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The Obesity Paradox Existing in Idiopathic Pulmonary Arterial Hypertension

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Abstract

Objectives: Our purpose was to evaluate the association between idiopathic pulmonary arterial hypertension (PAH) and obesity, as indicated by the body-mass index (BMI), in terms of the all-cause mortality in a group of patients from a specialized center.

Materials and Methods: In this study, we retrospectively analyzed 78 consecutive adult patients with idiopathic PAH. The patients were classified into two groups as the deceased (D) and the survived (S). A set of data was collected for each patient, including gender, age, weight, height, BMI (kg/m^2), World Health Organization functional class (WHO FC), brain natriuretic peptide (BNP), hemoglobin, the presence of atrial fibrillation (AF), 6-minute walking distance (6MWD), echocardiographic and hemodynamic parameters.

Results: The mean follow-up period was 33.7 months (maximum: 128 months), 38 deaths (48.7%) were noted. The two groups were found to be similar in terms of gender, age, and the presence of AF. The median BNP level in group D was significantly higher than that in group S ($p<0.001$). Baseline WHO FC III-IV was significantly more common in group D than that in group S (89.5% vs 57.5%, $p=0.003$). Group D had significantly lower BMI and 6MWD compared to those in group S ($p<0.001$ and $p=0.017$, respectively). Multivariate logistic regression analysis showed that BMI [Odds ratio (OR)=0.632, 95% confidence interval (CI)=0.478-0.837, $p=0.001$] and 6MWD (OR=0.981, 95% CI=0.970-0.993, $p=0.002$) were independent predictors of mortality in this cohort. The receiver operating characteristic curve analysis was performed to assess the utility of BMI as a predictor of mortality. The optimal BMI cut-off was 24.25 kg/m^2, with 60.5% sensitivity and 82.5% specificity (area under the curve=0.759, 95% CI=0.654-0.864, $p<0.001$) and the

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Abstract

patients with a BMI of ≤24.25 had worse prognosis based on the Kaplan Meier analysis survival curves (log-rank p<0.004).

Conclusion: BMI seems to be linearly but inversely related to all-cause mortality among patients with idiopathic PAH.

Keywords: Pulmonary arterial hypertension, obesity paradox, body-mass index, mortality

Introduction

Pulmonary arterial hypertension (PAH) is characterized by the dynamic obstruction of pulmonary vasculature by vasoconstriction, pathologically non-compliant arteries, and adverse vascular re-modelling due to vascular fibrosis and stiffening. Pulmonary vascular resistance (PVR) is increased because of obstruction, hyperproliferation in pulmonary vascular bed and the vasoconstriction of pre-capillary arterioles, resulting in increased right ventricular (RV) afterload and right heart failure, which are the major causes of mortality in patients with PAH[1].

On the other hand, there has been a marked increase in the worldwide prevalence of obesity over recent decades, which has increased the overall disease burden and resulted in millions of deaths annually[2]. Obesity is associated with several health problems, including the increased risk of cardiovascular and respiratory diseases[3-5].

In this study, our purpose was to evaluate the association between idiopathic PAH and obesity, as indicated by the body-mass index (BMI), in terms of the all-cause mortality in a group of patients from a specialized center.

Materials and Methods

Study population

The study was approved by the Non-invasive Research Ethics Board of Dokuz Eylul University (number: 2018/07-31). In this study, we retrospectively analyzed 78 consecutive adult patients with idiopathic PAH, who met the diagnostic criteria for definitive PAH based on the European Society of Cardiology/European Respiratory Society Guideline, between January 2008 and December 2019. In the guideline, PAH is defined by a mean pulmonary artery pressure (PAP) of ≥25 mmHg (at rest), a pulmonary capillary wedge pressure of ≤15 mmHg, and a PVR of >3 Wood units in the right heart catheterization (RHC) assessments[6]. A set of data was collected for each patient, including gender, age, weight, height, BMI (kg/m^2), World Health Organization functional class (WHO FC), brain natriuretic peptide (BNP), hemoglobin, the presence of atrial fibrillation (AF), 6-minute walking distance (6MWD), echocardiographic and hemodynamic parameters. All-cause mortality (ACM) was noted during the follow up with 3-month intervals. The BMI was calculated at the time of baseline RHC by dividing the mass in kilograms by the square of the height in meters[7]. Patients with unreported height or weight at admission were excluded. All patients had diagnostic RHC at rest by an experienced cardiologist.

A thorough transthoracic echocardiography that specifically focused on investigating the function, dimension and the pressure within the right side of the heart was performed. The tricuspid annular plane systolic excursion (TAPSE) and the RV end-diastolic diameter were measured. Systolic PAP was calculated. The existence of pericardial effusion was recorded.

Statistical Analysis

Statistical analyses were performed using SPSS 25.0 (SPSS Inc., Chicago, USA). The normality was assessed with the Kolmogorov-Smirnov test, and the data were

reported as percentages for categorical variables, mean ± standard deviation for continuous variables, and median (IQR) when the distribution was not normal. Student's *t*-test and the appropriate chi-square test were used for comparing the groups for continuous and categorical variables, respectively. In order to predict mortality in PAH patients, the optimal cut-off threshold for the BMI was obtained by analyzing the receiver operating characteristic (ROC) curve. The Kaplan-Meier analysis with a BMI cut-off value of 24.25 was provided to designate survival curves in the whole cohort and a patient subgroup. To determine the independent predictors for mortality, a multivariate logistic regression model with the backward selection method was used. The variables with p<0.1 in Table 1 were entered the multivariate logistic regression and were reported in Table 2.

Results

The study included 78 patients: 11 men and 67 women. The mean age was 58.35±15.3 years; the mean follow-up period was 33.7 months (maximum: 128 months). The patients were classified into two groups as the deceased (D) and the survived (S); 38 deaths (48.7%) were noted during the follow-up. The comparison of the two groups regarding the demographic, clinical, echocardiographic, and hemodynamic characteristics at the baseline was presented in Table 1. The two groups were found to be similar in terms of gender, age, and the presence of AF. The median BNP level in group D was significantly higher than that in group S (p<0.001). Baseline WHO FC III-IV was significantly more common in group D than that in group S (89.5% vs 57.5%, p=0.003). Group D had significantly lower BMI and 6MWD compared to those

Table 1. Baseline clinical, echocardiographic and hemodynamic characteristics of the study population

Characteristics	Survived (n=40)	Deceased (n=38)	p
Age	57.73±14.58	59.03±16.21	0.710
Gender (female) (%)	36 (90%)	31 (81.6%)	0.458
Atrial fibrillation (%)	10 (25%)	13 (34.2%)	0.520
WHO FC 3-4 (%)	23 (57.5%)	34 (89.5%)	**0.003**
Height (m)	160.72±8.78	160.10±8.16	0.748
Weight(kg)	78.55±16.07	63.23±13.69	**<0.001**
BMI (kg/m^2)	30.46±6.20	24.71±5.36	**<0.001**
6MWD (m)	330 (300-390)	270 (140-320)	**0.017**
Echocardiographic characteristics			
TAPSE (mm)	18 (15-21)	16 (13-18)	0.061
RVEDD (cm)	3.61±0.95	3.76±0.77	0.519
Pericardial effusion (%)	10 (25%)	19 (50%)	**0.040**
Hemodynamic characteristics at heart catheterization			
Systolic PAP (mmHg)	72 (54.5-84.75)	70 (62.5-82.75)	0.673
Mean PAP (mmHg)	44 (31.25-52)	42 (38-54)	0.539
RAP (mmHg)	9 (6-13)	8 (5-12.25)	0.463
CO (L/m^2)	4.89±1.60	4.67±2.05	0.607
CI (L/min/m^2)	2.68±0.91	2.68±1.11	0.996
PVR (wood unit)	7 (4.03-9.55)	8.72 (5-13.1)	0.076
BNP (pg/mL)	207 (100-433)	614 (281-1436)	**<0.001**
Hemogram (mg/dL)	11.93±1.96	11.98±2.32	0.927

WHO FC: World Health Organization Functional class, BMI: Body mass index, 6MWD: 6-minute walking distance, TAPSE: Tricuspid annular plane systolic excursion, RVEDD; Right ventricular end diastolic diameter; PAP: Pulmonary arterial pressure, RAP: Right atrial pressure, CO: Cardiac output, CI: cardiac index, PVR: Pulmonary vascular resistance, BNP: Brain natriuretic peptide

in group S (p<0.001 and p=0.017, respectively). Of note, the rate of those with a BMI of ≥30 was 21.1 % in group D and 50% in group S (p=0.002). The distribution of ACM during the follow-up period among different BMI categories was presented in Figure 1. (ACM rates were 100, 59.3, 40 and 28.6% for BMI categories ≤20, 20.01-24.99, 25-29.99, and ≥30 respectively, p=0.002).

While the two groups had similar mean TAPSE, and RV end diastolic diameter, pericardial effusion was significantly more frequent in group D.

Multivariate logistic regression analysis showed that BMI [odds ratio (OR)=0.632, 95% confidence interval (CI)=0.478-0.837, p=0.001] and 6MWD (OR=0.981, 95% CI=0.970-0.993, p=0.002) were independent predictors of mortality in this cohort (Table 2). The ROC curve analysis was performed to assess the utility of BMI as a predictor of mortality. The optimal BMI cut-off was 24.25 kg/m^2, with 60.5% sensitivity and 82.5% specificity [area under the curve (AUC)=0.759, 95% CI=0.654-0.864, p<0.001] (Figure 2). As shown in Figure 3, the patients with a BMI of ≤24.25 had worse prognosis based on the Kaplan Meier analysis survival curves (log-rank p<0.004).

Table 2. Multivariate logistic regression analysis to predict mortality in patients with idiopathic pulmonary arterial hypertension

	p	OR	CI 95%
6MWD (m)	0.002	0.981	0.970-0.993
BMI (kg/m^2)	0.001	0.632	0.478-0.837

Variable(s) entered the model: Pericardial effusion, WHO FC3-4, 6MWD, BNP, PVR, BMI, TAPSE
WHO FC: World Health Organization Functional class, 6MWD: 6-minute walking distance, BNP: Brain natriuretic peptide, PVR: Pulmonary vascular resistance, BMI: Body mass index, TAPSE: Tricuspid annular plane systolic excursion, OR: Odds ratio, CI: Confidence interval

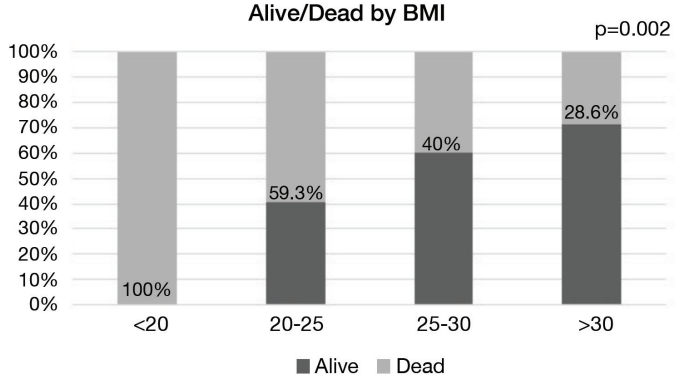

Figure 1. Distribution of ACM during follow-up among different BMI categories

ACM: All-cause mortality, BMI: Body mass index

Discussion

In this study, lower BMI was showed to be an independent predictor of death in patients with idiopathic PAH, which suggests an "obesity paradox" in these patients along with a different threshold. Specifically, a BMI of ≤24.25 kg/m^2 was the indicative of ACM although there was a linear decrease in ACM with increasing BMI categories.

Though increased BMI is a leading health problem, trials have shown favorable survival prognosis in obese patients in comparison with non-obese patients with various chronic disease such as hypertension, chronic obstructive lung disease, atherosclerotic cardiovascular disease and heart failure[8-13].

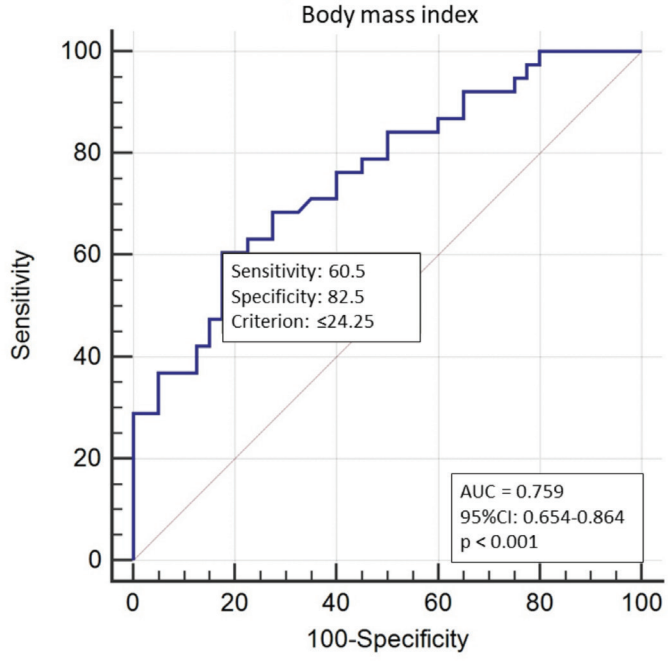

Figure 2. Receiver operating characteristic curves of BMI for predicting mortality

BMI: Body mass index, AUC: Area under the curve, CI: Confidence interval

The inverse relationship between obesity and ACM, which has been demonstrated in various cardiovascular conditions, challenged the simple clinical reasoning and created the term "obesity paradox"[14]. This protective effect of obesity is particularly evident in heart failure patients with recent data supporting the concept of obesity paradox. This paradox is explained in part by the greater metabolic reserve of obese patients to cope with the increased oxidative stress, catabolic burden, and systemic inflammation associated with heart failure. The factors that were suggested to have a role in the relationship of low BMI with high mortality include abnormal secretion of cytokines and neurohormones, cardiac cachexia, and higher catabolic burden. Thus, the additional adipose tissue reserve might also provide a buffer for cytokines and improve the prognosis in patients with PAH[10,15-20]. Moreover, recent experimental studies have found that the upregulation of the renin-angiotensin system is strongly associated with the mortality in PAH.

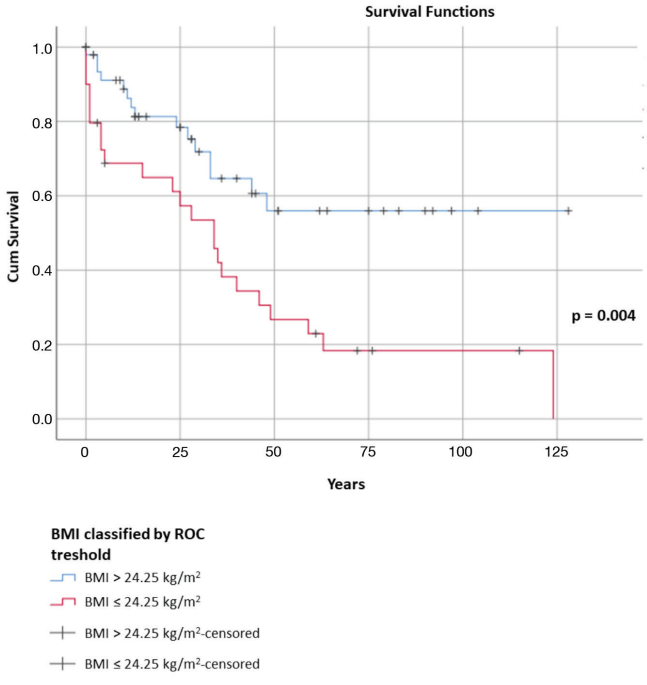

Figure 3. Kaplan–Meier survival estimates of mortality in patients with idiopathic pulmonary arterial hypertension by on admission BMI of ≤24.25 vs >24.25

BMI: Body mass index, ROC: Receiver operating characteristic

Since obese patients have a weaker response to the renin-angiotensin system, they might have an advantage in terms of mortality[20].

It should be noted that there is no consensus regarding the paradox. Some studies reported similar findings and called it the "overweight paradox" rather than the "obesity paradox"[21]. Others argue against it, reporting no survival advantage for obese patients[22]. On the contrary, the French network demonstrated a survival disadvantage for younger and morbidly obese patients[23]. Overall, these diverging opinions might be related to the cohort characteristics. Although we had a small number of patients with a BMI of ≥35 (n=12) in our study, we did not observe any increase in the ACM but, rather, a continuing trend for decreasing ACM (16.7%).

An important prognostic marker to assess the exercise capacity in patients with various pulmonary and cardiac diseases is 6MWD[24,25]. 6MWD was reported to be a predictor of mortality in PAH[26]. Similarly, we found that 6MWD was an independent predictor of ACM in this cohort of patients (OR=0.981, 95% CI=0.970-0.993, p=0.002).

Study Limitations

There are some limitations of the current analysis. First of all, the retrospective nature of the study is a limiting factor although the patients were closely monitored with regular follow-up visits at a specialized center in the region. Edema and diuretic treatment might have influenced the BMI, which was measured only at the time of diagnosis, and the patients' BMI might have changed over time. While BMI is the most commonly used measure of obesity, it does not report the distribution of adipose tissue throughout the body, and our study did not include data about the waist or hip circumference. Therefore, other measures of obesity, including waist-to-hip ratio or waist circumference, might be considered and compared to BMI in future studies to investigate the relationship between obesity and prognosis in PAH.

Conclusion

BMI seems to be linearly but inversely related to all-cause mortality among patients with idiopathic PAH.

Ethics

Ethics Committee Approval: The study was approved by Noninvasive Research Ethics Board of Dokuz Eylül University (desicion number: 2018/07-31).

Informed Consent: Because of the study's retrospective design, no patients' consents were added.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: B.Ş., B.A., E.Ö., M.B.Y., B.Ö.K., D.S., K.C.T., C.S., Design: B.Ş., B.A., E.Ö., M.B.Y., B.Ö.K., D.S., K.C.T., C.S., Data Collection or Processing: B.Ş., B.A., E.Ö., M.B.Y., D.S., C.S., Analysis or Interpretation: B.Ş., B.A., M.B.Y., B.Ö.K., D.S., K.C.T., Literature Search: B.Ş., B.A., E.Ö., M.B.Y., D.S., Writing: B.Ş., B.A., M.B.Y., B.Ö.K., K.C.T., C.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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