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Relation Between Obesity and Survival in Patients Hospitalized for Pulmonary Arterial Hypertension (from a Nationwide Inpatient Sample Database 2003 to 2011)

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There have been numerous studies reporting lower mortality rates in obese patients with various cardiovascular disorders than in nonobese patients, a phenomenon known as the "obesity paradox." Limited data exist regarding the effect of obesity on prognosis in patients with pulmonary arterial hypertension (PAH). We used the National Inpatient Sample database for years 2003 to 2011 to identify all patient hospitalizations aged ≥18 years with a primary diagnosis of PAH. Patients with a diagnosis of obesity were identified using Elixhauser co-morbidity measure provided in Nationwide Inpatient Sample database, based on *International Classification of Diseases, Ninth Revision, Clinical Modification*, codes and the diagnosis-related groups. Multivariable logistic regression was used to compare in-hospital mortality between obese and nonobese patients with PAH. Of the 18,450 patients with a primary diagnosis of PAH, 14.7% were obese. Obese patients with PAH were younger, more often women, and more often black compared with nonobese white patients. After risk adjustment for demographics, hospital characteristics, and baseline co-morbidities, obese patients with PAH had lower observed in-hospital mortality compared with nonobese patients with PAH (3.5% vs 8.1%; adjusted odds ratio 0.66, 95% confidence interval 0.51 to 0.85, p = 0.001). In conclusion, from a 9-year nationwide cohort of patients with PAH, we observed significantly lower risk-adjusted in-hospital mortality in obese patients compared with nonobese patients. **(Am J Cardiol 2017;120:489−493)**

Although obesity is an important independent cardiovascular (CV) risk factor, data exist supporting better survival outcomes for obese compared to non-obese patients in multiple clinical conditions, including coronary heart disease, heart failure, hypertension, and chronic obstructive pulmonary disease.[1−6] This epidemiologic observation has been termed the "obesity paradox." Pulmonary arterial hypertension (PAH), the result of pathophysiological changes in pulmonary vasculature leading to abnormally high pulmonary artery pressures, is an important CV condition leading to poor outcomes including right-sided heart failure and death. Little is known about the effect of obesity on prognosis in patients with PAH, and the need for studies examining the role of obesity in pulmonary vascular diseases has been emphasized previously.[7−10] Hence, we analyzed the association of obesity with mortality in the Nationwide Inpatient Sample (NIS) databases from 2003 to 2011.

Methods

We used NIS of the Healthcare Cost and Utilization Project, the largest publicly available all-payer inpatient care database in the United States with discharge-level data available for approximately 8 million hospital stays each year and which is designed to approximate a 20% stratified sample of US hospitals.[11] The first diagnosis is referred to as the "principal diagnosis" and is considered the primary reason for admission to the hospital. The NIS also provides ≤25 secondary diagnoses during that hospitalization and carries information on patient demographics, hospitalization characteristics, insurance status, co-morbidities, hospitalization outcome, and length of stay and cost of hospitalization. The internal and external validity of the NIS database are maintained through annual data quality assessments and comparison with other databases, such as National Hospital Discharge Survey and MedPar Statistics. These reports are published on the NIS Web site: http://www.hcupus.ahrq.gov/db/nation/nis/nisrelatedreports.jsp.

All hospitalizations with the principal diagnosis of PAH in patients with age ≥18 years were identified using the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes 416.0, as used previously.[12] Obese patients were identified using the Agency for Healthcare Research and Quality−defined co-morbidity measure, CM_Obese.[11] Agency for Healthcare Research and Quality co-morbidities that are provided in NIS were originally described by Elixhauser et al[13] using *ICD-9-CM* diagnoses and the diagnosis-related group in effect on the discharge/death date.[11] The definition of

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See page 492 for disclosure information.

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Table 1
Baseline demographics, hospital characteristics, and comorbidities of pulmonary artery hypertension patients

Variable	Overall	Obesity		*p*-value
		NO	YES	
	n=18,450	n=15,735	n=2,715	
Age, mean ± SD (years)	55.4± 17.5	55.8 ±17.9	53.1±14.8	<0.001
Women	76.8%	75.6%	83.9%	<0.001
White	65.7%	66.0%	64.0%	
Black	17.2%	16.5%	20.7%	
Hispanic	9.8%	9.9%	9.3%	
Asian or Pacific Islander	2.3%	2.4%	1.5%	
Native American	1.3%	1.3%	1.3%	
Other	3.7%	3.8%	3.1%	
Payer status				
Primary expected payer				<0.001
Medicare	45.4%	46.6%	38.8%	
Medicaid	16.4%	15.9%	19.0%	
Private insurance	32.1%	31.8%	33.8%	
Self-pay	3.5%	3.2%	5.0%	
No charge	0.4%	0.3%	0.7%	
Other	2.2%	2.1%	2.7%	
Median household income (percentile)				<0.001
0 to 25th	25.6%	25.4%	27.1%	
26th to 50th	25.6%	25.2%	27.7%	
51st to 75th	25.8%	25.7%	26.3%	
76th to 100th	23.0%	23.7%	18.8%	
Admission characteristics				
US Region				<0.001
Northeast	23.8%	24.3%	20.8%	
Midwest	19.6%	19.6%	19.8%	
South	31.9%	32.2%	30.2%	
West	24.7%	23.9%	29.2%	
Bed size				0.68
Small	7.3%	7.3%	7.6%	
Medium	18.0%	18.0%	18.4%	
Large	74.7%	74.8%	74.0%	
Urban location	92.5%	92.5%	92.7%	0.68
Teaching Hospital	68.9%	69.9%	63.2%	<0.001
Elective admission	20.3%	20.7%	18.5%	0.01
Weekend admission	14.3%	14.1%	15.6%	0.04
Comorbidities*				
Smoking	17.8%	17.4%	20.3%	<0.001
Diabetes mellitus (uncomplicated)	18.8%	16.4%	32.6%	<0.001
Diabetes mellitus (complicated)	4.3%	3.4%	9.1%	<0.001
Hypertension	36.3%	33.9%	49.9%	<0.001
Dyslipidemia	15.5%	14.4%	21.8%	<0.001
Alcohol abuse	2.3%	2.4%	1.4%	<0.001
Prior myocardial infarction	2.9%	2.8%	2.9%	0.84
Atrial fibrillation	15.5%	16.1%	12.1%	<0.001
Congestive heart failure	36.0%	35.7%	38.1%	0.01
Chronic Pulmonary Disease	30.1%	28.9%	36.9%	<0.001
Obstructive Sleep Apnea	10.1%	6.4%	31.4%	<0.001
Peripheral vascular disease	3.4%	3.2%	4.4%	<0.01
Renal Failure	12.6%	12.3%	14.6%	0.001
Valvular heart disease	14.4%	14.9%	11.8%	<0.001
Acquired immune deficiency syndrome	0.7%	0.8%	0.7%	0.60
Deficiency anemia	16.6%	16.0%	20.6%	<0.001
Rheumatoid arthritis/collagen vascular diseases	8.1%	8.7%	4.8%	<0.001
Chronic blood loss anemia	0.8%	0.7%	1.2%	0.01
Coagulopathy	10.0%	10.5%	7.5%	<0.001
Depression	9.8%	9.3%	12.6%	<0.001
Drug abuse	2.7%	2.8%	2.4%	0.29
Hypothyroidism	14.1%	13.5%	17.5%	<0.001

(*continued*)

Table 1
(*continued*)

Variable	Overall	Obesity		*p*-value
		NO	YES	
	n=18,450	n=15,735	n=2,715	
Liver disease	7.0%	7.3%	5.4%	<0.001
Lymphoma	1.0%	1.1%	0.8%	0.14
Fluid and electrolyte disorder	26.0%	26.0%	25.7%	0.78
Metastatic cancer	0.5%	0.5%	0.0%	<0.001
Other neurologic disorders	4.6%	4.7%	3.9%	0.06
Paralysis	0.9%	0.9%	0.6%	0.07
Psychoses	2.7%	2.2%	5.3%	<0.001
Solid tumor without metastasis	0.8%	0.9%	0.6%	0.08
Weight loss	2.5%	2.6%	1.4%	<0.001

SD = standard deviation.

* Co-morbidities were extracted using the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) and Clinical Classifications Software (CCS) Codes.[11]

Table 2
In-hospital mortality, mean length of stay and average cost of hospitalization of pulmonary artery hypertension patients

In-Hospital Outcomes	Overall	Non-Obese	Obese	p-value
Number of cases (weighted)	18,450	15,735	2,715	
In-hospital Mortality	7.4%	8.1%	3.5%	
Unadjusted OR (95% CI)	—	Reference	0.41 (0.33 to 0.51)	<0.001*
Adjusted OR† (95% CI)	—	Reference	0.66 (0.51 to 0.85)	0.001‡
Median Length of Stay (days)	5(3,8)	5(2,8)	5(3,10)	<0.001§
Median cost of hospitalization (US$)	25121(13550,49733)	24226 (12886,47946)	28991 (17413,61001)	<0.001*

CI = confidence interval; OR = odds ratio.

* p value calculated using chi-square test.

† Adjusted for patient demographics, hospital characteristics and clinical comorbidities.

‡ p value calculated using multivariate logistic regression.

§ p value calculated using Mann Whitney U test.

obesity includes the following *ICD-9-CM* codes: 278.0, 278.00, 278.01, 278.03, 649.10 to 649.14, 793.91, V85.30 to V85.39, V85.41 to V85.45, and V85.54 and excludes the following diagnosis-related group: 288, 296 to 298, 619 to 621, and 640 to 641.[11] Patient-level characteristics included age, gender, race, primary payer status, weekday versus weekend admission, all Elixhauser co-morbidities[11,13] provided as part of database (except obesity and pulmonary circulation disorders)—acquired immune deficiency syndrome, alcohol abuse, deficiency anemia, rheumatoid arthritis/collagen vascular diseases, chronic blood loss anemia, congestive heart failure, chronic renal failure, coagulopathy, depression, diabetes (uncomplicated), diabetes (with chronic complications), drug abuse, hypertension, hypothyroidism, liver disease, lymphoma, fluid and electrolyte disorders, metastatic cancer, other neurologic disorders, paralysis, peripheral vascular disease, psychosis, solid tumor without metastasis, valvular heart disease, and weight loss and other relevant CV co-morbidities (smoking, dyslipidemia, previous myocardial infarction, obstructive sleep apnea, and atrial fibrillation). Hospital-level characteristics included the following: location (urban or rural), bed size (small, medium, or large), region (Northeast, Midwest, South, or West), and teaching status. The principal outcome measure was in-hospital mortality. In addition to all variables listed in Table 1, obesity was used as an independent variable in a multivariable regression model to examine predictors of in-hospital mortality, labeled as "died" in the NIS.

All analyses were performed on weighted data using NIS-provided weights to create national estimates. Categorical variables are expressed as percentages and continuous variables as mean ± SD or median (interquartile range) as applicable. We initially compared the baseline patient and hospital characteristics between the 2 groups (nonobese and obese). The Pearson chi-square test was used for categorical variables and the Student's *t* test or Mann-Whitney *U* test for continuous variables. Multivariate unconditional logistic regression was then used to compare in-hospital mortality between patients with obesity and those without obesity, where we adjusted for patient demographics, hospital characteristics, all clinical co-morbidities, and hospital characteristics as mentioned earlier. Adjusted odds ratios and 95% confidence intervals were used to report the results of logistic regression. Statistical analysis was performed using IBM SPSS Statistics 23.0 (IBM Corp., Armonk, New York). A 2-sided p value of <0.05 was considered significant.

Results

In all, 18,450 hospitalized patients with a primary diagnosis of PAH at discharge or at death were identified. Table 1 describes the patient demographics, hospital characteristics, and clinical co-morbidities in the overall cohort and subgroups based on obesity diagnosis. In the overall cohort of patients with PAH, obesity was associated with lower in-hospital mortality (3.5% vs 8.1%; unadjusted odds ratio 0.41, 95% confidence interval [CI] 0.33 to 0.51, p <0.001). This unadjusted mortality difference reduced markedly but remained statistically significant, even after risk adjustment for demographics, hospital characteristics, and baseline co-morbidities (adjusted odds ratio 0.66, 95% CI 0.51 to 0.85, p = 0.001) (Table 2).

Discussion

In this largest nationalized "real-world" study of patients with PAH to-date, a coexisting discharge diagnosis of obesity (present in 14.7% of the PAH patient cohort) was associated with lower in-hospital mortality even after extensive adjustment for patient demographics, hospitalization characteristics, and clinical co-morbidities.

Obesity has been shown to adversely impact right ventricular end-diastolic pressures, mean pulmonary artery pressures, and pulmonary vascular resistance and CV structure and function.[14–17] Thus, survival would be expected to be lower in obese patients with PAH, the opposite of what we found in our analysis, suggestive of obesity paradox in PAH. Although many studies have reported the impact of obesity on pulmonary hemodynamics and development of PAH, until now, scant literature existed with respect to mortality. Zafrir et al[9] reported significantly improved survival in obese pulmonary hypertension patients during a follow-up duration of 19 ± 13 months (hazard ratio [HR] 0.2, 95% CI 0.1 to 0.6; p = 0.004). Similarly, in another study based on analysis of a subcutaneous treprostinil database, a 10 kg/m^2 increase in body mass index was reported to significantly decrease 10-year mortality (HR 0.68, 95% CI 0.52 to 0.89, p = 0.005).[8] Poms et al[7] found significantly higher survival in obese patients with PAH during long-term follow-up in 2,959 patients with PAH from Registry to Evaluate Early and Long-term PAH Disease Management Registry (HR 0.73, 95% CI 0.61 to 0.86, p <0.001). In a recent animal model-based study, the association of obesity and enhanced sympathetic adrenergic state was recently hypothesized as a potential explanation for the obesity paradox in PAH.[18] To the best of our knowledge, our study is the first study to report the protective effect of obesity on in-hospital mortality in patients with PAH at a large, nationwide level.

Multiple clinical studies have reported the protective effect of obesity on mortality in other CV and pulmonary diseases.[3,6,19] Although no clear explanations exist for this phenomenon, improved prognosis in obese patients compared with nonobese has been related to the excess adipose tissue and higher circulating lipoproteins.[20] Given that patients with chronic diseases, such as heart failure, coronary heart disease, and chronic obstructive pulmonary disease, have higher baseline inflammatory state, with high levels of inflammatory markers, such as interleukin-1, interleukin-6, tumor necrosis factor-alpha levels, they live with higher catabolic burden and cachexia. Similar to the earlier mentioned chronic diseases, PAH has also been reported to have higher levels of tumor necrosis factor-alpha and interleukins.[21] Hence, as hypothesized in other diseases, the extra adipose reserve might potentially provide a buffer for these cytokines in PAH too, thereby positively influencing the prognosis. Other investigators have suggested that obese patients in diseases such as heart failure might present earlier in their disease course because of factors, such as poorer functional status and reduced expression of circulating natriuretic peptides, which can lead to medical care and initiation of follow-up at a younger age.[22,23] Additionally, given renin-angiotensin system upregulation in recent experimental PAH studies has been strongly related to mortality, obese patients might have an advantage as they have attenuated response to renin-angiotensin system.[23] It is critically important to emphasize that this strong paradoxical association of obesity with favorable survival does not assume causation and should not be seen as encouragement for weight gain. Clearly extensive literature supports that obesity is an established risk factor for the epidemiology of CV diseases and its morbidity and mortality.[24] However, the existence of obesity paradox should stimulate research to elucidate the mechanism(s) behind this interesting observation and use it for potentially improving patient care and prognosis.

This study has several limitations. Obesity and PAH were identified based on *ICD-9* codes, and information on clinical variables, body mass index, laboratory values, hemodynamics, and pulmonary vasoactive medications was not available. Hence, addressing specific issues such as differences in the prescription and clinical impact of medications between 2 groups is not possible. Also there is a risk that pulmonary hypertension secondary to left heart disease or lung disease might have been misclassified as PAH, given dependency on *ICD-9* codes. The prevalence of obesity in our study was lower (14.7%) in comparison with those reported by earlier studies (33% to 48%).[25,26] Others using Behavioral Risk Factor Surveillance System direct survey have previously shown that obesity is underreported in NIS.[27] NIS is prone to coding errors and is limited to all cause in-patient mortality, and the primary discharge diagnosis may not reliably represent the condition responsible for hospital admission. Also the possibility of residual measured or unmeasured confounding should be noted. Nonetheless, the NIS database provided a large nationalized sample of the real-world data and high statistical power to study the impact of obesity on in-hospital mortality in patients with PAH. Finally, we do not have data on physical activity, exercise, or fitness, which affects many patients with CV diseases, including potentially those with PH.[5,20,28–30]

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Disclosures

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1. Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX, Eckel RH. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss. *Arterioscler Thromb Vasc Biol* 2006;26:968−976.
2. Lainscak M, von Haehling S, Doehner W, Sarc I, Jeric T, Ziherl K, Kosnik M, Anker SD, Suskovic S. Body mass index and prognosis in patients hospitalized with acute exacerbation of chronic obstructive pulmonary disease. *J Cachexia Sarcopenia Muscle* 2011;2:81−86.
3. Fonarow GC, Srikanthan P, Costanzo MR, Cintron GB, Lopatin M, Committee ASA. Investigators. An obesity paradox in acute heart failure: analysis of body mass index and inhospital mortality for 108, 927 patients in the Acute Decompensated Heart Failure National Registry. *Am Heart J* 2007;153:74−81.
4. Chittal P, Babu AS, Lavie CJ. Obesity paradox: does fat alter outcomes in chronic obstructive pulmonary disease? *COPD* 2015;12:14−18.
5. Lavie CJ, Sharma A, Alpert MA, De Schutter A, Lopez-Jimenez F, Milani RV, Ventura HO. Update on obesity and obesity paradox in heart failure. *Prog Cardiovasc Dis* 2016;58:393−400.
6. Uretsky S, Messerli FH, Bangalore S, Champion A, Cooper-Dehoff RM, Zhou Q, Pepine CJ. Obesity paradox in patients with hypertension and coronary artery disease. *Am J Med* 2007;120: 863−870.
7. Poms AD, Turner M, Farber HW, Meltzer LA, McGoon MD. Comorbid conditions and outcomes in patients with pulmonary arterial hypertension: a REVEAL registry analysis. *Chest* 2013;144:169−176.
8. Benza RL, Gomberg-Maitland M, Naeije R, Arneson CP, Lang IM. Prognostic factors associated with increased survival in patients with pulmonary arterial hypertension treated with subcutaneous treprostinil in randomized, placebo-controlled trials. *J Heart Lung Transplant* 2011;30:982−989.
9. Zafrir B, Adir Y, Shehadeh W, Shteinberg M, Salman N, Amir O. The association between obesity, mortality and filling pressures in pulmonary hypertension patients; the "obesity paradox". *Respir Med* 2013;107:139−146.
10. Robbins IM, Moore TM, Blaisdell CJ, Abman SH. Improving outcomes for pulmonary vascular disease. *Am J Respir Crit Care Med* 2012;185:1015−1020.
11. Healthcare Cost and Utilization Project (HCUP). Overview of the National (nationwide) Inpatient Sample (NIS), Rockville. Available at: https://www.hcup-us.ahrq.gov/nisoverview.jsp. Accessed on January 10, 2016.
12. Anand V, Roy SS, Archer SL, Weir EK, Garg SK, Duval S, Thenappan T. Trends and outcomes of pulmonary arterial hypertension-related hospitalizations in the United States: analysis of the nationwide inpatient sample database from 2001 through 2012. *JAMA Cardiol* 2016;1:1021−1029.
13. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care* 1998;36:8−27.
14. Alpert MA. Obesity cardiomyopathy: pathophysiology and evolution of the clinical syndrome. *Am J Med Sci* 2001;321:225−236.
15. Vasan RS. Cardiac function and obesity. *Heart* 2003;89:1127−1129.
16. Alpert MA, Omran J, Mehra A, Ardhanari S. Impact of obesity and weight loss on cardiac performance and morphology in adults. *Prog Cardiovasc Dis* 2014;56:391−400.
17. Oktay AA, Lavie CJ, Milani RV, Ventura HO, Gilliland YE, Shah S, Cash ME. Current perspectives on left ventricular geometry in systemic hypertension. *Prog Cardiovasc Dis* 2016;59:235−246.
18. Diong C, Jones PP, Tsuchimochi H, Gray EA, Hughes G, Inagaki T, Bussey CT, Fujii Y, Umetani K, Shirai M, Schwenke DO. Sympathetic hyper-excitation in obesity and pulmonary hypertension: physiological relevance to the 'obesity paradox'. *Int J Obes (Lond)* 2016;40: 938−946.
19. Lainscak M, von Haehling S, Doehner W, Anker SD. The obesity paradox in chronic disease: facts and numbers. *J Cachexia Sarcopenia Muscle* 2012;3:1−4.
20. Parto P, Lavie CJ, Arena R, Bond S, Popovic D, Ventura HO. Body habitus in heart failure: understanding the mechanisms and clinical significance of the obesity paradox. *Future Cardiol* 2016;12:639−653.
21. Groth A, Vrugt B, Brock M, Speich R, Ulrich S, Huber LC. Inflammatory cytokines in pulmonary hypertension. *Respir Res* 2014;15:47.
22. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Woo MA, Tillisch JH. The relationship between obesity and mortality in patients with heart failure. *J Am Coll Cardiol* 2001;38:789−795.
23. Lavie CJ, Alpert MA, Arena R, Mehra MR, Milani RV, Ventura HO. Impact of obesity and the obesity paradox on prevalence and prognosis in heart failure. *JACC Heart Fail* 2013;1:93−102.
24. Bastien M, Poirier P, Lemieux I, Despres JP. Overview of epidemiology and contribution of obesity to cardiovascular disease. *Prog Cardiovasc Dis* 2014;56:369−381.
25. Taraseviciute A, Voelkel NF. Severe pulmonary hypertension in postmenopausal obese women. *Eur J Med Res* 2006;11:198−202.
26. Badesch DB, Raskob GE, Elliott CG, Krichman AM, Farber HW, Frost AE, Barst RJ, Benza RL, Liou TG, Turner M, Giles S, Feldkircher K, Miller DP, McGoon MD. Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. *Chest* 2010;137:376−387.
27. Al Kazzi ES, Lau B, Li T, Schneider EB, Makary MA, Hutfless S. Differences in the prevalence of obesity, smoking and alcohol in the United States nationwide inpatient sample and the Behavioral Risk Factor Surveillance System. *PLoS One* 2015;10:e0140165.
28. Arena R, Lavie CJ, Borghi-Silva A, Daugherty J, Bond S, Phillips SA, Guazzi M. Exercise training in group 2 pulmonary hypertension: which intensity and what modality. *Prog Cardiovasc Dis* 2016;59:87−94.
29. Lavie CJ, De Schutter A, Parto P, Jahangir E, Kokkinos P, Ortega FB, Arena R, Milani RV. Obesity and prevalence of cardiovascular diseases and prognosis-the obesity paradox updated. *Prog Cardiovasc Dis* 2016;58:537−547.
30. Lavie CJ, McAuley PA, Church TS, Milani RV, Blair SN. Obesity and cardiovascular diseases: implications regarding fitness, fatness, and severity in the obesity paradox. *J Am Coll Cardiol* 2014;63: 1345−1354.