality assessment of the software consisted of a relatively small number of patients with CLAD. Specifically, patients with 12-month follow-up were few, especially regarding the cohort of nonresponders, as only 3 were available (8 out of 14 patients died within 12 months, 2 were unable to perform PFTs due to clinical reasons, and 1 did not undergo measurements at the 12-month time frame). Lastly, since ours was a retrospective monocentric cohort study, there were no specific inclusion criteria and protocol visits.

In conclusion, informatics is an integral part of medical science and an indispensable tool for clinical decision-making in many circumstances, reducing costs and improving patient outcomes. The "Siena ECP Database" showed good data collection capacity for pre- and post-transplant information in patients with CLAD undergoing ECP. It fosters characterization of responder patients and deeper insights into the prognostic factors associated with ECP response. Functionality assessment of our tool reports a rate of response rate to ECP of about 50% in CLAD patients in our cohort. Although no clear clinical profile of responders has yet been defined, BOS phenotype and absence of recurrent respiratory infections before the diagnosis of CLAD seem to be associated with a positive response to ECP therapy. Further validation with a multicenter LTX cohort is warranted.

CRediT authorship contribution statement

David Bennett: conception and design of the study, acquisition of data, analysis and interpretation of data, drafted the article and revising it critically for important intellectual content. Matteo Fanetti and Maddalena Messina: acquisition of data, analysis and interpretation of data, drafted the article. Barbara Toniella Corradini and Asma Bendjeddou: software development; implementation of the computer code and supporting algorithms. Samuele Ferrari, Felice Perillo, Luca Luzzi, Piero Paladini, Elena Marchini, Elena Bargagli, Antonella Fossi: critical revision for important intellectual content. All authors approved the final version of the article.

Disclosure statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: David Bennett reports a relationship with Mallinckrodt Pharmaceuticals that includes funding grants. No other authors declare competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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