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Original Article

Mortality association between obesity and pneumonia using a dual restricted cohort model

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ABSTRACT

Background: An obesity survival paradox has been reported among obese patients with pneumonia.
Aims: To determine the impact of obesity on pneumonia outcomes and analyze the correlation between in-hospital all-cause mortality and obesity among patients with pneumonia.
Methods: The United States Nationwide Readmissions Database (NRD) was retrospectively analyzed for patients with pneumonia from 2013 to 2014. We used a step-wise restricted and propensity score matching cohort model (dual model) to compare mortality rates and other outcomes among pneumonia patients based on BMI. Mortality was calculated by a Cox proportional hazard model, adjusted for potential confounders with propensity score matched analysis.
Results: A total of 70,886,775 patients were registered in NRD during the study period. Of these, 7,786,913 patients (11.0%) were considered obese and 1,652,456 patients (2.3%) were admitted to the hospital with pneumonia. Based on the step-wise restricted cohort model, the hazard ratio comparing the mortality rates among obese pneumonia patients to mortality rates among normal BMI pneumonia patients was 0.75 (95% CI 0.60–0.94). The propensity score matched analysis estimated a hazard rate of 0.84 (95% CI 0.79–0.90) and the hazard ratio estimated from the dual model was 0.82 (95% CI 0.63–1.07).
Conclusions: With the application of a dual model, there appears to be no significant difference in mortality of obese patients with pneumonia compared to normal BMI patients with pneumonia.

Introduction

According to data from the National Health and Nutrition Examination Survey, the overall prevalence of obesity and morbid obesity in the US is respectively 38% and 8% [1,2]. The survey also showed significant increasing linear trends in obesity for both adults and youth [2,3]. Obesity has multiple health outcomes including a higher incidence of infection, chronic disease, and organ failure [4–8]. Obesity has been associated with decreased lung function and increased prevalence of lung disease such as asthma, chronic obstructive pulmonary disease, sleep apnea, and pneumonia [9–11]. Persons with obesity have higher risk of acquiring pneumonia and subsequently higher hospital admission rates, longer intensive care unit stays, and increased mechanical ventilation requirements [12–16]. However, their hospital all-cause mortality has been reported to be lower than that of non-obese individuals [14,15,17]. Such observations have been described as the "obesity survival paradox" within the literature [17–19].

The obesity survival paradox has been discussed both in human and animal studies with controversial findings [17,20–25]. In animal studies, neutrophil-impaired chemotaxis was observed in obese mice, resulting in an increased risk of respiratory infection. There was also observed an impaired host response to lung infections in obese subjects [23]. Neutrophil CXCR2 expression was significantly lowered in obese mice which subsequently attenuated murine acute lung injury [24]. Similarly, obese rats has less lung function deterioration, secondary to anti-inflammatory and anti-fibrotic effects [25]. Such animal studies addressed, in part,

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the mechanisms of the obesity survival paradox with lung infections. In clinical studies, results are more mixed [17,22,26,27]. Most studies that support the obesity survival paradox either analyzed general data and adjust for potential confounders or used a stepwise restricted cohort analysis for specific diseases. These methods may be subject to patient selection bias [14,19,28]. Studies that counter the obesity survival paradox typically use a large-scale sample size and assess for overall all-cause mortality by a restricted cohort model [27,29]. These two large-scale epidemiological studies reported a step-wise diminished trend of the obesity survival paradox among successive restriction cohort models [27,29]. A subsequent secondary data analysis combining this data further supported such findings [26]. Using this model requires a significant amount of data to satisfy the final analysis. At present, most studies focusing on a mortality correlation between obesity and pneumonia included only small sample size, which prevents using this large-scale restricted cohort model [15,18,22]. Therefore, it is necessary to apply a large-scale national sampling database to this analysis method which has not been reported in the literature to date.

Proper interpretation of survival benefit in patients with obesity will eventually help guide the appropriate evaluation and managements of these patients. We aim to apply and expand this successive restricted model to the US national database to analyze the impact of obesity on pneumonia outcomes and further determine the correlation between all-cause mortality and pneumonia in the obese patient population.

Methods

Study design and participants

This was a retrospective observation study using a large-scale sample database. We used the Nationwide Readmissions Database (NRD) data from 2013 to 2014. NRD is one of the largest inpatient databases publicly available in the US and is sponsored by the Agency for Healthcare Research and Quality (AHRQ) as a part of the Healthcare Cost and Utilization Project (HCUP). To reflect the target universe, weights were calculated and applied through poststratification by hospital and discharge characteristics [30]. We included all patients in the NRD who were hospitalized with their primary or secondary discharge diagnoses listed as pneumonia. We excluded patients who 1) had missing outcomes (e.g., mortality) or gender since both variables were important for final data analysis; 2) uncertain disposition (e.g., left against medical advice, transferred to another facility, etc.); 3) age <18; and 4) obese patients with no further grading information (e.g., unknown BMI to differentiate level of obesity to include overweight or obese). Detailed inclusion and exclusion criteria is shown in Fig. 1. This study was waived by the local institutional review board based on analysis of de-identified, publicly available datasets.

Coding

We used the International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) codes 480–487 to identify all-cause pneumonia patients. See Appendix A Table A1 for the entire list of the diagnostic codes used in this study. The definition of obesity includes the following ICD-9-CM codes: 278.0, 278.00, 278.01, 278.02, 278.03, and 649.10–649.14. Obesity was identified when any of these ICD-9-CM codes were listed in NRD. In addition, ICD-9-CM code V85.21–V85.25, V85.30–V85.49, and V85.53–V85.54 were used for different classifications of obesity based on BMI (Body Mass Index). We classified patients as underweight (<18.5 kg/m^2), normal (18.5–<25.0 kg/m^2), overweight (25.0–<30.0 kg/m^2), and obese (30.0-kg/m^2) categories. Other codes for patients with history of smoking (305.1, 649.0, 989.84), chronic alcoholism (303, 305.0, 790.3, 980, E860), or any of the chronic diseases defined by the Charlson Comorbidity scale were also used in this study (Appendix A Table A1).

Variables

To classify obesity, this studied grouped patients into the following categories: underweight, normal, overweight, and obese. We included age, sex, patient income level, geographic location, chronic disease conditions (e.g., Charlson Comorbidity Score) and other clinically relevant conditions (smoking, alcoholism, patient level of disease severity by APR-DRG) as a baseline for patient characteristics. Specifically, we included hospital quality metrics (e.g. length of hospitalizations, 30-day readmission rate), and hospital cost for sub-group analysis.

Outcome measurements

Our primary outcome of interest was in-hospital all-cause mortality among pneumonia patients. Our secondary outcome measurements included subgroup mortality analysis among pneumonia patients with hospital quality metrics (length of hospital stay and 30-day readmission) and costs (hospital total and daily cost).

Dual restricted cohort models

Dual restricted cohort models were used in this study. An initial step-wise successive restricted cohort model was selected to compare mortality differences among patients with different BMIs (underweight, normal, overweight, and obese) by excluding those with history of smoking, chronic alcoholism, and any chronic diseases in a stepwise manner. Subsequently, a propensity score matching all variables except obesity was applied to the initial restricted cohort model to further minimize potential confounders. Standardized differences among all variables after propensity score matching are listed in Appendix A Fig. A1.

Study protocol

Study patients were divided into four groups [underweight (<18.5 kg/m^2), normal (18.5–<25.0 kg/m^2), overweight (25.0–<30.0 kg/m^2), and obese (30.0-kg/m^2)]. Patient baseline characteristics, primary, and secondary outcomes were compared among the four groups. Dual restricted cohort models were applied to patients within the four groups for in-hospital mortality comparisons. Mortality comparisons were also analyzed among subgroups including patients with different levels of obesity, different age groups, and patients with different levels of disease severity.

Data analysis

Univariate comparisons among groups were performed with Chi-square test for categorical variables and Mann–Whitney U test for continuous variables. Outcome comparisons were performed with the full, restricted, and restricted with propensity score matching cohorts separately. Propensity score was estimated by a logistic regression model in which obesity was the dependent variable and all other potential covariates listed in Appendix A Table A2 were the independent variables. This method of analysis is the one used in current literature [31]. Post-match comparisons were shown in Appendix A Fig. A1. Effect size of obesity on pneumonia all-cause in-hospital mortality was estimated via Cox proportional hazard model adjusted for all potential confounders and propensity score matched analysis. Adjusted hazard ratio was

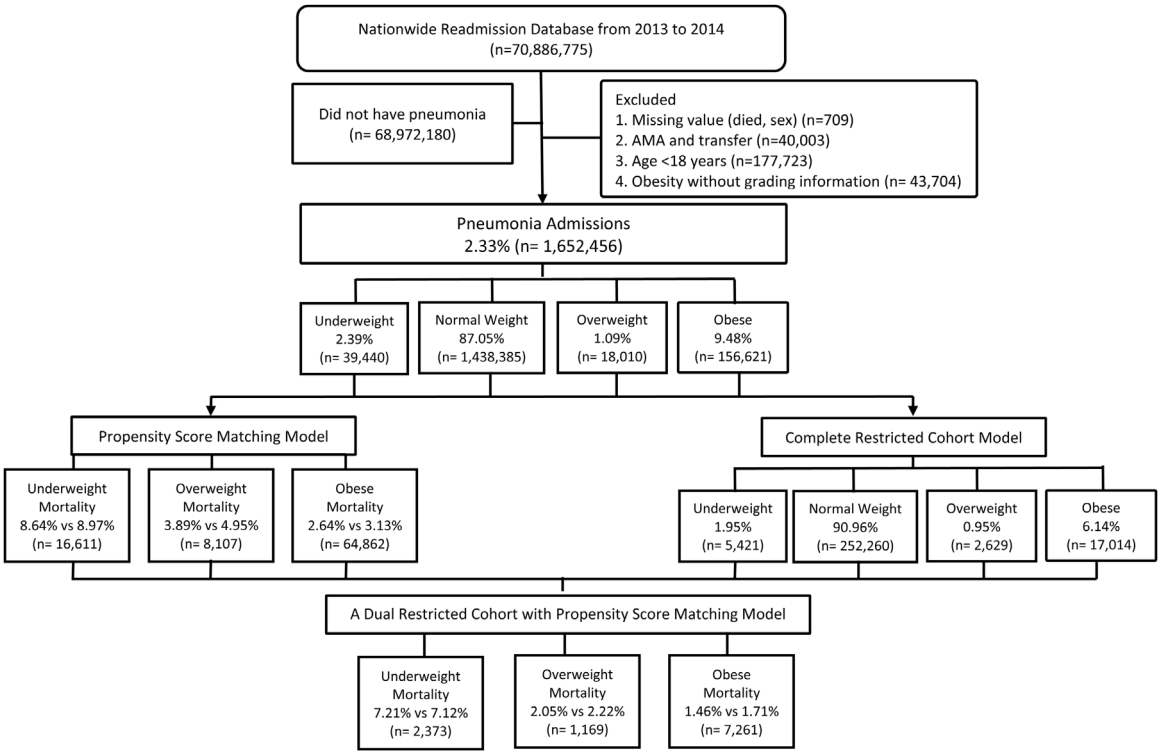

Fig. 1. Flow chart of patient population.

estimated for subgroup analyses including patients of different BMI categories, age, ventilation requirement, and severity of diseases, then presented in line chart and forest plot formats respectively. All descriptive and statistical analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC). A p value less than 0.05 was considered statistically significant.

Results

A total of 70,886,775 patients were registered in NRD during the study period. Of these 7,786,913 patients (11.0%) were considered obese, 6,144,989 patients (8.7%) were BMI $\geq$ 30, and 1,652,456 patients (2.3%) were admitted to hospital with a diagnosis of pneumonia and considered eligible for enrollment in the final analysis. Among the entire final analysis cohort, only 9.5% (156,621) of patients were deemed to be obese, whereas 87% were non-obese (Fig. 1). Detail comparisons were analyzed among patients with different BMI categories (e.g., underweight, normal weight, overweight, and obese patients respectively). Briefly, patients with obesity tended to be younger, predominantly female, had less alcohol abuse but had more comorbidities. Clinically, in-hospital mortality and 30-day readmission of the obese group were lower in comparison to non-obese groups. Economically, daily hospital cost was slightly higher in the obese group, whereas total length of stay in hospital and total hospital cost among patients with obesity was similar when compared with non-obese groups (Table 1).

Outcome analyses from step-wise restricted cohort model

When a step-wise restricted model was applied to the entire cohort, in-hospital mortality dropped consistently among all patients with different BMI categories (Table 2). When compared to non-obese groups, patients with obesity had significantly lower in-hospital mortality. Final in-hospital mortality from the completed restricted model in the obese group was 1.37% with a hazard ratio of 0.75 (95% CI 0.60–0.94) in comparison to the non-obese group (2.60%, Table 2). Neither overweighed nor underweighted group in our study showed significant difference in terms of mortality.

Outcome analyses from propensity score matched model

When propensity score matching was applied to the entire cohort, a pair of 64,862 patients were matched between non-obese and obese groups. In-hospital mortality was 2.64% in patients with obesity with a hazard ratio of 0.84 (95% CI 0.79–0.90) as compared to 3.13% in non-obese patients ($p < 0.001$, Table 3). In terms of length of hospitalization stay, hospital cost, and 30-day readmissions, patients with obesity had similar findings in comparison to the normal weight patient group (Table 3). Meanwhile, when overweighed group is compared to the normal weight group, the HR is 0.78 (95% CI 0.67–0.91).

Outcome analyses from restricted propensity score matching (dual restricted) model

Among the entire cohort, 6.1% of obese and 91% of non-obese patients were identified when a restricted cohort model was applied. Further application of propensity score matching (1:1) yielded 43% (7,261/17,014) of paired-patient comparisons between non-obese and obese groups (Fig. 1). When a dual restricted model was applied, the obesity survival paradox (mortality benefit) subsided. In-hospital mortality was 1.46% with hazard ratio of 0.82 (95% CI 0.63–1.07) in patients with obesity when compared to 1.71% in non-obese patients (Table 4, $p > 0.05$). Similar trends were noted among the different sub-group analyses showing less mortality benefits (e.g. the mortality difference between overweighed group and normal weighted one disappeared when applying this statistic method, Table 4). Overall, the obesity survival paradox was noted when only one restricted model was applied. This mortality benefit

Table 1
Comparison of characteristics among patients with four different BMI categories.

	Underweight N = 39,440	Normal weight N = 14,38385	Overweight N = 18,010	Obese N = 15,6621	p-Value
Demographics					
Gender male (%)	16,440 (41.68%)	692,973 (48.18%)	8870 (49.25%)	58,341 (37.25%)	<0.0001
Age Group					
18–44	2492 (6.32%)	123,430 (8.58%)	1389 (7.71%)	25,026 (15.98%)	
45–64	8770 (22.24%)	344,842 (23.97%)	4807 (26.69%)	66,067 (42.18%)	
65–74	8164 (20.7%)	288,715 (20.07%)	4248 (23.59%)	37,650 (24.04%)	<0.0001
75–84	10,075 (25.55%)	355,956 (24.75%)	4418 (24.53%)	21,581 (13.78%)	
≥85	9939 (25.20%)	325,442 (22.63%)	3149 (17.48%)	6297 (4.02%)	
Income quartile					
Lowest quartile	12,849 (33.05%)	434,154 (30.69%)	5722 (32.29%)	51,155 (33.16%)	
Quartile 2	10,722 (27.58%)	407,029 (28.77%)	5001 (28.22%)	46,502 (30.14%)	<0.0001
Quartile 3	8440 (21.71%)	321,403 (22.72%)	3984 (22.48%)	34,547 (22.39%)	
Highest quartile	6868 (17.67%)	252,175 (17.82%)	3012 (17.00%)	22,077 (14.31%)	
Residence					
Metro	18,017 (45.68%)	631,041 (43.87%)	9490 (52.69%)	72,789 (46.47%)	
County	12,751 (32.33%)	433,602 (30.15%)	5217 (28.97%)	49,539 (31.63%)	<0.0001
Rural	8583 (21.76%)	370,351 (25.75%)	3241 (18%)	34,028 (21.73%)	
Comorbidities					
Number of comorbidities (median, IQR)	3.66 (2.49,4.93)	2.83 (1.58,4.25)	3.95 (2.63,5.43)	4.33 (3.05,5.76)	<0.0001
Charlson score	2.27 ± 3.58	2.1 ± 3.2	2.42 ± 3.37	2.35 ± 2.94	<0.0001
COPD	19,067 (48.34%)	486,338 (33.81%)	5949 (33.03%)	53,162 (33.94%)	<0.0001
Lung cancer	2953 (7.49%)	52,328 (3.64%)	730 (4.05%)	2028 (1.29%)	<0.0001
Tuberculosis	116 (0.29%)	826 (0.06%)	18 (0.10%)	28 (0.02%)	<0.0001
Asthma	2753 (6.98%)	153,016 (10.64%)	2340 (12.99%)	35,147 (22.44%)	<0.0001
Congestive heart failure	7748 (19.65%)	345,093 (23.99%)	4507 (25.02%)	49,006 (31.29%)	<0.0001
Pulmonary disease	2889 (7.33%)	87,830 (6.11%)	1229 (6.82%)	15,772 (10.07%)	<0.0001
Peripheral vascular	3436 (8.71%)	103,683 (7.21%)	1624 (9.02%)	8726 (5.57%)	<0.0001
Disease					
Diabetes with chronic complications	959 (2.43%)	70,464 (4.90%)	1373 (7.62%)	18,006 (11.50%)	<0.0001
Metastatic cancer	2818 (7.15%)	53,853 (3.74%)	911 (5.06%)	2534 (1.62%)	<0.0001
Solid tumor without metastasis	2699 (6.84%)	58,115 (4.04%)	800 (4.44%)	3100 (1.98%)	<0.0001
Hypertension	19,716 (49.99%)	898,691 (62.48%)	12,550 (69.68%)	112,932 (72.11%)	<0.0001
Alcohol abuse	1997 (5.06%)	42,407 (2.95%)	578 (3.21%)	3246 (2.07%)	<0.0001
Tobacco abuse	8973 (22.75%)	220,715 (15.34%)	2813 (15.62%)	26,973 (17.22%)	<0.0001
Severity Index					
All patient refined DRG median (IQR)	2.58 (2.12,3.08)	1.98 (1.38,2.61)	2.28 (1.63,2.79)	2.25 (1.65,2.74)	<0.0001
Type of infection					
Bacteremia	553 (1.4%)	19,970 (1.39%)	279 (1.55%)	2269 (1.45%)	0.4591
Streptococcal pneumonia	866 (2.2%)	23,609 (1.64%)	316 (1.75%)	2133 (1.36%)	<0.0001
Influenza	945 (2.4%)	56,131 (3.9%)	759 (4.21%)	7619 (4.86%)	<0.0001
Outcome measurements					
In-hospital mortality (n, %)	3271 (8.29%)	60,339 (4.19%)	688 (3.82%)	4048 (2.58%)	<0.0001
Pleural effusion	4176 (10.59%)	106,470 (7.40%)	1850 (10.27%)	8615 (5.50%)	<0.0001
Empyema	342 (0.87%)	7008 (0.49%)	138 (0.76%)	945 (0.60%)	<0.0001
Use of ventilator	4338 (11.00%)	107,052 (7.44%)	1912 (10.62%)	23,400 (14.94%)	<0.0001
Length of hospital stay median (IQR), days	5.84 (3.86, 8.99)	4.48 (3.07, 6.85)	5.15 (3.45, 8.14)	4.78 (3.24, 7.46)	<0.0001
Readmission rate within 30 days, N (%)	3493 (8.86%)	113,577 (7.90%)	1432 (7.95%)	11,122 (7.10%)	<0.0001
Total cost of 1 st hospital stay median (IQR), USD	9004.34 (5705.51, 15,069)	7113.6 (4597.97, 11,670)	8394.09 (5296.18, 13,767)	8029.44 (5128.32, 13,442)	<0.0001
Cost per day for 1 st hospital stay, median (IQR), USD	1715.07 (1306.87, 2305.95)	1807.46 (1367.38, 2459.33)	1810.11 (1370.94, 2481.14)	1900.52 (1454.37, 2562.50)	<0.0001

subsided with application of dual restricted models whereby more robust control is applied across the cohort.

Discussion

In recent years, studies focusing on the association between pneumonia and all-cause mortality among patients with obesity have been reported with diverse results and conclusions [14,17]. Our study found that in-hospital mortality among pneumonia patients was lower in obese patients as compared to those without with no restriction applied. However, when dual restrictions (both step-wise restricted and propensity score matching cohort model) was applied to the database, the obesity survival paradox was less significant. Therefore, we believe our findings support recent debates regarding the obesity paradox and recommend such interpretations should be used with caution [20,32]. This study adds to the current literature pool on the obesity survival paradox specific to pneumonia by using an advanced statistical methodology for bias control. To the best of our knowledge, a study with this method of analysis has not been reported.

Our study's strengths are: 1) use of the US national database which provides a large-scale patient sample inclusive of different locations, races, genders, and ethnicities; 2) performing mortality and hospital metrics analysis using a dual restricted propensity

Table 2
Comparison of pneumonia related outcomes among patients in four different BMI categories using a step-wise restricted cohort model.

Step-wise restricted cohort	Underweight	Normal weight	Overweight	Obesity	p Value
In-hospital mortality (n/N, %, HR, 95% CI)					
Patients without chronic disease	394/6335 (6.21%)*** 0.89 (0.75–1.07)	6843/300,020 (2.28%) 1	59/3229 (1.82%) 0.62 (0.38–1.02)	263/20,892 (1.26%) 0.80 (0.65–0.99)*	
Non-smoker patients without chronic disease	365/5530 (6.59%)*** 0.87 (0.73–1.04)	6646/256,813 (2.59%) 1	57/2694 (2.12%) 0.64 (0.39–1.05)	238/17,311 (1.37%)*** 0.76 (0.61–0.94)*	
Non-smoker, non-alcohol consuming patients without chronic disease	363/5421 (6.70%)*** 0.88 (0.73–1.06)	6547/252,260 (2.60%) 1	57/2629 (2.17%) 0.65 (0.40–1.08)	233/17,014 (1.37%)*** 0.75 (0.60–0.94)*	
[a]Complete restricted cohort	N = 5421	N = 252,260	N = 2629	N = 17,014	
Pleural effusion	480 (8.86%)	16,766 (6.65%)	271 (10.29%)	1149 (6.75%)	<0.0001
Empyema	61 (1.12%)	1624 (0.64%)	21 (0.79%)	205 (1.21%)	<0.0001
Use of ventilator	418 (7.70%)	10,142 (4.02%)	141 (5.37%)	1465 (8.61%)	<0.0001
Length of hospital stay, median (IQR), days	5.28 (3.53, 8.33)	3.82 (2.68, 5.64)	4.46 (3.1, 6.83)	3.87 (2.7, 5.97)	<0.0001
Readmission rate within 30 days, N (%)	396 (7.30%)	14,236 (5.64%)	135 (5.14%)	618 (3.63%)	<0.0001
Total cost of 1 st hospital stay, median (IQR), USD	7666.05 (4851.7, 12,740)	5742.9 (3810.55, 9098.07)	6834.38 (4540.4, 10,820)	6197 (4048.59, 10,016)	<0.0001
Cost per day for 1 st hospital stay, median (IQR), USD	1630.64 (1224.95, 2216.58)	1745.43 (1299.37, 2410.72)	1757.91 (1293.48, 2379.47)	1845.65 (1379.16, 2529.3)	<0.0001

Abbreviations: BMI, body metabolic index; n, number of deceased patients; N, total number of patients within group; HR, hazard ratio; CI, confidence interval. *p < 0.05, **p < 0.01; *** p < 0.001 when compared with normal weight group.
[a] Complete restricted cohort refers to the full cohort excluding patients with chronic illness defined by Charlson Comorbidity Index, as well as smokers and alcoholics.

Table 3
Comparison of pneumonia related outcomes among patients in four different BMI categories using propensity score matching model.

Propensity score matching cohort	Underweight versus normal weight N = 16,611 versus 16,611	Overweight versus normal weight N = 8107 versus 8107	Obese versus normal weight N = 64,862 versus 64,862
Primary outcome measurement	1435 vs. 1490	315 vs 401	1711 vs. 2028
	8.64% vs. 8.97%	3.89% vs. 4.95%	2.64% vs. 3.13%
In-hospital mortality (n, %, HR, 95% CI)	0.95(0.88–1.03)	0.78(0.67–0.91)	0.84(0.79–0.90)
Second outcome measurements			
Pleural effusion	1800(10.84%) vs. 2184(13.15%)***	841(10.37%) vs. 771(9.51%)	3704(5.71%) vs. 5086(7.84%)***
Empyema	144(0.87%) vs. 155(0.93%)	58(0.72%) vs. 63(0.78%)	417(0.64%) vs. 407(0.63%)
Use of ventilator	1950(11.74%) vs. 2541(15.3%)***	901(11.11%) vs. 833(10.28%)	10,012(15.44%) vs. 6399(9.87%) ***
Length of hospital stay, median (IQR), days	6(4,10) vs. 6(4,9)***	6(4,9) vs. 5(4,8)***	5(4,8) vs. 5(4,8) ***
Readmission rate within 30 days, N (%)	1449(8.72%) vs. 1494(8.99%)	624(7.7%) vs. 686(8.46%)	4471(6.89%) vs. 5286(8.15%) ***
Total cost of 1 st hospital stay, median (IQR), USD	9219(5788,15542.24) vs. 9152(5617,15756)	8486(5352,14178) vs. 7931(4960,13321)***	8093(5146,13659) vs. 7641(4866,12781)***
Cost per day for 1 st hospital stay, median (IQR), USD	1731(1308,2365) vs. 1845(1384,2550)***	1832(1374,2550) vs. 1872(1395,2549)*	1914(1449,2602) vs. 1892(1423,2579)***

Abbreviations: BMI, body metabolic index; n, number of deceased patients; N, total number of patients within group; HR, hazard ratio; CI, confidence interval. *p < 0.05, **p < 0.01; *** p < 0.001 when compared with normal weight group.

score matching cohort model; and 3) including sub-group analyses (extremely elderly and overall disease severity). Our study showed similar mortality in patients with pneumonia who required hospitalization regardless of their obesity statuses, especially when disease severity was balanced. Emergency physicians may have biases about outcome risk in obesity patients, resulting in higher admissions among this population [33,34]. Analyzing hospital metrics including length of stay, in-hospital mortality, and average cost does not support such a practice pattern in this study. Based on our findings, obesity might not be an independent risk to affect in-hospital mortality in pneumonia patients. We may be able to recommend similar medical management among this cohort despite their obesity.

Our study provides valuable insight into why the paradox may indeed be a statistical artifact by introducing a dual restriction model to minimize patient selection bias. We validated mortality among obese patients with pneumonia by using the national large-scale NRD database. Meanwhile, this study findings challenge the potential necessity of intensive body nutrition consumption in acute infectious diseases. In a recent TARGET trial, no mortality benefit was found in patients with high daily calorie intake (1.5 Kcal) in comparison to their routine controls (1.0 Kcal) [35]. Though we are not able to show evidence that high body fat is a protective factor against acute diseases, at least, this study shows such purported protective effect is exaggerated.

Dual restrict model for large scale data analysis shows advantages to other non-matched models. Given that long-term weight loss among alcoholics, smokers, and patients with chronic diseases subsequently affects mortality, exclusions of these patients minimizes potential patient selection bias [26]. Recent studies comment on the methodological inaccuracy of applying a restricted cohort model for analysis stating that such analyses are more like subgroup

Table 4
Comparison of pneumonia related outcomes among patients in four different BMI categories using a dual restricted propensity score matching model.

[a]Dual restricted propensity score matching cohort	Underweight versus normal weight	Overweight versus normal weight	Obese versus normal weight
	N = 2373 vs 2373	N = 1169 vs 1169	N = 7261 vs 7261
Primary outcome measurement	171 vs. 169	24 vs. 26	106 vs. 124
In-hospital mortality	7.21% vs. 7.12%	2.05% vs. 2.22%	1.46% vs. 1.71%
(n, %, HR, 95% CI)	1.00(0.81–1.24)	0.88(0.50–1.55)	0.82(0.63–1.07)
Second outcome measurements			
Pleural effusion	212(8.93%) vs. 331(13.95%) ***	111(9.5%) vs. 97(8.3%)	498(6.86%) vs. 720(9.92%)***
Empyema	26(1.1%) vs. 41(1.73%)	8(0.68%) vs. 9(0.77%)	97(1.34%) vs. 101(1.39%)
Use of ventilator	194(8.18%) vs. 272(11.46%)***	65(5.56%) vs. 58(4.96%)	636(8.76%) vs. 385(5.3%)***
Length of hospital stay, median	6(4,9) vs. 5(4,8)***	5(4,7) vs. 4(3,7)***	4(3,6) vs. 4(3,6)
(IQR), days			
Readmission rate within 30 days,	169(7.12%) vs. 164(6.91%)	57(4.88%) vs. 69(5.9%)	256(3.53%) vs 418(5.76%) ***
N (%)			
Total cost of 1 st hospital stay,	7771(4919,13380) vs.	6750(4537,10858) vs.	6244(4076,10142) vs.
median (IQR), USD	7595(4883,13209)	6195(4194,10064)**	6096(4047,9862) *
Cost per day for 1 st hospital	1674 (1233,2288) vs.	1749(1291,2412) vs.	1871(1388,2574) vs.
stay, median (IQR), USD	1771(1311,2435)***	1799(1311,2495)	1831(1356,2546)*
Subgroup in-hospital mortality analysis			
Elderly patients (≥75 years of age)	130(8.98%) vs. 132(9.12%)	14(2.97%) vs. 23(4.88%)	24(2.85%) vs. 36(4.28%)
	0.96(0.75–1.23)	0.58(0.29–1.16)	0.66(0.39–1.11)
Young patients (18–75 years of age)	41(4.43%) vs. 51(5.51%)	10(1.43%) vs. 11(1.58%)	82(1.28%) vs. 99(1.54%)
	0.77(0.50–1.18)	0.91(0.39–2.14)	0.79(0.58–1.08)
Ventilated patients	118(5.42%) vs. 113(5.19%)	14(1.27%) vs. 17(1.54%)	21(0.32%) vs. 45(0.68%)**
	1.03(0.79–1.33)	0.82(0.41–1.67)	0.48(0.28–0.80)**
Non-ventilated patients	53(27.32%) vs. 54(27.84%)	10(15.38%) vs. 13(20%)	85(13.60%) vs. 120(19.2%)**
	0.97(0.66–1.45)	0.67(0.28–1.56)	0.65(0.49–0.87)**
[b]Less severe patients	14(2.06%) vs. 10(1.47%)	2(0.29%) vs. 2(0.29%)	4(0.09%) vs. 12(0.26%)*
	1.30(0.57–2.97)	1.00(0.14–7.09)	0.33(0.11–1.03)
[c]More severe patients	156(9.23%) vs. 162(9.59%)	22(4.56%) vs. 34(7.05%)	102(3.94%) vs. 126(4.87%)
	0.95(0.76–1.19)	0.63(0.36–1.08)	0.79(0.60–1.04)

Abbreviations: BMI, body metabolic index; n, number of deceased patients; N, total number of patients within group; HR, hazard ratio; CI, confidence interval. *p < 0.05, **p < 0.01; *** p < 0.001 when compared with normal weight group.

[a] Dual restricted propensity score matching cohort refers to the full cohort excluding patients with chronic illness defined by Charlson Comorbidity Index, smokers, and alcoholics and then subsequently paired with propensity score matching (referred to as a dual restricted propensity score matching model).

[b] Refers to patients with minor or moderate severity by all patient refined DRG.

[c] refers to patients with major and extreme severity by AHR-DRG.

comparisons which could lead to collider stratification bias [36,37]. This, in part, could be due to other unmeasured confounders [38]. Therefore, the addition of propensity score matching allows for inclusion of patients paired with similar conditions except obesity, thus minimizes these confounders to a better level. Our study followed the same step-wise restriction method as the GBMC (The Global BMI Mortality Collaboration) reported with the addition of propensity score matching after such restrictions were applied [27]. This restriction control might further minimize patient selection bias.

As for underweight populations, Starr suggested short-term dietary restriction improved survival outcome in abdominal sepsis mice and proposed a possible mechanism [39]. Analyzing nationwide health survey in the UK, Hamer suggested an increased mortality in underweight and decreased mortality in overweight and stage I obese patients [40]. In our study, the underweighted groups showed no statistically significant mortality difference when comparing to healthy group.

Our study has its limitations. First, given the nature of the retrospective study design, limited and potentially incorrect information, missing data, and potential patient population selection bias cannot be avoided. Second, this study relied heavily on proper coding. Potential miscoding of patients might place them in an inappropriate category which could subsequently affect the accuracy of results. The prevalence of overweight and obesity in this study is very low in comparison to the national average. Since our obesity classifications are largely depending on ICD-9-CM code, such underestimation of obesity will inevitably occur in this type of study [41]. Third, the potential exists that obese patients having less severe pneumonia may be admitted more frequently than non-obese patients with similar disease which could lead to disease severity bias. Due to a retrospective analysis design we are unable to analyze relative pneumonia severity among groups. However, our subgroup analysis on severity of illness based on APR-DRG classification showed a similar mortality trend regardless of overall disease severity among obese patients. Fourth, even after applying a dual restricted propensity score matching cohort model, we are unable to eliminate patient selection bias completely nor be able to include all independent variables for comparisons. Fifth, this study only addressed short-term mortality among pneumonia patients with obesity. We did not investigate the obesity survival paradox in terms of long-term mortality. Sixth, the dual restricted model further reduced the sample size and widened the 95% confidence interval to 0.63–1.07. In this range, the hazard ratio (0.75) from the step-wise restricted cohort model was included. Expanding the sample size may provide better statistic power to show statistical difference. Lastly, BMI is not the perfect way to measure adiposity and obesity [42]. However, it is easily measured and widely recorded in the nationwide database to analyze. Further investigation would be needed as the obesity is defined by other central obese measures. Therefore, future multicenter prospective large-scale studies with robust controls is warranted to further identify whether a mortality benefit is present among obese populations.

Conclusion

When analyzing recent US national inpatient data, short-term in-hospital mortality tended to be lower in patients with obesity without any restrictions. However, when a dual restricted propensity score matching cohort model was applied the mortality benefit among patients with obesity who sustained pneumonia was diminished. Therefore, in obese patients with acute pneumonia, an obesity survival paradox must be interpreted with caution.

Author agreement

All authors approved the final version of the manuscript to be published. All authors agreed to be accountable for all aspects of the work in ensuring the questions related to the accuracy or integrity of any part of the work. CLL takes final responsibility for the paper.

Conflict of interest

No potential conflicts of interest exist.

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None.

Ethical statement

This study was waived by the local institutional review board based on analysis of de-identified, publicly available datasets.

CRediT authorship contribution statement

Hao Wang: Investigation, Methodology, Project administration, Supervision, Validation, Writing - original draft, Writing - review & editing. **Chien-Chang Lee:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing - original draft, Writing - review & editing. **Eric H. Chou:** Writing - original draft, Writing - review & editing. **Wan-Ting Hsu:** Conceptualization, Data curation, Formal analysis. **Richard D. Robinson:** Investigation, Methodology, Writing - original draft, Writing - review & editing. **Ke-Ying Su:** Conceptualization, Data curation, Formal analysis. **Jessica J. Kirby:** Writing - review & editing. **Dahlia Hassani:** Writing - review & editing.

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Appendix A.

Table A1
ICD-9 codes.

Demographics
Gender male (%)
Age group
18–44
45–64
65–74
75–84
≥85
Residence
Metro
Counties
Rural
Comorbidities
Number of comorbidity (median, IQR)
Charlson score
COPD
Lung cancer
Tuberculosis
Asthma
Congestive heart failure
Pulmonary circulation disease
Peripheral vascular disease
Diabetes with chronic complications
Metastatic cancer
Solid tumor without metastasis
Hypertension
Alcohol abuse
Tobacco use
Severity index
All patient refined DRG. Median (IQR)
Type of infection
Bacteremia
Streptococcal pneumonia
Influenza
Outcomes
Pleural effusion
Empyema
Use of ventilator
Underweight (<18.5 kg/m^2) ICD-9 V85.0, V85.51
Overweight (25.0–<30.0 kg/m^2) ICD-9 V85.21–V85.25, V85.53,278.02
Obesity grade 1 (30.0–<35.0 kg/m^2) ICD-9 V85.30–V85.34
Obesity grade 2 (35.0–<40.0 kg/m^2) ICD-9 V85.35–V85.39
Obesity grade 3 (40.0–<60.0 kg/m^2) ICD-9 V85.40–V85.49, V85.54,278.01

Table A2
Empirical predictors of obesity and odds ratios.

Standardized difference (%)	Underweight vs. normal	Overweight vs. normal	Obesity vs. normal
Demographic			
Female	Reference	Reference	Reference
Male	0.74(0.71–0.77)	1.03(0.98–1.09)	0.62(0.61–0.64)
Age			
18–44	Reference	Reference	Reference
45–64	1.12(1.01–1.24)	1.05(0.94–1.17)	0.61(0.59–0.63)
65–74	1.26(1.12–1.41)	1.06(0.94–1.19)	0.35(0.33–0.36)
75–84	1.40(1.26–1.56)	0.91(0.81–1.03)	0.16(0.15–0.16)
≥85	1.66(1.49–1.85)	0.74(0.64–0.85)	0.05(0.05–0.05)
Income			
Income quartile 1	Reference	Reference	Reference
Income quartile 2	0.85(0.80–0.90)	0.93(0.84–1.03)	1.11(1.07–1.15)
Income quartile 3	0.79(0.74–0.85)	0.85(0.75–0.96)	1.07(1.02–1.11)
Income quartile 4	0.78(0.72–0.85)	0.75(0.64–0.88)	0.96(0.91–1.01)
Patient Location			
Metro	Reference	Reference	Reference
Counties	0.95(0.88–1.03)	0.78(0.68–0.90)	0.98(0.94–1.03)
Rural	0.81(0.74–0.89)	0.58(0.49–0.69)	0.86(0.82–0.91)
Comorbidities			
Chronic obstructive pulmonary disease	1.44(1.37–1.50)	0.89(0.84–0.95)	0.99(0.97–1.02)
Lung cancer	1.10(1.00–1.21)	0.88(0.74–1.04)	0.62(0.56–0.68)
Tuberculosis	4.22(3.00–5.94)	1.63(0.72–3.70)	0.30(0.17–0.53)
Asthma	0.77(0.71–0.84)	1.17(1.08–1.26)	1.65(1.60–1.70)
Congestive heart failure	0.56(0.54–0.59)	0.91(0.85–0.97)	1.53(1.49–1.57)
Valvular disease	0.94(0.86–1.02)	0.94(0.85–1.06)	0.76(0.73–0.80)
Pulmonary circulation disease	0.81(0.76–0.87)	0.94(0.85–1.04)	1.48(1.42–1.55)
Peripheral vascular disease	1.19(1.12–1.28)	1.13(1.04–1.24)	0.76(0.73–0.80)
Hypertension	0.64(0.62–0.67)	1.31(1.23–1.39)	1.72(1.68–1.76)
Paralysis	0.82(0.75–0.91)	0.94(0.81–1.08)	0.61(0.57–0.65)
Other neurological disorders	1.02(0.96–1.07)	0.92(0.84–0.99)	0.72(0.69–0.74)
Diabetes w/o chronic complications	0.42(0.39–0.44)	1.34(1.26–1.43)	2.46(2.40–2.51)
Diabetes w/ chronic complications	0.43(0.38–0.48)	1.40(1.26–1.56)	2.66(2.56–2.78)
Hypothyroidism	0.87(0.83–0.92)	1.00(0.93–1.08)	1.21(1.18–1.25)
Renal failure	0.62(0.59–0.66)	0.87(0.81–0.93)	0.89(0.86–0.91)
Liver disease	0.88(0.79–0.97)	1.09(0.95–1.25)	0.90(0.85–0.95)
Peptic ulcer disease × bleeding	2.19(1.09–4.40)	0.36(0.05–2.47)	0.78(0.41–1.50)
Lymphoma	0.63(0.53–0.74)	0.83(0.68–1.01)	0.52(0.47–0.57)
Metastatic cancer	1.16(1.07–1.26)	1.19(1.04–1.36)	0.44(0.41–0.48)
Solid tumor w/out metastasis	1.24(1.14–1.36)	1.11(0.95–1.30)	0.69(0.63–0.74)
Rheumatoid arthritis/collagen vas	1.01(0.93–1.10)	0.94(0.83–1.07)	0.78(0.74–0.81)
Coagulopthy	0.68(0.63–0.73)	0.98(0.88–1.09)	0.86(0.82–0.90)
Fluid and electrolyte disorders	1.13(1.08–1.18)	1.05(0.99–1.11)	0.81(0.79–0.83)
Chronic blood loss anemia	1.20(0.96–1.51)	1.22(0.94–1.59)	1.04(0.92–1.17)
Deficiency anemias	1.37(1.31–1.43)	1.25(1.18–1.32)	0.78(0.76–0.80)
Drug abuse	1.21(1.09–1.35)	0.88(0.75–1.04)	0.63(0.60–0.67)
Psychoses	0.94(0.86–1.01)	1.20(1.05–1.37)	1.20(1.15–1.26)
Depression	1.02(0.97–1.08)	1.16(1.08–1.25)	1.16(1.13–1.20)
Severity (functional class)			
Minor loss	Reference	Reference	Reference
Moderate	3.32(2.77–3.99)	1.29(1.14–1.46)	3.68(3.44–3.94)
Major loss	12.22(10.14–14.72)	2.09(1.84–2.38)	6.08(5.67–6.54)
Extreme loss	26.89(22.16–32.63)	2.49(2.10–2.96)	6.21(5.73–6.73)

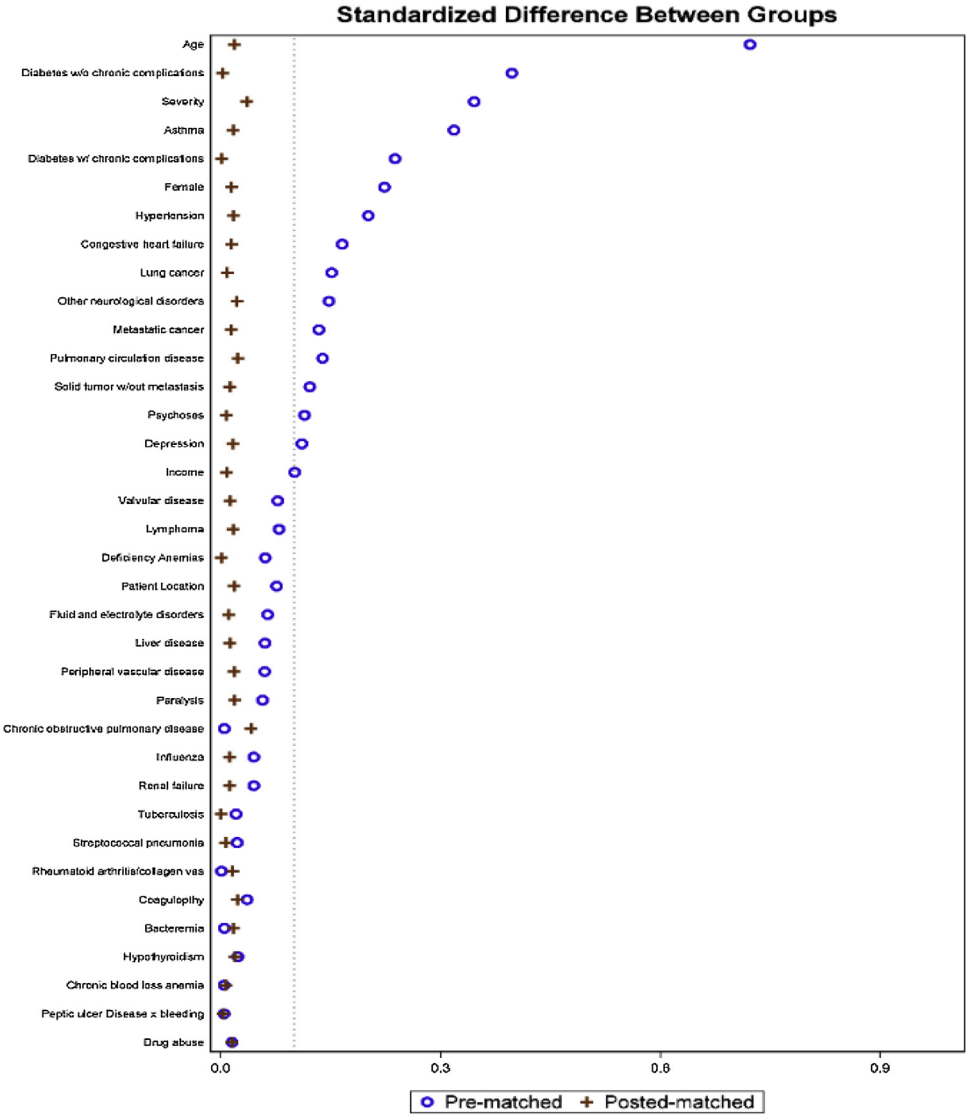

Fig. A1. Standardized differences in the baseline covariates after propensity score matching (normal weight versus obese groups).

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