CHEST Online Supplement

# Latent Class Analysis Identifies Distinct Phenotypes of Primary Graft Dysfunction After Lung Transplantation

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**e-Appendix 1.** IRB Approval Details by Site:

Columbia University IRB:
Approved, protocol number IRBAAAC1924.

University of Pennsylvania IRB:
Approved, protocol number 806468.

Vanderbilt University IRB:
Approved, protocol number 030089.

Stanford University IRB:
Approved, protocol number 13554.

University of Alabama IRB:
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Johns Hopkins University IRB:
Approved, protocol number NA_00009182.

University of Michigan IRB:
Approved, protocol number HUM00016290.

Duke University IRB:
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University of Chicago IRB:
Approved, protocol number 14756A.

University of Pittsburgh IRB:
Approved, protocol number 0703089.



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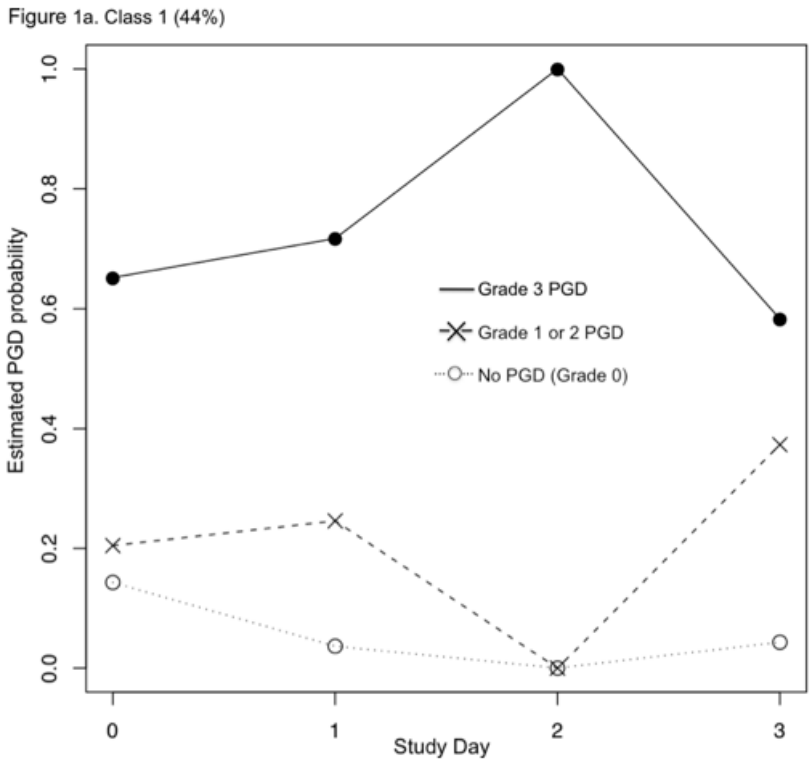
**e-Figure 1**. 4 Class model generated using latent class analysis. The y-axis indicates the probability of ISHLT PGD grade on a given day. The x-axis is the post-operative day. A given probability of PGD grade for each day is represented by symbols connected by corresponding lines (solid circle is grade 3, X is grade 1 or 2, hollow circle is grade 0). The line with the highest probability generated from the model indicates that members of that class are most likely to have a particular grade on a particular day.




**e-Figure 1a**. Latent Class 1 (44% of grade 3 PGD population): Grade 3 PGD present on day 0 that persists to day 3. Grade 3 (solid circles) has the highest probability on all study days in this class.



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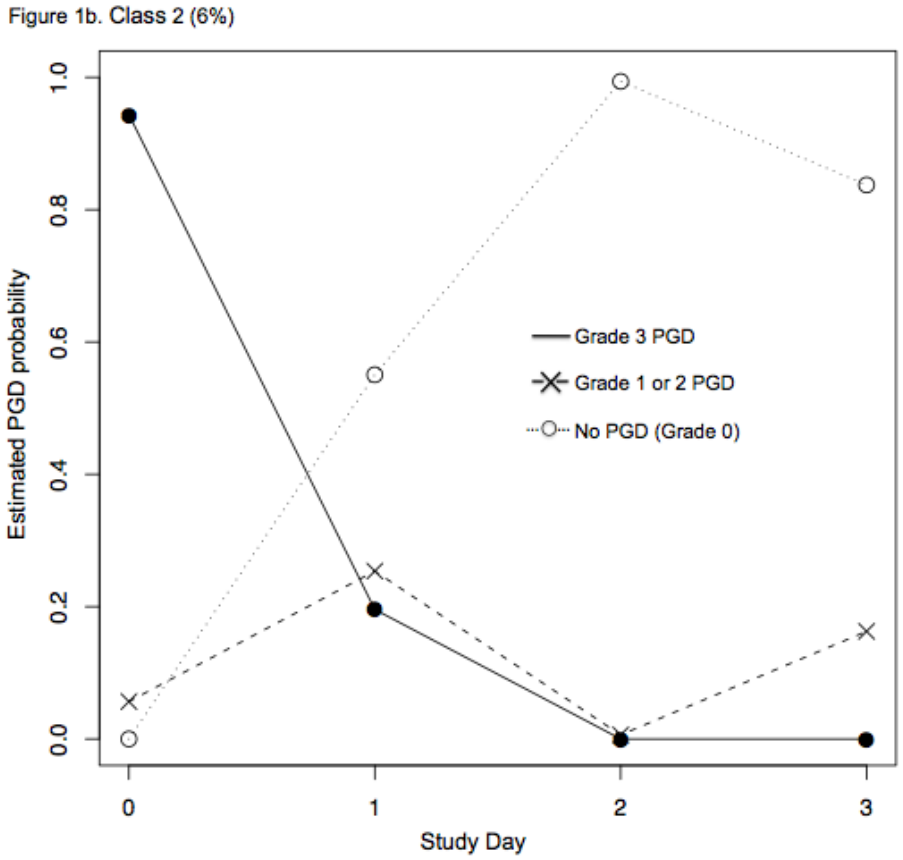


**e-Figure 1b.** Grade 3 PGD present on day 0 that resolves completely to grade 0 by day 3. On day 0, grade 3 (solid circles) has the highest probability, but the probability of grade 3 decreases by day 1, and on days 2 and 3, grade 0 has the highest probability (hollow circle).



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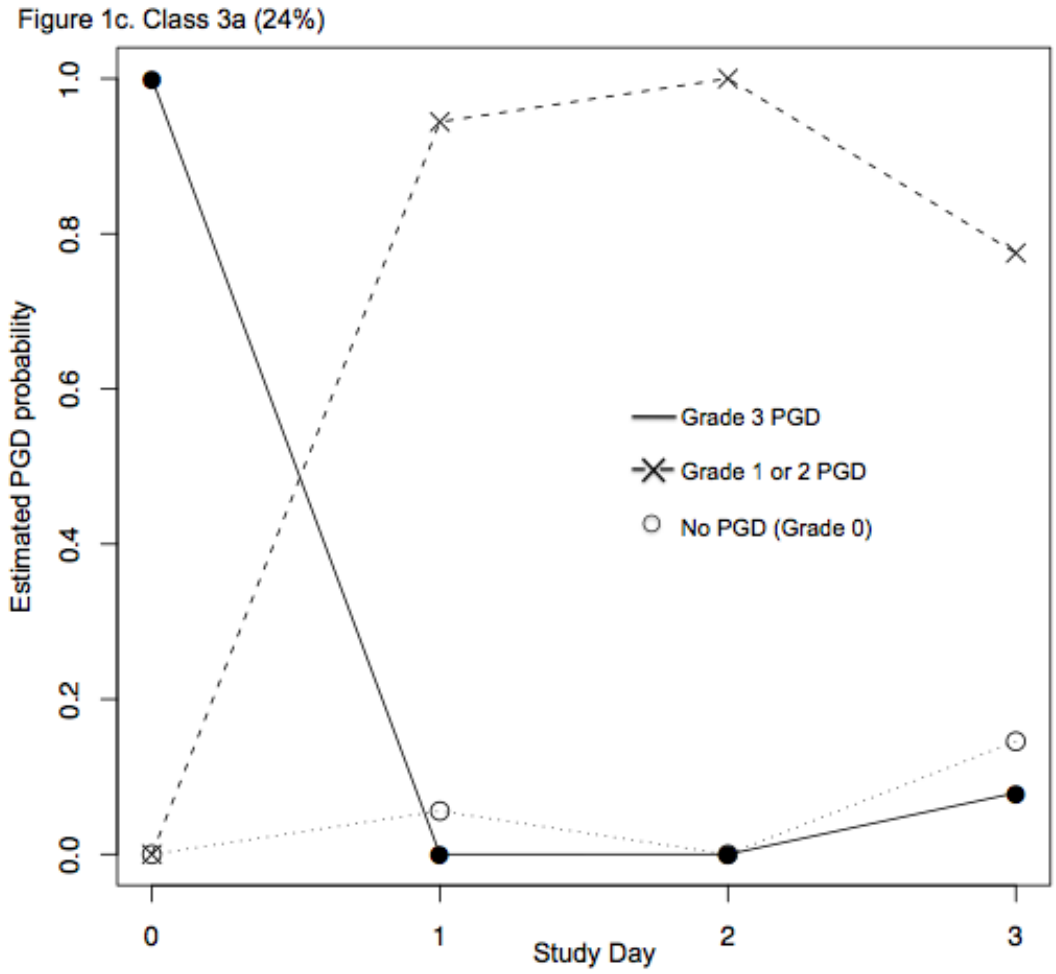


**e-Figure 1c.** Latent Class 3a (24% of grade 3 PGD population) Grade 3 PGD on day 0 that attenuates to lower grades 1 and 2 by day 1, but does not completely resolve by day 3. On day 0, grade 3 (solid circles) has the highest probability, but decreases by day 1, and on days 1, 2, and 3, intermediate grades (1, 2, denoted by X) have the highest probability.



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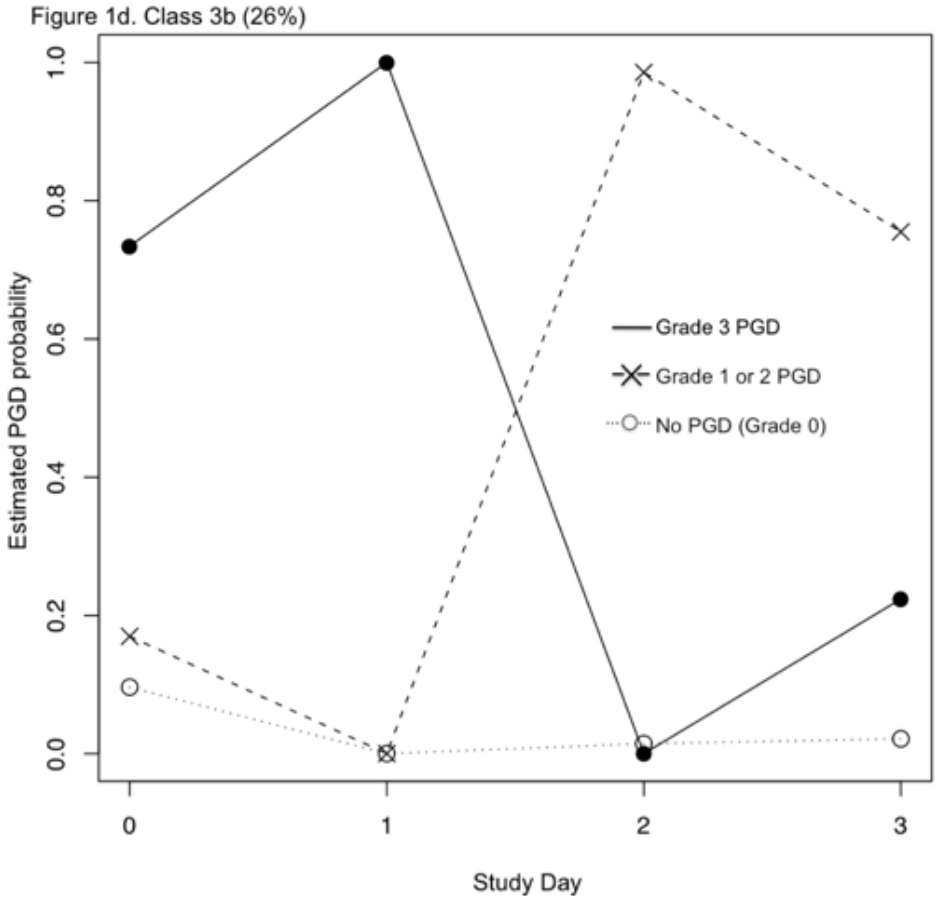


**e-Figure 1d**. Latent Class 3b (26% of grade 3 PGD population) Grade 3 PGD on day 0 that attenuates to lower grades 1 and 2 later, by day 2, but does not completely resolve by day 3. On day 0, grade 3 (solid circles) has the highest probability, but decreases by day 2, and on days 2 and 3, intermediate grades (1, 2, denoted by X) have the highest probability.



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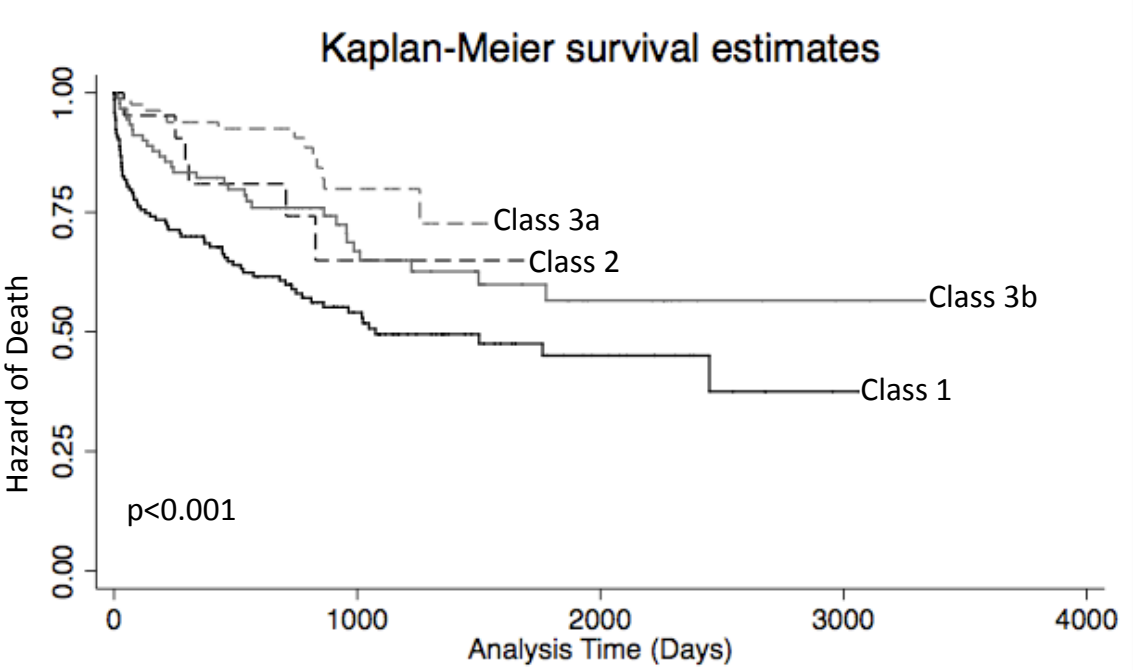
**e-Figure 2.** Association of classes with time to death in the 4 class model. P value generated using the log rank test.



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**e-Table 1.** Frequencies of demographic characteristics between classes in the 4 class model. P values generated using chi square and t-tests. PRBC=volume of packed red blood cells transfused within 24 hours. PAP=pulmonary artery pressure at the time of transplantation.

| | *Class 1 (n=157)* | *Class 2 (n=23)* | *Class 3a (n=87)* | *Class 3b (n=94)* | *p Value* |
|---|---|---|---|---|---|
| **Recipient Characteristics** | | | | | |
| ***Recipient Age*** | 53.7 ± 11.4 | 50.8 ± 15.1 | 54.4 ± 12.6 | 50.7 ± 12.6 | 0.27 |
| ***Native Disease*** | | | | | |
| *COPD* | 39 (25%) | 2 (9%) | 27 (31%) | 25 (27%) | 0.13 |
| *CF* | 9 (6%) | 5 (22%) | 11 (13%) | 13 (14%) | |
| *IPF* | 67 (43%) | 12 (52%) | 38 (44%) | 37 (40%) | |
| *PPH* | 11 (7%) | 1(4%) | 3 (3%) | 5 (5%) | |
| *Sarcoid* | 17 (11%) | 1(4%) | 2 (2%) | 4 (4%) | |
| *Other* | 14 (9%) | 2 (9%) | 6 (7%) | 9 (10%) | |
| ***Female Recipient*** | 72 (46%) | 9 (39%) | 37 (43%) | 45 (48%) | 0.83 |
| ***Prior Pregnancy*** | 60 (83%) | 5 (56%) | 26 (70%) | 29 (64%) | 0.07 |
| ***Recipient Race*** | | | | | |
| *Caucasian* | 120 (76%) | 16 (70%) | 69 (79%) | 75 (80%) | 0.36 |
| *African American* | 28 (18%) | 6 (26%) | 10 (11%) | 12 (13%) | |
| *Hispanic* | 3 (2%0 | 1 (4%) | 6 (7%) | 4 (4%) | |
| *Asian* | 4 (3%) | 0 (0%) | 0 (0%) | 3 (3%) | |
| *Other* | 2 (1%) | 0 (0%) | 2 (2%) | 0 (0%) | |
| ***BMI Recipient*** | 27.1 ± 4.8 | 24.6 ± 5.1 | 26.1 ± 4.8 | 25.9 ± 6.3 | 0.01 |
| ***LAS (n=312)*** | 46.4 ± 15.7 | 46 ± 11.8 | 45.5 ± 15.7 | 48.0 ± 15.7 | 0.46 |
| **Donor Characteristics** | | | | | |
| ***Female Donor*** | 76 (48%) | 12 (52%) | 32 (37%) | 41 (44%) | 0.30 |
| ***Donor Age*** | 35.9 ± 14.9 | 28.6 ± 10.4 | 35.2 ± 13.6 | 35.3 ± 13.1 | 0.17 |
| ***Donor Race*** | | | | | 0.42 |
| *Caucasian* | 108 (69%) | 15 (65%) | 62 (71%) | 56 (60%) | |
| *African American* | 31 (20%) | 6 (26%0 | 12 (14%) | 20 (21%) | |
| *Hispanic* | 12 (8%) | 2 (9%0 | 8 (9%) | 15 (16%) | |
| *Other* | 6 (4%) | 0 (0%) | 5 (6%) | 3 (3%) | |
| ***Donor Vent Days*** | | | | | |
| *One* | 52 (33%) | 5 (22%) | 18 (21%) | 20 (21%) | 0.36 |
| *Two* | 46 (29%) | 5 (22%) | 26 (30%) | 26 (28%) | |
| *Three* | 27 (17%) | 7 (30%) | 18 (21%) | 22 (23%) | |
| *Four* | 32 (20%) | 6 (26%) | 25 (29%) | 26 (38%) | |
| ***Donor Smoking*** | 80 (51%) | 6 (26%) | 36 (41%) | 45 (48%) | 0.11 |
| ***Donor Mode of Death*** | | | | | |
| *Trauma* | 61 (39%) | 8 (35%) | 41 (47%) | 40 (43%) | 0.10 |
| *Stroke* | 71 (45%) | 9 (39%) | 32 (37%) | 40 (43%) | |
| *Anoxia* | 48 (5%) | 3 (13%) | 12 (14%)) | 5 (5%) | |
| *Other* | 17 (11%) | 3 (13%) | 2 (2%) | 9 (10%) | |



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|---|---|---|---|---|---|
| **Operative Characteristics** | | | | | |
| ***Bilateral Transplant*** | 104 (66%) | 14 (61%) | 53 (61%) | 70 (74%) | 0.24 |
| ***Cardiopulmonary Bypass*** | 94 (60%) | 10 (43%) | 34 (39%) | 56 (60%) | 0.007 |
| ***Intra-Op Crystalloids*** | 973.4 ± 1542 | 1637.0 ± 2179.3 | 1680.5 ± 1971 | 1333.0 ± 2030.8 | 0.01 |
| ***Intra-Op Nitric Oxide*** | 95 (61%) | 15 (65%) | 55 (63%) | 61 (65%) | 0.90 |
| ***Reperfusion FiO2*** | 67.4 ± 28.7 | 71.8 ± 27.3 | 69.3 ± 29.8 | 64.0 ± 28.8 | 0.95 |
| ***Tidal Volume (cc/kg)*** | 7.0± 3.1 | 7.9 ± 2.7 | 7.1 ± 2.7 | 6.9 ± 2.8 | 0.39 |
| ***PRBC (mL)*** | 1123.8 ± 1522 | 732.6 ± 1014.5 | 989.4 ± 1317.3 | 958.3 ± 1390.5 | 0.09 |
| ***mean PAP (mmHg)*** | 35.5 ± 17.2 | 29.7 ± 13.5 | 27.9 ± 12.8 | 31.0 ± 11.3 | <0.01 |

**e-Table 2.** Frequencies of demographic characteristics using the 3 class analysis in the non-imputed dataset. Chi square and t tests were used to generate p values. . PRBC=volume of packed red blood cells transfused within 24 hours. PAP=pulmonary artery pressure at the time of transplantation.

| | *Number with data* | *Class 1 (n=197)* | *Class 2 (n=25)* | *Class 3 (n=139)* | *P Value* |
|---|---|---|---|---|---|
| **Recipient Characteristics** | | | | | |
| ***Recipient Age*** | 358 | 53.0 ± 12.3 | 51.5 ± 14.6 | 53.4 ± 12.4 | 0.48 |
| ***Native Disease*** | 359 | | | | 0.50 |
| *COPD* | | 50 (26%) | 3 (12%) | 39 (28%) | |
| *CF* | | 17 (9%) | 5 (20%) | 16 (12%) | |
| *IPF* | | 81 (41%) | 13 (52%) | 60 (43%) | |
| *PPH* | | 11 (6%) | 1 (4%) | 8 (6%) | |
| *Sarcoid* | | 17 (9%) | 1 (4%) | 6 (4%) | |
| *CHD* | | 3 (2%) | 0 (0%) | 0 (0%) | |
| *Other* | | 17 (9%) | 2 (8%) | 9 (7%) | |
| ***Female Recipient*** | 360 | 92 (47%) | 10 (40%) | 61 (44%) | 0.76 |
| ***Prior Pregnancy*** | 251 | 40 (33%) | 6 (27%) | 32 (30%) | 0.97 |
| ***Recipient Race*** | 360 | | | | |
| *Caucasian* | | 152 (77%) | 18 (72%) | 109 (78%) | 0.29 |
| *African American* | | 32 (16%) | 6 (24%) | 18 (13%) | |
| *Hispanic* | | 4 (2%) | 1 (4%) | 9 (7%) | |
| *Asian* | | 6 (3%) | 0 (0%) | 1 (1%) | |
| *Other* | | 3 (2%) | 0 (0%) | 1 (1%) | |



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| | | | | | |
|---|---|---|---|---|---|
| ***Recipient Weight*** | 354 | 75.8 ± 19 | 70 ± 15.7 | 75.2 ± 17.9 | 0.52 |
| ***LAS*** | 312 | 46.9 ± 15.9 | 47.6 ± 14.2 | 45.7 ± 15 | 0.65 |
| **Donor Characteristics** | | | | | |
| ***Female Donor*** | 359 | 91 (47%) | 14 (56%) | 57 (41%) | 0.52 |
| ***Donor Age*** | 359 | 36.0 ± 14.5 | 27.8 ± 10.4 | 35.5 ± 13.1 | 0.09 |
| ***Donor Race*** | 358 | | | | 0.64 |
| *Caucasian* | | 127 (65%) | 16 (67%) | 96 (69%) | |
| *Black* | | 42 (22%) | 6 (25%) | 20 (14%) | |
| *Hispanic* | | 17 (9%) | 2 (8%) | 18 (13%) | |
| *Asian* | | 7 (4%) | 0 (0%0 | 2 (2%) | |
| *Other* | | 2 (1%) | 0 (0%) | 2 (1%) | |
| **Donor Vent Days** | 315 | | | | |
| *One* | | 44 (27%) | 6 (25%) | 26 (21%) | 0.36 |
| *Two* | | 52 (31%) | 6 (25%) | 31 (22%) | |
| *Three* | | 32 (20%) | 7 (29%) | 32 (26%) | |
| *> 4* | | 69 (60%) | 6 (5%) | 40 (35%) | |
| ***Donor Smoking*** | 350 | 92 (60%) | 6 (24%) | 56 (36%) | 0.11 |
| ***Donor Mode of Death*** | 360 | | | | 0.13 |
| *Trauma* | | 79 (40%) | 10 (40%) | 59 (42%) | |
| *Suicide* | | 6 (3%) | 1 (4%) | 0 (0%) | |
| *Stroke* | | 83 (42%) | 9 (36%) | 59 (39%) | |
| *Anoxia* | | 10 (5%) | 2 (8%) | 14 (11%) | |
| *Unknown* | | 1 (0.5%) | 1 (4%) | 5 (4%) | |
| *Other* | | 16 (8%) | 2 (8%) | 2 (1%) | |
| **Operative Characteristics** | | | | | |
| ***Bilateral Transplant*** | 356 | 133 (69%) | 15 (63%) | 91 (66%) | 0.78 |
| ***Cardiopulmonary Bypass*** | 357 | 118 (61%) | 10 (42%) | 63 (46%) | 0.05 |
| ***Intra-Op nitric oxide*** | 359 | 119 (60%) | 15 (63%) | 85 (62%) | 0.96 |
| ***Intra-Op Crystalloids (mL)*** | 166 | 2391 ± 1596 | 3229 ± 1958 | 3156 ± 1950 | 0.20 |
| ***Reperfusion FiO2*** | 200 | 72.6 ± 29.8 | 68.7 ± 28.4 | 70.2 ± 30.7 | 0.91 |
| ***Tidal Volume (cc)*** | 191 | 587.7 ± 125 | 560.5 ± 107 | 612.1 ± 115 | 0.64 |
| ***PRBC (mL)*** | 277 | 1398 ± 1604 | 1157 ± 1041 | 1252 ± 1323 | 0.03 |
| ***mean PAP (mmHg)*** | 285 | 33.7 ± 16.8 | 29.7 ± 12.6 | 29.2 ± 12.4 | 0.002 |



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**e-Table 3.** Frequencies of demographic characteristics between the 4 classes in the non-imputed dataset. Chi square and t tests were used to generate p values. . PRBC=volume of packed red blood cells transfused within 24 hours. PAP=pulmonary artery pressure at the time of transplantation. Numbers with data are presented in supplemental table 2.

| | *Class 1 (n=157)* | *Class 2 (n=23)* | *Class 3a (n=87)* | *Class 3b (n=94)* | *p Value* |
|---|---|---|---|---|---|
| **Recipient Characteristics** | | | | | |
| ***Recipient Age*** | 53.6 ± 11.4 | 50.8 ± 15.1 | 54.5 ± 12.7 | 51.1 ± 13.1 | 0.22 |
| ***Native Disease*** | | | | | |
| *COPD* | 39 (25%) | 2 (9%) | 26 (30%) | 25 (27%) | 0.13 |
| *CF* | 9 (6%) | 5 (22%) | 11 (13%) | 13 (14%) | |
| *IPF* | 67 (43%) | 12 (52%) | 38 (44%) | 37 (40%) | |
| *PPH* | 11 (7%) | 1(4%) | 3 (3%) | 5 (5%) | |
| *Sarcoid* | 17 (11%) | 1(4%) | 2 (2%) | 4 (4%) | |
| *CHD* | 3 (2%) | 0 (0%) | 0 (0%) | 0 (0%) | |
| *Other* | 11 (7%) | 2 (9%) | 6 (7%) | 9 (10%) | |
| ***Female Recipient*** | 72 (46%) | 9 (39%) | 37 (43%) | 45 (48%) | 0.85 |
| ***Prior Pregnancy*** | 30 (32%) | 5 (25%) | 27 (31%) | 16 (31%) | 0.84 |
| ***Recipient Race*** | | | | | 0.36 |
| *Caucasian* | 52 (33%) | 7 (30%) | 27 (31%) | 32 (34%) | |
| *African American* | 120 (76%) | 16 (70%) | 68 (79%) | 75 (80%) | |
| *Hispanic* | 28 (18%) | 6 (26%) | 10 (12%) | 12 (13%) | |
| *Asian* | 3 (2%) | 1 (4%) | 6 (7%) | 4 (4%) | |
| *Other* | 4 (3%) | 0 (0%) | 0 (0%) | 3 (3%) | |
| ***Recipient Weight*** | 76.7 ± 17.6 | 70.5 ± 15.3 | 75.2 ± 17.3 | 73.7 ± 20.7 | 0.16 |
| ***LAS*** | 46.4 ± 15.7 | 46 ± 11.8 | 45.5 ± 15.7 | 48.0 ± 15.7 | 0.46 |
| **Donor Characteristics** | | | | | |
| ***Female Donor*** | 76 (49%) | 12 (52%) | 33 (38%) | 41 (44%) | 0.57 |
| ***Donor Age*** | 36.5 ± 14.8 | 28.6 ± 10.4 | 34.8 ± 13.2 | 35.3 ± 13.2 | 0.17 |
| ***Donor Race*** | | | | | 0.65 |
| *Caucasian* | 107 (69%) | 14 (64%) | 62 (71%) | 56 (60%) | |
| *Black* | 30 (19%) | 6 (27%) | 12 (14%) | 20 (21%) | |
| *Hispanic* | 12 (8%) | 2 (9%) | 8 (9%) | 15 (16%) | |
| *Asian* | 4 (3%) | 9 (0%) | 4 (5%) | 2 (2%) | |
| *Other* | 2 (1%) | 0 (0%) | 1 (1%) | 1 (1%) | |
| ***Donor Days on Ventilator*** | | | | | |
| ***One*** | 41 (26%) | 5 (22%) | 15 (17%) | 15 (16%) | 0.51 |
| ***Two*** | 45 (29%) | 5 (22%) | 24 (28%) | 25 (37%) | |
| ***Three*** | 24 (15%) | 7 (30%) | 19 (22%) | 21(22%) | |
| ***≥ 4*** | 47 (30%) | 6 (26%) | 29 (33%) | 33 (35%) | |



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| | | | | | |
|---|---|---|---|---|---|
| ***Donor Smoking*** | 75 (50%) | 6 (26%) | 32 (37%) | 41 (45%) | 0.25 |
| ***Donor Mode of Death*** | | | | | 0.39 |
| *Trauma* | 62 (39%) | 8 (35%) | 40 (47%) | 40 (43%) | |
| *Suicide* | 4 (3%) | 1 (4%) | 1 (1%) | 1 (1%) | |
| *Stroke* | 71 (46%) | 9 (39%) | 31 (36%) | 40 (43%) | |
| *Anoxia* | 8 (5) | 2 (9%) | 11 (13%) | 5 (5%) | |
| *Other* | 10 (6%) | 2 (9%) | 1 (1%) | 7 (7%) | |
| **Operative Characteristics** | | | | | |
| ***Cardiopulmonary Bypass (n=194)*** | 93 (59%) | 10 (43%) | 33 (38%) | 55 (60%) | 0.020 |
| ***Bilateral Transplant*** | 103 (66%) | 14 (61%) | 53 (62%) | 69 (75%) | 0.27 |
| ***Intra-Op Nitric Oxide*** | 95 (61%) | 15 (65%) | 55 (63%) | 61 (65%) | 0.90 |
| ***Intra-Op Crystalloids (mL)*** | 2351 ± 1583 | 3422.7 ± 1930 | 2850 ± 1807 | 3132.5 ± 2013.1 | 0.39 |
| ***Tidal Volume (cc)*** | 597.5 ± 119 | 567.6 ± 106 | 614.6 ± 118 | 575.8 ± 125 | 0.62 |
| ***Reperfusion FiO2*** | 73.8 ± 30.2 | 69.3 ± 29.2 | 69 ± 31.2 | 71.3 ± 28.0 | 0.90 |
| ***PRBC (mL)*** | 1389.8 ± 1579 | 1203.5 ± 1063.6 | 1526 ± 1372 | 1126 ± 1443.9 | 0.26 |
| ***mean PAP (mmHg)*** | 34.3 ± 17.7 | 29.7 ± 13 | 28.6 ± 12.9 | 30.3 ± 11.7 | <0.01 |



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