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The association between obesity, mortality and filling pressures in pulmonary hypertension patients; the "obesity paradox"

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Summary

Background: The term "obesity paradox", refers to lower mortality rates in obese patients, and is evident in various chronic cardiovascular disorders. There is however, only scarce data regarding the clinical implication of obesity and pulmonary hypertension (PH). Therefore, in the current study, we evaluated the possible prognostic implications of obesity in PH patients.
Methods: We assessed 105 consecutive PH patients for clinical and hemodynamic parameters, focusing on the possible association between Body Mass Index (BMI) and mortality. Follow-up period was 19 ± 13 months.
Results: Sixty-one patients (58%) had pre-capillary PH and 39 patients (37%) out-of-proportion post-capillary PH. During follow-up period, 30 patients (29%) died. Death was associated with reduced functional-class, inverse-relation with BMI, higher pulmonary artery and right atrial pressures, pulmonary vascular resistance and signs of right ventricular failure. In multivariate analysis, obesity (BMI $\geq$ 30 kg/m^2), was the variable most significantly correlated with improved survival [H.R 0.2, 95% C.I 0.1—0.6; $p = 0.004$], even after adjustment for baseline characteristics. Obese and very-obese (BMI $\geq$ 35 kg/m^2) patients had significantly less mortality rates during follow-up (12% and 8%, respectively) than non-obese patients (41%), $p = 0.01$. The tendency of survival benefit for the obese vs. non-obese patients was

maintained both in the pre-capillary (10% vs. 46% mortality, $p = 0.008$) and disproportional post-capillary PH patients (11% vs. 40% mortality, $p = 0.04$).

Conclusions: Obesity was significantly associated with lower mortality in both pre-capillary and disproportional post-capillary PH patients. It seems that in PH, similarly to other chronic clinical cardiovascular disease states, there may be a protective effect of obesity, compatible with the "obesity paradox".

Introduction

Pulmonary hypertension (PH) is defined as mean pulmonary artery pressure (PAP) $\geq$25 mmHg at rest as assessed by right heart catheterization. The clinical classification of PH comprises heterogeneous conditions with different clinical presentations, pathophysiology and management.[1,2] Untreated, it is commonly associated with reduced prognosis, leading to right ventricular failure.[3–5]

Hemodynamic classification of PH includes both pre-capillary PH, typically in pulmonary arterial hypertension (PAH) patients, and post-capillary PH which is evident in patients with left heart dysfunction, and is probably the most common etiology for elevated PAP. Most of the post-capillary PH patients will have a passive increase in PAP due to the backward transmission of the elevated left atrial pressure. However, a subset of patients will have an increase of mean PAP with increased trans-pulmonary gradient (TPG; defined as mean PAP-PCWP $\geq$12 mmHg) and pulmonary vascular resistance (PVR). As opposed to the "passive" form, lowering the pulmonary capillary wedge pressure (PCWP) to normal may not normalize the PAP. These patients can develop severe PH which is also defined as "reactive" or "out-of-proportion" post-capillary PH.[6–9]

Over the last several decades numerous studies identified specific prognostic variables associated with prognosis in PH, especially in patients with PAH. Most of these parameters were either hemodynamic or clinically based.[10–13] Parameters such as functional class and exercise capacity measures, right atrial pressure (RAP), PVR, cardiac index, presence of pericardial effusion, and laboratory markers including brain natriuretic peptides and troponin levels were reported with varying results.[14–16]

Body Mass Index (BMI), is an indicator of relative weight for height (kg/m^2) and a frequently used surrogate for assessment of excess body fat. Although measuring total body mass does not measure fat distribution directly, BMI is adopted by the World Health Organization (WHO) as a valuable measure of obesity.[17]

The relationship between BMI and total mortality risk is controversial. Obesity is a well-recognized independent cardiovascular risk factor. In the general population, a higher BMI is associated with an increased risk for cardiovascular events and death, and obesity has reached epidemic proportions in developed countries.[18] On the other hand, BMI was shown to be inversely associated with long term mortality in several chronic diseases, including coronary artery diseases, peripheral vascular disease, chronic obstructive pulmonary disease and hemodialysis patients.[17,19–23] This phenomenon was even more prominent in heart failure patients, a disease with high mortality in both reduced and preserved systolic function.[24–29]

This unexpected manifestation of reverse epidemiology, known as the "obesity paradox", promoted several suggested hypotheses trying to clarify the obesity paradox.[19,30] However, the relationship between high BMI and mortality remains a topic of considerable controversy.[31–36]

Data regarding the possible prognostic values of BMI in PH is scarce. Recently, an NHLBI workshop in PH establishing priorities for specific clinical research needed to advance care of patients with PH, recommended to examine the role of obesity with pulmonary vascular disease and RV dysfunction.[37] Considering the lack of data and referring to PH as a chronic progressive disorder with heart failure manifestations, the aim of our study was to evaluate the impact of BMI on mortality, focusing on two groups of patients with PH, the pre-capillary PH patients as opposed to patients with post-capillary PH.

Methods

Study population and data collection

Study population included 105 consecutive PH patients, who underwent echocardiographic and hemodynamic evaluation, at our PH referral tertiary medical center. PH was defined as mean PAP of more than 25 mmHg, measured by right heart catheterization. Study was approved by Carmel Medical Center institutional review board (CMC 09-0095; approval number 021-8109). Data collected for each patient included: age, gender, weight, height and BMI (kg/m^2), WHO functional class (I–IV), signs of clinical right heart failure, and laboratory values of blood creatinine and hemoglobin levels. Obesity was defined as BMI of 30 kg/m^2 or higher, according to the WHO definitions. BMI values were calculated during the right heart catheterization. Co-morbidities and risk factors were recorded according to patients' diagnoses, and included: smoking, hypertension, diabetes mellitus, coronary artery disease, heart failure, and renal dysfunction. Comprehensive two-dimensional echocardiographic studies were performed in all patients.

Hemodynamic measurements

Diagnostic right heart catheterization was performed in all patients, at rest, using Swan-Gantz catheter, according to standard protocols.[38] Baseline hemodynamic variables were calculated at end-expiration, and included systemic arterial pressure, mean RAP, PAP — (systolic, diastolic, mean),

PCWP, blood oxygen saturations (mixed venous, pulmonary artery and systemic artery), and measures of PVR and TPG. Cardiac output and indexes were measured both by the Fick's and Thermodilution method.

PH was further classified by the hemodynamic definitions of PH according to the European Society of Cardiology (ESC) PH guidelines.[1] Pre-capillary PH which was specified as mean PCWP ≤15 mmHg, while post-capillary PH as PCWP >15 mmHg, and was further classified into 2 types, depending on the Trans-Pulmonary Gradient (TPG = mean PAP-PCWP); Reactive (out-of-proportion) post-capillary PH with TPG >12 mmHg, and passive post-capillary PH with normal TPG ≤12 mmHg. All the patients with pre-capillary and out-of-proportion post-capillary PH had in addition an elevated PVR of >3 Wood units.

Data analysis

Continuous data are presented as means ± standard deviation (SD), and categorical variables as numbers or percentages. The Independent-Samples T-test was used to compare continuous variables, and the Chi-square tests were used to compare categorical variables. Fisher's exact test was used in cases of small sample sizes. We analyzed the clinical, echocardiographic and hemodynamic characteristics of our PH patients and examined the relation of all variables measured, with subsequent mortality during follow-up period. Survival curves were plotted by the Kaplan–Meier method using the Log-rank test for comparison between variables. Multivariate analysis was performed by the Cox proportional – hazards regression analysis. Hazard ratios for death were calculated, with 95% confidence intervals (CI) between brackets. To determine if the significant variables that differ between the obese and non-obese patients remained significant, adjustment was made for other risk factors and baseline characteristics such as age, gender, smoking, diabetes mellitus and heart failure measures. Survival analysis according to BMI values of obesity, was further carried out in the two discrete groups of patients with pre-capillary (n = 61) and out-of-proportion post-capillary (n = 39) PH.

The results were considered statistically significant when the p-value was <0.05. The SPSS statistical software was used to perform all statistical analyses.

Results

A total of 105 PH patients were included in the study. Mean age of the study population was 66 ± 12 years. Fifty-eight percent of the patients were female. Patients' characteristics and major co-morbidities are presented in Table 1. Half of the study cohort had evidence of clinical right heart failure and the mean WHO functional class was 2.9 ± 0.7. Echocardiography and right heart catheterization were accomplished in all study population, displaying PH hemodynamics (Table 2). Sixty patients (57%) had an enlarged right ventricular size, and 27 (26%) a reduced right ventricular function, as assessed by 2-dimensional echocardiography. The majority of the patients had preserved left ventricular ejection fraction, with only 7% systolic heart failure (LVEF < 45%). In addition, mean cardiac output indices were in the low-normal range.

Mean follow up period was 19 ± 13 months (median 17 months), during which 30 (29%) of the patients had died. We performed univariate analysis to identify several factors out of the patients characteristics that were associated with increased mortality risk during follow up. Mortality was associated with reduced WHO functional class (3.4 ± 0.7 vs. 2.8 ± 0.7, p = 0.001), a trend toward higher incidence of pericardial effusion (20% vs. 7%, p = 0.06) and an inverse association with BMI values (26 ± 4 vs. 30 ± 5, p = 0.003), demonstrating lower mortality rates in higher BMI patients (Table 1). Major co-morbid conditions such as hypertension and diabetes mellitus had no significant association.

Hemodynamic parameters of echocardiogram and right heart catheterization, demonstrated several parameters in correlation with mortality during follow-up. Smaller left ventricular dimensions, higher PAP and RAP, echocardiographic findings of right ventricle enlargement and systolic dysfunction, lower systolic blood pressure, and elevated PVR and TPG measurements, were all associated with

Table 1 Baseline characteristics and co-morbidities in patients with PH, according to survival during follow-up.

Variable	All patients (n = 105)	Alive (n = 75)	Dead (n = 30)	p Value
Age (years)	66 ± 12	65.6 ± 11.8	68.9 ± 10.8	0.18
Gender (F)	61 (58%)	41 (55%)	20 (66%)	0.28
World health organization functional class (1–4)	2.9 ± 0.7	2.8 ± 0.7	3.4 ± 0.7	0.001
Smoking	16 (15%)	11 (16%)	5 (16%)	1.00
Diabetes	39 (37%)	27 (37%)	12 (41%)	0.66
Hypertension	69 (65%)	49 (65%)	20 (67%)	0.64
Coronary artery disease	35 (33%)	27 (36%)	8 (27%)	0.26
Pericardial effusion	11 (11%)	5 (7%)	6 (20%)	*0.06*
Right heart failure	56 (53%)	37 (51%)	19 (63%)	0.28
BMI (kg/m²)[a]	28.7 ± 5.0	30 ± 5	26 ± 4	0.003
Creatinine (mg/dl)	1.18 ± 0.5	1.15 ± 0.4	1.24 ± 0.5	0.37
Hemoglobin (g/dl)	12.5 ± 2.3	12.8 ± 2.3	11.8 ± 2.2	0.09

[a] BMI = body mass index.

Table 2 Echocardiographic and hemodynamic variables in patients with PH, according to survival during follow-up.

Variable[a]	All patients ($n = 105$)	Alive ($n = 75$)	Dead ($n = 30$)	p-Value
LVEF (%)	57 ± 9	52 ± 10	59 ± 3	0.1
LVEDD (cm)	4.5 ± 0.8	4.6 ± 0.8	4.1 ± 0.6	0.007
LVESD (cm)	3.0 ± 0.8	3.2 ± 0.9	2.7 ± 0.5	0.006
Left atrial dimension (cm)	4.2 ± 0.8	4.2 ± 0.7	4.1 ± 0.9	0.54
Estimated systolic PAP (mmHg)	69 ± 19	66 ± 18	78 ± 18	0.003
RAP (mmHg)	9.9 ± 4.8	9 ± 4	12 ± 5	0.02
Moderate—severe T.R	54 (51%)	33 (46%)	21 (70%)	0.04
Enlarged RV size	60 (57%)	36 (49%)	24 (80%)	0.008
Reduced RV function	27 (26%)	13 (18%)	14 (47%)	0.006
Systolic blood pressure (mmHg)	133 ± 21	134 ± 23	123 ± 17	0.03
RAP (mmHg)	11 ± 6	10 ± 5	13 ± 7	0.09
Systolic PAP (mmHg)	69 ± 21	66 ± 20	77 ± 20	0.01
PCWP (mmHg)	15 ± 7	16 ± 7	15 ± 7	0.15
	10 ± 3			
Trans-pulmonary gradient (mmHg)	26 ± 13	24 ± 12	31 ± 12	0.018
PA saturation (%)	60 ± 10	60 ± 10	58 ± 12	0.39
C.O[a] — fick (l/min)	4.4 ± 1.1	4.6 ± 1.1	4.3 ± 1.0	0.11
C.O — thermodilution (l/min)	4.5 ± 1.2	4.6 ± 1.1	4.3 ± 1.2	0.29
C.I[a] — fick (l/min/m^2)	2.5 ± 0.6	2.4 ± 0.5	2.4 ± 0.5	0.66
C.I — thermodilution (l/min/m^2)		2.4 ± 0.6	2.4 ± 0.6	0.77
SVR (wood)	20 ± 6	20 ± 6	21 ± 6	0.50
PVR (wood)	7.3 ± 4	6 ± 3	8 ± 5	0.004

[a] LVEF = Left Ventricular Ejection Fraction; LVEDD = Left Ventricular End Diastolic Dimension; LVESD = Left Ventricular End Systolic Dimension; TR = Tricuspid Regurgitation; PA = pulmonary Artery; CO = Cardiac Output; CI = Cardiac Index; SVR = Systemic Vascular Resistance; PVR = Pulmonary Vascular Resistance.

mortality (Table 2). In contrast, cardiac output and elevated left heart filling pressures had no significant association with mortality.

In a multi-variable stepwise Cox regression analysis, out of all the univariate correlated variables, only BMI and WHO functional class measures were independently associated with mortality (Table 3). Obesity (BMI ≥ 30 kg/m^2) was the best marker for survival prediction [H.R 0.2, 95% C.I 0.1—0.6; $p = 0.004$], and was not affected by adjusting for baseline characteristics or heart failure measures.

Dividing the study population to defined BMI groups according to the WHO definitions, displayed that the obese (BMI ≥ 30 kg/m^2) and very-obese (BMI ≥ 35 kg/m^2) patients had significantly lower mortality rates during follow-up (12% and 8%, respectively) than the non-obese patients (41% mortality; $p = 0.01$). Accordingly, the Kaplan—Meier
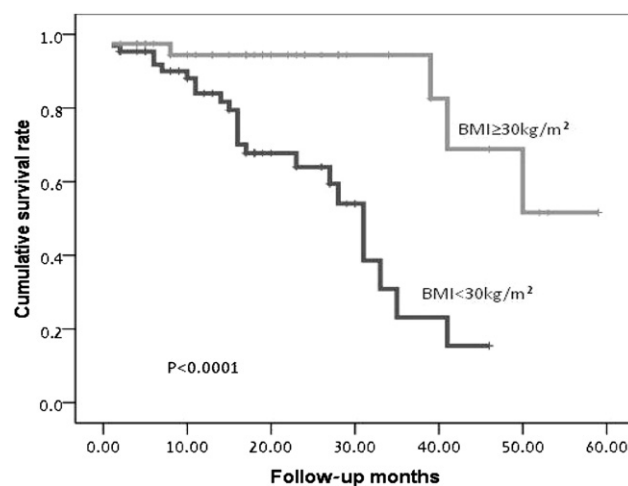
survival curves demonstrates significantly better survival rates for the obese vs. the non-obese patients (Log rank test, $p < 0.001$; Fig. 1).

The distribution of the BMI values in the study cohort displayed a bell-shaped, normal appearance (Fig. 2). Correlating the obese (41% of patients; BMI ≥ 30 kg/m^2) and non-obese patients (59% of patients; BMI < 30 kg/m^2) for baseline characteristics, there were no significant differences, except for a trend toward lower age in the obese patients (64 ± 12 vs. 67 ± 11 years, $p = 0.06$; Table 4).

**Table 3** Adjusted multivariate analysis of variables associated with all-cause mortality during follow-up.

Variable[a]	x^2	p-Value	Adjusted hazard ratio	95% C.I
BMI	8.9	0.004	0.2	0.1—0.6
WHO functional class	6.7	0.01	1.9	1.2—3.4

[a] The following variables were entered the multi-variable Cox model: Functional class, pericardial effusion, BMI, moderate—severe T.R, right ventricular dysfunction, Systolic blood pressure, PAP, PVR, RAP, Hemoglobin level. Risk adjustment was made for age, gender, baseline risk factors and heart failure measures.

Figure 1 Kaplan—Meier survival curves, for obese (BMI ≥ 30 kg/m^2) and non-obese (BMI < 30 kg/m^2) patients.
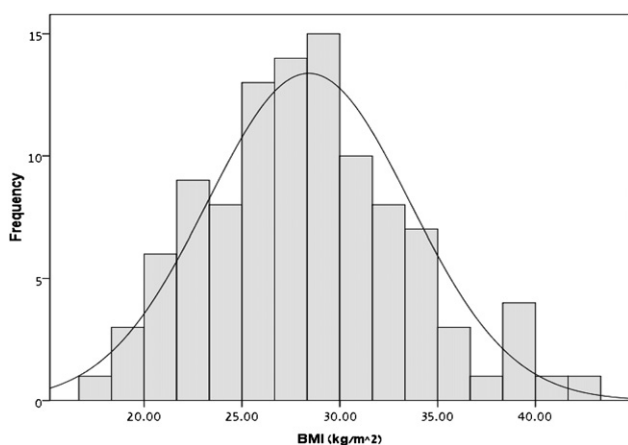
Figure 2 Distribution of BMI values in the study cohort.

There was no significant difference between follow-up duration of the obese and non-obese patients (21 ± 15 vs. 17 ± 11 months, $p = 0.13$).

In the current study we classified our patients based on hemodynamic classification.

This classification is noted in several documents and guidelines of major European and non-European Societies and is the basis for treatments options evaluation and serve as the platform for the clinical sub-classification for PH working groups .In pre-capillary PH the left heart filling pressure is ≤ 15 mmHg and pulmonary resistance is usually increased to >3 Wood units. In post-capillary PH the left heart filling pressure is increased to values >15 mmHg. Pre-capillary PH includes the clinical groups 1, 3, 4, and 5, while post-capillary PH is represented by the clinical group 2 [1, 6, 7, 14].

Performing a sub-group classification of the study population according to the hemodynamic definitions of PH, we were able to divide most of our patients into two major groups: the pre-capillary PH group with 61 (58%) of the patients, and post-capillary group with 39 (37%) patients which were all reactive, out-of-proportion PH patients. The sub-group analysis demonstrates that the same tendency of survival benefit for the obese patients is maintained in the two discrete groups of patients, the pre-capillary and the

Table 4 Characteristics and co-morbidities of obese vs. non-obese patients.

Variable	Non-obese (59% of patients)	Obese (41% of patients)	p-Value
Age (years)	67 ± 11	64 ± 12	0.06
Sex (F)	34 (56%)	26 (62%)	0.55
Smoking	10 (17%)	6 (14%)	0.65
Diabetes	21 (34%)	18 (44%)	0.27
Hypertension	40 (65%)	29 (66%)	0.68
Coronary artery disease	19 (31%)	16 (38%)	0.40
Right heart failure	30 (49%)	26 (61%)	0.23
LVEF (%)	57 ± 9	56 ± 10	0.63
Systolic PAP (mmHg)	71 ± 20	66 ± 22	0.23
Cardiac output (l/min)	4.42 ± 1.1	4.56 ± 1.1	0.53

disproportional post-capillary patients. Mortality during follow-up was observed in 10% and 11% of the obese patients in these two groups, in comparison to 40% and 46% mortality in the non-obese patients ($p = 0.008$ and $p = 0.04$, respectively; Fig. 3).

Discussion

The main finding of this study is that obesity is associated with lower mortality in PH patients suggesting the existence of the "obesity paradox" in these patients, irrespectively of their left heart filling pressures. Specifically, we demonstrated the importance of BMI evaluation in PH patients as BMI ≥ 30 kg/m^2 was strongly correlated with improved survival, independent to other well-known prognostic parameters including echocardiographic, hemodynamic, functional assessment or demographic parameters. In fact, comparing with all of these parameters, BMI was found to be the strongest prognostic marker for mortality. The survival advantage of the obese PH patients was maintained in both patients with pre-capillary and disproportional post-capillary PH, suggesting that higher BMI serve as a protective marker in PH patients irrespectively of their left heart filling pressures.

There are conflicting data regarding the correlation between obesity and PH. Of note, even the possible association between obesity and elevated pulmonary pressures is controversial.[39,40] Recently, an analysis of the wide-scale REVEAL registry in PAH patients, demonstrated that mean BMI values are similar to a normal comparison group.[41] However, in other studies, pulmonary venous hypertension was found to be associated with metabolic syndrome, with higher BMI values in comparison with PAH patients.[42] Yet, the vast majority of these studies had traditionally concentrated on the relationship between obesity and PH rather on the possible association between obesity and mortality in PH patients.

Interestingly, Benza et al. demonstrated that a higher BMI values with elevation of 10 kg/m^2, were associated with better survival in patients with pulmonary arterial hypertension, supporting the notion of obesity protective role in this sub-population of PH patients.[43]
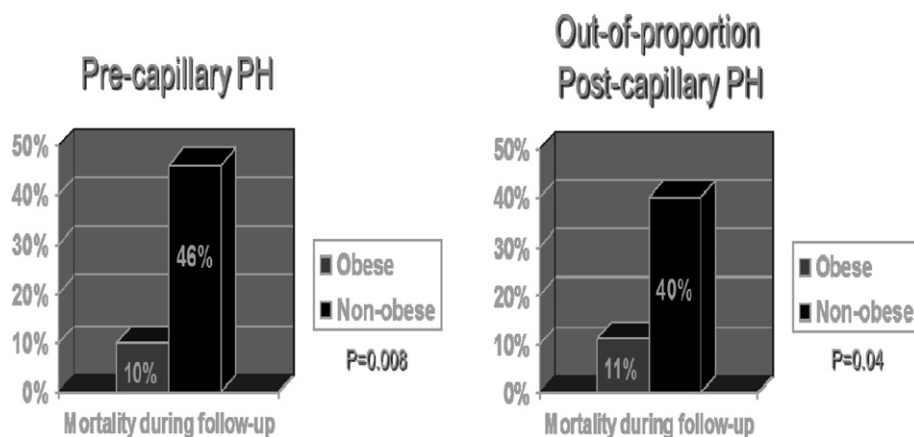
Nevertheless, to the best of our knowledge, this current study is the first to focus on the BMI as a prognostic parameter in predicting mortality in PH patients; both pre and post-capillary PH, representing a "real world" cohort of patients, demonstrating the "obesity paradox" presents irrespectively of the left heat filling measurements.

Data emerged in a variety of chronic cardiovascular diseases, suggested that patients with higher BMI have better survival rates comparing with normal and under-weight patients.[17,19] This replicated data of inverse relationship between obesity and all-cause mortality, challenged clinical reasoning and generated the concept of the "obesity paradox".[31] The growing evidence supporting the protective effect of obesity in chronic diseases is particularly recognized in heart failure patients, in which the observations supporting obesity paradox are accumulating in recent years.[24−28,30] Higher catabolic burden, cardiac cachexia, and abnormal cytokine and neurohormonal secretion, were all signaled to play a role in the linkage between low BMI and high

Figure 3 Correlation of obesity with mortality during follow-up, according to subgroup analysis: pre-capillary and out-of-proportion post-capillary PH patients.

mortality.[30] As several biological mechanisms are involved in heart failure pathogenesis and disease progression including oxidative stress and systemic inflammation,[44,45] it was suggested that patients with higher BMI also have a metabolic reserve, and with increased adipose tissue they may have reduced systemic inflammation.[25,30]

Of note, albeit the vast data, the "obesity paradox" is still far from being a consensus. It was suggested that bias selection may play a role as obese patients often present earlier in their disease course and thus treated more appropriately than other patients. Interestingly, a trend of lower age in the obese patients group was observed in our study population as well. The lower BNP values seen in the obese patients may also be a potential explanation for their better prognosis in heart failure. Other critics of the "obesity paradox" refer to small sample sizes of patients with short follow-up periods and a U-shaped BMI-survival curve relationship was also pointed out.[32,33] In addition, it is important to note that BMI and obesity are not identical terms. BMI parameter is not a good surrogate for body fat in certain populations as the elderly. Accordingly, other parameters may be more accurate in quantifying and defining obesity such as adiposity distribution, the degree of visceral and ectopic fat burden, and percent body fat.[46,47] It is also conceivable that BMI clinical implications are different in health and disease states, and thus the observation of inverse relation between BMI and mortality in populations of chronic diseases may not be generalized to healthy populations.[31] Albeit BMI may not be the ideal parameter to reflect obesity, it has significant advantages as being easily calculated parameter with proven overall risk prediction capabilities in a wide variety of medical disorders.[35]

Our study has several limitations. As stated above, BMI represents total body mass and other adiposity markers may better define obesity. The number of patients in each PH subtype category was not large and therefore might have influenced on the survival analyses of obese vs. non-obese patients in those subgroups.

As noted throughout this article, in the current study we categorized PH patients based on a hemodynamic classification. Therefore, the pre-capillary PH group might have different demographic characteristics than cohorts of WHO group 1 PH patients, such as the REVEAL registry, in which

the mean age of subjects was younger, with less co-morbidities, and even a higher percentage of women.[48]

The prevalence of obesity in our patients' cohort (41%) was high. However, it is not significantly higher than in the REVEAL registry, in which the percentage of obesity was 33%, and even 38% in the idiopathic PAH group, suggesting that the high rate of obesity does not reflect a selection bias of a less severe PH cohort.

Larger prospective and longitudinal studies are needed in order to better evaluate the association between BMI values, obesity, and mortality in various subgroups of PH patients.

In conclusion, in a cohort of PH patients, higher BMI values were significantly associated with lower mortality risk, independent to other prognostic variables, both in pre-capillary and out-of-proportion post-capillary PH patients. Similar to several other chronic cardiovascular diseases, including heart failure, the "obesity paradox" seems to exist in PH patients as well.

Acknowledgments

Authors contributions

Dr. Zafrir: Had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the results. Contributed to study concept and design, data analysis and interpretation, drafting of the manuscript, and critically revising the article, and approving the final version of the manuscript.

Dr. Adir: Contributed to study concept and design; data abstraction, critical revision of the manuscript, and approving the final version of the manuscript.

Dr. Shehadeh: Contributed to acquisition of data, data analysis, critical revision of the manuscript, and approving the final version of the manuscript.

Dr. Shteinberg: Contributed to study concept, acquisition of data and data interpretation, critical revision of the manuscript, and approving the final version of the manuscript.

Dr. Salman: Contributed to study concept, acquisition of data, critical revision of the manuscript, and approving the final version of the manuscript.

Dr. Amir: Contributed to study concept and design, data analysis and interpretation, data abstracting, critically revising the article, and approving the final version of the manuscript.

Conflict of interest statement

The authors report no potential conflicts of interests.

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