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META-ANALYSIS

Underweight and obesity increase the risk of mortality after lung transplantation: a systematic review and meta-analysis

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Keywords
body mass index, lung transplantation, obesity, primary graft dysfunction, underweight.

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Summary

Many studies have found an association between abnormal body mass index (BMI) and poor outcomes among lung transplant recipients. We performed a systematic review and meta-analysis to identify outcomes associated with an abnormal pretransplant BMI after lung transplantation (LTx). The MEDLINE and EMBASE databases were searched from inception to May 2015 with focus on original observational studies with post-transplant survival data in candidates with abnormal BMI (underweight, overweight, or obese). We performed meta-analyses examining survival and primary graft dysfunction after LTx. We identified 866 citations; 13 observational cohort studies involving 40 742 participants met our inclusion criteria for systematic review. Seven of the 13 were included in the meta-analysis. There was a significant risk of mortality after LTx in candidates with underweight and obesity (underweight versus normal, relative risk [RR] 1.36, 95% confidence interval [CI] 1.11–1.66, I^2 = 0%; obesity vs. normal, RR 1.90, 95% CI 1.45–2.56, I^2 = 0%; overweight vs. normal, RR 1.36, 95% CI 1.11–1.66, I^2 = 0). There was also a significant risk of primary graft dysfunction in obese (RR 1.92, 95% CI 1.39–2.65, I^2 = 0%) and overweight (RR 1.72, 95% CI, 1.32–2.24, I^2 = 0%) candidates. Lung transplant candidates who are underweight or obese have a higher risk of post-transplant mortality than recipients with a normal BMI.

Introduction

Lung transplantation is the primary treatment for patients with a variety of advanced-stage lung diseases [1–3]. Many factors are reportedly associated with poor post-transplant outcomes [4,5]. The body mass index (BMI) is an important factor that influences the survival and mortality rates of such patients [6–11].

An association between BMI and post-transplantation outcome has been demonstrated in many studies. Several studies have shown that pretransplant obesity is associated with poor lung transplantation outcomes independent of other risk factors [6–10]. For example, the United Network for Organ Sharing (UNOS) database demonstrated 15% higher mortality rates for overweight recipients (BMI = 25.0–29.9 kg/m^2) and 22% higher mortality rates for obese recipients than normal-weight recipients [8]. Furthermore, the guideline for recipient selection from the International Society of Heart and Lung Transplantation (ISHLT) stated that severe obesity (BMI $\geq$ 30 kg/m^2) is a relative contraindication for lung transplantation [9,11,12]. However, no association between the predicted ideal body weight or BMI and overall survival was found in one large cohort of lung transplant recipients, although obese recipients had an increased risk for 90-day mortality [13].

Although a low pretransplant BMI is not considered to be a risk factor for mortality after transplantation according to the ISHLT Registry [11,14], some studies have found that a low pretransplant BMI can increase the risk of mortality, especially in patients with cystic fibrosis (CF)

and chronic obstructive pulmonary disease (COPD) [15–17]. Therefore, many centers have considered a low BMI to be a contraindication for lung transplantation. Additionally, other studies have demonstrated worse lung transplantation outcomes in recipients who are underweight or obese [8,10]. Therefore, identifying the specific poor outcomes associated with a low or high BMI may be clinically relevant. We conducted a systematic review and meta-analysis of observational studies that assessed an association between a low (underweight) or high (overweight, obese) pretransplant BMI with poor lung transplant outcomes in adult recipients.

Methods

This systematic review and meta-analysis was conducted and reported according to the Meta-analysis Of Observational Studies in Epidemiology statement [18] and was registered in PROSPERO (registration number: CRD42014014982).

Data sources

Two authors (AS, SU) independently searched published studies indexed in the MEDLINE and EMBASE from database inception to May 2015. No filters for date, language, or any other parameter were used. References of all selected studies were also examined. The following main search terms were used: overweight, obesity, underweight, body mass index, and lung transplantation. The full search terms used are detailed in Appendix S1.

Study selection criteria

This review included all available published observational studies, regardless of language, including prospective cohort, retrospective cohort, case–control, and cross-sectional studies, that assessed the association of BMI, nutritional status, being underweight, overweight or being obese with lung transplantation outcomes. Reviews, case reports, letters, commentaries, abstracts, and unpublished studies were excluded.

Studies had to investigate adult participants $\geq$ 16 years of age who underwent lung transplantation with or without other organ transplantation. Studies including children or mixed child and adult populations were excluded unless data were presented separately.

Risk factors

We used the World Health Organization International Classification of adult underweight, overweight, and obesity [19]. Underweight, overweight, and obese were defined as BMI $<$ 18.5, $\geq$ 25.0, and $\geq$ 30.0 kg/m^2, respectively. Obesity class I and class II were defined as BMI 30–34.9 and $\geq$ 35, respectively.

Outcome measures

The primary outcome of the meta-analysis was post-transplant mortality at 12 months. If studies did not have outcome data at 12 months, we used the available data at closest to 12 months. The secondary outcome was the occurrence of primary graft dysfunction (PGD).

Study selection

Two authors (AS, SU) independently reviewed the titles and abstracts of all citations identified. Reviewers were not blinded to the authors, institutions, or article journals. Abstracts that did not provide enough information regarding the inclusion and exclusion criteria were retrieved for full-text evaluation. After all studies were reviewed, data comparisons between the two investigators were conducted to ensure completeness and reliability. The inclusion criteria were independently applied to all identified studies. Reasons for exclusion were noted. Differing decisions were resolved by consensus between both authors.

Data extraction and management

Full-text versions of potentially relevant papers identified in the initial screening were retrieved. Data extraction included author's name, year of publication, study design, source of data, cohort start and end date, center/countries, number of participants, follow-up length, primary lung disease and severity, comorbidities, BMI classification, covariates included in the multivariable analysis, and outcome (mortality, PGD). If overlapping data were presented in several publications from the same data source, only the latest published article was included in the meta-analysis. Earlier publications using the same data source were considered companion reports. We had a plan to contact the authors of the primary reports to request any unpublished data. As we extracted all necessary data from published information, we did not contact any authors. The extracted studies were excluded from the meta-analysis if they did not compare an outcome with a control group or did not have enough information for data comparison.

Quality assessment

The quality of the observational studies was evaluated using the checklist of including nonrandomized studies in

systematic reviews [20]. This checklist assesses four major issues of included studies: study design features, risk of unmeasured and residual confounding, risk of selective outcome or analysis reporting, and directness of evidence with respect to our study objective. We used this checklist to assess the risk of bias and determine whether to include observational studies to our review. We excluded any study that had high risk of bias on one of the four features.

Statistical methods

Data analysis was performed using Comprehensive META-ANALYSIS 3.3 software from the Biostat, Inc[21]. We used the adjusted hazard ratio (HR) or relative risks (RR) from multivariate analysis, if available, and calculated pooled RRs with 95% confidence intervals (CI), to report the estimate for the outcomes of mortality and PGD. If HR or RR was not reported, dichotomous data on the outcome of interest were pooled to calculate RRs[22]. A relative risk > 1 suggests abnormal BMI (underweight, overweight or obesity) as risk factors. We excluded any study from meta-analysis and only presented the result with narrative description when there were not sufficient comparable data available for outcome of interest. The heterogeneity of effect size estimates across these studies was quantified using the I^2 statistic. An I^2 of 0–40% was considered to exclude heterogeneity, of 30–60% was considered to represent moderate heterogeneity, of 50–90% was considered to represent substantial heterogeneity, and of 75–100% was considered to represent considerable heterogeneity [23]. We used a random-effects model for all analyses. All tests were two-tailed, and a P value of < 0.05 was deemed statistically significant.

Results

Description of included studies

The initial search yielded 866 articles (Fig. 1); 839 articles were excluded on the basis of title and abstract because they were not observational studies ($n = 145$), did not provide BMI data ($n = 269$), did not involve lung transplantation ($n = 244$), or did not have a post-transplantation primary outcome ($n = 181$). A total of 27 articles underwent full-length review. Data were extracted from 13 studies [7–9,13,14,24–31] involving 40 742 participants and underwent qualitative analysis.

The included studies varied in design, source of data, primary lung disease, type of transplantation, and follow-up duration. The population sizes of the included studies, all published from 1998 to 2015, varied from 85 to 11 411 individuals. The study duration ranged from 1 to 11 years. All studies were cohort studies and published in English. Four studies [7,8,27,29] derived from the UNOS database. Two studies derived from the LTOG database [25,28]. Others were single center studies. The indications for transplantation included COPD, CF, alpha-1 antitrypsin deficiency, pulmonary fibrosis, primary and secondary pulmonary hypertension, and others. In almost all studies, the recipients underwent only lung transplantation (single and bilateral); some recipients in one study [24] underwent heart–lung transplantation. The characteristics of the 13 extracted studies included in this review are outlined in Table 1.

Quality assessment

Quality assessment of the included studies using checklists of methodological issues of the included studies was performed. None of the studies had high risk of bias on either feature (Appendix S2).

Outcome

Mortality

Five studies were included in the meta-analysis of post-transplant mortality (Fig. 2). Singer *et al.* had the most recent data among studies that used UNOS database and was included in the meta-analysis. Data from other studies that used UNOS database and had mortality outcome (Allen and Lederer *et al.*) were not the most recent, so these studies were not included in the analysis. The pooled RR of post-transplant mortality was associated with underweight, and obesity. Being underweight increased risk of mortality, with a pooled RR of 1.36 (95% CI, 1.11–1.66, $I^2 = 0\%$). Being obese also increased mortality risk, with a pooled RR of 1.90 (95% CI, 1.42–2.56, $I^2 = 0\%$). Overweight also tended to increase mortality risk, but the association was not significant [pooled RR = 1.16 (95% CI, 1.00–1.36)].

PGD

Two studies were included in a meta-analysis of PGD (Fig. 3). Kuntz *et al.* and Diamond *et al.* had the most recent data among studies that used UNOS and LTOG database, respectively, and were included in the meta-analysis. Lederer *et al.* was not included in the analysis because their data were not recent. There was a significant association of overweight and obesity with PGD. Subgroup analysis revealed that obesity has the strongest association with PGD, with a pooled RR of 1.92 (95% CI, 1.39–2.65, $I^2 = 0\%$). Being overweight also had a significant association with PGD, with a pooled RR of 1.72 (95% CI, 1.32–2.24, $I^2 = 0\%$). However, underweight was not associated

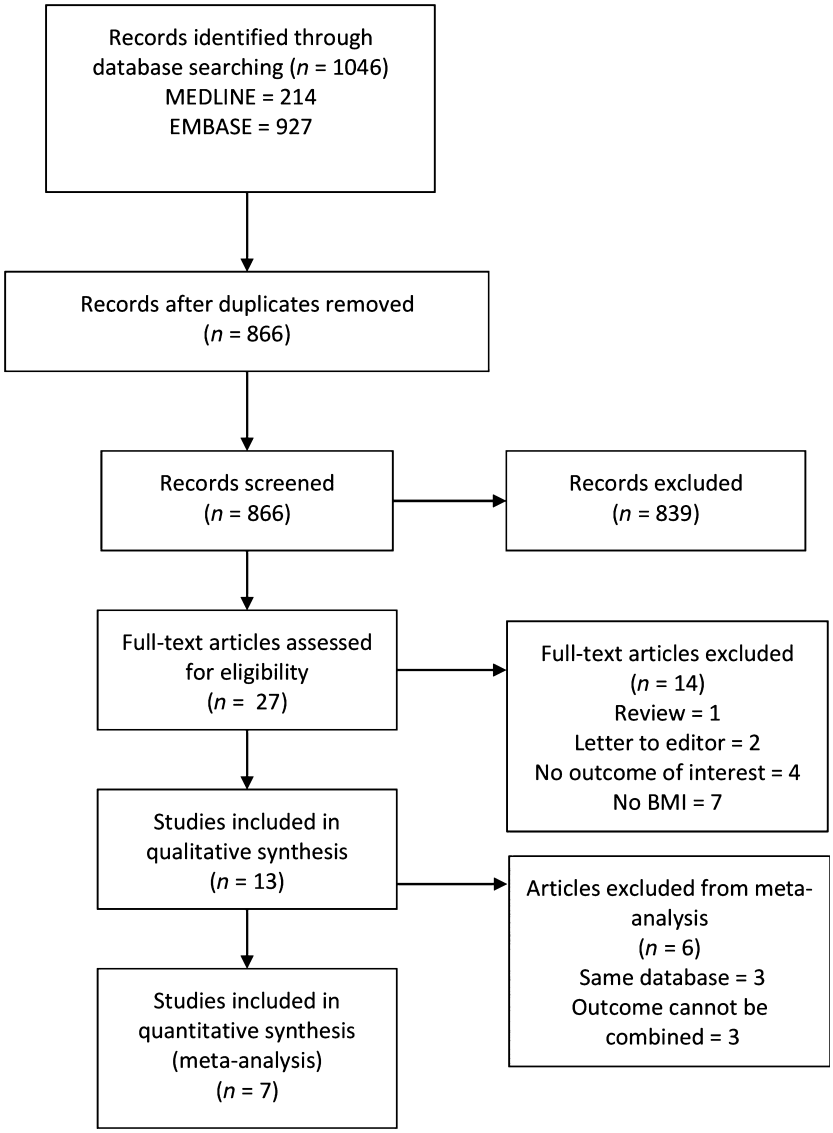

Figure 1 Results of information search.

with PGD after transplantation (RR = 0.69, 95% CI, 0.23–2.09, I^2 = 86%).

Sensitivity analysis and publication bias

We did not perform sensitivity analysis or publication bias analysis because of too few included studies in the meta-analysis.

Discussion

Summary of main results

Our systematic review and meta-analysis among post-lung transplant recipients found that underweight and obesity before transplantation were significantly associated with higher mortality than recipients who have normal BMI. Overweight and obesity also had an association with a higher risk of PGD.

Our findings are consistent with those of a previously published meta-analysis of recipient-related clinical risk factors for PGD after lung transplantation [32]. That meta-analysis showed a significant association between an elevated BMI (BMI $\geq$ 25 kg/m^2) and PGD. Our meta-analysis added more studies and evidence of the associations of being obese (BMI $\geq$ 30 kg/m^2) with a higher risk of PGD. Additionally, our mortality results are in agreement with the results of another meta-analysis of the association between BMI and mortality in other solid

Table 1. Characteristics of included studies.

Study	Study design	Follow-up (years)	Participant characteristics	Country	Participants (*n*)	BMI classification	Primary lung disease	Severity of primary lung disease	Transplantation	Covariates included in multivariable analysis
Culver (2005) [13]	Retrospective cohort	5	Adults aged > 18 years from Cleveland Clinic Foundation between 1990 and 2002	USA	283	Underweight (15%) Normal (42%) Overweight (26%) Obese (16%)	Obstructive (49%) Restrictive (28%) Cardiovascular (21%) Bronchiectatic (2%)	N/A	Single LTx (70%) Bilateral LTx (30%)	Age, sex, race, underlying disease category, and type of transplantation (unilateral or bilateral)
Chandrashekaran (2015) [31]	Retrospective cohort	5	Adults aged > 18 years from 2 centers (Mayo clinic Rochester and Jacksonville)	USA	355	Underweight (5.6%) Normal (42.8%) Overweight (42.2%) Obese (9.4%)	COPD (36.5%) IPF (37.6%) Bronchiectasis (9%) Pulmonary fibrosis other (11.5%) Other (5%)	LAS (39.8)	Single LTx (51.7%) Bilateral LTx (48.3%)	Age, gender, Race, BMI baseline, BMI reduced, days spent on mechanical ventilator
Gries (2015) [30]	Retrospective cohort	90 days	Adults aged > 18 years form OPTN database between 2000 and 2010	USA	3389	Normal (24%) Overweight (47%) Obese (29%)	IPF (100%)	mPAP (22–26) CO2 (41 mmHg) FVC, %predicted (45–48) FEV1, %predicted (48–52) PAP systolic (36–41) LAS (42.01–46.3)	Single LTx (58%) Bilateral LTx (42%)	Age, gender, pretransplant FVC and FEV1, pretransplant mean PA and systolic PA pressure
Allen (2010) [7]	Retrospective cohort	3	Adults aged > 17 years from UNOS database between 1998 and 2008	USA	11 411	Underweight (11.9%) Normal (43.8%) Overweight (32.1%) Obese (12.2%)	COPD (37.1%) CF (14.3%) IPF (25.2%) Other (23.5%)	6-min walk distance < 150 ft (3.4%) FEV_1, % predicted (26.6–45) FVC, % predicted (43.3–52.1) FEV/FVC (0.51–0.67)	Single LTx (45.6%) Bilateral LTx (54.4%)	BMI strata, gender, donor–recipient gender mismatch, age>60, creatinine, history of diabetes, transplant year, CF, IPF, ICU care and hospitalization before LTx, 6-min walk distance<150 feet, insurance/self-pay, bilateral LTx, ischemic time

Table 1. continued

Study	Study design	Follow-up (years)	Participant characteristics	Country	Participants (*n*)	BMI classification	Primary lung disease	Severity of primary lung disease	Transplantation	Covariates included in multivariable analysis
Burton (2005) [24]	Retrospective cohort	11	Adults aged < 65–70 years from National Heart and Lung Transplantation Center between January 1992 and December 2003	Denmark	362	Normal (80.8%) Overweight (19.2%)	COPD (47%) α_1AT deficiency (23%) CF (9.7%) IPF (5.4%) Sarcoidosis (1.8%) Silicosis (1%) Bronchiectasis (0.2%) Eisenmenger + SPH (6.5%) PPH (2.1%) GVHD (0.2%) Other (3.1%)	N/A	Single LTx (63%) Bilateral LTx (31%) Heart–lung Tx (5.8%) One-lobe LTx (0.2%)	Recipient age, donor age ≥ 50 years, recipient BMI ≥ 25
Diamond (2013) [25]	Prospective cohort	9	Adults aged 18–80 years from The Lung Transplant Outcomes Group (LTOG) between March 2002 and December 2010	USA	1257	Underweight (9.5%) Normal (40.5%) Overweight (35.0%) Obese (15.0%)	COPD (37.7%) IPF (36.2%) CF (14%) Sarcoidosis (3.4%) PPH (3.2%) Other (5.5%)	mPAP: normal (41%), mild (44.3%), moderate (10.8%), severe (3.9%)	Single LTx (34%) Bilateral LTx (66%)	Transplant type, cardiopulmonary bypass use, gender, BMI, total ischemic time, primary lung disease, PRBC transfusion, mPAP, reperfusion FI_{O2}, onor smoking
Gonzalez-Castro (2006) [26]	Retrospective cohort	6	Patients from the intensive care service of Hospital Universitario Marques de Valdecilla between January 1999 and June 2005	Spain	114	Underweight (8.3%) Normal (57.5%) Overweight (15.7%) Obese (18.5%)	Emphysema (43%) IPF (32%) α_1AT deficiency (9%) CF (3%) Other (18%)	PaO_2/FI_{O2} at ICU admission (198–242) PaO_2/FI_{O2} at 24 h (281–316)	Single LTx (38.6%) Bilateral LTx (61.4%)	Level of serum albumin and serum prealbumin, pretransplantation BMI
Kanasky (2002) [9]	Retrospective cohort	5	Adults aged <55 for single LTx or < 65 for bilateral LTx from University of Florida Health Science Center between March 1994 and October 1998	USA	85	Underweight (22.0%) Normal (44.0%) Overweight (22.0%) Obese (12.0%)	COPD (52.9%) IPF (27.1%) CF (10.6%) Other (9.4%)	FEV_1 for obstructive lung disease = 20.5% predicted FVC for restrictive lung disease = 46% predicted	Single LTx (70.6%), Bilateral LTx (29.4%)	Age, gender, disease, transplantation type, time spent on transplantation list, obliterative bronchiolitis, pretransplantation BMI

Table 1. continued

Study	Study design	Follow-up (years)	Participant characteristics	Country	Participants (*n*)	BMI classification	Primary lung disease	Severity of primary lung disease	Transplantation	Covariates included in multivariable analysis
Kuntz (2009) [27]	Retrospective cohort	9	All LTx recipients from UNOS database between January 1994 and December 2002	USA	6984	Underweight (12.6%) Normal (50.8%) Overweight (26.4%) Obese (10.2%)	With PGD Obstructive (38.6%) PPH (11.3%) CF (14.6%) IPF (20.7%) SPH (3.9%) SPF (9.4%) Without PGD obstructive (53.9%) PPH (3.9%) CF (17.8%) IPF (15.5%) SPH (1.3%) SPF (6.6%)	N/A	Single LTx (56.6%), Bilateral LTx (43.4%)	gender, recipient BMI, systolic PAP, age, donor cause of death, single lung transplant, Eurocolins solution, and ischemic time
Lederer (2009) [8]	Retrospective cohort	4.2	Adults aged ≥ 18 years from UNOS database between January 1995 and December 2003	USA	5978	Underweight (14.5%) Normal (47.9%) Overweight (27.5%) Obese (10.1%)	CF (16.2%) COPD (63%) DPLD (20.8%)	Lung allocation score (32–35)	Single LTx (43.9%) Bilateral LTx (56.1%)	Age, sex, height, diagnosis, transplant procedure, transplant year, transplant center, donor characteristics, lung allocation score, cardiovascular risk factors hospitalization at transplant, CMV mismatch status, HLA mismatch, use of steroid before transplant, graft ischemic time
Lederer (2011) [28]	Prospective cohort	8	Adults from nine transplant centers in Lung Transplant Outcomes Group (LTOG) between March 2002 and July 2009	USA	512	Underweight (43.8%) Overweight (38.5%) Obese (17.8%)	COPD (51%) ILD (49%)	Systolic PAP (39–46 mmHg)	Single LTx (47.9%), Bilateral LTx (52.1%)	Diagnosis, use of cardiopulmonary bypass, transplant procedure, systolic PAP, ischemic time, donor oxygenation and donor age
Ruttens (2014) [14]	Retrospective cohort	10	Adults from a single transplant center between 1991 and 2010	Belgium	546	Underweight (28.0%) Normal (47.0%) Overweight (18.0%) Obese (7%)	COPD/α_1AT (46.2%) ILD (16.8%) CF (15.6%)	N/A	N/A	Age, sex, type of lung transplant, BMI, underlying disease, lymphocytic bronchiolitis, chronic rejection, azithromycin use, acute rejection

Table 1. continued

Study	Study design	Follow-up (years)	Participant characteristics	Country	Participants (*n*)	BMI classification	Primary lung disease	Severity of primary lung disease	Transplantation	Covariates included in multivariable analysis
Singer (2014) [29]	Retrospective cohort	1	Adults aged > 18 years from UNOS database between May 2005 and June 2011	USA	9814	Underweight (9.9%) Normal (40.2%) Overweight (34.7%) Obese class I (14.0%) Obese class II–III (1.2%)	N/A	N/A	N/A	Recipient factors (age, sex, height, previous cardiac surgery, lung allocation score, center, diagnosis, previous lung transplantation, mechanical ventilation), donor factors (age, sex, height, BMI, arterial partial pressure of oxygen, alcohol use, smoking history, pulmonary infection, cause of death, diabetes, donor–recipient height interaction, donor–recipient sex interaction), procedural factors (ischemic time, transplant type)

BMI, body mass index; LTx, lung transplantation; OPTN, Organ Procurement and Transplantation Network; UNOS, United Network for Organ Sharing; α_1AT, alpha-1 antitrypsin; CF, cystic fibrosis; DPLD, diffuse parenchymal lung disease; IPF, interstitial pulmonary fibrosis; SPF, secondary pulmonary fibrosis; SPH, secondary pulmonary hypertension; PPH, primary pulmonary hypertension; GVHD, graft-versus-host disease; mPAP, mean pulmonary artery pressure; PRBC, packed red blood cell; $FI_{O2,}$ reperfusion fraction of inspired oxygen; ISHLT, International Society of Heart and Lung Transplantation; ILD, interstitial lung disease; HR, hazard ratio; OR, odds ratio; CI, confidence interval; PAP, pulmonary arterial pressure; PGD, primary graft dysfunction.

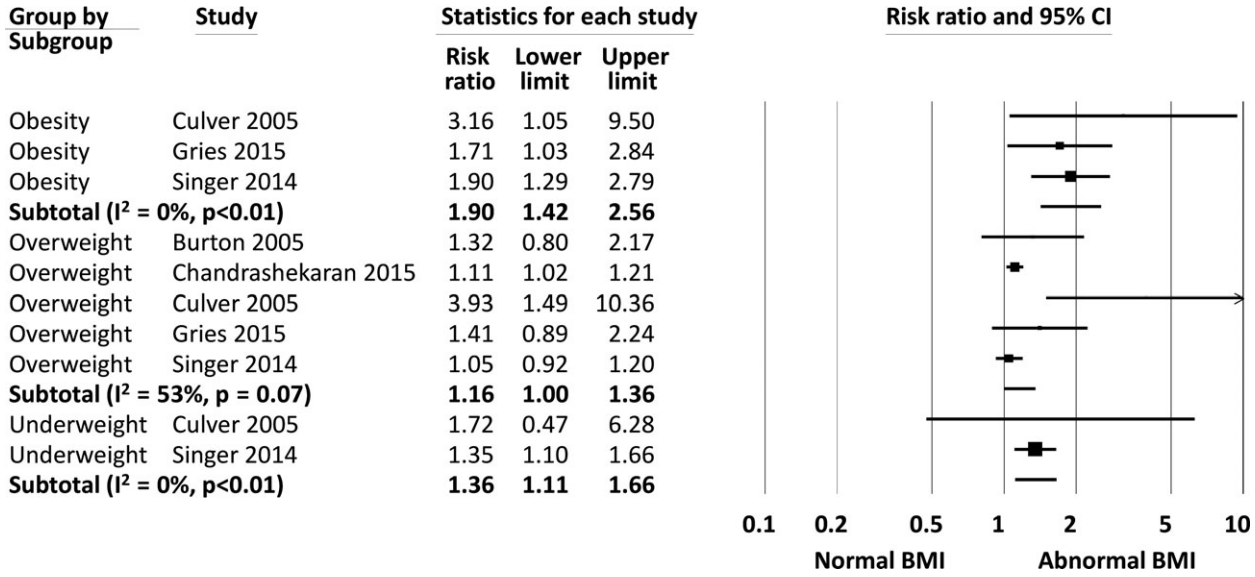

Figure 2 Forest plot of pooled analysis of post-transplant mortality between abnormal BMI and normal BMI cohorts.

organ transplant recipients. A meta-analysis of kidney transplantation [33] showed that being underweight and obese were associated with higher all-cause mortality. A review of the effect of pretransplant obesity on the candidacy for and outcomes of various organ transplantations by Hasse [34] found that there are few data available on the influence of obesity on lung transplant outcomes. The author concluded that an elevated BMI is a risk factor for reduced short-term survival. However, there is no difference in long-term survival according to BMI. On the other hand, obesity was not identified as a risk factor for mortality in a review of recipient risk factors for mortality in heart transplantation [35].

In 2014, the ISHLT updated its guidelines for the selection of lung transplant candidates [12]. Absolute contraindications for lung transplantation include patients with recent malignancy, life-threatening extrapulmonary disease, or psychiatric factors that could impact the outcome. Obesity, defined as a BMI of > 30 kg/m^2, was listed as a relative contraindication by some centers. Previous studies found controversial results regarding the association between BMI and mortality risk among different diagnoses. A greater BMI is associated with mortality only in diffuse parenchymal lung disease, but not COPD or CF [36,37]. Being underweight is a risk factor for death among patients with COPD [38]. Earlier studies found that death among underweight patients with COPD might be attributable to diaphragmatic weakness and respiratory failure related to a poor nutritional status [39]. The results from our quantitative analysis add to these previous data by demonstrating an association of being underweight, and obese with the risk of death and being overweight and obese with the risk PGD after lung transplantation.

In a recent retrospective cohort study [30], a reduction in BMI in obese patients prior to lung transplantation is associated with improved survival and decreased perioperative morbidity. However, underweight transplant candidates did not achieve weight gain after dietary intervention in pretransplantation state. After lung transplantation, they successfully gain weight [40]. The finding from this study supported the idea that pretransplant obesity is a modifiable risk factor of mortality. An additional study should be carried out to assess whether dietary intervention in underweight patients improves survival after lung transplantation.

Strengths and limitations

Our study has several strengths. First, we included all indications for lung transplantation in adults and performed a comprehensive search of the MEDLINE and EMBASE databases. Second, we analyzed the pooled RR in a multivariate analysis of each study, if available, so that most of the results were adjusted for potential confounders from the baseline characteristics of the recipients.

There is also limitation in our meta-analysis, and our results should thus be interpreted with caution. As we used only data from the most recent study that used the same database, there are a small number of studies

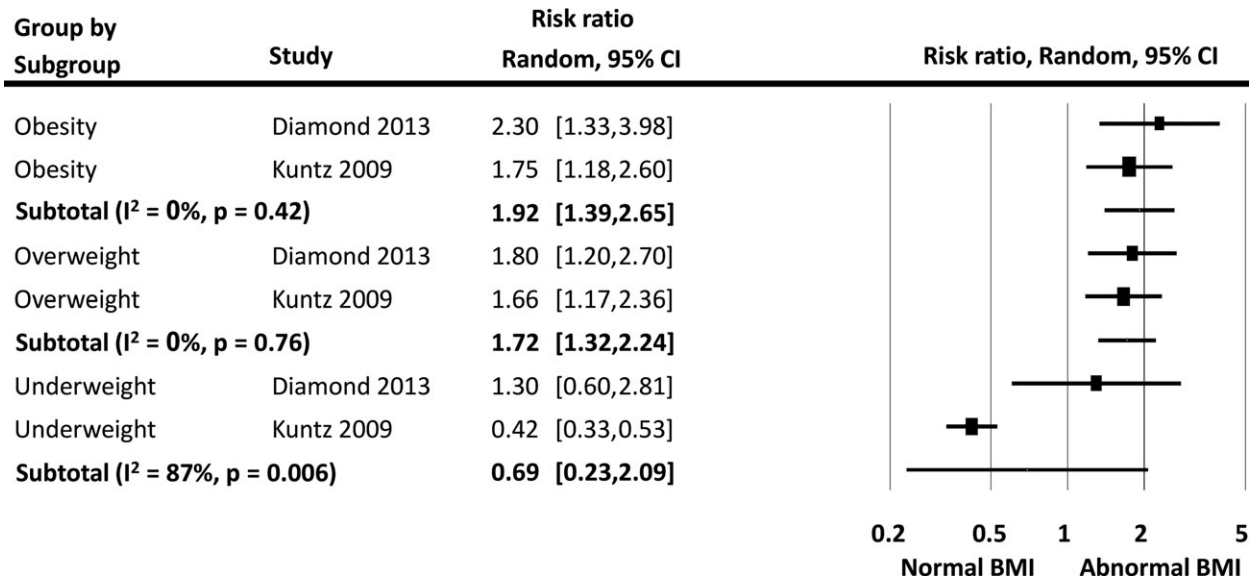

Figure 3 Forest plot of pooled analysis of primary graft dysfunction between abnormal BMI and normal BMI cohorts.

included in the meta-analysis. Therefore, we are not be able to provide a strong conclusion from the result. We used the recipients' pretransplant BMI as a risk factor after lung transplantation; this BMI does not allow for differentiation between visceral adiposity and higher muscle mass. A study of kidney transplantation suggested that waist circumference may be a better marker to capture the adverse effects of obesity, possibly because of its reflection of visceral adiposity [41]. Measurement of the body fat distribution using the waist-to-thigh ratio or waist-to-hip ratio may also help to predict mortality [42]. The best tool to assess abdominal obesity as a risk factor for lung transplantation remains unknown because no studies on lung transplantation have compared the various body composition measurement techniques.

Conclusions

Our results add evidence to the current body of knowledge by showing that overweight and obesity are associated with an increased risk of post-transplant mortality and PGD. Each transplant center should weigh the risks and benefits of having candidates with an abnormal BMI. Physicians should emphasize to candidates that they should improve their nutritional status and optimize their BMI. They should also assess whether the patient is ready to undertake the measures necessary to succeed in these efforts, such as undergoing a comprehensive lifestyle intervention [43]. Further studies that evaluate the risk of a low or high BMI on lung transplantation outcomes with longer follow-up periods are necessary. Such studies will provide more definitive information on what guidelines the transplant center should develop regarding exclusion criteria for lung transplant candidates.

Authorship

SU: conceptualized the study, performed the literature search and screening, and wrote and reviewed the manuscript. AS: performed the literature search and screening, analyzed the data, and wrote and reviewed the manuscript. TP: performed the literature search, analyzed the data, and reviewed the manuscript. KW and VJ: wrote and reviewed the manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Search Strategy.

Appendix S2. Quality assessment.

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