



# Selection of Candidates for Lung Transplantation: The First Italian Consensus Statement

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## ABSTRACT

Lung transplantation is a well-established treatment for selected patients with advanced chronic respiratory insufficiency. Recognizing those patients with end-stage lung disease who might benefit from lung transplantation is a crucial task. Considering the presence of inadequate evidence-based practice, international and national scientific societies provided consensus opinions regarding the appropriate timing of listing. The Study Group for Thoracic Organs Transplantation (branch of the Italian Society for Organs Transplantation) promoted and realized a Delphi conference among the Italian lung transplantation centers to provide guidance to clinical practice based on international recommendations. The experts from the nine Italian centers completed two rounds of standardized questionnaires (answer rate, 100%): 42 statements received a consensus  $\geq 80\%$ . The selected statements presented in this article are intended to assist Italian clinicians in selecting patients for lung transplantation.

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**L**UNG transplantation (LT) is a valuable and worldwide accepted treatment option for patients with end-stage respiratory diseases who are refractory to conventional therapies [1]. Despite the fact that the first experimental activities on animals date back to 1950 [2], LT has been implemented in humans in Italy only since the early 1990s with approximately 120–130 procedures per year currently performed. Considering that the rate of LTs is roughly 2.2 per million inhabitants, the Italian National Transplantation Centre has encouraged clinicians to develop standard operating procedures to optimize the management of these patients. One of the most important challenges physicians working in a LT center encounter in everyday clinical practice is the identification of the proper candidate for LT.

Over the past decade, international societies attempted to define criteria for recipient selection. In light of the absence of strong evidence, guidelines suggested a variety of criteria and most of the recommendations are based on expert opinions [3]. How the Italian scientific community has accepted these recommendations and translated them into clinical practice is unknown. It might be reasonable to

hypothesize a very heterogeneous approach in following these recommendations across the country. One of the first challenges for the Italian community of surgeons and pulmonologists taking care of LT patients would be to reach a consensus on criteria for recipient selection published by international societies.

The aim of this study was to use a modified Delphi process among physicians working in nine Italian LT centers to identify the level of agreement on criteria for recipient selection recently suggested by international societies.

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## METHODS

This study was endorsed by the Italian Society for Pulmonology (SIP/IRS) and the Italian Society for Thoracic Surgery (SICT). A steering committee was proposed and approved by the Study Group for Thoracic Organs Transplantation during the 39<sup>th</sup> National Congress of the Italian Society for Organ Transplantation (SITO) in 2015. The committee included one pulmonologist (O.T.), two thoracic surgeons (N.M., D.D.), and one cardiothoracic surgeon (D.A.) from different Italian geographic areas.

A review of the currently available literature was conducted on PubMed. The search included articles published in English from 1985 to June 2016. The search included the following terms: “lung transplantation candidates” OR “lung transplant candidates” OR “recipient selection” AND “lung transplantation”. A total of 180 potentially relevant articles were identified and analysed by the steering committee. Full texts were obtained for nine papers that contained clear statements related to a general indication for recipient selection [3–11]. The Committee was asked to draft a list of these statements plus the national criteria for emergency LT. A total of 67 statements were finally selected and split into six separate sections, including general principles for listing, indications and absolute contraindications for LT, relative contraindications for LT, preoperative extracorporeal support, national emergency, and retransplantation. The grading of scientific evidence and recommendations was avoided to allow the expression of free judgment during the conference.

The Committee contacted the nine Italian Lung Transplantation centers to identify both pulmonologists and surgeons with greater clinical experience in LT. A total of 18 clinicians (9 pulmonologists and 9 surgeons) constituted the panel of experts who participated in a modified Delphi process [12]. All of the process was carried out anonymously. Experts were asked to grade each recommendation using a 3-level scale (agreement, disagreement, or indifference). Two rounds of voting were organized from July to October 2016. Consensus was defined as more than 80% agreement or disagreement among the panel of experts. The first round took place in July 2016; therefore, the anonymous ratings as well as comments were tabulated. Statements for which consensus was not reached were modified according to experts' comments and underwent second-round voting in September 2016. Results of both the first- and the second-round voting comprise the body of the present consensus statement.

## RESULTS

All experts participated in both Delphi rounds; a final consensus among the experts was reached on 42 statements. During the first Delphi round, 40 statements received a consensus with  $\geq 80\%$  of agreement, while none of the statements reached 80% disagree consensus. The remaining 27 statements were reformulated according to experts' comments. During the second Delphi round 2 more statements reached consensus with more than 80% of agreement.

## General Principles for Listing

Experts agreed on the indication for LT in patients with progressive respiratory failure despite maximal medical therapy. The 3 general criteria expressed in the consensus document from the International Society for Heart and

Table 1. General Principles for LT

| Statements   | Consensus |
|--|-----------|
| LT is indicated in:  |           |
| Patients with progressive respiratory failure despite maximal medical therapy  | 100%      |
| Patients with <50% of life expectancy at 2 y for their respiratory failure   | 94.4%     |
| Patients who have 80% chance of surviving 5 y after LT provided that the graft will retain good function   | 88.9%     |
| Patients who have 80% chance of surviving at 90 d after LT   | 88.9%     |
| The objective of the LT is to increase survival of the patient with respiratory disease and to increase the survival and/or quality of life of patients with pulmonary emphysema | 88.9%     |
| Patients with pulmonary disease with poor quality of life, intractable symptoms, and frequent hospital admissions  | 83.3%     |

Lung Transplantation (ISHLT) received high consensus. Two additional approved statements were related to patients' quality of life (Table 1).

## Indications and Absolute Contraindications

A summary of statements regarding indications and absolute contraindications for LT is presented in Table 2. Consensus was achieved on the following items: patients should be able to understand the risks for the procedure and fit enough to complete the preoperative examinations; age limits were entrusted to physiological judgment; organ insufficiency should be limited to the lung; coronary artery disease with ventricular impairment is a contraindication except in the case where an adequate revascularization is possible and ventricular function is restorable; left ventricular ejection fraction should be  $>45\%$ ; transplantation is contraindicated in case of highly unstable medical conditions, such as sepsis, myocardial infarction, and acute liver failure, and in the case of uncorrectable bleeding diathesis; LT is contraindicated in case of untreatable extrapulmonary infections or *Mycobacterium tuberculosis* active infection; transplantation is contraindicated in the case of a positive history for malignancy in the last 5 years; transplantation is contraindicated in case of chest wall deformity or progressive neuromuscular disorders; body mass index (BMI)  $\geq 35$  kg/m<sup>2</sup> is a contraindication; LT is contraindicated in the case of documented nonadherence to treatment; transplantation is contraindicated in the case of uncontrolled psychiatric disorders or absence of adequate social support; transplantation is contraindicated when adequate rehabilitation appears improbable; and, finally, LT is contraindicated in the case of substance abuse.

## Relative Contraindications

Statements regarding relative contraindications for LT are presented in Table 3. Consensus was achieved on the following matters: age limits, severe malnutrition and osteoporosis, colonization with highly resistant micro-organisms

**Table 2. Indications and Absolute Contraindications**

| Statements  | Consensus |
|---|-----------|
| <b>Basic conditions:</b>  |           |
| Patients should be able to understand the risks and long-term implications of LT  | 100%      |
| The patient should be able to undergo the clinical investigations for enrollment on the waiting list  | 100%      |
| <b>Age:</b>   |           |
| The patient being considered for single LT must demonstrate physiological age not >65 y   | 88.9%     |
| The patient candidate for double LT must demonstrate physiological age not >60 y  | 88.9%     |
| <b>Comorbidity:</b>   |           |
| LT is contraindicated in the case of severe impairment of other organs (heart, kidney, liver, and so on) except in patients who are candidates for double transplantation   | 100%      |
| LT is contraindicated in the case of coronary heart disease with decreased ventricular function. The treatment of coronary heart disease is allowed provided it is effective, does not report sequelae, and results in acceptable ventricular function. | 100%      |
| LT is contraindicated in the case of left ventricular ejection fraction <45%  | 88.9%     |
| LT is contraindicated in the case of the highly unstable medical conditions, such as sepsis, myocardial infarction, acute liver failure   | 88.9%     |
| LT is contraindicated in the case of uncorrectable bleeding diathesis   | 94.4%     |
| <b>Infection:</b>   |           |
| LT is contraindicated in the cases of untreatable extrapulmonary infection  | 88.9%     |
| LT is contraindicated in case of <i>Mycobacterium tuberculosis</i> active infection   | 94.4%     |
| <b>Oncology:</b>  |           |
| LT is contraindicated in case of a positive history for malignancy in the last 5 y (never in melanoma)  | 88.9%     |
| <b>Thoracic wall deformity:</b>   |           |
| LT is contraindicated in case of chest wall deformity or progressive neuromuscular disorders  | 94.4%     |
| <b>BMI:</b>   |           |
| LT is contraindicated in case of BMI $\geq 35$ kg/m <sup>2</sup>  | 100%      |
| <b>Compliance:</b>  |           |
| LT is contraindicated in the case of documented nonadherence to treatment   | 100%      |
| <b>Psycho-social conditions:</b>  |           |
| LT is contraindicated in case of psychiatric disorders, such as uncontrolled depression or psychosis  | 100%      |
| LT is contraindicated in the case of absence of adequate social support   | 83.3%     |
| <b>Rehabilitation:</b>  |           |
| LT is contraindicated when the general decline and the muscle conditions of the patient raise serious questions about the possibility of rehabilitation after extubation  | 88.9%     |
| <b>Substance abuse:</b>   |           |
| LT is contraindicated in case of substance abuse. The documented attendance at a special rehabilitation program and the confirmation of serological samples of complete abstinence are required.  | 100%      |

**Table 3. Relative Contraindications**

| Statements  | Consensus |
|---|-----------|
| <b>Age:</b>   |           |
| LT may be contraindicated in patients >65 y associated with relative contraindications. Patients >75 y are unlikely to be in the circumstances to overcome transplantation. | 94.4%     |
| <b>BMI:</b>   |           |
| LT may be contraindicated in the case of progressive and severe malnutrition  | 94.4%     |
| <b>Bone metabolism:</b>   |           |
| LT may be contraindicated in patients with severe and symptomatic osteoporosis  | 94.4%     |
| <b>Infection:</b>   |           |
| LT may be contraindicated in patients colonized with highly resistant micro-organisms that would imply a worsening in the postoperative course                              | 94.4%     |
| LT may be contraindicated in patients infected with hepatitis C and B if the infection or cirrhosis are not under control   | 100%      |
| LT may be contraindicated in patients with HIV except in cases of HIV-RNA not titratable, disease under control, and demonstrated compliance to antiviral therapy           | 88.9%     |
| <b>Comorbidity:</b>   |           |
| LT may be contraindicated in patients with atherosclerosis. Patients treatable with percutaneous coronary procedures can be treated and re-evaluated for transplantation.   | 94.4%     |
| LT may be contraindicated in patients suffering from serious diseases that do not have adequate treatment options or are not adequately controlled with medical therapy     | 94.4%     |

that would imply a worsening in the postoperative course, hepatitis C and B that are not under control and infection with human immunodeficiency virus (HIV) except in cases of HIV-RNA not titratable, disease under control, and demonstrated compliance to antiviral therapy. LT may be contraindicated in patients with atherosclerosis but patients treatable with percutaneous coronary procedures can be treated and re-evaluated for transplantation. Finally, LT may be contraindicated in patients suffering from serious diseases that do not have adequate treatment options.

#### Miscellanea

The experts approved six statements to manage extracorporeal support as a bridge to LT (Table 4). Statements were related to the following points: indication to extracorporeal support as bridge to LT is indicated in young patients, without multiple organ dysfunctions and with a rehabilitation potential; extracorporeal support should preferably be maintained with conscious and autonomously breathing patients; and, finally, severe occlusive atherosclerosis and heparin-induced thrombocytopenia should be considered contraindication to extracorporeal support.

Table 4 also shows statements for National Emergency listing. The two approved sentences are related to the

**Table 4. Miscellanea**

| Statements  | Consensus |
|---|-----------|
| Extracorporeal support as bridge to LT:   |           |
| Extracorporeal support is indicated in young patients   | 88.9%     |
| The extracorporeal support is indicated in patients without multiple organ dysfunctions   | 94.4%     |
| The extracorporeal support is indicated in patients with rehabilitation potential   | 100%      |
| Extracorporeal support should preferably be maintained with conscious and autonomously breathing patients   | 88.9%     |
| The extracorporeal support is not indicated in patients with severe occlusive atherosclerosis   | 100%      |
| The extracorporeal support is not indicated in patients with heparin-induced thrombocytopenia   | 83.3%     |
| National Emergency list:  |           |
| The National Emergency list can be activated for patients aged <50 y, with extracorporeal support (excluding DECAP), on the waiting list, and admitted to the intensive care unit of the transplantation center | 100%      |
| The National Emergency list cannot be activated for patient with severe sepsis, multi-organ failure, hemorrhagic shock, or neurological damage  | 100%      |
| Retransplantation:  |           |
| Lung retransplantation should be reserved for young patients  | 94.4%     |

following: the list can be activated for patients aged <50 years, with extracorporeal support (excluding DECAP®); and the patient must be on the waiting list and admitted to the intensive care unit of the transplantation center. The list cannot be activated for patient with severe sepsis, multi-organ failure, hemorrhagic shock, or neurological damage.

In the end, [Table 4](#) reports that consensus was reached on the indication for lung retransplantation; such a procedure should be reserved for young patients.

## DISCUSSION

Considering that LT is mainly limited by the scarcity of suitable donor organs, recipient selection is crucial in a national program for transplantation. This conference meant to share opinions and homogenize general indications and contraindications to LT across Italy. The Delphi conference is a useful tool for evaluation and found consensus among a board of experts with repeated rounds of internet-based anonymous surveys [13]. The present project involved 18 clinicians who represented the nine LT centers in Italy. The response rate was 100% in both survey rounds and this may be related to the strong interest from the participating experts in this project.

There was full agreement among the expert panel on the general principle that LT is indicated in patients with progressive respiratory failure despite maximal medical therapy. The three general criteria prompted by the ISHLT in the 2014 consensus document also received a high consensus from the Italian expert panel, despite some concerns regarding the possibility to predict the percentage of survival as required by those criteria [3].

Age limit is a frequently debated issue among clinicians taking care of LT patients. The panel approved a selection of recipient according to a “physiological” age rather than a rigid age limit. Conversely, the experts approved the ISHLT age limit in the contest of the relative contraindications. A complete consensus was reached on the absolute contraindication to LT if the patient had a severe impairment of other organs, except for patients who are candidates for double transplantation. The experts agreed on the possibility to treat the coronary syndrome to overcome the contraindication related to ischemic heart disease. Concerning oncological matters, the panel disagreed on statements that favored a liberal approach and a limit of a 5-year disease-free interval after radical treatment for an oncological disease was considered essential. The panel expressed high consensus on absolute contraindication to LT in patients with *Mycobacterium tuberculosis* active infection or untreatable extrapulmonary infections; on the contrary, highly resistant micro-organisms, hepatitis virus, and HIV were quoted among relative contraindications.

Extracorporeal support as a bridge to LT found a consistent consensus among the experts, establishing that such rescue treatment must be offered to young patients without extrapulmonary diseases; possibly, the support should be maintained with conscious and autonomously breathing patients. The panel reached total consensus with the rules established for national emergency listing except the limit on the duration of the emergency list (15 days) and the upper and lower limits of BMI. Statements with indications and limits for retransplantation received a very low consensus except for the statement that such a procedure should be reserved for young patients.

In conclusion, the present Delphi conference represents a collective agreement among 18 clinicians from the nine LT centers in Italy. The recommendations outlined in this document represent expert opinion, considering the presence of inadequate evidence-based practice. The selected statements presented in this article are intended to assist Italian clinicians in making the difficult and weighty decision to enlist a patient for LT. Nevertheless, operators should be aware that, by their very nature, these statements cannot be considered final.

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