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ISHLT CONSENSUS REPORTS
PRIMARY LUNG GRAFT DYSFUNCTION

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

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Primary graft dysfunction (PGD) refers to the syndrome of acute lung injury early after lung transplantation (LTx).[1] In 2005, based on the need for a reliable and valid definition with clear taxonomy, the first International Society for Heart and Lung Transplantation (ISHLT) Working Group on PGD proposed a consensus-based standardized definition and grading system.[1] This definition has since been used to characterize PGD clinically by diffuse alveolar infiltrates on chest X-ray imaging, with the degree of associated hypoxemia determining its severity (Table 1).[1]

PGD in its "purest" form has no proven, singular etiology; rather, the clinical PGD syndrome represents the result of mechanical, immune, inflammatory, possible microbial, and other contributors associated with LTx.[1,2] The original description of PGD aimed to be inclusive and allowed characterization of any LTx recipient while still allowing for exclusion or sub-group analyses of specific contributing etiologies, such as infection or cardiogenic edema, for particular study purposes.[1,2]

[1]A list of the International Society for Heart and Lung Transplantation Primary Graft Dysfunction Working Group Members can be found in the online version of this article at www.jhltonline.org.

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Table 1 Features of the 2005 International Society for Heart and Lung Transplantation Primary Graft Dysfunction Definition and Severity Grading

Grade	Pulmonary edema on chest X-ray	Pao_2/FIO_2 ratio
PGD grade 0	No	> 300
PGD grade 1	Yes	> 300
PGD grade 2	Yes	200 to 300
PGD grade 3	Yes	< 200

Grade severity notes: grade 1—nasal cannula oxygen $Fio_2 < 0.3$, or ventilator $FIO_2 < 0.3$, = grade 1 if edema present on chest X-ray. These settings and no X-ray edema = grade 0. Grade 3—use of extracorporeal lung support or mechanical ventilation with $FIO_2 > 0.5$ on nitric oxide > 48 hours from lung transplant = grade 3.
FIO_2, fraction of inspired oxygen; Pao_2, partial pressure of arterial oxygen; PGD, primary graft dysfunction.
Time window notes: PGD is graded at 4 time points, every 24 hours, over the first 72 hours after transplantation (T0, T24, T48, and T72 hours). T0: within 6 hours of final lung reperfusion. T24, T48, and T72 have time windows ± 6 hours.
Other notes: If multiple blood gas values are available, use the worst Pao_2/FIO_2 ratio. The Pao_2/FIO_2 should ideally be measured on positive end-expiratory pressure of 5 cm H_2O at FIO_2 of 1.0 while patients are on mechanical ventilation. For altitudes higher than 1,000 m, use an appropriate correction factor. If $FIO_2 > 0.3$ and patient not ventilated, grade according to Pao_2/FIO_2 ratio.

PGD is one of the most important and common complications of LTx, being strongly linked to both early mortality[3] and late outcomes, including the bronchiolitis obliterans syndrome (BOS) and late mortality.[4,5] Furthermore, as novel technologies are being developed, PGD has emerged as an important consideration for clinical trial design. Therefore, continued research into the etiology, pathogenesis, prevention, and therapy of PGD remains highly relevant to the practice of clinical LTx in 2016.

Rationale and methods for the 2016 consensus PGD definition

Since the publication of the 2005 ISHLT PGD consensus documents, multiple studies have validated the PGD definition, estimated the incidence of PGD, and described its risk factors. However, as detailed below, questions have arisen regarding the terminology, sub-phenotypes, optimal timing of measurement, and range of the grading scale. In addition, the 2012 Berlin definition of grading of the adult respiratory distress syndrome (ARDS) raised some relevant issues to PGD grading, including the potential for expanded severity grading.[6] Furthermore, since 2005, clinical trials of novel organ preservation technologies and other therapeutics have proposed PGD as a trial outcome.

Thus, based on these considerations and the potential to improve the reliability, validity, and clarity of the PGD definition, the International Society for Heart and Lung Transplantation (ISHLT) convened a second PGD Consensus Group in 2015. The Consensus Group conducted a rigorous literature review, undertook sub-group discussions in an in-face meeting at the 2015 ISHLT conference in Nice, France, held group teleconferences, solicited and included wider consensus of ISHLT members and councils, included review of on-line submissions, and then incorporated focused discussion from a specially convened meeting at the 2016 ISHLT conference in Washington DC. The final work product was then reviewed by a committee of 4 external experts, relevant ISHLT councils, the ISHLT Standards and Guidelines Committee, and approved by the Board of Directors. This consensus approach paralleled the methods used by the original ISHLT working group in 2005.[7]

Validity of the 2005 ISHLT PGD definition

Epidemiologic studies have validated the PGD definition by confirming the discriminant (predictive) validity PGD for clinical outcomes (Table 2). Christie et al[3] in 2005 demonstrated that PGD at the 72 hour time point (T72) grade 3 compared with no PGD was associated with 30-day mortality relative risk of 6.95 and that the increased mortality risk persisted to conditional survival at 1 year, with a relative risk of death in the same PGD group of 1.35. Prekker et al[8] demonstrated higher 90-day mortality by PGD grade at T48 and that PGD 3 was associated with increased long-term mortality, with PGD 3 at the time the second recipient lung cross-clamp is removed (T0) being the best predictor of long-term mortality.

Similarly, Daud et al[4] showed that PGD grades 1 to 3 were associated with higher 90-day mortality, PGD 3 was associated with higher mortality conditional on survival to 90 days, and all grades of PGD were associated with greater risk of BOS development in survivors. Whitson et al[9] reported an increased long-term mortality and BOS development in patients with PGD 3, although this finding was only present in bilateral LTx and not single LTx recipients. Huang et al[5] demonstrated that all grades of PGD at T24, T48, and T72 hours were associated with BOS development and that PGD 2 at T48 and 72 hours and PGD 3 at all time points were associated with increased mortality. Similarly, Kreisel et al[10] reported increased short- and long-term mortality as well as development of BOS in lung recipients with PGD compared with those who did not have PGD. In a more recent large prospective multicenter study, Diamond et al[11] found increased 30-day, 90-day, and 1-year mortality with PGD 3 at T48 to T72, with attributable mortality risks ranging from 18% to 22%.

In addition to mortality prediction, PGD 3 has also shown discriminant (divergent) validity for the most severely altered lung injury plasma biomarker profiles, regardless of the time point of grading.[2] Multiple clinical translational studies have demonstrated association between PGD 3 and plasma biomarkers that reflect injury to the epithelium, dysregulated fibrinolysis/coagulation, endothelial injury, and activation of cell adhesion molecules. Plasminogen activator inhibitor type-1, soluble receptor for advanced glycation end-products, Clara cell secretory protein, protein C, and intercellular adhesion molecule-1 have all been associated with PGD. In sum, these findings support the conclusion that PGD 3 is associated with the most clear differences in lung injury markers compared with lesser grades of PGD.[2,12–16]

Table 2 Summary of Key Studies After 2005 Relating Primary Graft Dysfunction to Clinical Outcomes

Study	Study population	Subjects No.	PGD definition	BOS development	Mortality
Christie et al,[3] 2005	ISHLT Registry	5,262	T72 grade 3 equivalent	Not reported	Increased at 30 days; Increased conditional on 1-year survival
Prekker et al,[8] 2006	Single center (Minneapolis)	402	T0–48 grade 1–3	Not reported	Increased at 90 days for all PGD; Increased at 1 year for grade 3
Daud et al,[4] 2007	Single center (St. Louis)	334	T0 grade 0–3	Increased in all PGD grades	Increased at 90 days for all PGD; Increased conditional on 90-day survival for grade 3
Whitson et al,[9] 2007	Single center (Minneapolis)	374	T0–48 grade 0–3	Increased conditional on 90-day survival in grade 3 (only bilateral recipients)	Increased conditional on 90-day survival in grade 3 (only bilateral recipients)
Huang et al,[5] 2008	Single Center (St. Louis)	334	T24–72 grade 0–3	Increased in all PGD grades at each time point	Increased for T48–72 grade 2; Increased for T24–72 grade 3
Christie et al,[2] 2010	LTOG Registry	450	T48–72 grade 3	Not reported	Increased at 30 days for T48–72 grade 3
Kreisel et al,[10] 2011	Single center (St. Louis)	1,000	PGD vs. no PGD	Increased in PGD	Increased in PGD
Diamond et al,[11] 2013	LTOG Registry	1,255	T48–72 grade 3	Not reported	Increased at 90 days for T48–72 grade 3

BOS, bronchiolitis obliterans syndrome; ISHLT, International Society for Heart and Lung Transplantation; LTOG, Lung Transplant Outcomes Group; PGD, primary graft dysfunction; T, time in hours.

Together these findings indicate that the 2005 ISHLT consensus PGD definition has predictive validity in the ability to discriminate mortality and BOS, convergent and divergent validity for concurrent lung injury biomarkers, and that PGD 3 appears to be the major driver of these differences.

Potential areas of refinement of the PGD definition and classification

Differential grading according to selected key potential PGD risk factors

Several groups have suggested that PGD should be graded separately according to select clinical factors (e.g., underlying recipient diagnosis, transplant procedure type, or donor characteristics). On the basis of the presence or absence of specific pre-LTx features, there is currently insufficient evidence to exclude or partition particular donor sub-groups from post-LTx PGD analyses; however, transplant and recipient characteristics warrant further consideration and should be the subject of future investigation.

Several publications have raised the possibility of separate grading of PGD for bilateral and single LTx recipients, contributing evidence that single LTx may have a higher overall incidence of PGD 3 at all time points.[8,11,17] In support of this, single LTx had a less robust correlation between PGD 3 and outcomes than bilateral LTx. The potential mechanisms for elevated PGD 3 incidence in single LTx include the diluting effect of poor oxygenation associated with shunting in the remaining native lung, higher cardiac output through the graft vasculature, greater capillary stress in cases of size mismatch, and an increased grading score relevance of any changes in the unilateral transplanted lung seen on X-ray imaging. Lobar transplants[18] and significantly undersized bilateral LTx transplants[19] might also contribute to blood flow and pressure-related capillary stress, particularly if recipient ventilator strategies are not targeted at the donor predicted body weight.[20] Therefore, the Consensus Group concluded that there is sufficient evidence to consider the mechanisms and analyses of PGD in single LTx separately from those of bilateral LTx[8,11,17]; however, there is insufficient evidence to routinely change the PGD grading system within each transplant procedure type. Furthermore, insufficient evidence currently exists to routinely exclude lobar, size-reduced, or significantly undersized allografts from pooled analyses. Future studies testing whether the validity of PGD grading is affected by transplant procedure type are recommended.

Given the multifactorial and likely additive nature of PGD risk factors, clinicians are recommended to consider post-LTx complications that may confound and/or amplify PGD (Table 3). Nonetheless, at this time, there is insufficient evidence to separately analyze PGD grading according to the presence or absence of specific recipient complications or confounding issues. Future studies are

Table 3 Key Post-Lung Transplant Factors That May Confound and/or Amplify a Diagnosis of Primary Graft Dysfunction[a]

Airway
Blocked endotracheal tube/poor positioning
Blocked bronchus/distal airways with sputum or blood
Vascular
Arterial anastomotic obstruction
Venous anastomotic obstruction
Cardiac
Acute left ventricular cardiac dysfunction
Right and left ventricular dys-synchrony in patients with significant pre-operative pulmonary hypertension
Parenchymal
Infection
Rejection
Aspiration
Hemorrhage
Transfusion-related acute lung injury
Systemic inflammatory response syndrome
Pleural
Hemorrhage
Effusion
Pneumothorax
Open chest

[a]Not exhaustive and not listed in order of frequency.

warranted to understand the ways in which these contributing factors may influence the classification of PGD.

Operational considerations in defining PGD

Timing of measurement

The optimal timing for grading PGD has been debated.[8,21,22] The 2016 Consensus Group clarified that the PGD timing starts at the point of reperfusion after release of the second lung recipient pulmonary arterial cross-clamp. This typically occurs approximately 2 hours after the first lung reperfusion and approximately 2 hours before arrival into the intensive care unit, where the T0 point can be assessed by the P/F ratio, which is the partial pressure of arterial oxygen/fraction of inspired oxygen (F_{IO_2}), and chest X-ray (which is typically $<$ 6 hours after reperfusion).[8,11,17] Extracorporeal conditioning of donor lungs before recipient implantation challenges this time course and requires further consideration in future studies. Pending further research, the Consensus Group recommends that the recipient second lung cross-clamp release time should still be used as the initiation point for the timing of grading.

T0 has been suggested as having less predictive validity than subsequent times.[2,8,23] It can be argued that the hemodynamics, including pulmonary pressures, cardiac index, and systemic blood pressure, are still in flux. In addition, the effect of cardiopulmonary bypass on right ventricular function, instilled fluid, blood loss, and variable renal function can influence volume status considerably, potentially elevating the PGD grade.[8,23]

Prekker et al[8] demonstrated that T0 PGD data were the most complete, whereas arterial blood gases were not measured at T72 in most of their patients. However, the authors found that long-term mortality was higher based on the T24 or T48 time points and the presence of PGD grade 3, rather than T0 or the PGD grade 1. Subsequent studies likewise have suggested that T48 and T72 best capture the most clinically significant forms of PGD.[2,24] Furthermore, using latent class analyses, Shah et al[24] described that patients with T0 PGD 3 who continued to have PGD 3 at T48 and T72 had the greatest risk of mortality compared with those patients with PGD 3 only at earlier time points.

Oto et al[22] further noted that the T0 assessment might be problematic because it invariably includes the effect of a time gap between first and second lung reperfusion. To minimize operative variables and early post-LTx instability, this group suggested additional assessments at T6 and T12. T6 significantly predicted immediate post-LTx duration of intubation and intensive care unit stay, whereas T12 predicted 90-day mortality.[21,22] Gohrbandt et al[25] assessed PGD at T24 and associated PGD 2 and 3 (not grade 1) with early mortality.

Based on the current literature on timing of grading, the Consensus Group proposes that no changes be made to the grading time points of T0, T24, T48, and T72. There was some consideration that T0 grading be omitted because of issues of altered hemodynamics and physiologic changes that may be transient with little long-term effect; however, it was noted that T0 grading demonstrates discriminant validity for longer-term outcomes (although not as strong as later time points) and that early identification of patients may have merit in some circumstances. Because of high data completeness, T24 may have robustness and allow assessment of the effect of perioperative PGD management strategies; however, PGD 3 present at later times (T48 and T72) appears to have the greatest effect on long-term outcomes, including BOS and mortality. Thus, PGD 3 present at T48 and/or T72 seems to be most suited for use as an outcome in clinical trials because of its clinical impact.

Conversely, LTx registries may be able to optimize data accuracy and capture by standardizing to earlier time points for data completeness or may choose to standardize to later time points for greater clinical effect. For practical reasons, we also propose the timing windows continue to have a 6-hour margin (i.e., plus or minus 6 hours). In specific individual studies, additional assessment at T6 or T12 may allow for analysis of the PGD presentation dynamics or features but are not routinely recommended for addition to the grading scheme by the Consensus Group.

Severity grading

The severity of PGD is graded based on the P/F ratio. Studies have validated PGD grades by showing worsening outcomes with each grade increase,[2,3,9,26,27] but nuances have been noted. Furthermore, the 2012 revised Berlin definition of ARDS[6] provides rationale for the possibility of additional severity thresholds. Reflecting the revised ARDS Berlin definition, the Consensus Group considered the

suggestion of adding an extra grade for a P/F ratio of < 100 and concluded that the current literature does not support the addition of this extra category; however, future studies could consider this.

PGD grade 0 is intended to represent absence of acute lung injury.[28] The 2005 consensus definition was unclear on the grading of patients without diffuse pulmonary edema on chest X-ray imaging, who also have P/F ratios of < 300. Subsequently the 2005 Executive Committee clarified in a letter that absence of pulmonary edema on X-ray imaging (in the case of bilateral transplants involving both lungs) should be interpreted as PGD grade 0.[28] The 2016 Consensus Group reaffirms this approach and now clarifies that "any" P/F ratio is to be considered grade 0 in the absence of diffuse pulmonary edema on X-ray imaging.

PGD grades 0 and 1 have similar short-term outcomes, yet may have divergent longer-term outcomes.[2] Christie et al[2] described PGD 1 at T72 (but not earlier time points) as being associated with a slightly higher 30-day mortality (5%) than grade 0 (3.5%), with divergent longer-term mortality curves. Furthermore, PGD 3 was associated with the worst mortality and the most severely altered plasma biomarker profiles. Daud et al[4] and Huang et al[5] noted all PGD grades (including grade 1) were associated with a significantly increased risk of BOS above grade 0. Prekker et al[8] noted only PGD 3 was associated with an increased risk of short- and long-term mortality and hospital length of stay. Therefore, maintaining the current grading cutoffs appears prudent at this time; however, consideration of collapsing PGD 0 and PGD 1 for some purposes warrants further investigation.

PGD grading in patients who are not receiving mechanical ventilation through an endotracheal tube (extubated patients) has generated considerable controversy. P/F ratios may be influenced by positive end-expiratory pressure, delivered through an endotracheal tube or mask ventilation.[22,29,30] However, grading of extubated patients was not directly addressed in the 2005 ISHLT PGD definition. This issue has become more significant with the expansion of noninvasive ventilation strategies and other forms of support such as high-flow nasal cannula delivery systems. Because the transplant literature does not address these issues directly, the next best available evidence can be found in ARDS definitions.[6] The Consensus Group recommends that any noninvasive ventilation strategy or high-flow oxygen delivery system should be graded using the same method as for mechanically ventilated patients. The Consensus Group noted that there is little evidence to suggest that extubated patients with F_{IO_2} > 40% should be graded differently than those requiring non-invasive ventilation and recommends further research on these patients.

Similar to the consensus ARDS definitions, and noting the instability of the P/F ratio at lower F_{IO_2}, the Consensus Group recommends that patients with F_{IO_2} < 40% not be considered as grade 3 patients. However, it was acknowledged that there are sparse data on the best method to grade patients with F_{IO_2} < 40%, and future research is needed. Furthermore, noting the potential for missing data in the event that a partial pressure of arterial oxygen value is not available for calculation of the P/F ratio, the oxygen saturation/F_{IO_2} ratio should be calculated and the 200 and 300 PGD grading cutoffs adjusted to 235 and 315 when arterial blood gas measures are not available.[31]

Peri-LTx extracorporeal lung support (ECLS) is increasingly being used. The use of ECLS post-LTx has historically been considered equivalent to PGD 3. Acknowledging that the indications for ECLS are changing (including routine use for bridging strategies), that practice variability exists, and that the decision for ECLS use depends on the choices of the care team, there is potential for ECLS use to affect the numbers of PGD 3 patients. The Consensus Group recommends continued use of PGD 3 for patients with consistent abnormalities on X-ray imaging in whom the indication for ECLS is hypoxemia. In the cases where the chest X-ray images are clear and/or the indication for ECLS is not for primarily hypoxemia (such as right ventricular failure), then it is not certain that the PGD grade 3 is appropriate, and the Consensus Group recommends that these patients be viewed as "ungradeable" and accounted for separately in analyses. Given the potential of ECLS therapy to affect PGD 3 rates for registry reporting and clinical trials, the Consensus Group recommends that the use of ECLS should explicitly be recorded and accounted for in

Table 4 The 2016 International Society for Heart and Lung Transplantation Primary Graft Dysfunction Definition

Grade	Pulmonary edema on chest X-ray	Pa_{O_2}/F_{IO_2} ratio
PGD grade 0	No	Any
PGD grade 1	Yes	>300
PGD grade 2	Yes	200 to 300
PGD grade 3	Yes	<200

Grade severity notes: Patients with no evidence of pulmonary edema on chest X-ray are considered grade 0. Absence of invasive mechanical ventilation should be graded according to the Pa_{O_2}/F_{IO_2} ratio, using methods similar to those receiving mechanical ventilation.

F_{IO_2}, fraction of inspired oxygen; Pa_{O_2}, partial pressure of arterial oxygen; PGD, primary graft dysfunction.

If Pa_{O_2} is not available for calculation of a Pa_{O_2}/F_{IO_2} ratio, then an oxygen saturation/F_{IO_2} ratio should be calculated and the 200 and 300 PGD grading cutoffs should be adjusted to 235 and 315. Use of nitric oxide, aerosolized epoprostenol, or other pharmacologic agents that may improve oxygenation should not change grading methods. Use of extracorporeal lung support (ECLS) with bilateral pulmonary edema on chest X-ray image should be graded as grade 3 and ECLS use should be explicitly recorded. The use of ECLS for non-hypoxic indications without pulmonary edema on chest X-ray imaging should be considered ungradable and explicitly recorded separately.

Time window notes: PGD is graded at 4 time-points, every 24 hours, over the first 72 hours after transplantation (T0, T24, T48, and T72 hours). Time starts at reperfusion of second lung. T0, T24, T48, and T72 have time windows ± 6 hours. If multiple blood gas values are available, the worst Pa_{O_2}/F_{IO_2} ratio on a given calendar day should be used.

Other notes: Pa_{O_2}/F_{IO_2} should ideally be measured on positive end-expiratory pressure of 5 cm H_2O at F_{IO_2} of 1.0 while patients are on mechanical ventilation; however, grading should not be altered for other settings. For altitudes higher than 1,000 m, use of an appropriate correction factor is recommended. For comparative purposes, single lung transplantation is recommended to be reported separately from bilateral lung transplant without change in grading methodology.

Table 5 Suggested Topics for Future Research on Primary Graft Dysfunction Grading Methods

- Performance of grading methods within procedure type
- Impact of extracorporeal lung support on grading
- Validity of grading methods in patients not receiving invasive mechanical ventilation
- Effect of donor, recipient, and transplant contributing factors on grading validity
- Addition of higher severity grades, such as proposed in the Berlin acute respiratory distress syndrome definition
- Utility of grade 0 primary graft dysfunction
- Optimal methods for grading of patients with fraction of inspired oxygen $< 40\%$
- Effect of pharmacologic agents on grading

reporting and analyses as well as be the focus of future investigation.

Inhaled nitric oxide and aerosolized epoprostenol may improve P/F ratios, but how these therapies apply to the PGD grading has not been studied.[32] The Consensus Group recommends these patients be graded as those patients who are not given these agents, pending further research.

A summary of recommended changes to the ISHLT PGD definition and grading classification

Table 4 summarizes recommended changes to PGD terminology, severity cutoffs, and grade assignments. This revision should allow almost all LTx recipients to be graded.

For particular study or clinical trial purposes, the Consensus Group recommends standardization of the time points and key variables, such as oxygenation and ventilation mode or pressure settings, as well as explicitly and separately reporting the use of inhaled nitric oxide, prostacyclin, or ECLS. Furthermore, the Consensus Group recommends consideration of reporting single and bilateral LTx separately without changes in grading according to procedure type, pending future research.

In conclusion, the concepts and measures of PGD expounded in the original 2005 ISHLT PGD consensus document have proved feasible, valid, and clinically relevant. In adapting and applying lessons learned since then, the current revised definition includes minor refinements that will support clinical and experimental LTx for the next decade and beyond. Furthermore, the group has identified key areas for future study to improve classification (Table 5).

Disclosure

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

Supplementary data

A list of the International Society for Heart and Lung Transplantation Primary Graft Dysfunction Working Group Members can be found in the online version of this article at www.jhltonline.org.

References

1. Christie JD, Carby M, Bag R, et al. Report of the ISHLT Working Group on Primary Lung Graft Dysfunction part II: definition. A consensus statement of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2005;24:1454-9.
2. Christie JD, Bellamy S, Ware LB, et al. Construct validity of the definition of primary graft dysfunction after lung transplantation. J Heart Lung Transplant 2010;29:1231-9.
3. Christie JD, Kotloff RM, Ahya VN, et al. The effect of primary graft dysfunction on survival after lung transplantation. Am J Respir Crit Care Med 2005;171:1312-6.
4. 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 2007;175:507-13.
5. Huang HJ, Yusen RD, Meyers BF, et al. Late primary graft dysfunction after lung transplantation and bronchiolitis obliterans syndrome. Am J Transplant 2008;8:2454-62.
6. Force AD, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307:2526-33.
7. Christie JD, Van Raemdonck D, de Perrot M, et al. Report of the ISHLT Working Group on Primary Lung Graft Dysfunction part I: introduction and methods. J Heart Lung Transplant 2005;24:1451-3.
8. Prekker ME, Nath DS, Walker AR, et al. Validation of the proposed International Society for Heart and Lung Transplantation grading system for primary graft dysfunction after lung transplantation. J Heart Lung Transplant 2006;25:371-8.
9. Whitson BA, Prekker ME, Herrington CS, et al. Primary graft dysfunction and long-term pulmonary function after lung transplantation. J Heart Lung Transplant 2007;26:1004-11.
10. Kreisel D, Krupnick AS, Puri V, et al. Short- and long-term outcomes of 1000 adult lung transplant recipients at a single center. J Thorac Cardiovasc Surg 2011;141:215-22.
11. Diamond JM, Lee JC, Kawut SM, et al. Clinical risk factors for primary graft dysfunction after lung transplantation. Am J Respir Crit Care Med 2013;187:527-34.
12. Covarrubias M, Ware LB, Kawut SM, et al. Plasma intercellular adhesion molecule-1 and von Willebrand factor in primary graft dysfunction after lung transplantation. Am J Transplant 2007;7:2573-8.
13. Christie JD, Shah CV, Kawut SM, et al. Plasma levels of receptor for advanced glycation end products, blood transfusion, and risk of primary graft dysfunction. Am J Respir Crit Care Med 2009;180:1010-5.
14. 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 2012;31:942-9.
15. Christie JD, Shah CV, Kawut SM, et al. Plasma levels of receptor for advanced glycation end products, blood transfusion, and risk of primary graft dysfunction. Am J Respir Crit Care Med 2009;180:1010-5.
16. Pelaez A, Force SD, Gal AA, et al. Receptor for advanced glycation end products in donor lungs is associated with primary graft dysfunction after lung transplantation. Am J Transplant 2010;10:900-7.
17. Oto T, Griffiths AP, Levvey BJ, Pilcher DV, Williams TJ, Snell GI. Definitions of primary graft dysfunction after lung transplantation: differences between bilateral and single lung transplantation. J Thorac Cardiovasc Surg 2006;132:140-7.
18. Mitilian D, Sage E, Puyo P, et al. Techniques and results of lobar lung transplantations. Eur J Cardiothorac Surg 2014;45:365-9: discussion 369-70.
19. Dezube R, Arnaoutakis GJ, Reed RM, et al. The effect of lung-size mismatch on mechanical ventilation tidal volumes after bilateral lung transplantation. Interact Cardiovasc Thorac Surg 2013;16:275-81.

20. Beer A, Reed RM, Bolukbas S, et al. Mechanical ventilation after lung transplantation. An international survey of practices and preferences. Ann Am Thorac Soc 2014;11:546-53.
21. Oto T, Levvey BJ, Pilcher DV, Bailey MJ, Snell GI. Evaluation of the oxygenation ratio in the definition of early graft dysfunction after lung transplantation. J Thorac Cardiovasc Surg 2005;130:180-6.
22. Oto T, Levvey BJ, Snell GI. Potential refinements of the International Society for Heart and Lung Transplantation primary graft dysfunction grading system. J Heart Lung Transplant 2007;26:431-6.
23. Shigemura N, Orhan Y, Bhama JK, et al. Delayed chest closure after lung transplantation: techniques, outcomes, and strategies. J Heart Lung Transplant 2014;33:741-8.
24. Shah RJ, Diamond JM, Cantu E, et al. Latent class analysis identifies distinct phenotypes of primary graft dysfunction after lung transplantation. Chest 2013;144:616-22.
25. Gohrbandt B, Simon AR, Warnecke G, et al. Lung preservation with Perfadex or Celsior in clinical transplantation: a retrospective single-center analysis of outcomes. Transplantation 2015;99:1933-9.
26. Suzuki Y, Cantu E, Christie JD. Primary graft dysfunction. Semin Respir Crit Care Med 2013;34:305-19.
27. Whitson BA, Nath DS, Johnson AC, et al. Risk factors for primary graft dysfunction after lung transplantation. J Thorac Cardiovasc Surg 2006;131:73-80.
28. Christie J, Keshavjee S, Orens J, et al. Potential refinements of the International Society for Heart and Lung Transplantation primary graft dysfunction grading system. J Heart Lung Transplant 2008; 27:138.
29. Ferguson ND, Kacmarek RM, Chiche JD, et al. Screening of ARDS patients using standardized ventilator settings: influence on enrollment in a clinical trial. Intensive Care Med 2004;30:1111-6.
30. Villar J, Perez-Mendez L, Lopez J, et al. An early PEEP/FIO2 trial identifies different degrees of lung injury in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2007;176: 795-804.
31. Rice TW, Wheeler AP, Bernard GR, et al. Comparison of the SpO2/FIO2 ratio and the PaO2/FIO2 ratio in patients with acute lung injury or ARDS. Chest 2007;132:410-7.
32. Dzierba AL, Abel EE, Buckley MS, Lat I. A review of inhaled nitric oxide and aerosolized epoprostenol in acute lung injury or acute respiratory distress syndrome. Pharmacotherapy 2014;34:279-90.