Interobserver variability impairs radiologic grading of primary graft dysfunction after lung transplantation

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ABSTRACT

Objectives: The current score for primary graft dysfunction after lung transplantation relies heavily on chest radiographs, and radiologic judgment can make the difference between the lowest (primary graft dysfunction 0) and the highest (primary graft dysfunction 3) grade. This study aimed to evaluate interobserver variability of the scoring of postoperative chest radiographs and its impact on primary graft dysfunction grades in a large single-center cohort.

Methods: We retrospectively analyzed 497 lung transplantations performed between January 2010 and July 2016 at the Medical University of Vienna. Five trained thoracic radiologists were asked to independently examine postoperative chest radiographs performed at 0 to 6 hours, 24 hours, 48 hours, and 72 hours after arrival at the intensive care unit. Interobserver variability was calculated using Fleiss' kappa (κ) statistics.

Results: A total of 1988 chest radiographs were evaluated. Consensus among all 5 radiologists was found in only 826 cases (43.0%). At 0 to 6 hours and 24 hours, only a moderate agreement was found among the 5 radiologists ($\kappa = 0.456$ and 0.456 , respectively), and agreement was even worse at 48 and 72 hours ($\kappa = 0.405$ and $\kappa = 0.409$). On the basis of this high interobserver variability, best and worst case scenarios were calculated leading to primary graft dysfunction 3 rates of 8.4% versus 28.4% at 0 to 6 hours, 1.8% versus 4.8% at 24 hours, 2.0% versus 5.3% at 48 hours, and 0.2% versus 3.1% at 72 hours. A high recipient body mass index and size-reduced transplants were found to be factors associated with higher rates of interobserver variability.

Conclusions: The substantial interobserver variability found in this retrospective analysis underlines the difficulty to adequately grade post-transplant organ function. Future revisions of the primary graft dysfunction grading should take this problem into consideration. (J Thorac Cardiovasc Surg 2019;158:955-62)

High interobserver variability of chest radiograph diagnosis after LTx significantly impairs grading of PGD.

Central Message

Current PGD grading relies heavily on the binary radiologic component. Interobserver variability in grading chest radiographs after LTx is substantial and therefore impairs the assessment of PGD scores. Future revisions of the PGD score should take this issue into consideration.

Perspective

The clinical significance of the ISHLT PGD score remains controversial because the grading is impaired by a high degree of interobserver variability in interpreting chest radiographs. An improved scoring system should place more weight on functional measurements and redefine the central role of the radiologic component.

See Commentaries on pages 963 and 965.

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Read at the 98th Annual Meeting of The American Association for Thoracic Surgery, San Diego, California, April 28-May 1, 2018.

Received for publication May 21, 2018; revisions received Feb 11, 2019; accepted for publication Feb 14, 2019; available ahead of print June 14, 2019.

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0022-5223/\$36.00

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<https://doi.org/10.1016/j.jtcvs.2019.02.134>

Although outcomes after lung transplantation (LTx) have constantly improved over the last decades, primary graft dysfunction (PGD) still remains one of the main obstacles in the early perioperative period.¹ PGD is currently graded

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Abbreviations and Acronyms

ARDS	= acute respiratory distress syndrome
BMI	= body mass index
ECMO	= extracorporeal membrane oxygenation
ISHLT	= International Society for Heart and Lung Transplantation
LTx	= lung transplantation
P/F	= partial pressure of arterial oxygen/fraction of inspired oxygen
PGD	= primary graft dysfunction
t0	= 0 to 6 hours
t24	= 24 hours
t48	= 48 hours
t72	= 72 hours

using a scoring system that was proposed by the International Society for Heart and Lung Transplantation (ISHLT) in 2005² and revised in 2016.³ According to these recommendations, PGD grades should be measured at different time points: 0 to 6 hours (t0), 24 hours (t24), 48 hours (t48), and 72 hours (t72) after transplantation. Grading is based on the ratio of arterial partial pressure of oxygen and fraction of inspired oxygen and the presence or absence of bilateral infiltrations consistent with reperfusion edema in chest radiographs. The judgment of chest radiographs has a major impact on PGD grading and can make the difference between the lowest (PGD 0) and highest (PGD 3) scores.

We aimed to determine the agreement rate of trained radiologists on postoperative chest radiographs and its impact on PGD grades studying a contemporary, large single-center cohort of LTx recipients.

MATERIALS AND METHODS**Patient Cohort and Study Outline**

A total of 497 patients who received double LTx in our institution between January 2010 and July 2016 were included in this retrospective, single-center analysis. Single LTx and multiorgan transplantations were excluded from this study. Patient demographics, operative parameters, and outcome data were extracted from our institutional LTx database and the hospital patient data management system.

Five thoracic radiology specialists with several years of experience in assessing chest radiographs in LTx recipients participated in the study. The raters were asked to retrospectively judge postoperative chest radiographs of all included patients at 4 time points (t0, t24, t48, and t72 hours) after transplantation, resulting in a total of 1988 x-rays. The experts were blinded to the clinical details, course, and outcome of the patients. Only the patient's name, date of birth, and time of transplantation were provided to the raters to facilitate viewing radiographs using the institution's standard image viewing software (IMPAX EE, Agfa Healthcare, Mortsel, Belgium). Raters were asked to independently assess the radiographs for presence or absence of bilateral infiltrations consistent with reperfusion edema and answer in binary form (yes/no).

Subgroup Analysis

To address potential bias introduced by the blinding of raters to preoperative and intraoperative details, the radiologists were asked to reevaluate

the radiographs of a subgroup of patients a second time. For this purpose, a random subgroup of 100 patients was drawn from the original cohort and radiologists were provided with basic preoperative and intraoperative characteristics for each patient (underlying diagnosis, recipient age, urgency status, intubation before transplantation, extracorporeal life support bridging, recipient body mass index [BMI], last donor partial pressure of arterial oxygen, use of ex vivo lung perfusion, total surgery time, number of administered erythrocyte and fresh-frozen plasma concentrates, and total graft ischemic time).

Statistical Analysis and Primary Graft Dysfunction Scoring

Percentages of full agreement among the 5 raters were calculated for each of the 4 time points. Chance-corrected agreement was calculated using Fleiss' kappa method.

PGD scores were calculated for all time points according to ISHLT guidelines using partial pressure of arterial oxygen/fraction of inspired oxygen (P/F) ratios and chest radiograph interpretation (Table E1). For patients on postoperative extracorporeal membrane oxygenation (ECMO), the PGD score was ungradable in case of a clear x-ray or PGD 3 in case of bilateral infiltrations. Extubated patients were not assigned a PGD score, but their radiographs at all time points were included in the interobserver agreement analysis.

To highlight the maximal impact of interobserver variability on PGD scoring, PGD grades were assigned using both a best case and a worst case scenario of chest x-ray diagnosis. In cases of full agreement among raters, their unanimous decision was used for calculating the score. For the remaining cases with a discordant x-ray reporting, PGD grading was simulated assuming a most favorable x-ray (no infiltrations) for the best case scenario or a nonfavorable x-ray (infiltrations present) for the worst case scenario. Furthermore, a subgroup analysis on patients with a P/F ratio lower than 200 at the respective time points was performed.

In an additional set of analyses, chance-corrected agreement between subgroups was calculated on the basis of the patient's BMI and type of transplantation (whole lungs vs atypical size reduction vs lobar transplantation).

Data were analyzed using IBM SPSS Statistics (New York, NY) software version 24.0. For calculation of Fleiss' kappa, a free SPSS software extension was used.⁴ To interpret kappa values, guidelines proposed by Altman⁵ and Landis and Koch⁶ were used (Table E2). Figures 1 and 2 were produced with GraphPad Prism 6 (GraphPad Software, San Diego, Calif).

RESULTS**Descriptive Analysis**

The study cohort consisted of 497 LTx recipients. The main underlying diagnoses were COPD (36.0%), pulmonary fibrosis (24.7%), and cystic fibrosis (24.5%). Twenty-eight patients (5.6%) were bridged to LTx by short-term mechanical ventilation, and 18 patients (3.6%) were bridged by extracorporeal life support. In 53 patients (10.7%), ex vivo lung perfusion of the donor lung was performed. Overall mean ischemic time was 345 ± 72 minutes, and the mean duration of surgery was 281 ± 56 minutes. ECMO was used for intraoperative support in 393 patients (79.1%), and 100 patients (20.1%) underwent transplantation without support. Cardiopulmonary bypass was used in 4 patients (0.8%). A total of 231 patients (46.5%) received whole lungs, and 197 (39.6%) transplants were size-reduced by extra-anatomic resection of the middle lobe or

FIGURE 1. Percentages of full agreement on the diagnosis of chest radiographs among 5 experienced radiologists at different time points after LTx. *t0*, 0 to 6 hours; *t24*, 24 hours; *t48*, 48 hours; *t72*, 72 hours.

the lingula. Sixty-nine patients (13.9%) received tri-lobar or bi-lobar transplantations. Detailed patient demographics are shown in [Table 1](#).

Interobserver Agreement

A total of 1988 chest radiographs were independently examined by 5 radiologists. Full agreement of all 5 raters was found in 826 cases (43.0%). In 266 (32.2%) of these radiographs, the uniform diagnosis was “presence of infiltrations,” whereas in 560 cases (67.8%) no infiltrations were found. At *t0*, radiologists were in full agreement in 224 cases (46.3%). They agreed on 216 radiographs (45.2%) at *t24*, 191 radiographs (40.0%) at *t48*, and 195 radiographs (40.9%) at *t72*. Percentages of agreement at different time points are depicted in [Figure 1](#).

Fleiss’ kappa statistics were calculated to quantify chance-corrected agreement. For both *t0* and *t24*, Fleiss’ kappa was 0.456, corresponding to a moderate agreement. At *t48* and *t72*, agreement was worse with a kappa of 0.405 and 0.409, respectively. An in-depth analysis revealed that these poor agreement rates were not due to a single outlier (data not shown). Because radiologists were completely blinded to all clinical parameters, and detailed background knowledge might have changed their judgment, we asked the raters to reevaluate a randomly created subgroup of 100 patients, this time having full information on preoperative and intraoperative patient data. Kappa values did not improve, and raters only reached “fair” chance-corrected agreement levels across all time points (0.335 at *t0*, 0.322 at *t24*, 0.365 at *t48*, and 0.358 at *t72*) ([Table 2](#)). In a next set of analyses, we determined whether certain preoperative and intraoperative factors were associated with inter-rater variability. Atypical size reductions (middle lobe and lingula resections) and lobar transplantations led to markedly lower kappa values of agreement at *t0* with 0.396 and 0.311, respectively, compared with whole LTxs with 0.520. In addition, high patient BMI greater than 25 was associated with reduced interobserver agreement. This difference was most pronounced at *t48* and *t72* with a kappa of 0.224 and 0.248 compared with 0.445 and 0.455 for BMI 18 to 25 or 0.457 and 0.429 for BMI less than 18 ([Table 3](#)).

Primary Graft Dysfunction Scores

Across all time points, 231 cases (11.6%) with a P/F ratio of less than 200 mm Hg were identified (n = 160 at *t0*,

FIGURE 2. Rates of PGD were calculated for all time points according to best and worst case scenarios of the radiologic judgment. In cases of full agreement, the unanimous x-ray diagnosis was used for calculating the PGD score. For the remaining cases with a discordant x-ray reporting, PGD was graded assuming a favorable x-ray (no infiltrations) for a best case scenario and a nonfavorable x-ray (infiltrations present) for a worst case scenario. This led to a large variation in PGD rates highlighting the heavy reliance of the current PGD scoring system on the radiologic component. *PGD*, Primary graft dysfunction; *t0*, 0 to 6 hours; *t24*, 24 hours; *t48*, 48 hours; *t72*, 72 hours.

TABLE 1. Summary of patient demographics for the full cohort (n = 497) and the random subgroup of 100 patients

	Full cohort (n = 497)	Random subgroup (n = 100)
Age (mean ± SD)	45.8 ± 16.0	47.0 ± 15.0
Gender (m%/w%)	51.1/48.9	52.0/48.0
Height (cm) (mean ± SD)	167 ± 11	169 ± 10
Weight (kg) (mean ± SD)	61 ± 16	62 ± 15
BMI (mean ± SD)	22 ± 4	21 ± 4
Diagnosis (n; %)		
COPD	179 (36.0)	38 (38.0)
Fibrosis	123 (24.7)	20 (20.0)
Cystic fibrosis	122 (24.5)	22 (22.0)
Primary pulmonary hypertension	8 (1.6)	2 (2.0)
A1AD	25 (5.0)	6 (6.0)
Bronchiectasis	9 (1.8)	4 (4.0)
LAM	9 (1.8)	2 (2.0)
Sarcoidosis	6 (1.2)	3 (3.0)
Other	16 (3.2)	3 (3.0)
Pulmonary hypertension (n; %)	35 (7.0)	8 (8.0)
Waiting time (d) (mean ± SD)	168 ± 177	173 ± 182
High urgent recipients (n; %)	47 (9.5)	7 (7.0)
Intubation before transplant (n; %)	28 (5.6)	4 (4.0)
Extracorporeal life support bridging (n; %)	18 (3.6)	4 (4.0)
Donor last PaO ₂ at FiO ₂ = 1.0 (mean ± SD)	448 ± 100	438 ± 100
Donor last PaCO ₂ at FiO ₂ = 1.0 (mean ± SD)	38.8 ± 6.4	38.6 ± 5.9
Ex vivo lung perfusion (n; %)	53 (10.7)	16 (16.0)
Ischemic time (mean ± SD)	345 ± 72	347 ± 75
Type of transplant (n; %)		
Whole lungs	231 (46.5)	48 (48.0)
Size reduction	197 (39.6)	40 (40.0)
Lobar transplant	69 (13.9)	12 (12.0)
Type of circulatory support (n; %)		
no ECMO	100 (20.1)	22 (22.0)
intraoperative ECMO	372 (74.8)	73 (73.0)
postoperative prolonged ECMO	3 (0.6)	1 (1.0)
preoperative and intraoperative ECMO	18 (3.6)	3 (3.0)
cardiopulmonary bypass	4 (0.8)	1 (1.0)
Surgery duration (min) (mean ± SD)	281 ± 56	282 ± 60
Intraoperative transfusions (mean ± SD)	4.0 ± 2.7	4.3 ± 3.0
FFP (mean ± SD)	10.6 ± 4.8	11.7 ± 6.0
Induction (n; %)	382 (76.9)	78 (78.0)

SD, Standard deviation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; A1AD, alpha-1-antitrypsin deficiency; LAM, lymphangioleiomyomatosis; PaO₂, partial pressure of arterial oxygen; FiO₂, fraction of inspired oxygen; PaCO₂, partial pressure of arterial carbon dioxide; ECMO, extracorporeal membrane oxygenation; FFP, fresh-frozen plasma.

n = 24 at t24, n = 27 at t48, and n = 20 at t72). By definition, in these cases the chest radiograph diagnosis is the decisive factor between the highest and lowest PGD scores. In 134 of those 231 cases (58.0%), no full agreement on the presence and absence of infiltrations was found among the 5 radiologists. In 92 cases (n = 72 at t0, 6 at t24, 9 at t48, 5 at

t72), the majority of raters diagnosed infiltrations and the minority rated a clear chest radiograph. Therefore, a PGD grade of 3 would have been calculated according to 3 or more radiologists, but according to the other(s) a PGD 0 would have been documented. On the other hand, in 42 cases (23 at t0, 6 at t24, 5 at t48, 8 at t72), the majoritarian

TABLE 2. Kappa values representing interobserver agreement for the full cohort and random subgroup

	Full cohort (n = 497) kappa (95% CI)	Random subgroup (n = 100) kappa (95% CI)
0-6 h	0.456 (0.43-0.48)	0.335 (0.27-0.40)
24 h	0.456 (0.43-0.48)	0.322 (0.26-0.38)
48 h	0.405 (0.38-0.43)	0.365 (0.30-0.43)
72 h	0.409 (0.38-0.44)	0.358 (0.29-0.42)

CI, Confidence interval.

interpretation was “no infiltrations” but the dissenting radiologist(s) stated “infiltrations.” This means that the PGD grading would have changed from 0 to 3 following the interpretation of the disagreeing rater(s).

Furthermore, we calculated PGD rates for a best case and a worst case scenario of radiologic judgment (Figure 2). The biggest difference for PGD 3 was found at t0 (best case: 8.4% vs worst case: 28.4). This discrepancy was less pronounced at t24 (1.8% vs 4.8%), t48 (2.0% vs 5.3%), and t72 (0.2% vs 3.1%). Five patients (1.0%) were on postoperative ECMO at t0. According to current PGD criteria, 2 of them were categorized as ungradable, and 3 were graded PGD 3. Extracorporeal support was still present in 3 patients at t24 (0.6%), 2 patients at t48 (0.4%), and 1 patient at t72 (0.2%). According to the majority judgment of the chest radiograph, 2 patients at t24 and 1 patient at t48 were found to be ungradable. One patient at t24, t48, and t72 was scored PGD 3. Results are summarized in Video 1.

DISCUSSION

To the best of our knowledge, this is the first large-scale study evaluating interobserver variability of chest radiographs after LTx and its impact on PGD rates. We found that radiologists blinded to the patient’s clinical course had only a moderate agreement rate. This inconsistency could have led to an up- or downgrading of PGD in a significant number of patients (Graphical Abstract). In addition, we identified high BMI and size reduction as risk factors associated with discordant grading of chest radiographs. However, providing radiologists with basic preoperative and intraoperative patient characteristics did not improve chance-corrected agreement rates.

Interobserver variability of chest radiographs has been described in several smaller studies on acute respiratory distress syndrome (ARDS), which also uses a radiology-based grading system.^{7,8} Sjöding and colleagues⁹ found only a “moderate” agreement among 8 clinicians who were asked to grade 205 patients with ARDS and attributed 67% of the disagreement to the low reliability of chest radiographs. Rubenfeld and colleagues¹⁰ analyzed the results of 21 clinical care experts reviewing the x-rays of 28 patients and found only moderate agreement with a kappa of 0.55. In addition, near-full agreement (20/21 observers) was found in 43% of cases. In a larger study by Meade and colleagues,¹¹ 2 intensivists and 1 radiologist assessed 778 chest x-rays of 99 patients. Two raters finished a training module on ARDS chest x-ray reporting before the study, whereas no specific training was offered to the third. In pairwise comparisons, the 2 trained raters achieved high kappa values of 0.72 to 0.88. For all other pairings, the authors found only a level of “moderate” agreement (kappa 0.38 to 0.55), concluding that specific training could improve reliability. In contrast, a recent multicenter prospective study by Peng and colleagues¹² found only minor improvement after specific training in 268 intensivists with a kappa of 0.133 before and 0.178 after training. Our results of interobserver variability are in line with these reports, showing only fair to moderate agreement among 5 specialist radiologists when assessing post-LTx chest radiographs.

Although the radiologic criteria of ARDS are identical to those in PGD, it is important to highlight that the latter is assessing a postoperative situation. Postoperative radiographs are often difficult to interpret because of a variety of confounders, even for radiologists specialized in thoracic radiology. For example, postoperative bleeding or pleural collections could mimic bilateral infiltrations, especially in bedside chest radiographs.

Other factors frequently leading to inconsistent x-ray interpretations are size reductions and a high recipient BMI. In patients with a high BMI, atelectasis can develop during weaning when ventilation pressures are reduced. An erroneous interpretation of atelectasis could explain impaired interobserver agreement in our study cohort at t48 and

TABLE 3. Kappa values of patients subgrouped according to body mass index and the type of transplantation/size reduction at each time point

	BMI < 18.5 (n = 125) kappa (95% CI)	BMI 18.5-25 (n = 253) kappa (95% CI)	BMI > 25 (n = 96) kappa (95% CI)	Full size (n = 231) kappa (95% CI)	Size reduced (n = 197) kappa (95% CI)	Lobar (n = 69) kappa (95% CI)
0-6 h	0.500 (0.44-0.56)	0.482 (0.44-0.52)	0.377 (0.31-0.44)	0.520 (0.48-0.56)	0.396 (0.35-0.44)	0.311 (0.23-0.39)
24 h	0.502 (0.45-0.56)	0.501 (0.46-0.54)	0.334 (0.27-0.40)	0.470 (0.43-0.51)	0.455 (0.41-0.50)	0.322 (0.25-0.40)
48 h	0.457 (0.40-0.51)	0.445 (0.40-0.49)	0.244 (0.18-0.31)	0.364 (0.32-0.40)	0.408 (0.36-0.45)	0.391 (0.31-0.47)
72 h	0.429 (0.37-0.49)	0.455 (0.41-0.50)	0.248 (0.18-0.31)	0.352 (0.31-0.39)	0.440 (0.40-0.49)	0.325 (0.27-0.40)

BMI, Body mass index; CI, confidence interval.

VIDEO 1. Summary of the study rationale and overview of the most important findings and results. Video available at: [https://www.jtcvs.org/article/S0022-5223\(19\)30974-2/fulltext](https://www.jtcvs.org/article/S0022-5223(19)30974-2/fulltext).

t72. Moreover, extra-anatomic size reduction, such as removal of the middle lobe and lingula, usually results in bilateral hilar opacities. This can be easily misjudged as bilateral infiltrations, especially because the lung parenchyma next to the resection line can sometimes be congested. To the best of our knowledge, extra-anatomic size reductions are not a risk factor for the development of a reperfusion edema^{13,14}; however, radiographs of patients with size-reduced LTx showed markedly lower chance-corrected agreement rates among the 5 observers.

In daily routine, radiologists often lack full clinical background information of patients at the time they report on chest radiographs. Therefore, in this study the 5 raters were primarily blinded to clinical patient details. Ideally, radiologists should have full access to each patient's clinical data. Therefore, in a second set of analysis, we aimed to determine whether basic knowledge on clinical parameters might improve interobserver variability. Surprisingly, information on clinical parameters failed to improve interobserver agreement rates. The reason for this remains unclear. Radiologists may ascribe different degrees of importance to the additional clinical information provided, thus leading to a higher discordance. This finding represents further evidence of the difficult and subjective nature of judging postoperative chest radiographs.

Another factor worthy of discussion is that severe reperfusion edema has become rare in the modern era of LTx. A complete white-out of the chest radiographs is hardly ever seen. Instead, radiologic edematous changes tend to be subtle and therefore may be more difficult to interpret. Several factors account for the low number of severe reperfusion edema in recent series of LTx: improved donor management, optimal graft handling, and understanding the importance of controlled reperfusion. Maximal controlled reperfusion is achieved by liberal use of intraoperative ECMO. Several studies have demonstrated the benefits of controlled reperfusion for early graft function.¹⁵⁻¹⁸ Additionally, with a routine application of ECMO in LTx,

extremely low numbers of reperfusion edema have been reported.^{19,20} Because this is especially true for the later time points, the discrepancies between best and worst case scenarios in our study are less profound at t72. This is mainly a result of the high number of patients who are already extubated and the low frequency of impaired P/F ratios at this time point. Difficulties in reporting PGD rates are further aggravated by the controversy of prophylactic postoperative venoarterial ECMO. According to the latest ISHLT recommendation, in these patients solely the radiograph decides between ungradable and PGD 3.³

The question remains how to address these radiologic flaws in a future revision of the PGD scoring system. An approach of a joint radiograph judgment of multiple observers might improve the validity of chest radiograph diagnoses, but will not be feasible for most transplant centers because of limited personal resources. Computed tomography for assessment of reperfusion edema has been proposed by Belmaati and colleagues,²¹ but is also of limited practicability in daily routine. Although PGD rates are broadly used to report outcomes, they are rarely used for treatment decisions in the early post-transplant period. Functional measurements of the transplant lungs are generally more useful. As in other reports,²²⁻²⁴ P/F ratios alone resulted in a good correlation with long-term survival in our study cohort. However, short-term outcomes such as duration of mechanical ventilation only mildly correlated with P/F ratios at the different time points. We are currently evaluating other ventilation parameters, such as peak or mean ventilation pressure, tidal volume, or dynamic pulmonary compliance, which could be used in a future PGD score. These variables seem to correlate better with actual graft performance.

Study Limitations

This study has several limitations. First, its retrospective nature poses a potential bias, and a prospective multicenter validation cohort is needed to confirm our results. Although the single-center approach guarantees a homogenous patient cohort and a consistent quality of radiologic films, variabilities between different transplant centers are neglected. In addition, our raters were not presented with single chest radiographs for grading but rather a chronologic series of x-rays for each patient. Although this study design is close to the clinical reality, knowledge on the temporal change of x-rays might have influenced the grading.

CONCLUSIONS

Interobserver variability in grading chest radiographs after LTx is substantial. This might have a considerable impact on clinical practice, as well as research, using the score as an outcome parameter. Future revisions of the PGD score should take this into consideration.

Webcast

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Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: interobserver variability, lung transplantation, primary graft dysfunction

Discussion

Dr Frank D'Ovidio (New York, NY). I will start by saying that grading tools are set to facilitate improved knowledge and understanding as in the case of LTx. Over time, they get refined and new classifications are generated, and your article clearly identifies one of the limitations of the current grading

system for PGD.

Now, going back, whenever there is a human interpretation of a finding, it is never going to be unanimous; our senses are going to be driven by our perceptions. So it would be surprising if this wasn't the case, and your article confirms this as other articles in the literature. And going along the presentation from the invited speaker today just from a methodological standpoint, did your reviewers, your radiologists, have the same monitors to review the x-rays; in other words, were their working tools standardized?

Dr Stefan Schwarz (Vienna, Austria). Yes, the working tools regarding the monitors and the viewing software were the standard equipment and software of our institution and were therefore the same for all raters.

Dr D'Ovidio. Was the subjective vision perception tested for color, in particular for the gray scale?

Dr Schwarz. No, this was not tested specifically beforehand. The raters were analyzing typical signs of pulmonary edema on chest x-ray, such as Kerley lines, and peribronchial cuffing and patchy bilateral infiltrates, gray scale was not separately taken into account.

Dr D'Ovidio. That was more of a perception, so understanding if the readers had the same capability to interpret the gray scale. Having said that, and your answer responds a bit to the next question that I had was, were accepted criteria set up front to differentiate pulmonary edema from other type of infiltrates as you depicted from the lobar nonanatomic resections?

Dr Schwarz. The task of the radiologists was to grade these chest x-rays according to the current PGD scoring system and its radiologic component, meaning bilateral infiltrations consistent with pulmonary edema and their respective features on chest x-ray. These were radiologists with years of experience in the field, specialist thoracic radiologists. Because they were working in a high-volume LTx center, they were dealing with post-LTx chest x-rays on a daily basis and were proficient in this assessment. But there was no special consensus training, if you are alluding to that, beforehand.

Dr D'Ovidio. There is also literature to suggest that if there is a certain training up front before starting the study that may be helpful in augmenting the unanimous understanding or interpretation of the findings.

Dr Schwarz. That is a good point, and this is something to keep in mind for future studies. There have been studies, for example, in the field of acute respiratory distress syndrome in which raters receiving consensus training showed improved agreement rates. However,

other studies did the same and didn't find this significant improvement.

Dr D'Ovidio. So are you and your group exploring other more objective tools to be implemented in the algorithm for PGD grading?

Dr Schwarz. That is an excellent point, and we are currently evaluating different parameters, for example ventilation parameters, that might be of use in future revisions of the PGD score. Peak pressure, mean pressure, tidal volume, and dynamic compliance are promising and might improve the score.

Dr D'Ovidio. Is your center using PGD as a clinical tool or a retrospective tool? In other words, are you currently prospectively evaluating the grade or is it just for reporting and interpretation of it?

Dr Schwarz. At our center, we prospectively report and document PGD at every time point for every patient and use it as a major outcome parameter for research.

Dr Marcelo Cypel (Toronto, Ontario, Canada). That is a great study. It is too bad that this was not really analyzed before the current classification just published recently. But it has been always I think my concern of underreporting of PGD grades in the literature because of this x-ray interpretation.

Just a few years ago I reviewed an article for donation after cardiac death LTx in which half of the patients had P/F ratios less than 200 but yet the PGD 3 rates were 10%, and I never could understand that. Really, a patient who arrives in the intensive care unit with a low P/F ratio after LTx, with rare exceptions, that's a PGD, and I don't know why we are still classifying them as PGD 0 if the P/F ratio was 150 and the x-ray is interpreted as clear. Do you think we should take the x-ray completely out of the classification as a solution?

Dr Schwarz. Well, that's something that has to be discussed in the next revisions of the score. The solution would be taking it completely out or at least introducing other parameters such as ventilatory parameters, as we have mentioned, to improve the score.

TABLE E1. Primary graft dysfunction grades according to current International Society for Heart and Lung Transplantation guidelines

PGD grade	Chest radiograph	PaO ₂ /FiO ₂ ratio
Grade 0	No infiltration	Any
Grade 1	Infiltration	>300
Grade 2	Infiltration	200-300
Grade 3	Infiltration	<200 or ECLS
Ungradable	No infiltration	ECLS

PGD, Primary graft dysfunction; PaO₂/FiO₂, partial pressure of arterial oxygen/fraction of inspired oxygen; ECLS, extracorporeal life support.

TABLE E2. Scale used for interpretation of kappa values and their corresponding level of chance-corrected agreement

Kappa value	Strength of agreement	
	Landis and Koch	Altman
<0.00	Poor	—
0.00-0.20	Slight	Poor
0.21-0.40	Fair	Fair
0.41-0.60	Moderate	Moderate
0.61-0.80	Substantial	Good
0.81-1.00	Almost perfect	Very good