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Procalcitonin accurately predicts lung transplant adults with low risk of pulmonary graft dysfunction and intensive care mortality☆

Cristopher Mazo, MD [a,b,c,d,f,*], Bárbara Borgatta, MD [a,b,c,d], Teresa Pont, MD, PhD [a,b,f], Alberto Sandiumenge, MD, PhD [a,c,f], Silvia Moyano, BSC [b], Antonio Roman, MD, PhD [b,c,d,e], Jordi Rello, MD, PhD [a,b,c,d]

[a] Critical Care Department, Vall d'Hebron University Hospital, Barcelona, Spain
[b] Vall d'Hebron Institut de Recerca, Barcelona, Spain
[c] CIBERES, Instituto de Salud Carlos III, Madrid, Spain
[d] Universitat Autònoma de Barcelona, Barcelona, Spain
[e] Pulmonary Department, Vall d'Hebron University Hospital, Barcelona, Spain
[f] Transplant Coordination Department, Vall d'Hebron University Hospital, Barcelona, Spain

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ABSTRACT

Purpose: We evaluated the association of procalcitonin (PCT), IL-6-8-10 plasma levels during the first 72 h after lung transplantation (LT) with ICU-mortality, oxygenation, primary graft dysfunction (PGD), and one-year graft function after LT.
Material and methods: Prospective, observational study. PCT and IL-6-8-10 plasma levels were measured at 24 h, 48 h and 72 h after LT from 100 lung transplant recipients (LTr). Patients were followed until one year after LT. End-points were ICU survival, grade 3 PGD at 72 h and one-year graft function.
Results: Higher PCT at 24 h was associated with lower PaO_2/F_IO_2 ratio and Grade 3 PGD over the first 72 h after LT ($p < 0.05$). PCT at 24 h was higher in the 9 patients who died (2.90 vs 1.47 ng/mL, $p < 0.05$), with AUC = 0.74 for predicting ICU-mortality. All patients with PCT < 2 ng/mL at 24 h following LT, survived in the ICU ($p < 0.05$). PCT and IL-10 at 48 h were correlated with FEV_1 (rho = −0.35) and FVC (rho = −0.29) one year after LT. ($p < 0.05$).
Conclusions: A breakpoint of PCT < 2 ng/mL within 24 h has a high predictive value to exclude grade 3 PGD at 72 h and for ICU survival. Moreover, both PCT and IL-10 within 48 h were associated with significantly better graft function one year after surgery.

1. Introduction

Primary graft dysfunction (PGD) is a form of acute lung injury presented by 11%–57% of lung transplant patients (LTr), being a leading cause of early post-transplantation mortality [1-2]. Recent studies have assessed the role of interleukin-6 (IL-6), interleukin-8 (IL-8) and interleukin-10 (IL-10) in the pathophysiology of PGD [3-4]. Procalcitonin (PCT) is a pro-peptide of calcitonin released in response to endotoxins from bacterial cell walls, cytokines and chemokines [5]. The use of PCT has been proposed in the decision-making process of antibiotic therapy [6] and stewardship [7-8]. Unfortunately, a major drawback is that PCT also increased in clinical situations not associated with infection, including major surgery, burns or trauma [9-17]. In transplant recipients, PCT has been shown to be a useful tool for infection detection [18-19], but data is lacking on its role in LT patients. It might be modified by several factors including recent surgical procedures, cardiopulmonary bypass (CPB), underlying end-organ disease, immunosuppression and type of agent, making its use and interpretation more complex than in non-transplant patients [9-13,20-26].

Our hypothesis was that PCT, IL-6, IL-8 and IL-10 plasma levels measured following LT may predict severity of early graft function and mortality. The primary objective was to establish the relationship between PCT, IL-6, IL-8 and IL-10 levels measured in the ICU at day one, two and

Abbreviations: PCT, procalcitonin; IL-6, interleukin 6; IL-8, interleukin 8; IL-10, interleukin 10; AUC, area under the curve; CI, confidence interval; ICU, intensive care unit; LT, lung transplantation; LTr, lung transplantation recipient; CPB, cardiopulmonary bypass; SLT, single lung transplant; BLT, bilateral lung transplant; OR, odds ratio; PGD, primary graft dysfunction; PF, pulmonary fibrosis; COPD, chronic obstructive pulmonary disease; Admission time, T0; 24 h, 24 hours; 48 h, 48 hours; 72 h, 72 hours.

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* Corresponding author at: Ps. Vall d'Hebron, 119-129, AMI - 11st floor, E08035 Barcelona, Spain.
E-mail addresses: cmazo@vhebron.net (C. Mazo), barbarabo@gmail.com (B. Borgatta), tpont@vhebron.net (T. Pont), asandiumenge@yahoo.com (A. Sandiumenge), silvia.moyano.vhir@gmail.com (S. Moyano), aroman@vhebron.net (A. Roman), jrello@crips.es (J. Rello).

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Table 1
Significant differences in 22 adults with Grade 3 primary graft dysfunction status, at 72 h after ICU admission.

Variables	Control (n = 77)*	Grade 3 PGD (n = 22)*	p value
Recipient age, median years (IQR)	55 (50–61)	52 (46–57)	0.080
CPB	19%	45%	0.028
Packed red blood cells transfusion	49%	73%	0.089
Mechanical ventilation days	6 (2−30)	32 (18–64)	<0.01
T0 Grade 3 PGD	39%	86%	<0.001
T24 Grade 3 PGD	18%	82%	<0.001
T48 Grade 3 PGD	12%	73%	<0.001
ICU days	11 (6–37)	37 (26–70)	<0.001
ICU mortality	5.1%	22.2%	0.013

APACHE = Acute Physiology and Chronic Health Evaluation; CPB = Cardiopulmonary Bypass; ICU = Intensive Care Unit; PGD = primary graft dysfunction; T0 = at ICU admission; T24 = 24 h from ICU admission; T48 = 48 h from ICU admission. Continuous variables are expressed as median (interquartile range), while categorical variables are expressed as percentages. Wilcoxon test and Chi-square test were used for comparisons of continuous and categorical variables, respectively.

three after LT with early oxygenation and different grades of PGD. The secondary objective was to assess PCT's prognostic value for ICU mortality and graft function one year after LT.

2. Materials and methods

2.1. Study population and design

Prospective single center study, including 100 adults consecutively admitted to the intensive care unit (ICU) of the Vall d'Hebron University Hospital after LT. Demographic, clinical data and sample collection has been reported elsewhere [28]. The study was approved by the Ethics Committee of the Vall d'Hebron University Hospital (reference code PR_AG_279-2013). Informed consent was obtained from the next of kin.

2.2. Determination of PGD grade

The PGD grade was determined using the International Society for Heart and Lung Transplantation consensus definition [1]. Chest X-ray images and arterial blood gases were assessed at the time of ICU admission (T0) and at 24 h, 48 h and 72 h after LT. Two different physicians examined chest X-ray images to assess the presence of diffuse infiltrates in the transplanted lungs. The severity of PGD was graded blinded to all biomarkers values and according to the ratio of partial pressure of arterial oxygen (PaO_2) to fraction of inspired oxygen (FIO_2). Grade 3 PGD was defined as a PaO_2/FIO_2 ratio of <200 mm Hg.

Table 2
Spearman rank correlation between procalcitonin levels at 24 h, 48 h, 72 h and PaO_2/FIO_2 ratio at 24 h, 48 h, 72 h.

	PaO_2/F_IO_2 ratio		
	24 h	48 h	72 h
Biomarker	Rho value	Rho value	Rho value
PCT T24	−0.363*	−0.335*	−0.311*
PCT T48	−0.327*	−0.298*	−0.265*
PCT T72	−0.288*	−0.273*	−0.247*

* Designates $p < 0.05$.

2.3. Biomarkers measurement

Blood samples were collected in sterile EDTA tubes (Vacutainer, Becton Dickinson, Cockeysville, Md). Tubes were immediately centrifuged at 3000 rpm for 10 min at 4 °C. Supernatant was withdrawn and kept refrigerated at −86 °C until samples were analyzed. PCT plasma levels were determined with B·R·A·H·M·S KRYPTOR/KRYPTOR compact, based on TRACE Technology (Time-Resolved Amplified Cryptate Emission). The assay has a detection limit of 0.02 ng/mL with a probability of 95%, sensitivity of 0.06 ng/mL (upper-reference-range 0.5 ng/mL in healthy subjects). ILs were analyzed using sandwich enzyme-linked immunosorbent assay kits (Human IL-6 Kit, Life Technologies, part of the Life Sciences Solutions Group of Thermo Fisher Scientific. Carlsbad, California, United States) and (Human IL-8 and 10 Kit, Tebu-bio, France).

2.4. Outcomes

Patients were followed until one year after LT. Time and cause of death were recorded. The primary endpoints were early allograft function and different grades of PGD. The secondary endpoints were ICU mortality, 1 year after LT mortality and graft function: forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC).

2.5. Statistical analysis

Continuous variables were expressed as mean and standard deviation or median and interquartile range. Categorical variables were expressed as frequencies and percentages. Continuous variables were compared with Student's *t*-test or the Mann-Whitney test, as appropriate. Differences between categorical variables were assessed with the chi-square test or Fisher's exact test. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) and Youden J index values were computed [27]. The optimal cut-off values were obtained from the best sensitivity/specificity ratios. A two-sided $p < 0.05$

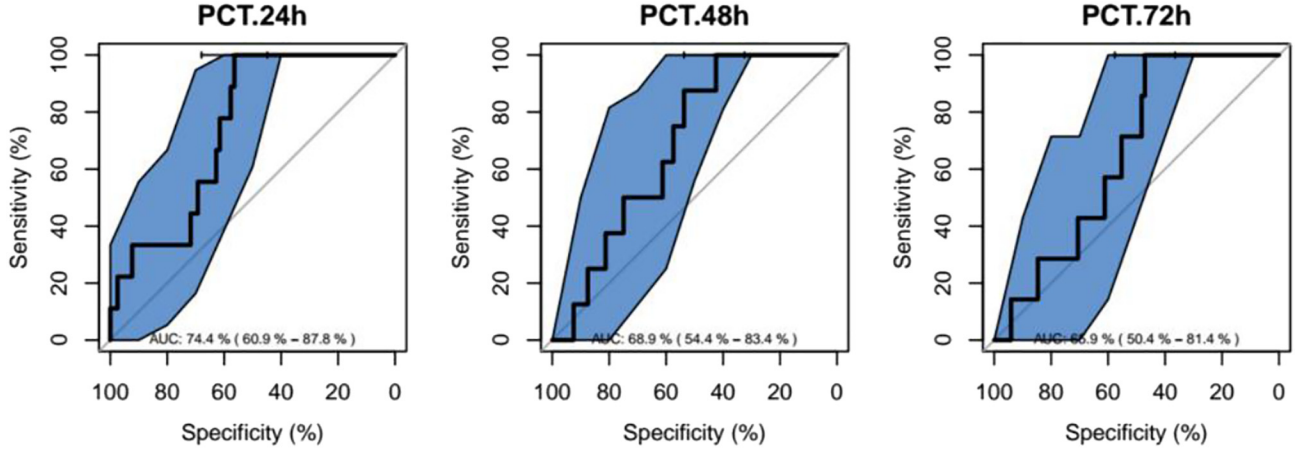

Fig. 1. PCT serum levels at 24, 48 and 72 h as predictors of ICU mortality.