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Body mass index and mortality following primary graft dysfunction: A Lung Transplant Outcomes Group study

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Higher body mass index (BMI) increases the risk of developing primary graft dysfunction (PGD) after lung transplantation; whether BMI is associated with decreased survival after PGD is unknown. We utilized the Lung Transplant Outcomes Group cohort of 1,538 subjects from 2011-2018. We evaluated the association between preoperative BMI and graft survival among subjects with severe PGD using Cox proportional hazards models with linear splines. Models were stratified by center and adjusted for sex, age, Lung Allocation Score, and diagnosis. PGD developed in 383 subjects. Among subjects with PGD, low BMI was associated with increased mortality while high BMI was not associated with differential mortality, compared to normal BMI. Results were similar for 90-day and 1-year survival. While high BMI increases the risk of developing PGD, it does not appear to be associated with survival after PGD. Future work should focus on PGD prevention rather than PGD management in patients with obesity.
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Primary graft dysfunction (PGD) is acute lung injury occurring within 72 hours of lung transplantation affecting 15% to 30% of recipients.[1] Death due to PGD partly accounts for excess post-transplant mortality among obese patients.[1-3] Yet, it is unknown whether this is due to increased PGD incidence in patients with obesity[1] or because body mass index (BMI) influences survival after PGD.

BMI could influence survival after PGD in multiple ways. Excess adipose tissue may have protective immunomodulatory effects,[4] alter intensive care unit management,[5] or lead to

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atelectasis with overestimation of lung injury. Alternatively, adipose tissue may produce proinflammatory cytokines that worsen lung injury.[6,7] Low BMI may also alter survival after PGD. Malnutrition may result in the inability to meet the metabolic demands of critical illness, alter immune function, or reflect greater disease severity.[8] We sought to evaluate the association between BMI and survival among subjects with PGD after lung transplantation. We hypothesized that both high and low BMI would be associated with an increased risk of death after PGD.

We performed a retrospective analysis of subjects enrolled in the multicenter Lung Transplant Outcomes Group cohort study between 2011 and 2018. We included subjects with severe PGD defined as the ratio of the partial pressure of oxygen in arterial blood (PaO_2) to the fraction of inspiratory oxygen concentration (FiO_2) (PaO_2/FiO_2) < 200 or extracorporeal membrane oxygen (ECMO) and bilateral infiltrates at 48 or 72 hours after transplantation.[1]

Our primary exposure variable was BMI at transplantation. Our primary outcome was graft survival defined as the time from transplantation to death or retransplantation. Subjects who were still alive were censored on October 9, 2021. Secondary outcomes were 90-day and 1-year survival. We used Cox proportional hazards models stratified by center, with linear splines to allow for nonlinear associations between BMI and graft survival. Knots were placed at values of 18.5, 24, 28, and 32 kg/m^2 to maintain consistency with the World Health Organization's definition of underweight, prior literature identifying potential inflection points at 24 and 28 kg/m^2, and reports of use of 32 kg/m^2 as threshold for candidate selection.[3,9] To maximize interpretability of spline models and demonstrate how the association differs over a range of BMI, we reported the hazards of death or retransplantation for an individual with a given BMI relative to the same subject if their BMI was 24 kg/m^2. We used the "pspline" function (R for statistical computing, v4.1) to display the relationship between BMI and survival. We confirmed the proportional hazards assumption via regression of Schoenfeld residuals over time. We used directed acyclic graphs to identify variables that

Table 1 Recipient, Donor, and Operative Characteristics of Subjects Who Developed PGD by Body Mass Index Group

Recipient characteristics	BMI < 18.5 kg/m^2	BMI 18.5-23.9 kg/m^2	BMI 24-27.9 kg/m^2	BMI 28-32 kg/m^2	BMI > 32 kg/m^2
	N = 25	N = 103	N = 109	N = 113	N = 32
Age, years	32 (23-51)	51 (37-62)	61 (52-66)	58 (53-64)	55 (50-61)
Sex, female	18 (72%)	53 (51%)	44 (40%)	41 (36%)	15 (47%)
LAS at transplantation	85 (52-90)	47 (37-69)	43 (37-53)	47 (38-64)	49 (41-85)
Race					
White	22 (92%)	86 (85%)	82 (80%)	88 (81%)	24 (77%)
Black	0 (0%)	9 (9%)	9 (9%)	17 (16%)	7 (23%)
Other	2 (8%)	6 (6%)	12 (12%)	4 (4%)	0 (0%)
Hispanic ethnicity	1 (4%)	5 (5%)	6 (6%)	13 (12%)	1 (3%)
Prior smoking	4 16%)	41 (44%)	56 (54%)	71 (65%)	20 (67%)
Diagnosis group					
Obstructive lung disease	1 (4%)	19 (18%)	17 (16%)	12 (11%)	5 (16%)
Pulmonary vascular disease	1 (4%)	16 (16%)	10 (9%)	9 (8%)	0 (0%)
Cystic fibrosis	10 (42%)	25 (24%)	4 (4%)	0 (0%)	0 (0%)
Interstitial lung disease	13 (52%)	43 (42%)	78 (72%)	92 (81%)	27 (84%)
Preoperative steroid	18 (75%)	57 (56%)	53 (51%)	58 (55%)	21 (66%)
Preoperative mechanical ventilation	8 (32%)	14 (14%)	6 (6%)	10 (9%)	3 (10%)
Operative characteristics					
Single lung transplant	2 (8%)	17 (17%)	18 (17%)	22 (19%)	9 (28%)
Intraoperative PRBC	23 (96%)	84 (83%)	84 (80%)	85 (80%)	26 (81%)
Total ischemic time, hours	6 (5-8)	6 (5-8)	6 (5-8)	6 (5-7)	6 (5-6)
Intraoperative bypass or ECMO	21 (84%)	76 (75%)	74 (70%)	86 (79%)	23 (74%)
Donor characteristics					
Donor age, years	39 (23-51)	35 (25-50)	38 (28-51)	35 (27-50)	34 (24-49)
Donor sex, female	12 (48%)	35 (35%)	51 (47%)	45 (40%)	12 (38%)
Donor smoking history	13 (57%)	47 (48%)	48 (53%)	43 (45%)	14 (47%)

Abbreviations: BMI, body mass index; ECMO, extracorporeal membrane oxygen; LAS, Lung Allocation Score; PGD, primary graft dysfunction; pRBC, packed red blood cell.

Continuous variables are reported as median (interquartile range).

Missing values: 14 (4%) for race and ethnicity; 19 (5%) for prior smoking; 16 (4%) for recipient preoperative steroid use; 10 (3%) for preoperative mechanical ventilation; 14 (4%) for intraoperative transfusion; 19 (5%) for intraoperative ECMO; 3 (1%) for donor age and sex; 47 (12%) for donor smoking history.

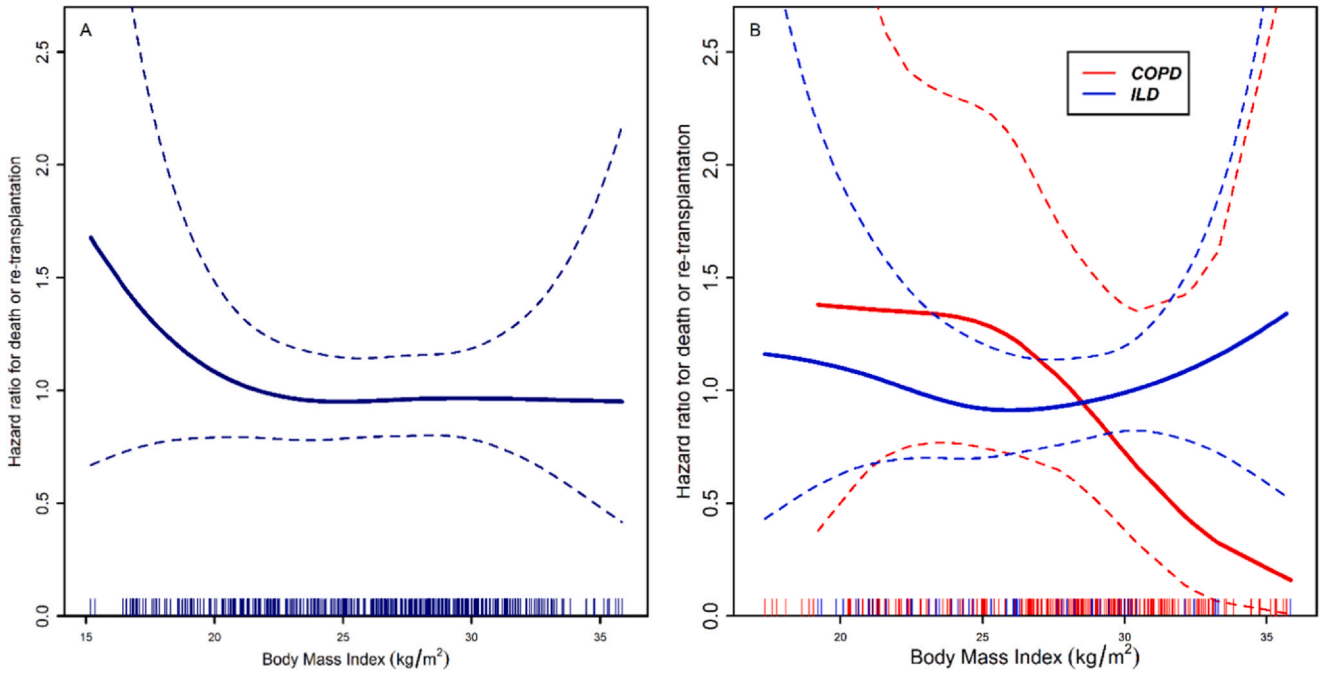

Figure 1 Hazard ratio for death or retransplantation (A) in all subjects with PGD, and (B) by diagnosis. Models are configured in a penalized spline function that smooths the line segments to allow for the curved transitions over ranges of BMI values; estimates may differ from primary models with linear splines. Dashed lines represent 95% confidence intervals. Vertical lines along the x axis each represent an individual subject. BMI, body mass index; PGD, primary graft dysfunction.

adequately adjust for confounding: age, sex, Lung Allocation Score (LAS), and diagnosis (Fig. S1). We used likelihood ratios to evaluate effect modification by LAS diagnosis category, age, intraoperative ECMO, and preoperative mechanical ventilation. Analyses were performed in STATA (STATA v17.0, StataCorp).

Of 1,528 subjects, 383 (25%) developed PGD. One subject was excluded due to missing BMI (Fig. S2). Eighteen subjects with missing vital status were discharged from their index hospitalization alive and were censored at hospital discharge. Subject characteristics are reported in Table 1. Subjects with lower BMI were younger, female, had higher LAS, and had cystic fibrosis as their transplant indication.

Thirty-six subjects (9%) died within 90 days, and 132 (35%) died over median (interquartile range) follow-up of 2.9 (1.3-4.0) years. Compared to a subject with a BMI of 24 kg/m^2, a subject with a BMI of 16 kg/m^2 was at 6.2 times increased risk of death or retransplantation (95% confidence interval (CI) 1.5-25.9, Fig. 1A, Table 2) while a subject with a BMI of 34 kg/m^2 was at similar risk of death or retransplantation (hazard ratio (HR) 1.1, 95% CI 0.5-2.5). Low BMI was associated with increased risk of death within 90 days of transplant in unadjusted but not adjusted models, and increased risk of death within 1 year in both unadjusted and adjusted models (Table 2). High BMI was not associated with 90-day or 1-year risk of death or retransplantation.

The association between BMI and survival was modified by LAS diagnosis group (p-for interaction = 0.0008). Higher BMI may be associated with decreased survival among those with interstitial lung disease but increased survival among those with chronic obstructive pulmonary disease, though small subgroups limit interpretation and preclude further investigation of other diagnoses (Fig. 1B, Supplemental Table). The association between BMI and survival was not modified by age (p-for interaction 0.25), preoperative mechanical ventilation ($p = 0.38$), preoperative ECMO ($p = 0.43$), or intraoperative ECMO ($p = 0.76$).

Among subjects with PGD, low BMI was associated with decreased survival, while high BMI was not associated with significantly different survival. Diagnosis may modify the association between BMI and survival though wide confidence intervals limit interpretation.

Our findings are consistent with prior work demonstrating that subjects with a low BMI are at increased risk of death from critical illness.[8] Low BMI subjects appeared sicker though findings were similar after adjustment for LAS. Underweight, frailty, and malnutrition may increase the risk of death due to failure to meet the catabolic demands of prolonged critical illness, impaired immunity, or increased risk of death due to acute insults after transplant.

We previously demonstrated that patients with obesity have decreased survival after lung transplantation partly attributable to death from PGD.[3] Results reported herein suggest that this excess obesity-related mortality is likely due to the increased risk of developing PGD rather than differential survival from PGD.[1,3] A similar association has previously been demonstrated with donor smoking.[10] Further research should therefore focus on PGD prevention in patients with obesity, as well as treatment of obesity in the preoperative period. Similar survival across normal and overweight/obese patients could also reflect the limitations of BMI as a measure of body composition, as we previously demonstrated that >50% of normal-weight lung transplant candidates were obese by dual-energy X-ray absorptiometry.[2]

Table 2 Association Between BMI and Hazards of Death or Retransplantation, Relative to Those With a BMI of 24 kg/m^2

	Risk of death or retransplantation within 90 days		Risk of death or retransplantation within 1 year		Risk of death or retransplantation overall	
BMI (kg/m^2)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
16	7.0 (1.1-45.1)	6.5 (0.6-66.8)	6.9 (1.7-28.2)	12.4 (1.9-79.0)	4.8 (1.6-14.1)	6.2 (1.5-25.9)
18.5	0.9 (0.2-4.2)	0.8 (0.1-5.1)	0.7 (0.2-2.4)	0.8 (0.2-3.0)	0.8 (0.3-1.9)	0.8 (0.3-2.0)
22	1.0 (0.6-1.7)	0.9 (0.5-1.8)	0.9 (0.6-1.4)	0.9 (0.5-1.5)	0.9 (0.7-1.3)	0.9 (0.6-1.3)
24	Ref	Ref	Ref	Ref	Ref	Ref
26	0.7 (0.4-1.5)	0.7 (0.3-1.6)	1.0 (0.6-1.6)	1.1 (0.6-1.9)	1.1 (0.8-1.5)	1.1 (0.8-1.5)
28	0.5 (0.1-2.1)	0.5 (0.1-2.6)	1.0 (0.4-2.6)	1.2 (0.4-3.6)	1.2 (0.6-2.3)	1.2 (0.6-2.4)
30	0.5 (0.2-1.5)	0.6 (0.2-2.0)	0.8 (0.4-1.8)	1.0 (0.4-2.6)	1.0 (0.6-1.7)	1.0 (0.5-1.8)
32	0.5 (0.2-1.5)	0.6 (0.1-2.7)	0.7 (0.3-1.8)	0.9 (0.3-2.6)	0.8 (0.4-1.6)	0.8 (0.4-1.7)
34	0.7 (0.1-3.7)	0.8 (0.1-4.7)	0.9 (0.3-2.9)	1.1 (0.3-3.8)	1.1 (0.5-2.5)	1.1 (0.5-2.5)

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio.

Estimates are from linear spline models. Adjusted models include covariates for age, sex, diagnosis, Lung Allocation Score at transplantation, and stratified by listing center. Unadjusted models are stratified by the listing center.

Our study has limitations. Our modest sample size may be underpowered to detect small differences in mortality. Analysis in diagnosis-specific subgroups was limited by small subgroup sizes with few deaths. We are unable to assess whether BMI influenced postoperative management. Cohort ascertainment by PGD status could induce collider bias if other PGD risk factors are associated with survival.

Low BMI was associated with increased risk of death and high BMI was associated with similar risk of death among subjects with PGD after lung transplantation. This may influence patient counseling in the preoperative and immediate postoperative periods. Further work should consider the use of advanced body composition measurements, evaluation within diagnosis groups, and interventions focused on PGD prevention in patients with obesity.

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CRediT authorship contribution statement

Conception and design: R.M.B, J.D.C, M.R.A. Acquisition, analysis, and interpretation of data: all authors. First draft: R.M.B. Drafting or revising the manuscript for important intellectual content: all authors. Statistical analysis: R.M.B, M.R.A. Final approval of the version to be published: all authors.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhlto.2024.100107.

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