ISHLT LUNG TRANSPLANTATION. December 2021
JOURNAL WATCH

CAROLINE PATTERSON, MD
EDITOR

Prangthip Charoenpong, MD, MPH

Tague LK, *et al*. Lung protective ventilation based on donor size is associated with a lower risk of severe primary graft dysfunction after lung transplantation

J Heart Lung Transplant. *2021 Oct;40(10):1212-1222. doi: 10.1016/j.healun.2021.06.016.*

STUDY HIGHLIGHTS

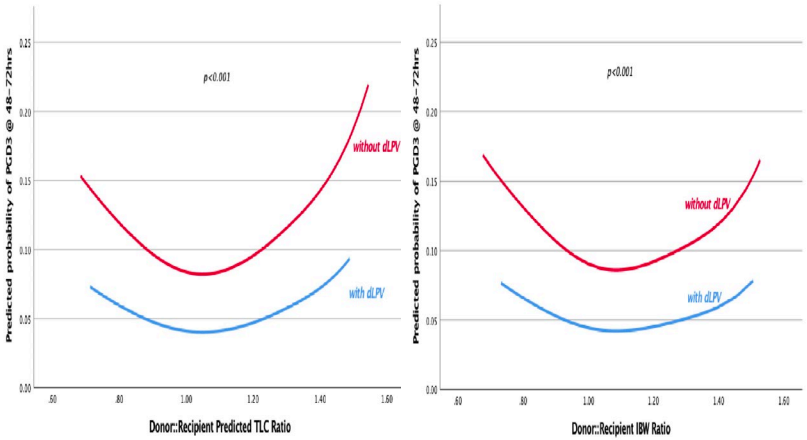
Question: Is donor-based lung protective ventilation (dLPV) associated with a lower risk of severe primary graft dysfunction (PGD) after lung transplantation?

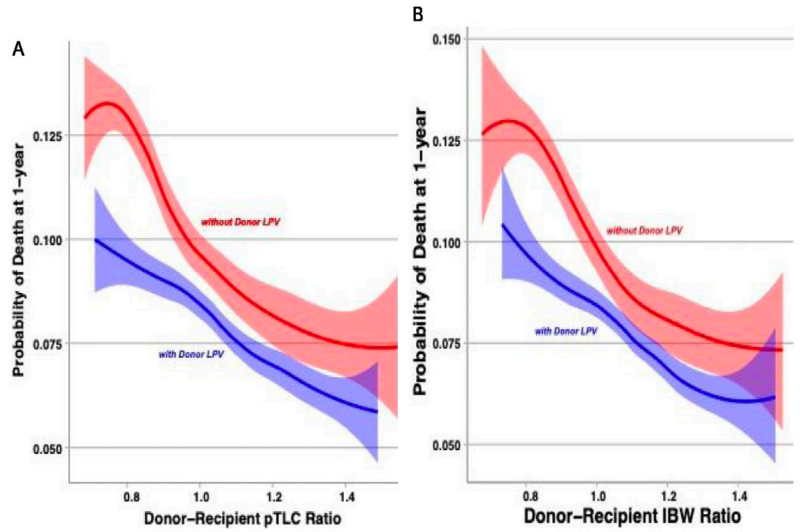
Background: Donor-recipient size mismatch is a risk factor for PGD. This may be related to ventilation strategies based on recipient rather than donor characteristics.
Design: Retrospective single center study
Inclusion: 373 adult bilateral lung recipients of whom 213 (57.3%) received dLPV
1^{o} Outcome: PGD grade 3 at 48-72hrs.
Results:
dLPV is associated with:

- **↓risk of PGD grade 3 at 48-72hrs for both pTLC ratio and IBW ratio**
- **↓ risk of death within the first year**

dLPV mitigates the association between size mismatch and PGD grade 3 at 48-72hrs and 1-year survival.
pTLC ratio appears to better correlate with clinical outcomes than IBW ratio.

FIGURES





REVIEWER'S COMMENTS

TAKE HOME MESSAGE: Post lung transplant ventilator settings should be based on donor characteristics, especially when the allograft is undersized.

- RCT is needed to confirm causal relationship.

Limitations:

- Retrospective, single center study
- pTLC calculated from ERS formula derived from normal population may not be accurate in diseased lungs.
- Clinically indicated changes to ventilation settings may introduce bias.
- Donor ventilator settings before retrieval and intraoperatively not included in analyses.
- Known risk factors for PGD (including donor age, recipient pulmonary hypertension, diastolic dysfunction) not addressed in multivariate analysis.

ISHLT LUNG TRANSPLANTATION. December 2021
JOURNAL WATCH

CAROLINE PATTERSON, MD
EDITOR

Anh Nguyen, MD, PhD

Jang MK, *et al*. Donor-derived cell-free DNA accurately detects acute rejection in lung transplant patients, a multicenter cohort study.

J Heart Lung Transplant. *2021 Aug;40(8):822-830. doi: 10.1016/j.healun.2021.04.009*

STUDY HIGHLIGHTS

Background: Transbronchial biopsies are invasive and subject to high intra-observer variability.

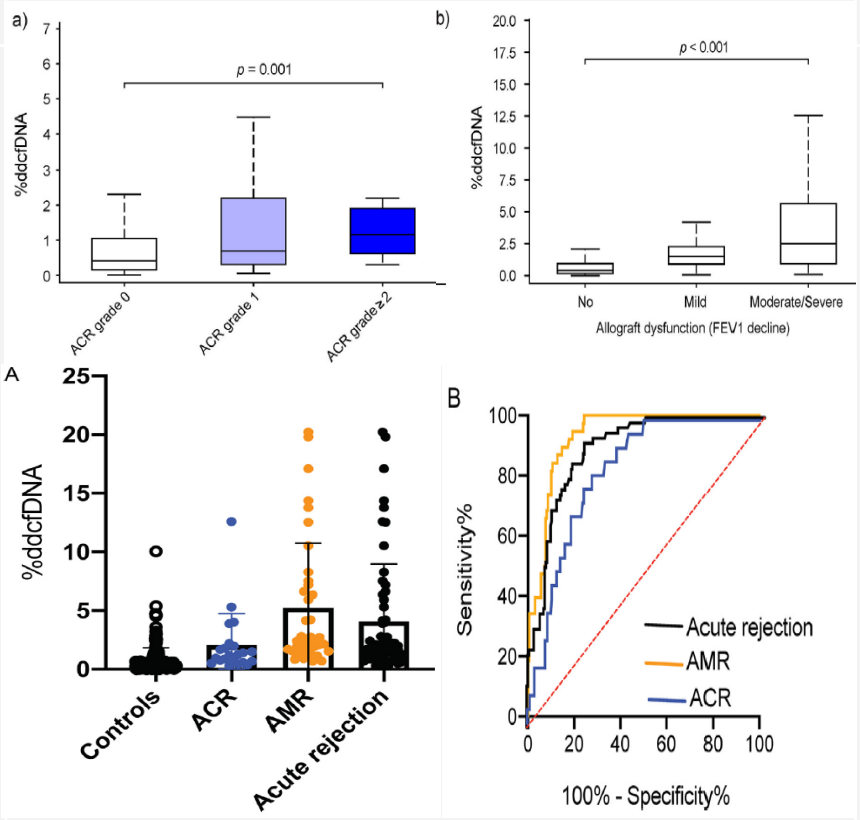
Objective: To assess %ddcfDNA, a non-invasive test, to detect acute rejection (AR).

Design: Multicenter cohort study. Analysis of clinical categories of acute rejection vs concurrent %ddcfDNA levels for 148 lung transplant recipients over median 19.6 months.

Results:

- %ddcfDNA 6x higher in AR than controls.
- %ddcfDNA 2x higher in AMR than ACR.
- %ddcfDNA correlates with spirometry decline and histological grading of AR.
- %ddcfDNA AUROC for AR, AMR, and ACR is 0.89, 0.93, and 0.83 respectively.
- %ddcfDNA levels of <0.5% and <1.0% show negative predictive value of 96% and 90% respectively for AR.

FIGURES



TAKE HOME MESSAGE: %ddcfDNA reliably detects acute rejection, with a high negative predictive value

REVIEWER'S COMMENTS

Selection bias due to exclusion of patients included in prior analyses or who died within 30 post-operative days (POD).

%ddcfDNA data before POD 45 excluded to account for post-transplant decay. Choice of POD 45 not sufficiently justified (why not 4 months when the %ddcfDNA was lowest?)

The study does not examine infection, because the clinical data needed to define infection was lacking.

Next-generation sequencing is a more practical option without the need for donor & recipient genotyping.

ISHLT LUNG TRANSPLANTATION. December 2021
JOURNAL WATCH

CAROLINE PATTERSON, MD
EDITOR

Vicky Gerovasili, MD, PhD

Viet T, *et al*. Letermovir in lung transplant recipients with cytomegalovirus infection: A retrospective observational study

Am J Transplant. 2021;21:3449–3455 DOI: 10.1111/ajt.16718

STUDY HIGHLIGHTS

Question: Is Letermovir effective in treating CMV infections in lung transplant recipients (LTR) failing on currently available antiviral agents?

Background:
CMV infection in LTR can be associated with graft failure. Current CMV treatments have toxic side effects. Letermovir is a viral terminase inhibitor approved for CMV prophylaxis post hematopoietic stem-cell transplant (HSCT).

Design: Retrospective single center observational study

Inclusion: 28 LTR with "difficult to treat CMV infection", defined as:

- Ganciclovir-associated side effects
- Ganciclovir-resistant CMV infection
- Refractory CMV infection

Outcomes:

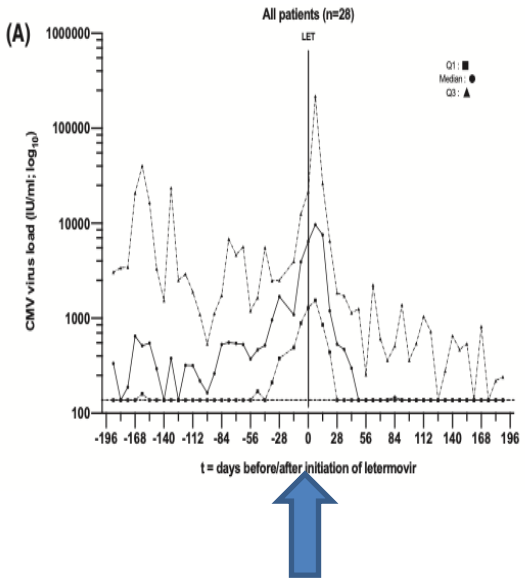
- Responders defined as patients with decrease (≥1 log10) in CMV viral load after 4 weeks of Letermovir

Results:

- In 23 patients (82.1%) CMV-viral load significantly decreased after median 17 days and cleared in all 23 patients after median 32 days of Letermovir.
- 5 patients (17.9%) were non responders, 3 (60%) of whom developed a Letermovir resistance mutation.

FIGURES

Course of CMV viral load before and after initiation of Letermovir in 28 LTR with difficult to treat CMV infection



REVIEWER'S COMMENTS

TAKE HOME MESSAGE: Letermovir was effective in treating CMV infection in >80% of LTR failing first line treatment.

- 5 patients were non-responders to Letermovir, of whom 3 developed resistance, which is concerning.
- Letermovir was dosed as described for CMV prophylaxis in HSCT recipients. Therapeutic dose and duration of treatment for LTR need to be defined.
- Letermovir was safe and well tolerated.

Limitations:

- Retrospective single centre observational study is not appropriate to assess efficacy but is suitable for hypothesis generation.
- Small study population without control group.
- Letermovir was used alone or in combination with immunosuppression adjustment and CMV IgG, which may confound the beneficial effects of Letermovir in this small cohort.