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ORIGINAL ARTICLE

Analysis of survival in lung transplantation: simple diagnostic tests in a new "SELeCT" Score used as prognostic tool. Results from a single center cohort study

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ABSTRACT

BACKGROUND: There are few validated scores evaluating outcomes of lung transplanted patients based on donor or recipient characteristic before or at the time of transplantation.

METHODS: In our study we evaluated a new, and easy to use, 5-item score on survival of patients who underwent lung transplantation. It was called SELeCT Score and was based on clinical, laboratoristic and radiological findings recorded at each observation.

RESULTS: We found higher scores in case of unscheduled observations and an inverse correlation with overall survival rate, even excluding patients who died within 60 days. We identified a threshold of 2 points as significant to predict patients' survival. Fungal and bacterial infections show scores higher than acute rejections and CMV and other viral infections.

CONCLUSIONS: SELeCT Score could represent a useful prognostic tool in guiding clinical choices, demonstrating that more compromised patients (routinely evaluated with clinic, laboratory test and radiological images) had a worse outcome, and that it could be important at least as much as the identification of the etiology.

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KEY WORDS: Lung transplantation; Pulmonary medicine; Survival.

Lung transplantation (LTx) is a valid therapeutical option for end-stage lung diseases.[1-4] The Lung Allocation Score (LAS), the Mortality After Lung Transplantation (MALT) Score and other studies identified recipient-, donor-, and transplant-specific characteristics associated with worst post-LTx prognosis.[5-10] Originally elaborated to shorten waiting list time, the Lung Allocation Score (LAS) has demonstrated acceptable predictive strength for outcomes after surgery.[7, 8] The Mortality After Lung Transplantation (MALT) Score represents the first known risk stratification tool that incorporates both recipient- and do-

nor-specific characteristics to predict 1-year mortality.[9]

However, all the tools proposed are based on characteristic assessed before or at the time of transplantation. Nevertheless, rejection, infections or other post-LTx events may influence the outcome predisposing to Chronic Lung Allograft Dysfunction (CLAD).[11-14]

The aim of this study was to find out a new "dynamic" score able to predict post-LTx transplantation survival by using data collected at each scheduled or un-scheduled follow-up visit.

Materials and methods

We conducted a retrospective observational single center study including all patients followed c/o Turin Lung Transplantation Center who underwent LTx between January 2015 and March 2017 and who underwent a complete, standardized 2-year follow-up. This follow-up program included: clinical evaluation, blood exams, pulmonary function tests, fiberoptic bronchoscopy with bronchoalveolar lavage and/or biopsy, microbiological and cyto-histological examinations, all performed at 1st-3rd-6th-9th-12th-18th-24th month after surgery. In addition, data collected at each unscheduled visit performed for suspected pulmonary infection or acute rejection have been evaluated to refine the calculation of the prognostic score. For each post-transplant observation, a score (SELeCT) based of the following five items was calculated: 1) symptoms and signs (S) (presence or worsening of cough, dyspnea, thoracic pain, hyperthermia or hypothermia, fatigue, tachypnea, new findings at chest examination); 2) blood gases evaluation (E) (hypoxemia defined as drop of PaO_2 below 15% of baseline); 3) leukocytosis (WBC>10.000×106/mm^3) or leukopenia (WBC<4.000×106/mm^3) (Le); 4) increased C-reactive protein (>10 mg/mL) (C); and 5) thoracic radiological findings (chest X-ray or high-resolution CT scan) (T) (evidence of pulmonary consolidations or cavitations, ground-glass opacities, nodules, pleural effusion, worsening of disease in the native lung).

The SELeCT Score showed values ranging from one to five. For each patient we calculated the mean of his scores (total, scheduled and unscheduled).

Statistical analysis

In the descriptive analysis, we included sample size and frequency for categorical data, means (±standard deviations). We performed ordinary one-way ANOVA for comparison of three or more means, and Tukey Test for multiple comparisons when appropriate. SELeCT Score was correlated with 2-year survival rate by using the Pearson Correlation Index (r) and the median value of our cohort was tested and used as cut-off. All P values were two-tailed and a P value <0.05 was considered statistically significant.

Results

We included 54 patients: 21 (38.9%) with end stage obstructive disease, 11 (20.4%) with cystic fibrosis (CF) and 22 (40.7%) with end stage interstitial lung disease (ILD). We collected 325 observations, whose 223 (68.6%) on follow-up schedule and 102 (31.4%) for unexpected events. study population characteristics are reported in Table I.

SELeCT Score calculated during unscheduled events was significantly higher than the one observed during scheduled observations (3.31±1.75 *vs.* 1.1±1.43, P<0.01) and it was negatively correlated with post-LTx survival (r=-0.701, CI: -0.81 to -0.53, P<0.001) (Figure 1). Even excluding early post-LTx deaths (possible bias inducing factor related to highest SELeCT scores

TABLE I.—*Demographics of patients included in the study.*

Variables	N. (%)
Patients	54
Gender N. (%): female/male	13 (24%), 41 (76%)
Age at LTx, in years: mean (±SD)	51.2 (±14.9)
Bilateral LTx: N. (%)	38 (70.5%)
Indications for LTx: N. (%)	
Obstructive lung disease	21 (39%)
Cystic fibrosis	11 (20%)
ILDs	22 (41%)
Total observed events	325
Scheduled: N. (%)	223 (69%)
Unscheduled: N. (%)	102 (31%)
Mean SELeCT score (±SD)	
Scheduled event	3.31 (±1.75)
Unscheduled event	1.1 (±1.43)

ILD: Interstitial lung disease; LTx: lung transplantation; SD: standard deviation.

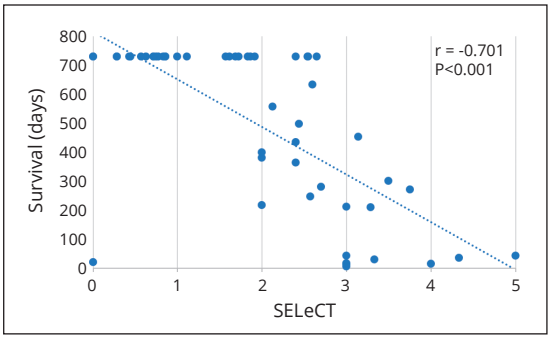

Figure 1.—SELeCT score.

observed in this cases), results showed the same significance level (P<0.001).

The median value score was calculated and a value of 2.0 and was arbitrarily considered as cut-off, since patients with a SELeCT Score >2 showed a significantly worse survival (P<0.001, sensitivity 83.3%, CI: 62.6-95.2, specificity 83.3%, CI: 65.2-94.3, PPV=80.0%, CI: 63.8-90.1, NPP=86.2%, CI: 71.6-93.9). When we considered only unscheduled evaluations, the score of each event divided per etiology (infective, acute rejection) did not correlate with survival (P>0.05).

For each episode was evaluated the presence of a microbiologic infection (bacterial, fungal or viral) on BAL as well as the presence of acute rejection on transbronchial biopsies. Significant differences between mean SELeCT scores were observed among bacteria and fungi when they were present (or absent) on BAL: when they were present the score was always greater than 2.

TABLE II.—*SELeCT scores results: difference between presence and absence of each factor (bacterial, viral, mycotic and acute rejection).*

Variables	N.	Present	Absent	P
Bacterial infection	142	2.02 (±1.58)	1.61 (±1.71)	0.018
Viral infection	165	1.63 (±1.73)	1.86 (±1.65)	0.177
Mycotic infection	58	2.41 (±1.66)	1.65 (±1.66)	0.001
Acute rejection	88	0.98 (±1.29)	1.39 (±1.59)	0.044

Interestingly, SELeCT Score was higher among patients without acute rejection on transbronchial biopsies (Table II).

We observed that mycotic infections had higher SELeCT scores than bacterial or viral ones (P=0.005) with a mean score of 2.41; in particular among pairwise comparison, the difference between fungal and viral SELeCT scores was significant (P=0.003). Among viral infections, CMV isolations had lower SELeCT scores than all other viruses (respectively 1.27±1.56 *vs.* 2.01±1.85, P=0.006). When we included in the analysis acute rejection scores, we observed that difference among groups was higher (P<0.00001) and that, after pairwise comparison, bacterial, viral and fungal SELeCT scores were all significantly higher than acute rejection ones (respectively P=0.00005, P=0.029, P<0.00001) (Table III).

Discussion

Since the first lung transplant in 1963, significant efforts have been made to identify predictive and prognostic factors useful in choosing the best therapeutic option and the correct timing for patients affected by end stage lung disease.[15, 16] LAS and MALT are both based on factors recordable before or immediately after the surgery.[17] However, one of the great limits to long term survival is represented by CLAD.[18] Acute rejection and infectious complications are known predisposing factors to CLAD but the real weight of each event on prognosis is far to be assessable.[19-24]

Well-known and widely employed clinical scoring systems (APACHE, CURB65, SIRS or Pneumonia Severity Index), validated in other clinical settings are not specific for transplanted patients and do not predict long-term survival.[25]

Bacterial and mycotic agents isolated on BAL had higher SELeCT scores than viral infection and acute rejections. In particular, bacteria and fungi

TABLE III.—*Microbiologic isolations and acute rejection at transbronchial biopsies; SELeCT scores' means differences.*

Values	Bacteria	Virus	Fungi	Acute rejection	P
N.	142	165	58	88	
Mean (±SD)	2.02 (±1.58)*	1.63 (±1.73)§	2.41 (±1.66)#	0.98 (±1.29)*§#	<0.0001

*P=0.0005; §P=0.029; #P<0.00001.

isolations had a mean score higher than 2 which is the threshold that we identified as correlated with a worse survival after lung transplantation, in accordance with other previously published data.[26] CMV infection as well acute rejection, had lower scores: this is probably correlated with accompaniment symptoms and biochemical and radiological findings in these two conditions as compared to bacterial and fungal infections.[27-29]

Moreover, it seems to be confirmed that acute rejections and CMV infections (without pneumonia) are rarely related to an increase of short time mortality, even if they are risk factors for chronic lung allograft disfunction (CLAD).[30]

This happens even if acute rejections are almost as frequently diagnosed in follow up transbronchial biopsies' evaluations (in absence of signs, symptoms and radiological opacities) as in acute "as needed" evaluations (34% *vs.* 30%) while CMV infections are more frequent in as needed evaluations (7% *vs.* 2.4%)

The SELeCT Score could represent a reliable prognostic tool to guide clinical decision making; in our cohort patients experiencing more clinically relevant events, independently from the etiology, had a worse long-term prognosis. Moreover, clinical events leading to at least two clinical impairments could significantly influence the outcome.[31] It might indicate who will benefit from a closer surveillance, a change in immunosuppressive therapy, a modification of therapeutic or prophylactic regimen of infections. Nevertheless, even if easy et sensitive, SELeCT Score need to be tested and validated with prospective trials in largest cohorts before to be suggested as tool in daily practice.

Limitations of the study

Limitations of this study include: its retrospective nature; and the fact that the score does not distinguish among infective or inflammatory cause of each event, but this is in line with the aim of its use. We assigned the same weight to each item, independently of its clinical implication.

Conclusions

In conclusion, giving more relevance to clinical presentation than etiopathogenesis of the single event, the proposed SELeCT Score correlates with patient's survival and it could be further developed to be a useful tool in diagnostic and therapeutic decisions too.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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