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Original article

## Risk Factors for Mortality in 272 Patients With Lung Transplant: A Multicenter Analysis of 7 Intensive Care Units

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### ABSTRACT

**Background:** One-year survival in lung transplant is around 85%, but this figure has not increased in recent years, in spite of technical improvements.

**Methods:** Retrospective, multicenter cohort study. Data from 272 eligible adults with lung transplant were recorded at 7 intensive care units (ICU) in Spain in 2013. The objective was to identify variables that might help to guide future clinical interventions in order to reduce the risk of death in the postoperative period.

**Results:** One patient (0.3%) died in the operating room and 27 (10%) within 90 days. Twenty (7.4%) died within 28 days, after a median of 14 ICU days. Grade 3 pulmonary graft dysfunction was documented in 108 patients, of whom 21 died, compared with 6 out of 163 without pulmonary graft dysfunction ( $P < .001$ ). At ICU admission, non-survivors had significantly lower ( $P = .03$ ) median PaO<sub>2</sub>/FiO<sub>2</sub> (200 mmHg vs 280 mmHg), and the difference increased after 24 hours (178 vs 297 mmHg,  $P < .001$ ). Thirteen required extracorporeal membrane oxygenation, and 7 (53.8%) died. A logistic regression model identified pulmonary graft dysfunction (OR: 6.77), donor age > 60yr (OR: 2.91) and SOFA > 8 (OR: 2.53) as independent predictors of 90-day mortality. At ICU admission, higher median procalcitonin (1.6 vs 0.6) and lower median PaO<sub>2</sub>/FiO<sub>2</sub> (200 vs 280 mmHg) were significantly associated with mortality.

**Conclusion:** Graft dysfunction remains a significant problem in lung transplant. Early ICU interventions in patients with severe hypoxemia or high procalcitonin are crucial in order to lower mortality.

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**Abbreviations:** CMV, Cytomegalovirus; ICU, Intensive Care Unit; LT, lung transplant; SLT, single lung transplant; BLT, bilateral lung transplant; PGD, primary graft dysfunction; ISHT, The International Society for Heart and Lung Transplantation; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; PCT, Procalcitonin; CRP, C-reactive protein; BAL, bronchoalveolar lavage.

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## Factores de riesgo de mortalidad en 272 pacientes sometidos a trasplante pulmonar: análisis multicéntrico de 7 unidades de cuidados intensivos

### R E S U M E N

#### Palabras clave:

Donante pulmonar  
EPOC  
Postoperatorio cuidados intensivos  
Disfunción del injerto pulmonar  
Procalcitonina

**Introducción:** La supervivencia anual del trasplante de pulmón está alrededor del 85% y este porcentaje no se ha incrementado recientemente, a pesar de mejoras técnicas.

**Métodos:** Estudio de cohortes, multicéntrico, retrospectivo. Se recogieron datos de 272 adultos con trasplante de pulmón en 7 unidades de cuidados intensivos españolas en 2013. El objetivo fue identificar variables que pudieran ser de utilidad para guiar futuras intervenciones clínicas para disminuir el riesgo de fallecer en el postoperatorio.

**Resultados:** Un paciente (0,3%) falleció en quirófano y 27 (10%) a los 90 días. Veinte (7,4%) fallecieron en 28 días, después de una mediana de 14 días en unidad de cuidados intensivos. La disfunción primaria grado 3 se documentó en 108 pacientes, de los cuales 21 fallecieron, comparado con 6 de 163 sin disfunción primaria grado 3 ( $p < 0,001$ ). Al ingreso en unidad de cuidados intensivos, los no supervivientes mostraban una significativa menor mediana ( $p = 0,03$ ) de PaO<sub>2</sub>/FiO<sub>2</sub> (200 vs. 280 mmHg); esta diferencia se incrementó a las 24 h (178 vs. 297 mmHg,  $p < 0,001$ ). Trece requirieron oxigenación con membrana extracorpórea (53,8%) y 7 fallecieron. Un modelo de regresión logística múltiple identificó la disfunción primaria grado 3 (OR: 6,77), edad donante > 60 años (OR: 2,91) y SOFA > 8 (OR: 2,53) como predictores independientes ( $p < 0,05$ ) de mortalidad a los 90 días. En el ingreso en unidad de cuidados intensivos, una mediana de procalcitonina plasmática superior (1,6 vs. 0,6 ng/mL) e inferior de PaO<sub>2</sub>/FiO<sub>2</sub> (200 vs. 280 mmHg) se asociaron independientemente ( $p < 0,05$ ) con la mortalidad.

**Conclusión:** La disfunción primaria del injerto continúa siendo un problema significativo en el trasplante pulmonar. Las intervenciones precoces dirigidas a mejorar la hipoxemia o la identificación de elevación de procalcitonina representan oportunidades para disminuir la mortalidad.

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### Introduction

Adult patients undergoing primary lung transplantation have unadjusted survival rates of 89% at 3 months, 80% at 1 year, 65% at 3 years, 54% at 5 years and 31% at 10 years.<sup>1</sup> The most frequently reported causes of death within the first 30 days are graft failure and non-cytomegalovirus (CMV) infections. Over the first year post-transplant, non-CMV infections are the major cause of death. After this time, bronchiolitis, graft failure, non-CMV infections and malignancy become important contributors to mortality. The primary objective of this study was to improve our understanding of the interaction between donor variables, recipients, surgical conditions, and immediate postoperative management variables and their effect on ICU survival in patients with LT. The secondary objective was to identify possible biomarkers of mortality in the immediate postoperative period.

### Methods

This is an analysis of a specific database which recorded all lung transplants performed in 2013 in Spain. Only adult patients who survived the intervention and for whom complete donor and recipient data were available were eligible for analysis of prognostic factors. This multicenter study was performed at 7 large general referral university hospitals (>700 beds) with active lung transplant programs. Ethical approval was obtained and the need for informed consent was waived at each center due to the observational nature of the study. All cases were recorded continuously.

### Definitions

The APACHE (Acute Physiology And Chronic Health Evaluation) II score was designed to measure severity of disease in adult patients admitted to intensive care units.<sup>2</sup> It generates a point score ranging from 0 to 71 based on 12 physiological variables (including PaO<sub>2</sub>, respiratory rate, heart rate, hematocrit and creatinine), age, and underlying health. The SOFA (Sequential Organ Failure Assessment) score is a composite score comprising 6 items: the

respiratory, coagulation, hepatic, cardiovascular, renal and neurological systems. It is used to track patient status during ICU stay and to establish the extent of organ function or failure.<sup>3</sup>

Pulmonary graft dysfunction (PGD) severity was graded according to the International Society for Heart and Lung Transplantation (ISHLT) consensus,<sup>4</sup> using the partial pressure of arterial oxygen (PaO<sub>2</sub>) to fraction of inspired oxygen (FiO<sub>2</sub>) ratio. Grade 3 PGD was defined as a PaO<sub>2</sub>/FiO<sub>2</sub> ratio of <200 mmHg.

Pneumonia was defined as new or progressive radiographic opacity,  $\geq 10^4$  colony forming units·mL<sup>-1</sup> in bronchoalveolar lavage (BAL) fluid and at least 2 of the following: fever >38 °C, leukocytosis ( $\geq 10,000$  cells mm<sup>-3</sup>) or leukopenia (<4000 cells mm<sup>-3</sup>) plus purulent secretions.<sup>5</sup> Acute rejection was determined using the ISHLT consensus.<sup>6,7</sup>

### Biomarkers

Blood samples were collected in sterile ethylenediaminetetraacetic acid tubes (Vacutainer; Becton Dickinson, Cockeysville, MD). Tubes were immediately centrifuged at 915,642×g for 10 min at 48 °C, and serum was kept refrigerated at -80 °C until assayed. Plasma procalcitonin serum concentration (PCT) was determined by immunofluorescent assay, using an automated sandwich-type immunoanalysis (Thermo Scientific™ BRAHMS™ KRYPTOR™; Hennigsdorf, Germany) with TRACE (Time-Resolved Amplified Cryptate Emission) technology.

### Statistical Analysis

All comparisons were unpaired. All tests of significance were two-tailed, and *P* values of .05 or less were regarded as indicating statistical significance. Continuous variables were compared using the Student's *t* test or ANOVA for normally distributed variables, and the Mann-Whitney *U* or Kruskal-Wallis test for non-normally distributed variables. The chi-square or Fisher's exact test was used to compare categorical variables. Values were expressed as medians (25th–75th percentile) (continuous variables) or as a frequency

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