



Blood Lactate During Double-Lung Transplantation: A Predictor of Grade-3 Primary Graft Dysfunction

Julien Fessler, Alexandre Vallée, Avit Guirimand, Edouard Sage, Matthieu Glorion, Antoine Roux, Olivier Brugière, François J.F. Parquin, Benjamin Zuber, Charles Cerf, et al.

► To cite this version:

Julien Fessler, Alexandre Vallée, Avit Guirimand, Edouard Sage, Matthieu Glorion, et al.. Blood Lactate During Double-Lung Transplantation: A Predictor of Grade-3 Primary Graft Dysfunction. Journal of Cardiothoracic and Vascular Anesthesia, 2022, 36 (3), pp.794-804. 10.1053/j.jvca.2021.10.043 . hal-03604070

HAL Id: hal-03604070

<https://hal.science/hal-03604070>

Submitted on 22 Jul 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Blood lactate during double-lung transplantation: A predictor of grade-3 primary graft dysfunction

Julien Fessler, MD,¹ Alexandre Vallée, MD, PhD,² Avit Guirimand, MD,³ Edouard Sage, MD, PhD,⁴
Matthieu Glorion, MD PhD,⁴ Antoine Roux, MD PhD,⁵ Olivier Brugiére, MD PhD,⁵
François Parquin, MD,⁴ Benjamin Zuber, MD,⁶ Charles Cerf, MD,⁶ Marc Vasse, MD, PhD,⁷
Tiffany Pascreau, MD, PhD,⁷ Marc Fischler, MD,¹ Carole Ichai, MD, PhD,⁸
Morgan Le Guen, MD, PhD¹

¹ Department of Anesthesiology, Hôpital Foch, 92150 Suresnes, France and Université Versailles-Saint-Quentin-en-Yvelines, 78000 Versailles, France

² Department of Clinical Research and Innovation, Hôpital Foch, 92150 Suresnes, France

³ Department of Anesthesiology, Hôpital Marie-Lannelongue, 92350 Le Plessis Robinson, France

⁴ Department of Thoracic Surgery, Hôpital Foch, 92150 Suresnes, France and Université Versailles-Saint-Quentin-en-Yvelines, 78000 Versailles, France

⁵ Department of Pneumology, Hôpital Foch, 92150 Suresnes, France and Université Versailles-Saint-Quentin-en-Yvelines, 78000 Versailles, France

⁶ Department of Intensive Care Medicine, Hôpital Foch, 92150 Suresnes, France

⁷ Department of Clinical Biology, Hôpital Foch, 92150 Suresnes, France and INSERM UMRS-1176, Université Paris-Sud, 91400 Orsay

⁸ Department of Intensive Care, Hôpital Pasteur, 06000 Nice, France and IRCAN (INSERM U1081, CNRS UMR7284), 06107 Nice, France

Corresponding author: Marc Fischler, MD, Department of Anesthesiology, Hôpital Foch, 40 rue Worth, 92150 Suresnes, France. E-mail: m.fischler@hopital-foch.com. Phone: 0033 1 46 25 24 42 (Business telephone) – 0033 6 09 68 78 54 (Mobile). Fax: 0033 1 46 25 240 88

E-mail addresses of each author:

Julien Fessler: j.fessler@hopital-foch.com

Alexandre Vallée: al.vallee@hopital-foch.com

Avit Guirimand: mail@avit.fr

Edouard Sage: e.sage@hopital-foch.com

Matthieu Glorion: m.glorion@hopital-foch.com:

Antoine Roux: a.roux@hopital-foch.com

Olivier Brugièr: o.brugiere@hopital-foch.com

François Parquin: f.parquin@hopital-foch.com

Benjamin Zuber: b.zuber@hopital-foch.com

Charles Cerf: c.cerf@hopital-foch.com

Marc Vasse: m.vasse@hopital-foch.com

Tiffany Pascreau: t.pascreau@hopital-foch.com

Marc Fischler: m.fischler@hopital-foch.com

Carole Ichai: ichai@unice.fr

Morgan Le Guen: m.leguen@hopital-foch.com

Declarations of interest: none in the relation with the present work

Funding source: This work was supported by the Clinical Research Department of Hôpital Foch which was not involved in the conduct of the study or development of the submission.

Acknowledgements : the authors would like to thank Polly Gobin for her linguistic assistance.

BLOOD LACTATE DURING DOUBLE-LUNG TRANSPLANTATION: A PREDICTOR OF GRADE-3 PRIMARY GRAFT DYSFUNCTION

INTRODUCTION

The main early postoperative risk after lung transplantation is the onset of primary graft dysfunction, a multifactorial injury to the transplanted lung that develops within the first 72 hours after transplantation.¹ Grade-3 primary graft dysfunction (PGD3) appears in 10%-30% of patients undergoing lung transplantation.² Of prime importance is the fact that patients with a PGD3 at day 3 (PGD3-T72) had an increased risk of 30-day and 5-year mortality.³

Blood lactate level (BLL) is a simple routine low-cost biologic parameter, and is routinely used as a point of-care to adapt intraoperative and intensive care therapy and to elaborate prognosis scoring. A cut-off value for BLL is usually considered normal in most studies between 2.0 and 2.5 mmol/l, and critical when superior to 4 mmol/l, which leaves an area of uncertainty.^{4, 5} Hyperlactatemia is also known to be an independent factor of poor prognosis in many surgical situations, such as major liver surgery,^{6, 7} vascular surgery,⁸ and cardiac surgery.⁹⁻¹¹ Conflicting results have been published regarding cardiac¹²⁻¹⁴ and liver transplantations.^{15, 16} In addition to this, lactate kinetics has gained a prominent place as a prognostic predictor in recent clinical studies.¹⁷

Major surgical procedures, cardiac surgery, cardiac, and liver transplantations have some points in common with lung transplantation: high-risk patients, ischemia-reperfusion phenomena, significant intraoperative bleeding, or catecholamine infusion. There are few data on variation of lactate level and significance of hyperlactatemia during lung transplantation except for two cohorts. The first included only cystic fibrosis patients¹⁸ and the second included 86 patients having undergone single and double lung transplantation, half of them underwent a conventional cardiopulmonary bypass.¹⁹ This study found that increased lactate levels were independently associated with longer intubation times, postoperative acute kidney injury, and longer length of stay.

The present retrospective study was done to test the hypothesis that intraoperative BLL, measured at each specific key time during surgery, could be a predictor of PGD3-T72 after double-lung transplantation.

METHODS

Ethics approval

This analysis of the prospectively maintained institutional Anesthesia Lung Transplant database was approved by the Ethics Committee of the French Society of Anesthesia and Critical Care (IRB00010254-2017-047; obtained January 29, 2018). It waived informed consent since patients were informed before their inscription on the waiting list that their medical information could be used for research. Our Lung Transplant group attests that they performed all procedures in strict compliance with the International Society for Heart and Lung Transplantation ethics statement.

Study subjects

All consecutive patients having undergone double-lung transplantation in our tertiary center between January 2012 and December 2019 were reviewed retrospectively from a prospective database. Patients having their second transplant during the study period, a multi-organ transplantation, under preoperative extracorporeal membrane oxygenation or under cardiopulmonary bypass were excluded from the analysis.

Procedures

The surgical technique was a bilateral sequential single-lung transplantation, without systematic use of circulatory assistance, as described first by Pasque et al.²⁰ Our team usually performs it via minimally invasive incisions (i.e. bilateral anterior thoracotomy. **The anesthetic management is fully described in the Supplementary file 1.** Briefly, our strategy lies in early rehabilitation after surgery leading to the extubation in the operating room of nearly a third of the patients.²¹ This is made possible i) by the infusion of short-acting anesthetic drugs, propofol and remifentanil, whose dosage is guided by the bispectral index; ii) an accurate hemodynamic assessment during all phases of the transplantation reducing fluid support and vasopressor drug doses; iii) optimal pain management achieved by thoracic epidural analgesia began before anesthetic induction apart from the usual contraindications; iv) and finally by non-invasive ventilation established immediately after extubation in the operating room. In

addition, intraoperative ECMO may be planned or unplanned in cases of a hemodynamic failure (e.g., right ventricular dysfunction, cardiac failure) or a respiratory failure (e.g., severe hypercarbia or hypoxemia refractory to standard medical treatment). Its modalities have been described previously.²²

Data collection

Table 1 summarizes the variables collected and their sources. In summary, they consist in patient and donor characteristics, intraoperative clinical variables and blood lactate levels, and postoperative data. The data were fully anonymized before extraction and analysis.

Primary and secondary outcomes

The primary outcome was the absolute value of blood lactate level measured at each of the six time-points and their evolution throughout surgery. The secondary outcome was the kinetic of lactate expressed as lactate variability and Δ Lactate. Lactate variability was calculated for each patient dividing the standard deviation of lactates by the mean of the lactates for all the measurements.²³ Δ Lactate was calculated for each patient as the difference between the highest lactate value measured during surgery and its value at the end of the surgical procedure and was expressed as a trend (increase or decrease in Δ Lactate). If maximal blood lactate level was observed at the last measurement, then the case was considered as having an increased Δ Lactate.

Statistical Analysis

Continuous data were described with mean \pm standard deviation and compared with Student test if the distribution was Gaussian. If not, they were described with median [25th percentile-75th percentile] and compared with the Mann-Whitney test. Categorical variables were described as number (percentage) and compared with Chi-Square test or Fisher's Exact test as appropriate.

The evolution of intraoperative BLL was evaluated with a paired T-test with Holm correction to compare lactate at different times. Missing data for BLL were replaced with multiple imputations which require that all variables had a continuous modeling type. The algorithm used least squares imputation. The covariance matrix was constructed using pairwise covariances. The variances (i.e.,

diagonal entries) were computed using non-missing value for each variable. The off-diagonal entries for any variables were computed using all observations that were non-missing for both variables.²⁴

We used an adjusted-repeated-measures mixed-model to test the relation between lactate level changes over time and the occurrence of PGD3-T72.

ROC analysis was performed for lactate parameters regarding their predictive ability to discriminate PGD grade 3. The maximum Youden index ($J = \max_c [Se(c) + Sp(c) - 1]$) was chosen to determine the optimal thresholds (c) of BLL for the discrimination. For each lactate parameter, the ability of the multiple logistic regression models to allow discrimination was quantified by the area under the ROC curve (AUC) which measures the ability of a classifier to distinguish between classes and is used as a summary of the ROC curve. The higher the AUC, the better the performance of the model at distinguishing between the positive and negative classes. Variables associated with p values lower than 0.20 were included in a multiple stepwise regression with forward - backward method. Each lactate parameter was independently adjusted for multivariate model. P value <0.05 was considered as significant.

Survival rate (time to death at one year) was estimated using the Kaplan–Meier estimator for each group of patients (lactates levels at the end of surgery < or \geq to 2.6 mmol/L) and compared by log-rank test.

All analyses were performed using SAS software (version 9.4; SAS Institute, Carry, NC).

RESULTS

Donors, recipients, and intraoperative characteristics

Transplant activity was stable in our center during the study period with an average of 65 procedures per year. From January 2012 to December 2019, 14 patients had a single-lung transplantation and 510 patients a double-lung transplantation. Among these, 61 patients were excluded from this study, some of them for more than one criterion (**Figure 1**). Consequently, the analysis was performed on a cohort of 449 patients. Seventy-two patients (16%) had a PGD3-T72 and constituted the PGD3-T72 group while 377 patients (84%) the No-PGD3-T72 group

Comparison of donors, recipients, and intraoperative characteristics (univariate analysis) is presented in **Table 2**.

Lactate levels during surgery

There were 240 (8.9%) missing data of BLL over 2.694 samples; they were replaced using multiple imputations.

In the entire study population, BLL reached a maximal point at T5 (2.4 [1.7-3.6] mmol/L), significantly higher than all other values ($p<0.001$) but not with T6 ($p=0.082$) (**Figure 2**). Repeated-measures mixed-model of lactate level during surgery presented a significant interaction between time and PGD-T72 group ($p<0.001$) (**Figure 3**).

Blood lactate levels of patients having required ECMO during surgery (199 cases) were compared to those measured in patients having not required ECMO during surgery (**Supplementary file 2**).

Prediction of PGD3-T72 using BLL alone

BLL were greater in No-PGD3-T72 group compared to PGD3-T72 group at all the six times during surgery. Lactate variability was greater in the PGD3-T72 group (0.5 [0.4-0.6] versus 0.4 [0.3-0.5], $p<0.001$). Δ Lactate increased in 34 cases (47.2%) in the PGD3-T72 group whereas it increased in 140 cases in the other group (37.1%); this difference was not statistically significant ($p=0.110$) (**Table 3**).

Prediction of PGD3-T72 was permitted by threshold values of BLL at T1 (0.8 mmol/L), T2 (1.3 mmol/L), T3 (2.0 mmol/L), T4 (1.7 mmol/L), T5 (2.6 mmol/L), and T6 (2.6 mmol/L) and by a threshold value of the variability (0.46). Threshold value of BLL at T6 was the best predictor since its AUC was significantly larger (**Table 4**).

Multivariable analysis for the prediction of PGD3-T72

Multiple multivariable analysis not including lactate parameters but including four independent factors (PaO₂/FiO₂ ratio 10 minutes after second lung implantation, intraoperative fluid support, end-stage lung disease (ESLD), and ECMO requirement during surgery) permitted prediction of PGD3-T72. Pulmonary fibrosis was the pulmonary disease which had the strongest relationship with the occurrence of PGD3-T72 (**Supplementary Table 1**). The AUC of this model was 0.860 (**Table 5**). Including separately threshold values of BLL at each time and threshold value of the variability (0.46) modifies slightly, or not at all, the AUC of this prediction model (**Table 5**).

But, when BLL cut-off at 2.6 mmol/L at the end-surgery status (T6) was included in the model, the AUC increased to 0.867, with a sensitivity = 76.9%, specificity = 85.4%. No significant difference was observed between the different lactate models (T6 vs T4, p=0.893, T6 vs T5, p=0.921) but the highest specificities were observed for the models including BLL threshold at T6 (85.4%), and highest sensitivity of BLL threshold was observed at T5 (83.1%).

ROC curves of the model including the four clinical independent factors and of the model adding the BLL at T6 were not statistically different (p=0.837; **Figure 4**). The red curve provides AUC under the ROC curve for multivariate analysis including four independent factors (PaO₂/FiO₂ ratio 10 minutes after second lung implantation, intraoperative fluid support, end-stage lung disease, and ECMO requirement during surgery) (AUC=0.860) showing a low positive predictive value (41.4%) but a high negative predictive value (95.4%). The blue curve provides AUC under the ROC curve for multivariate analysis including five independent factors (PaO₂/FiO₂ ratio 10 minutes after second lung implantation, intraoperative fluid support, end-stage lung disease, ECMO requirement during surgery and blood lactate level at the end-surgery status) (AUC=0.867) showing a low positive predictive value (51.4%) but a high negative predictive value (95.8%).

Among the predictive parameters, ECMO had the best accuracy ($AUC=0.794$, $p=0.041$) while BLL at T6 ($AUC=0.724$) had similar accuracy to ESLD ($AUC=0.698$, $p=0.795$) and P/F ratio ($AUC=0.682$, $p=0.628$), and better accuracy than fluid support ($AUC=0.588$, $p=0.027$) (**Supplementary Table 2**). The repeated-measures mixed-model of lactate during surgery remained significant after adjustment for covariates (F ratio= 4.22, $p<0.001$ for interaction).

Relation between one-year survival and BLL

Overall survival at one year was 10.5 % (95% confidence interval 8 – 13). Patients with a lactate level ≥ 2.6 mmol/L at T6 had significantly lower survival compared with patients with a lactate level < 2.6 mmol/L (Log rank, $p=0.005$) (**Figure 5**).

Sensitivity analysis

Sensitivity analysis was performed including patients with missing data, using only 2454 data of lactates out of 2694 data (8.9%).

The same results were observed for lactate information, in univariate analyses (T1, $p=0.001$, T2 $p=0.003$, T3 $p<0.001$, T4 $p<0.001$, T5 $p<0.001$, T6 $p<0.001$, variability of lactate $p=0.001$ and Δ Lactate $p=0.209$).

Repeated-measures mixed-model of lactate level during surgery presented a significant interaction between time and PGD-T72 group ($p<0.001$), which remained significant after adjustment on covariates ($p=0.001$).

Including threshold values of BLL at T1 (0.8 mmol/L), T2 (1.3 mmol/L), T3 (2.0 mmol/L), T4 (1.7 mmol/L), T5 (2.6 mmol/L), and T6 (2.56 mmol/L) and threshold value of the variability (0.47) modified slightly or not at all the AUC of this prediction model ($AUC=0.860$). OR of the model including T1=1.66 [0.88-3.16], $p=0.120$, $AUC=0.862$; T2=2.00 [0.62-2.31], $p=0.588$, $AUC=0.864$; T3=1.75 [0.88-3.47], $p=0.109$, $AUC=0.859$; T4=2.17 [0.99-4.78], $p=0.052$, $AUC=0.867$; T5=2.18 [1.08-4.41], $p=0.029$, $AUC=0.864$, T6=2.68 [1.32-5.41], $p=0.006$, $AUC=0.865$, and variability of lactate=1.68 [0.85-3.32], $p=0.136$, $AUC=0.863$.

DISCUSSION

Our study showed that blood lactate level increased progressively throughout surgery, to reach a maximum after the second graft implantation. The repeated mixed-model found a dynamic increase in the PGD3-T72 group to achieve a threshold value above 2.6 mmol/l at end-surgery status with the highest AUC predicting grade 3 primary graft dysfunction at 72 hours with a high negative predictive value (92.7%). However, it slightly improved a multivariate clinical model to predict PGD3-T72, but its weight in the model was overshadowed by other major factors such as ECMO during surgery. Its weight was similar to ESLD, and PaO₂/FiO₂ at second graft implantation, but better than intraoperative fluid support.

Andersen recently published a detailed review of studies of hyperlactatemia in cardiac surgical patients and stated that elevated BLL has relatively high specificity but only moderate sensitivity in predicting outcomes.¹⁰ Conflicting results have been published regarding cardiac transplantation: threefold increased mortality in the group with BLL above 4 mmol/l at ICU admission;¹² a variable of little interest because hyperlactatemia is mostly transient and benign.^{13, 14} Similarly, conflicting results have been published regarding liver transplantation: moderately predictive of BLL at ICU admission for 30-day and in-hospital mortality;¹⁵ strong prediction of early graft outcomes when arterial BLL at the end of liver transplantation is ≥ 5 mmol/l.¹⁶ Few publications have reported lactate evolution and prognostic significance during lung transplantation. Felten et al. reported that a median lactate level above 4.0 mmol/l [interquartile range 7.3] at the end of the procedure was related to PGD3 in cystic fibrosis patients receiving primary bilateral lung transplantation.¹⁸ In a recent study, Worrell et al. observed after adjustment in a cohort of 86 patients, that cardiopulmonary bypass duration, global ischemic time, and catecholamine use were associated with higher static lactate level during surgery, whereas inhaled nitric oxide and higher pulmonary artery pressures were associated with lower levels. Higher lactate level peaks in intensive care units were associated with longer length of stay after lung transplantation.¹⁹ Similarly, Xu et al. observed that postoperative peak lactate level measured in the

ICU within 72 h after lung transplantation was an independent predictor for 30-day and late mortality. However, their findings observed very high mean peak lactate levels around 5 mmol/L and pronounced early mortality (23% at 30 day).²⁵ The present study is the first to look specifically at lactate evolution during double-lung transplantation by having carried out dosages throughout the operation at precise moments corresponding to the main surgical steps. Specifically, this study looked for an association between intraoperative measurements of lactate levels and the diagnosis of PGD3 made 3 days later and regardless of postoperative events and treatments.

Lactate level and lactate clearance are commonly used as a hemodynamic biomarker and to target cellular perfusion, influenced by macro-circulation, microcirculation, and mitochondrial function.²⁶ BLL is especially interesting during lung transplantation because it reflects circulation impairment caused by two successive sequential single-LT procedures. It reveals the major hemodynamic repercussion of two successive pulmonary artery clampings, a variable depending on preoperative cardiac status and heart manipulation. These variations are particularly significant during left atrial cuff suture. BLL also bespeaks the ischemia-reperfusion after implantation of two successive ischemic organs. In addition, other major intraoperative events, such as bleeding, or cardiopulmonary assistance, may unbalance organ perfusion and oxygenation, leading to elevation of BLL. ECMO has increasingly replaced the traditional cardiopulmonary bypass roughly since the beginning of the last decade,²⁷ as it requires less heparin and it is less inflammatory and aggressive.²⁸⁻³⁰ Half of our cases were performed under ECMO, which may impact per se on lactate metabolism. It is difficult to distinguish which part of lactate modification may be due to the patient's severity and which part may be imputed to the ECMO itself. Some teams use repeated lactate measurements (i.e., every 30 minutes) to assess systemic perfusion when ECMO is used.³¹ Thus, it can be an overlap between transplant-specific events and ECMO effect on lactate levels per se. The increase in blood lactate levels in patients having required an intraoperative ECMO is difficult to analyze. Indeed, this increase may be due to the ECMO itself, the lactate level increasing in case of systematic perfusion failure, or to the cause of the ECMO initiation. Since we decided to use ECMO mostly in case of a major respiratory or hemodynamic failure,²² an increase in lactate levels can be attributed to this

complication or to ECMO. Furthermore, the analysis of the data is complicated by the fact that the initiation of ECMO is performed at different step of the surgery.

The originality of our study was to perform a dynamic view of lactate variability by a repeated-mixed-model showing a progressive increase of lactate across the time of surgery as a predictive marker of PGD3-T72. Our results suggest that BLL is an early negative biomarker for PGD3 since it significantly increased after lung implantations and since it predicted the absence of PGD3 if its level was below a threshold of 2.6 mmol/l at end-surgery status. BLL can be used routinely in clinical practice, as it is simpler and less expensive than other proposed biomarkers such as combination of biomarkers of impaired fibrinolysis (PAI-1, Protein C) with lung epithelial injury (RAGE and SP-D) and cell adhesion (ICAM-1),³² cytokine/chemokine levels (IL-6, IL-8, and IL-10, as well as monocyte chemoattractant protein (MCP)-1, matrix metalloprotease (MMP)-9),³³ and postreperfusion increase in sRAGE.³⁴

We approached lactate clearance using Δ Lactate and lactate variability as proposed by Vincent et al but our findings were less predictive than static lactate measurements or the repeated-measures mixed-model on outcomes.¹⁷ This can be explained at least in part by the chronological analysis during double-lung transplantation, where timing is not measured in minutes but by events (pulmonary artery clampings, first and second graft implantation, one or two lung ventilation...). Time duration between two set points was highly variable among patients but measurement set points were standard in our protocol.

We have reported a link between a BLL above 2.6 mmol/l at the end of surgery and the occurrence of PGD3. The latter has a poor prognosis as it is a major contributor to early morbidity and mortality after lung transplantation.³ Among the mechanisms evoked to explain this relation, a link between severe postoperative PGD and the development of bronchiolitis obliterans syndrome has been shown.³⁵ Thus, it is understandable that one-year mortality is higher in patients with BLL at or above the cut-off of 2.6 mmol/L since these patients have an increased risk of PGD3-T72. But an increase in BLL at the end of the procedure is also a sign of cellular perfusion failure whatever its origin.²⁶ This

probably has consequences for many organs and may help explain the increased mortality when BLL is high at the end of surgery.

Strengths and weaknesses of the study

The main strength of this study is the large size of the cohort with less than 9% missing lactate samples, which does not change the results as shown in the sensitivity analysis.

Our study presents several limitations.

The first limitation concerns the studied population. Patients who underwent preoperative ECMO or intraoperative cardiopulmonary bypass were excluded from the study since they represent few patients (31 for preoperative ECMO, and three for intraoperative cardiopulmonary bypass). In particular, patients who required preoperative ECMO have an initial severity greater than other transplant recipients. On the other hand, we treated a high proportion of cystic fibrosis patients and no patients with primary pulmonary hypertension, a consequence of our center's recruitment for lung transplantation.

Otherwise, epinephrine infusion could have overestimate BLL because of lactate release from skeletal muscle and gluconeogenesis. In our cohort, 51 patients required epinephrine during surgery; among them 36 patients were transferred to the ICU under epinephrine infusion.

Our patients' characteristics and our intraoperative management strategy prevent any external validation of our results but, more generally, the problem of external validity arises for most studies of lung transplant databases. This can be explained by the significant differences in donor selection, recipient recruitment, graft preservation, intraoperative conduct with variable use of ECMO, etc. Our study should lead other centers to evaluate the prognostic value of intraoperative lactate levels.

Conclusion

Blood lactate level increased during double-lung transplantation and reached a maximum after the second lung implantation. This increase was higher in the group of patients who will present grade 3

primary graft dysfunction at day 3. A value below the threshold of 2.6 mmol/L at the end of surgery had a high negative predictive value for the occurrence of a grade-3 primary graft dysfunction prognostic at post-operative day 3. This value should be part of other good prognostic factors encouraging intensivists to begin an early rehabilitation program adapted to lung transplantation.

REFERENCES

1. Snell GI, Yusen RD, Weill D, et al: Report of the ISHLT Working Group on Primary Lung Graft Dysfunction, part I: Definition and grading-A 2016 Consensus Group statement of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 36:1097-1103, 2017
2. Diamond JM, Arcasoy S, Kennedy CC, et al: Report of the International Society for Heart and Lung Transplantation Working Group on Primary Lung Graft Dysfunction, part II: Epidemiology, risk factors, and outcomes-A 2016 Consensus Group statement of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 36:1104-1113, 2017
3. Cantu E, Diamond JM, Suzuki Y, et al: Quantitative evidence for revising the definition of primary graft dysfunction after lung transplant. *Am J Respir Crit Care Med* 197:235-243, 2018
4. Kruse O, Grunnet N, Barfod C: Blood lactate as a predictor for in-hospital mortality in patients admitted acutely to hospital: a systematic review. *Scand J Trauma Resusc Emerg Med* 19:74, 2011
5. Rhodes A, Evans LE, Alhazzani W, et al: Surviving sepsis campaign: International guidelines for management of sepsis and septic shock: 2016. *Crit Care Med* 45:486-552, 2017
6. Vibert E, Boleslawski E, Cosse C, et al: Arterial lactate concentration at the end of an elective hepatectomy is an early predictor of the postoperative course and a potential surrogate of intraoperative events. *Ann Surg* 262:787-792, 2015
7. Lemke M, Karanicolas PJ, Habashi R, et al: Elevated lactate is independently associated with adverse outcomes following hepatectomy. *World J Surg* 41:3180-3188, 2017
8. Singhal R, Coghill JE, Guy A, et al: Serum lactate and base deficit as predictors of mortality after ruptured abdominal aortic aneurysm repair. *Eur J Vasc Endovasc Surg* 30:263-266, 2005
9. Renew JR, Barbara DW, Hyder JA, et al: Frequency and outcomes of severe hyperlactatemia after elective cardiac surgery. *J Thorac Cardiovasc Surg* 151:825-830, 2016

10. Andersen LW: Lactate elevation during and after major cardiac surgery in adults: a review of etiology, prognostic value, and management. *Anesth Analg* 125:743-752, 2017
11. Haanschoten MC, Kreeftenberg HG, Arthur Bouwman R, et al: Use of postoperative peak arterial lactate level to predict outcome after cardiac surgery. *J Cardiothorac Vasc Anesth* 31:45-53, 2017
12. Noval-Padillo JA, Serra-Gomez C, Gomez-Sosa L, et al: Changes of lactate levels during cardiopulmonary bypass in patients undergoing cardiac transplantation: possible early marker of morbidity and mortality. *Transplant Proc* 43:2249-2250, 2011
13. Nixon JL, Kfoury AG, McCubrey R, et al: Lactic acidosis after cardiac transplantation: foe or common innocent bystander? *Transplantation* 99:1216-1219, 2015
14. Hoshino Y, Kinoshita O, Ono M: The incidence, risk factors, and outcomes of hyperlactatemia after heart transplantation. *Int Heart J* 59:81-86, 2018
15. Kim DG, Lee JY, Jung YB, et al: Clinical significance of lactate clearance for the development of early allograft dysfunction and short-term prognosis in deceased donor liver transplantation. *Clin Transplant* 31:2017
16. Golse N, Guglielmo N, El Metni A, et al: Arterial lactate concentration at the end of liver transplantation is an early predictor of primary graft dysfunction. *Ann Surg* 270:131-138, 2019
17. Vincent JL, Quintairos ESA, Couto L, Jr., et al: The value of blood lactate kinetics in critically ill patients: a systematic review. *Crit Care* 20:257, 2016
18. Felten ML, Moyer JD, Dreyfus JF, et al: Immediate postoperative extubation in bilateral lung transplantation: predictive factors and outcomes. *Br J Anaesth* 116:847-854, 2016
19. Worrell SG, Haug K, Dubovoy A, et al: Is lactic acidosis after lung transplantation associated with worse outcomes? *Ann Thorac Surg* 110:434-440, 2020
20. Pasque MK, Cooper JD, Kaiser LR, et al: Improved technique for bilateral lung transplantation: rationale and initial clinical experience. *Ann Thorac Surg* 49:785-791, 1990
21. Fessler J, Fischler M, Sage E, et al: Operating room extubation: A predictive factor for 1-year survival after double-lung transplantation. *J Heart Lung Transplant* 40:334-342, 2021

22. Fessler J, Sage E, Roux A, et al: Is extracorporeal membrane oxygenation withdrawal a safe option after double-lung transplantation? *Ann Thorac Surg* 110:1167-1174, 2020
23. Nichol A, Bailey M, Egi M, et al: Dynamic lactate indices as predictors of outcome in critically ill patients. *Crit Care* 15:R242, 2011
24. Schäfer J, Strimmer K: A shrinkage approach to large-scale covariance matrix estimation and implications for functional genomics. *Stat Appl Genet Mol Biol* 4:Article32, 2005
25. Xu J, Qin Z, Wang Y, et al: The prognostic value of peak arterial lactate levels within 72 h of lung transplantation in identifying patient outcome. *J Thorac Dis* 12:7365-7373, 2020
26. Fuller BM, Dellinger RP: Lactate as a hemodynamic marker in the critically ill. *Curr Opin Crit Care* 18:267-272, 2012
27. Aigner C, Wisser W, Taghavi S, et al: Institutional experience with extracorporeal membrane oxygenation in lung transplantation. *Eur J Cardiothorac Surg* 31:468-473, 2007
28. Bermudez CA, Shiose A, Esper SA, et al: Outcomes of intraoperative venoarterial extracorporeal membrane oxygenation versus cardiopulmonary bypass during lung transplantation. *Ann Thorac Surg* 98:1936-1942, 2014
29. Biscotti M, Yang J, Sonett J, et al: Comparison of extracorporeal membrane oxygenation versus cardiopulmonary bypass for lung transplantation. *J Thorac Cardiovasc Surg* 148:2410-2415, 2014
30. Machuca TN, Collaud S, Mercier O, et al: Outcomes of intraoperative extracorporeal membrane oxygenation versus cardiopulmonary bypass for lung transplantation. *J Thorac Cardiovasc Surg* 149:1152-1157, 2015
31. Martin AK, Harrison BA, Fritz AV, et al: Intraoperative management of a hybrid extracorporeal membrane oxygenation circuit for lung transplantation. *J Card Surg* 35:3560-3563, 2020
32. Shah RJ, Bellamy SL, Localio AR, et al: A panel of lung injury biomarkers enhances the definition of primary graft dysfunction (PGD) after lung transplantation. *J Heart Lung Transplant* 31:942-949, 2012

33. Allen JG, Lee MT, Weiss ES, et al: Preoperative recipient cytokine levels are associated with early lung allograft dysfunction. Ann Thorac Surg 93:1843-1849, 2012
34. Pottecher J, Roche AC, Degot T, et al: Increased extravascular lung water and plasma biomarkers of acute lung injury precede oxygenation impairment in primary graft dysfunction after lung transplantation. Transplantation 101:112-121, 2017
35. Daud SA, Yusen RD, Meyers BF, et al. Impact of immediate primary lung allograft dysfunction on bronchiolitis obliterans syndrome. Am J Respir Crit Care Med 175:507–513, 2007

TABLES

Table 1. Variables collected

Table 2. Donors and preoperative recipients' characteristics and intraoperative data

Table 3. Values of blood lactate level and occurrence of primary graft dysfunction grade 3 at day 3

Table 4. Threshold values of blood lactate level and of variability of lactate level as predictors of primary graft dysfunction grade 3 at day 3

Table 5. Clinical models for pulmonary graft dysfunction grade 3 at day 3 (multivariable analysis)

FIGURE LEGENDS

Figure 1. Flow chart

* means that a single patient can have several criteria for exclusion from analysis.

Figure 2. Blood lactate levels throughout the procedure

- T1: before induction of anesthesia,
- T2: at first pneumonectomy
- T3: after first graft implantation,
- T4: second pneumonectomy,
- T5: after second graft implantation,
- T6: at end-surgery status

Boxplot and whisker presentation (2A and 2B) shows from bottom to top the 10th percentiles, the 25th percentile, the 50th percentile (median value), the 75th percentile, and the 90th percentile.

Figure 3. Blood lactate level throughout the procedure for No-PGD3-T72 group (white) and PGD3-T72 group (grey)

- T1: before induction of anesthesia,
- T2: at first pneumonectomy
- T3: after first graft implantation,
- T4: second pneumonectomy,
- T5: after second graft implantation,
- T6: at end-surgery status

Boxplot and whisker presentation (2A and 2B) shows from bottom to top the 10th percentiles, the 25th percentile, the 50th percentile (median value), the 75th percentile, and the 90th percentile.

Figure 4. Receiver operating characteristic curves (ROC curves) for two models of prediction of PGD3-T72

Figure 5. One-year survival. Kaplan-Meier survival curves with 95% confidence intervals.

Blue: Patients with a lactate level < 2.6 mmol/L at the end of surgery

Red: Patients with a lactate level ≥ 2.6 mmol/L at the end of surgery

The P value is presented for the overall comparison (log-rank test).

Double-lung transplantation 2012 – 2019 510 patients

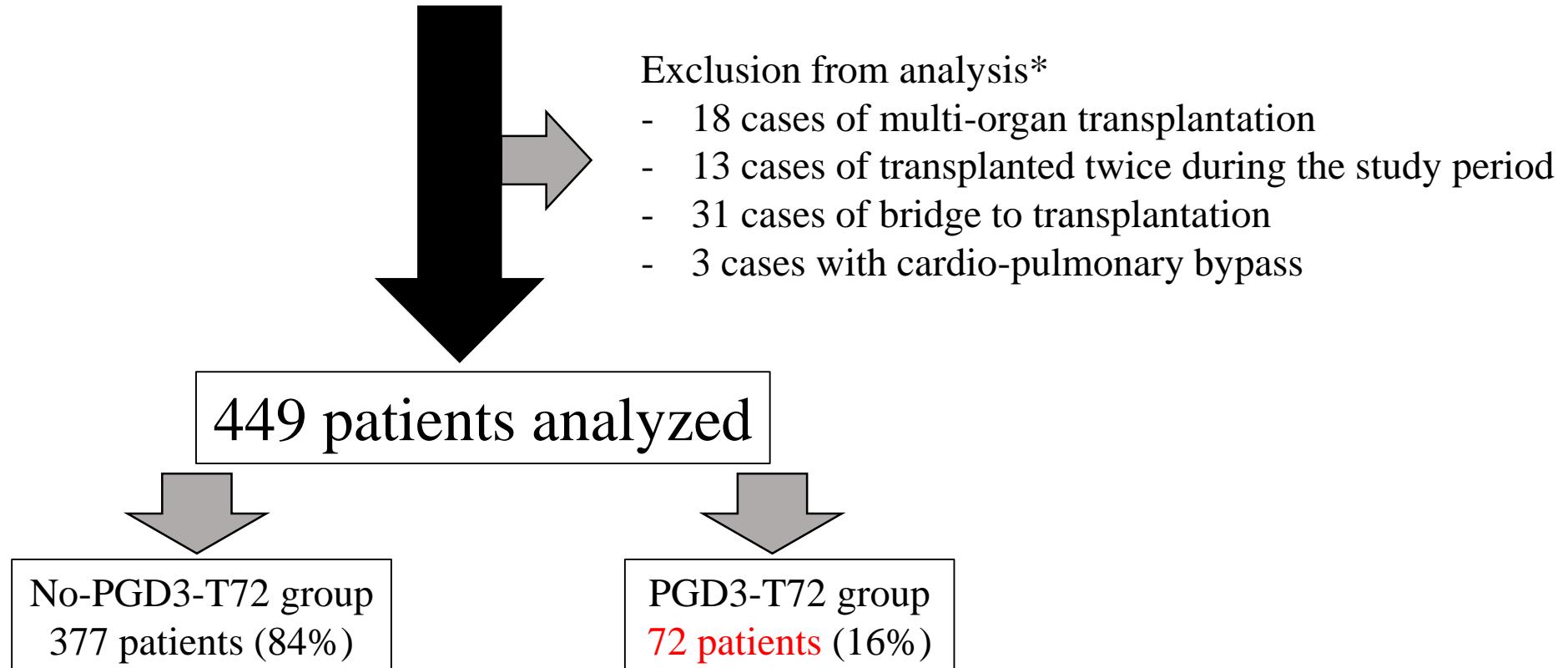


Figure 1

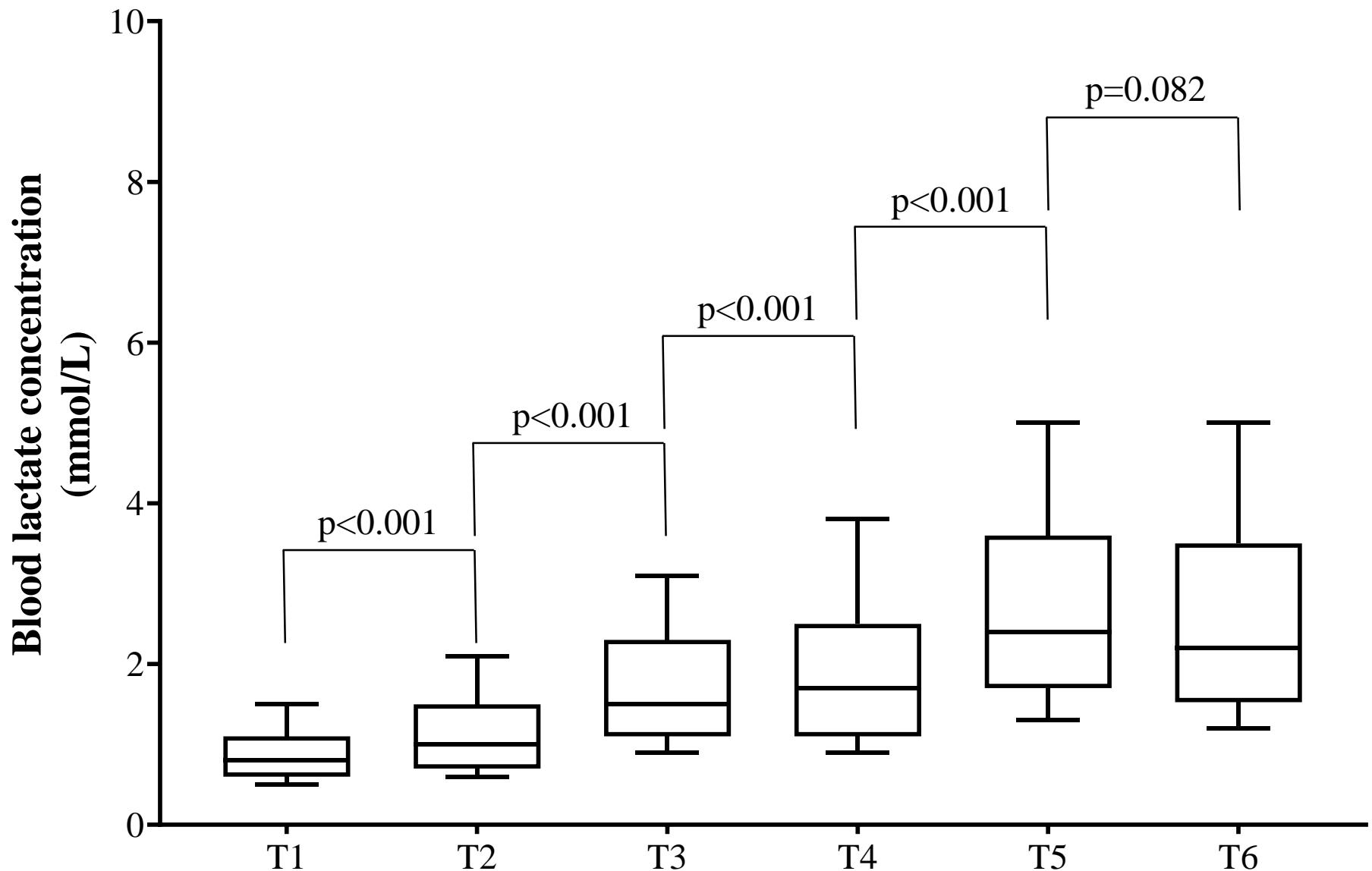


Figure 2

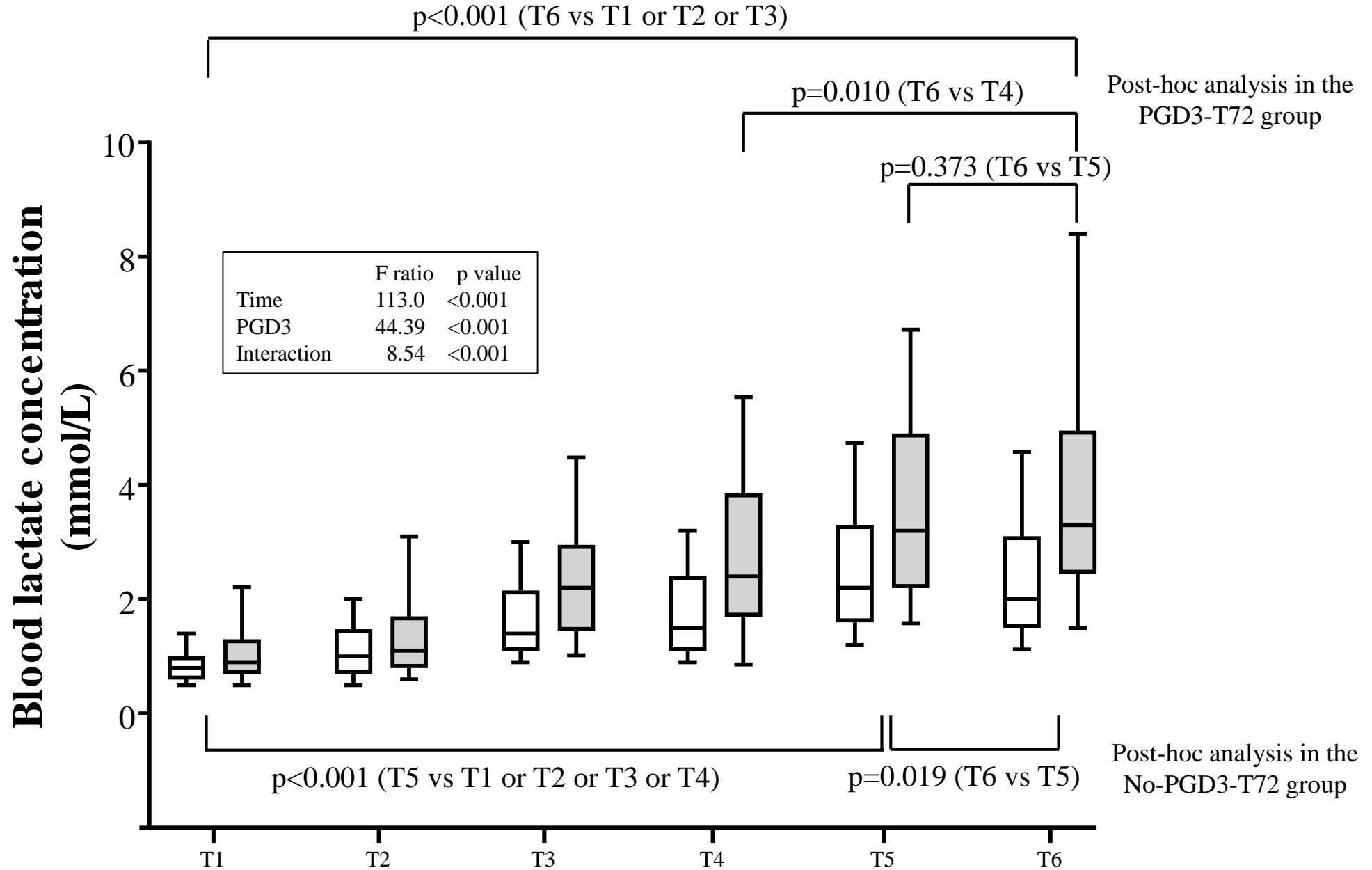


Figure 3

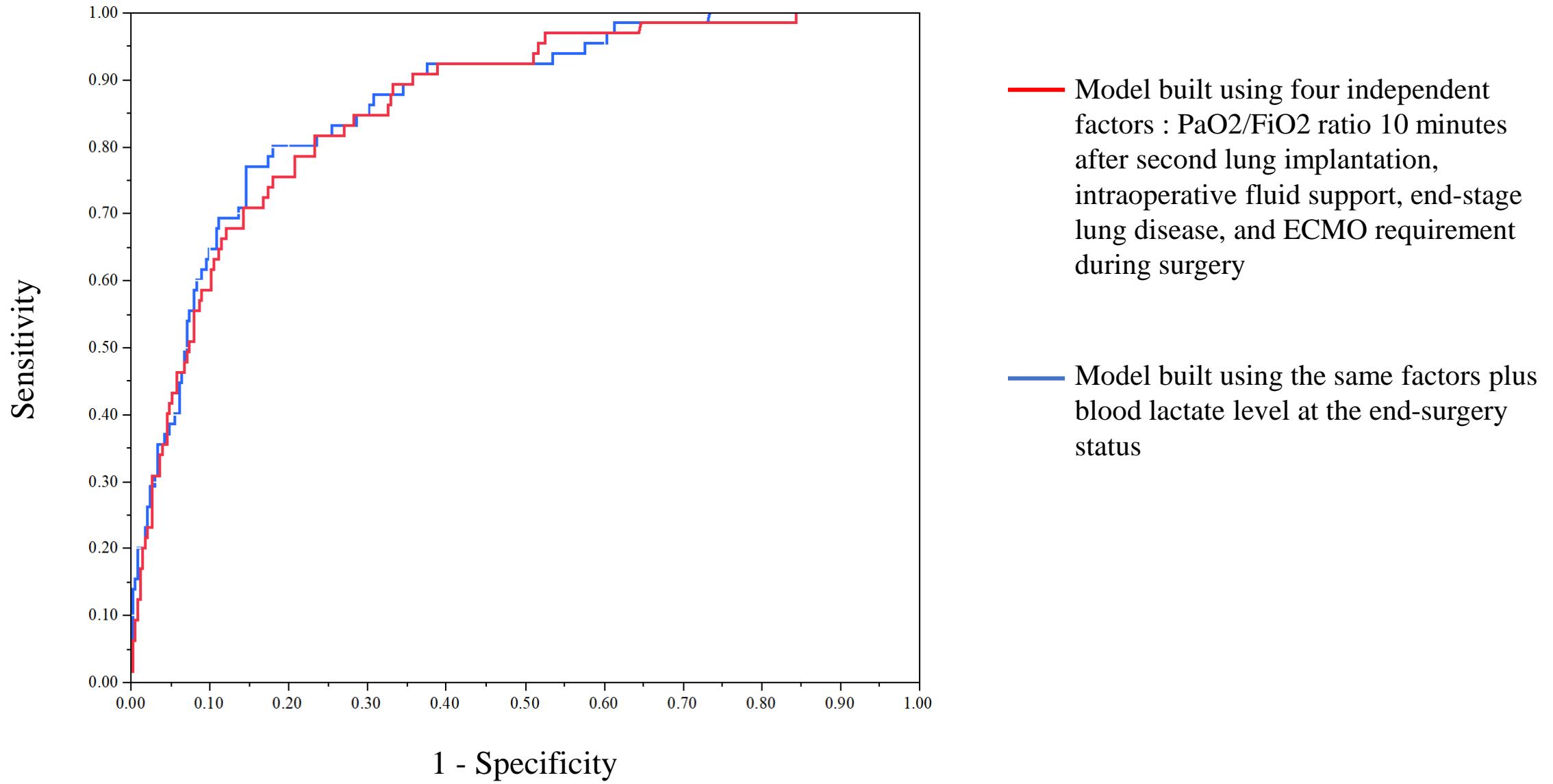


Figure 4

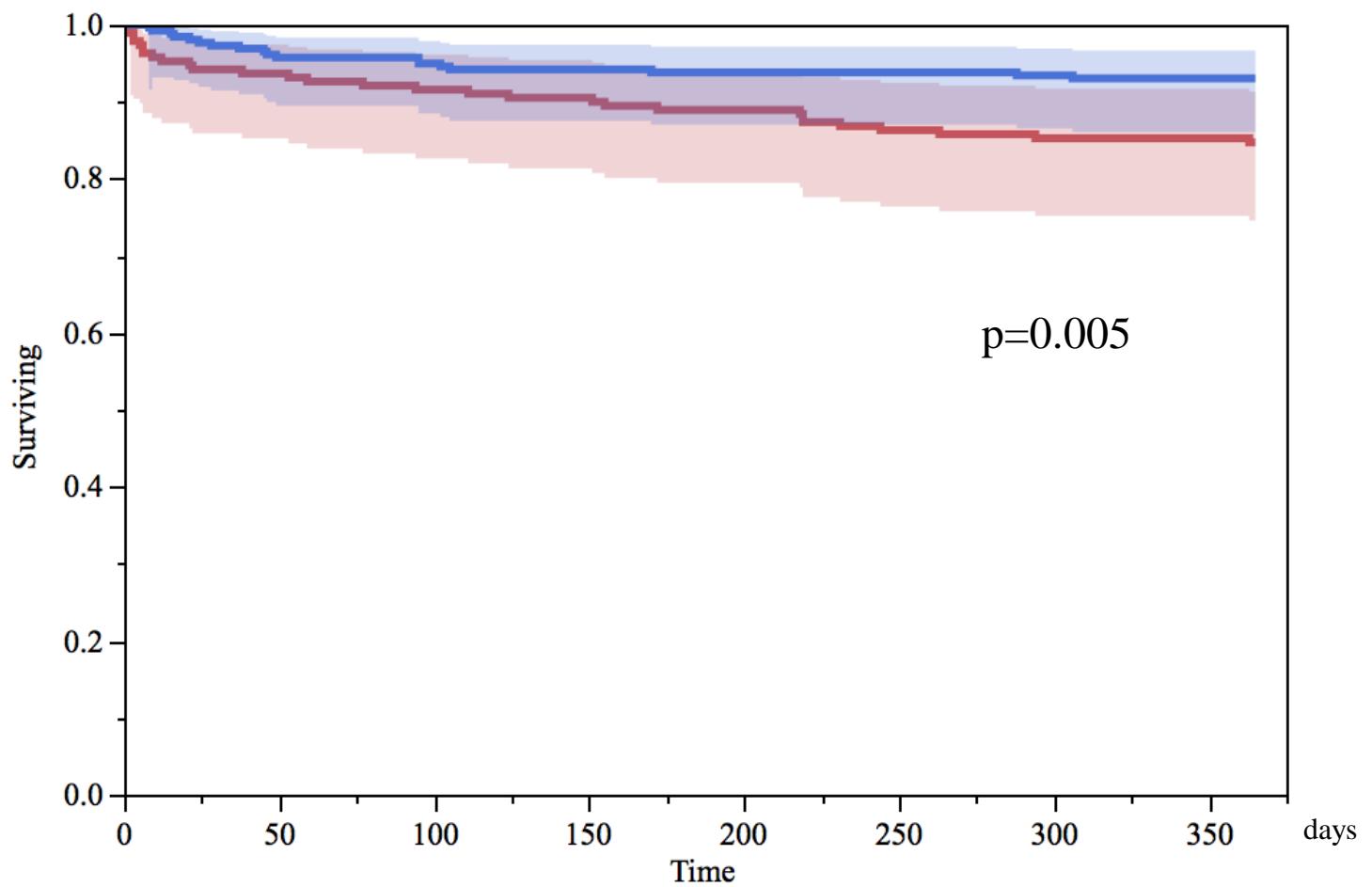


Figure 5

Table 1. Variables collected and their sources

Variable	Source
Patient and donor characteristics	Prospectively maintained database*
Intraoperative clinical variables	Prospectively maintained database*
surgery and ischemia durations	
intraoperative ventilator and hemodynamic parameters	
transfusion requirements	
ECMO	
Intraoperative lactate measurements (time points)	GEM4000 blood gas analyzer located in the operating room**
T1: after induction of anesthesia	
T2: at first pneumonectomy	
T3: 10 minutes after first graft implantation	
T4: at the second pneumonectomy	
T5: 10 minutes after second graft implantation	
T6: end-surgery status before transfer to the intensive care unit	
PGD on day 3***	Electronic medical records

* Encrypted database created using FileMaker Pro (FileMaker Company Santa Clara, California 95054) and accessible only on the local intranet with a personal password

** Internal control qualities (ProBioQual) of the GEM4000 Analyzer (Werfen, Le Pré Saint Gervais, France) were analyzed every 3 months, in accordance with the manufacturer's recommendations.

Reference values are 0.5 to 1.6 mmol/l

*** Classification of the 2016 Consensus Group statement of the International Society for Heart and Lung Transplantation¹

Table 2. Donors and preoperative recipients' characteristics and intraoperative data

	No-PGD3-T72 group (n=377)	PGD3-T72 group (n=72)	P value
Donor characteristics			
Age, year	49 [38-61]	50 [40-59]	0.639
Male gender	214 (56.8)	45 (62.5)	0.367
Body mass index	25 [22-28]	23 [21-26]	0.013
Tobacco use, pack-year	0 [0-15]	1 [0-15]	0.402
PaO ₂ /FiO ₂ ratio.	372.6 ± 87.3	356.9 ± 90.0	0.164
Oto score	8 [6-10]	9 [7-11]	0.232
Recipient preoperative characteristics			
Age, year	40 [28-55]	43 [28-55]	0.932
Male gender	190 (50.4)	37 (51.4)	0.877
Body mass index	20 [18-22]	21 [18-26]	<0.001
Diabetes	115 (30.5)	18 (25.0)	0.349
Preoperative ICU hospitalization	27 (7.2)	6 (8.3)	0.727
Vasopressor use prior to surgery	3 (0.8)	0 (0)	-
On mechanical ventilation	4 (1.0)	2 (2.8)	0.245
High emergency LT	17 (4.5)	3 (4.2)	0.897
Time on waiting list, days	19 [8-46]	18 [6-54]	0.981
Lung Allocation score	36.5 [34.1-40.2]	38.2 [35.9-44.7]	0.021
Re-transplantation	7 (1.9)	2 (2.8)	0.609
Thoracic surgery history	77 (20.4)	17 (23.6)	0.542
Pulmonary artery hypertension*	146 (38.7)	32 (44.4)	0.363
Patent foramen ovale	36 (9.6)	7 (9.7)	0.507
End-stage lung disease			<0.001
Cystic Fibrosis	203 (53.9)	28 (38.9)	
COPD/Emphysema	107 (28.4)	9 (12.5)	
Fibrosis	38 (10.1)	27 (37.5)	
Other pathology	29 (7.7)	8 (11.1)	

Table 2. Continued

	No-PGD3-T72 group (n=377)	PGD3-T72 group (n=72)	P value
Surgical procedure			
Preoperative plasmapheresis	149 (39.5)	31 (43.1)	0.575
Ex-vivo procedure	87 (23.1)	13 (18.1)	0.348
Pulmonary reduction	72 (19.1)	22 (30.6)	0.139
First lung ischemic time (min)	286 [236-383]	284 [230-398]	0.832
Second lung ischemic time (min)	412 [349-516]	441 [360-550]	0.373
ECMO during surgery	134 (35.5)	65 (90.3)	<0.001
PaO ₂ /FiO ₂ ratio at second graft implantation	233 [138-347]	135 [84-257]	0.002
Fluid and Transfusion			
Estimated blood loss (L)	1.0 [0.6-1.5]	1.3 [0.8-2.2]	0.003
Fluid support (L)	2.8 [2.0-3.5]	3.0 [2.5-4.0]	0.005
PRBC (units)	4 [3-6]	6 [4-9]	<0.001
FFP (units)	4 [3-6]	6 [4-8]	<0.001
Platelets (units)	0 [0-0]	0 [0-1]	<0.001
End-surgery status			
Vasopressors			
Epinephrine	21 (5.6)	15 (20.8)	<0.001
Norepinephrine (μg/kg/min)	0 [0-0]	0 [0-1.0]	0.002
PaO ₂ /FiO ₂ ratio at end-surgery status	257 [172-361]	156 [90-229]	<0.001
iNO dependence	47 (12.5)	12 (16.7)	0.334
ECMO continued after surgery	41 (10.9)	53 (73.6)	<0.001
Extubation in the OR	163 (43.2)	3 (4.2)	<0.001

Values are expressed as median (25th percentile-75th percentile), mean ± standard deviation, or n (%) as appropriate.

PGD-T72: Primary graft dysfunction grade 3 at day 3; PaO₂/FiO₂ ratio: ratio of arterial oxygen partial pressure to fractional inspired oxygen; ICU: Intensive care unit; LT: lung transplantation; COPD: Chronic obstructive pulmonary disease; ECMO: Extracorporeal Membrane Oxygenation; PRBC: packed red blood cells; FFP: fresh frozen plasma

Other pathology: this category includes patients having graft versus host disease, bronchial bronchiectasis, and bronchiolitis obliterans syndrome.

* means that mean pulmonary artery pressure was > 25 mmHg at rest at the preoperative evaluation

Table 3. Values of blood lactate level and occurrence of primary graft dysfunction grade 3 at day 3

	No-PGD3-T72 group (n=377)	PGD3-T72 group (n=72)	P value
Blood lactate level			
After induction of anesthesia (T1)	0.8 [0.6-1.0]	0.9 [0.7-1.3]	0.001
BLL at T1 \geq 0.8 mmol/L	193 (51.2)	47 (65.3)	0.027
At first pneumonectomy (T2)	1.0 [0.7-1.5]	1.2 [0.8-1.7]	0.003
BLL at T2 \geq 1.3 mmol/L	127 (33.7)	34 (47.2)	0.031
At first graft implantation (T3)	1.5 [1.1-2.1]	2.2 [1.4-3.9]	<0.001
BLL at T3 \geq 2.0 mmol/L	110 (29.2)	42 (58.3)	<0.001
At second pneumonectomy (T4)	1.6 [1.1-2.5]	2.4 [1.7-3.8]	<0.001
BLL at T4 \geq 1.7 mmol/L	177 (47.0)	57 (79.2)	<0.001
At second graft implantation (T5)	2.2 [1.6-3.2]	3.4 [2.3-5.0]	<0.001
BLL at T5 \geq 2.6 mmol/L	159 (42.2)	52 (72.2)	<0.001
At end-surgery status (T6)	2.0 [1.5-3.1]	3.4 [2.4-5.0]	<0.001
BLL at T6 \geq 2.6 mmol/L	137 (36.3)	53 (73.6)	<0.001
Variability of BLL			
Variability \geq 0.46	0.4 [0.3-0.5]	0.5 [0.4-0.6]	<0.001
Δ Lactate			0.110
Decreasing	237 (62.9%)	38 (52.8%)	
Increasing	140 (37.1%)	34 (47.2%)	

Values are expressed as median (25th percentile-75th percentile) or number (percentage).

PGD3-T72: Primary graft dysfunction grade 3 at day 3

BLL: blood lactate level

P values for absolute lactate level were adjusted because of multiple comparisons with Holm correction.

Δ Lactate, difference between the highest lactate level measured during surgery and its level at end-surgery status, is expressed as a trending: decreasing or increasing Δ Lactate. If maximal lactate level was observed at the last measurement, then the case was considered as having an increase.

Table 4. Threshold values of blood lactate level and of variability of lactate level as predictors of primary graft dysfunction grade 3 at day 3

	Threshold value	AUC	Sensitivity	Specificity	PPV	NPV	P value
							compared to T6
T1	0.8 mmol/L	0.600	56.9%	60.5%	21.6%	88.0%	0.033
T2	1.3 mmol/L	0.579	47.2%	66.3%	21.1%	86.8%	0.026
T3	2.0 mmol/L	0.663	58.3%	70.8%	27.6%	89.9%	0.573
T4	1.7 mmol/L	0.680	80.6%	53.1%	24.7%	93.5%	0.765
T5	2.6 mmol/L	0.696	72.2%	57.8%	24.6%	91.6%	0.882
T6	2.6 mmol/L	0.724	73.6%	63.7%	27.9%	92.7%	Reference
Variability	0.46	0.607	56.9%	62.3%	22.4%	88.3%	0.039

AUC: Area under the curve

PPV: Positive predictive value

NPV: Negative predictive value

T1: induction of anesthesia

T2: first pneumonectomy

T3: after first graft implantation

T4: second pneumonectomy

T5: after second graft implantation

T6: end-surgery status before transfer to the intensive care unit

Table 5. Clinical models for pulmonary graft dysfunction grade 3 at day 3 (multivariable analysis)

	OR [95%CI]	P value	AUC	Sensitivity	Specificity	PPV	NPV	P value for AUC comparison
Clinical variables								
PaO ₂ /FiO ₂ ratio at T5 (per 10 units) *	0.97 [0.95-0.99]	0.001	0.860	81.5%	76.6%	41.4%	95.4%	0.837
Fluid support (per 100 units) **	1.03 [1.01-1.05]	0.038						
End-stage lung disease		0.011						
Cystic Fibrosis	Reference							
COPD/Emphysema	0.92 [0.36-2.36]	0.863						
Fibrosis	3.28 [1.57-6.87]	0.002						
Other pathology	1.33 [0.44-3.97]	0.611						
ECMO during surgery	12.04 [4.49– 32.31]	<0.001						
Adding BLL threshold to the clinical model								
> 0.8 mmol/L at T1	1.75 [0.91-3.36]	0.094	0.865					
>1.3 mmol/L at T2	1.14 [0.59-2.17]	0.698	0.861					
>2.0 mmol/L at T3	1.61 [0.85-3.08]	0.145	0.863					
>1.7 mmol/L at T4	2.33 [1.11-4.92]	0.026	0.864	83.1%	77.3%	42.5%	95.8%	0.893
> 2.6 mmol/L at T5	2.13 [1.05-4.29]	0.017	0.866	83.2%	75.1%	40.3%	95.6%	0.921
> 2.6 mmol/L at T6	3.48 [1.29-5.15]	0.007	0.867	76.9%	85.4%	51.4%	95.8%	Reference
Variability>0.46	1.64 [0.82-3.29]	0.159	0.861					

Table 5: Continued

Each value of blood lactate level was independently adjusted on the predictive clinical variables.

AUC: Area under the curve; PPV: Positive predictive value; NPV: Negative predictive value

T1: induction of anesthesia; T2: first pneumonectomy; T3: 10 minutes after first graft implantation; T4: second pneumonectomy; T5: 10 minutes after second graft implantation; T6: end-surgery status before transfer to the intensive care unit

* Values of $\text{PaO}_2/\text{FiO}_2$ ratio at end-surgery status were divided by 10 to provide understandable odds ratios.

** Values of intraoperative fluid support have been transformed into fractions of 100 ml to provide understandable odds ratio

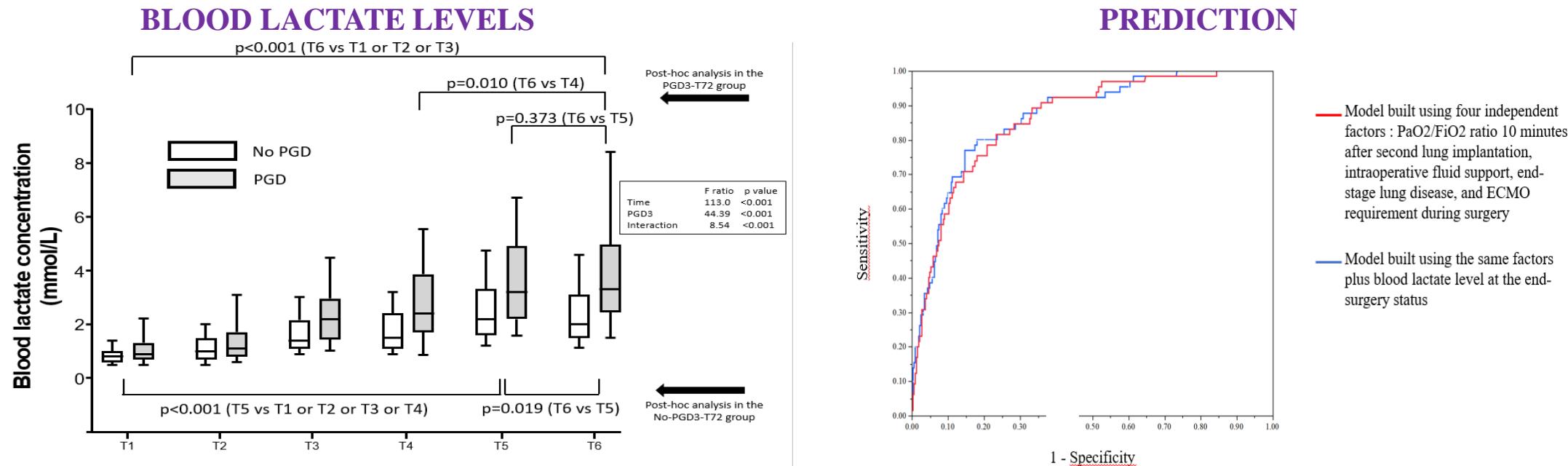
Blood lactate during double-lung transplantation: A predictor of grade-3 primary graft dysfunction (PGD)

QUESTIONS:

- 1) Describe the blood lactate levels at each major time-points during surgery.
- 2) Describe the kinetic of lactate expressed as lactate variability and Δ Lactate.
- 3) Test if intraoperative blood lactate levels could be a predictor of grade 3 pulmonary graft dysfunction at postoperative day 3

INTRAOPERATIVE MANAGEMENT: Combination of short-acting anesthetic drugs, thoracic epidural analgesia, ECMO for refractory hemodynamic or respiratory failure, and extubation at the end of the surgical procedure if possible

FINDINGS 449 patients transplanted from 2012 to 2019; 16% developed a grade 3 PGD at postoperative day 3



CONCLUSION: Blood lactate level increased during double-lung transplantation and this increase was higher in the group of patients who presented a grade 3 PGD. A value below 2.6 mmol/L measured at the end of surgery had a high negative predictive value.