ERJ open research
THE BEST IN OPEN ACCESS BASIC, TRANSLATIONAL & CLINICAL RESPIRATORY RESEARCH

Early View

Original article

Association between body mass index and mortality in hospitalised patients with community-acquired pneumonia

Richard Y. Kim, Connor Glick, Stephen Furmanek, Julio A. Ramirez, Rodrigo Cavallazzi

Please cite this article as: Kim RY, Glick C, Furmanek S, *et al*. Association between body mass index and mortality in hospitalised patients with community-acquired pneumonia. *ERJ Open Res* 2021; in press (https://doi.org/10.1183/23120541.00736-2020).

TITLE: Association between body mass index and mortality in hospitalized patients with community-acquired pneumonia

AUTHOR LIST: Richard Y. Kim[1], Connor Glick[2], Stephen Furmanek[2], Julio A. Ramirez[2], Rodrigo Cavallazzi[1]

AUTHOR AFFILIATIONS: 1. University of Louisville School of Medicine, Department of Medicine, Division of Pulmonary, Critical Care, and Sleep Disorders Medicine, Louisville, Kentucky 40202. 2. University of Louisville School of Medicine, Department of Medicine, Division of Infectious Diseases, Louisville, Kentucky 40202.

WORD COUNT:

Abstract Word Count: 249

Main Body Word Count: 2827 (excluding abstract, acknowledgements and references)

RUNNING HEAD: Obesity and Community Acquired Pneumonia

Abstract

The obesity paradox postulates that increased body mass index (BMI) is protective in certain patient populations. We aimed to investigate the association of BMI and different weight classes with outcomes in hospitalized patients with community-acquired pneumonia (CAP).

This cohort study is a secondary data analysis of the University of Louisville Pneumonia Study database, a prospective study of hospitalized adult patients with CAP from June of 2014 to May of 2016 in Louisville, KY. BMI as a predictor was assessed both as a continuous and categorical variable. Patients were categorized as weight classes based on WHO definitions: BMI < 18.5 (underweight), BMI of 18.5 to < 25 (normal weight), BMI of 25.0 to <30 (overweight), BMI of 30 to < 35 (obesity class I), BMI of 35 to < 40 (obesity class II), and BMI ≥ 40 (obesity class III). Study outcomes, including time to clinical stability, length of stay, clinical failure, and mortality, were assessed in hospital, at 30-days, at 6-months, and at 1-year. Clinical failure was defined as the need for noninvasive ventilation, invasive ventilation, or vasopressors within 1 week of admission. Patient characteristics and crude outcomes were stratified by BMI categories, and generalized additive binomial regression models were performed to analyze the impact of BMI as a continuous variable on study outcomes adjusting for possible confounding variables.

7449 patients were included in the study. Median time to clinical stability was 2 days for every BMI group. There was no association between BMI as a continuous predictor and length of stay <5 days (χ^2=1.83, EDF=2.74, p=0.608). Clinical failure was highest in the class III obesity group, and higher BMI as a continuous predictor was associated with higher odds of clinical failure. BMI as a continuous predictor was significantly associated with 30-day (χ^2=39.97, EDF=3.07, p<0.001), 6-month (χ^2=89.42, EDF=3.44, p<0.001) and 1-year (χ^2=83.97, EDF=2.89, p<0.001) mortalities. BMI ≤24.14 was a risk factor whereas BMI ≥26.97 was protective for mortality at 1-year. The incremental benefit of increasing BMI plateaued at 35.

We found a protective benefit of obesity on mortality in CAP patients. However, we uniquely demonstrate that the association between BMI and mortality is not linear, and no incremental benefit of increasing BMI levels is observed in those with obesity classes II and III.

INTRODUCTION

Background

The obesity paradox postulates that increased body mass index (BMI) is protective in certain patient populations, particularly the elderly and those with chronic diseases [1, 2]. The link between BMI and mortality is well established in medical literature with disease specific impacts on mortality. Obese individuals are known to have a significantly higher risk of all-cause mortality when compared to normal weight individuals [3, 4] Frasca stated, "In general, obesity decreases both the health span and lifespan, increases premature mortality and significantly increases global healthcare costs" [5].

The effect that BMI has on pneumonia and mortality, however, remains controversial. Literature exists on both sides of the argument to support and deny a positive effect of obesity on pneumonia and mortality. Some studies have identified an increased mortality risk in obese patients with pneumonia with H1N1 and more recently SARS-CoV-2.[6-10] However, other studies have shown a mortality benefit in obese patients with CAP. One meta-analysis performed by Nie et al suggested that obese individuals, though at higher risk for developing pneumonia, may have a lower mortality risk[11]. Several studies have also corroborated the "obesity paradox" and its positive effects on mortality in CAP[5, 12]. Despite these differences, it is generally accepted that underweight individuals are at increased risk of developing and dying from CAP [13-15].

Furthermore, current literature on the long-term mortality outcomes of obesity in CAP is limited, with most studies limited to short-term follow-up (less than 30 days) [12, 16, 17]. To our knowledge, there is only one study that investigates and demonstrates the mortality benefits of obesity in CAP over a longer time period [18]. Secondly, the studies on the mortality benefits of obesity in CAP stratified patients based primarily on only 4 BMI categories: underweight, normal, overweight, and obese. Current medical literature fails to specify the degree of mortality benefit in CAP in different classes of obesity or the continuous spectrum of BMI.

Thus, we aimed to investigate the association of BMI with mortality in hospitalized patients being treated for CAP in hospital, at 30-days, at 6 months, and at 1 year. We further investigated the effect of different classes of obesity and the continuous spectrum of BMI on the risk of mortality in patients with CAP.

METHODS

Study design and study population

This cohort study is a secondary data analysis of the University of Louisville Pneumonia Study (ULPS) database. ULPS was a prospective observational study of all hospitalized adult patients with CAP from June 1st, 2014 to May 31st, 2016 in the city of Louisville [19]. Data were prospectively collected by research associates from the division of infectious diseases at the University of Louisville, and quality control was performed.

Inclusion and Exclusion criteria

Patients were diagnosed with CAP if criteria 1, 2, and 3 were met: (1) presence of a new pulmonary infiltrate on chest radiograph and/or chest computed tomography scan at the time of hospitalization, defined by a board-certified radiologist's reading; (2) at least 1 of the following: new cough or increased cough or sputum production, fever >37.8°C (100.0°F) or hypothermia <35.6°C (96.0°F), changes in leukocyte count (leukocytosis: >11000 cells/μL; left shift: >10% band forms/mL; or leukopenia: <4000 cells/μL); (3) no alternative diagnosis at the time of hospital discharge that justified the presence of criteria 1 and 2. Patients were excluded if they were under the age of 18 years, did not have a valid Louisville address, did not possess a valid Social Security Number, or came from the correction system.[19, 20]

BMI Category Definitions

Patients were placed into the following categories based upon BMI: underweight, normal weight, overweight, and obese. Underweight individuals had a BMI < 18.5. Normal weight individuals had a BMI of 18.5 to < 25. Overweight individuals had a BMI of 25.0 to <30. Obese individuals had a BMI of 30.0 or higher. Patients within the obese class were further subclassified into class I, class II, and class III. Class I obese individuals had a BMI between 30 and < 35. Class II obese individuals had a BMI between 35 and < 40. Class III obese individuals had a BMI ≥40. These classifications are consistent with the World Health Organization BMI classifications [21].

Study variables

All patients were analyzed based on 4 main study outcome variables. Patient demographics were analyzed and include age, sex, and race. CAP patients were also categorized based on eight main comorbidities. Vital signs and laboratory values on admission were also included in our statistical analysis. Lastly, severity of disease was also

investigated based on the different clinical findings, such as altered mental status, pleural effusion, need for intensive care unit, need for vasopressors, and need for ventilatory support.

Study outcomes

Time of clinical stability (TCS): A patient was defined as clinically stable the day that the following four criteria were met: (1) improved cough and shortness of breath, (2) lack of fever for at least 8 hours, (3) improving leukocytosis (decreased at least 10% from the previous day), and (4) tolerating oral intake with adequate gastrointestinal absorption. Patients were evaluated daily within the first 7 days of hospitalization to determine the day when clinical stability was reached. Time to clinical stability was dichotomized as within three days (early stability) and after three days (late stability).

Length of stay (LOS): Length of stay was defined in days and calculated for each patient as the day of discharge minus the day of admission. Length of stay was dichotomized as within five days (early discharge) and after five days (late discharge).

Clinical failure: Clinical failure was defined as the need for noninvasive ventilation, invasive ventilation, or vasopressors within 1 week of admission.

Mortality: All-cause mortality was assessed during hospitalization, at 30 days after admission (early), at 6 months after admission (mid), and at 1 year (late) after admission. Mortality was assessed either through EMR records or vital statistics records from the Kentucky Department for Public Health Office of Vital Statistics.

Statistical Analysis

Baseline categorical explanatory variables were summarized as frequencies and percentages. Continuous variables were summarized as means and standard deviations. Differences in baseline patient characteristics between obese and non-obese patients were analyzed using a chi-squared test, Fisher's exact test, or Mann-Whitney U test when appropriate and warranted. Differences between obese and non-obese patients' TCS and LOS were analyzed with the Kaplan-Meier method, and log-rank tests were applied to evaluate differences between both groups. Generalized additive model (GAM) regression with dichotomous outcomes were performed with smooth curves produced. Generalized additive models are similar to generalized linear models, but instead of producing a coefficient estimate for continuous predictor variables, they may allow smooth curves to model the association of

predictor and outcome. For this analysis, all smoothed curves are plotted against the log odds of receiving an outcome with 95% confidence intervals. This way, BMI could be used to predict categorical outcomes in manner that does not require a linear relationship; the log odds, taken from a smoothed curve, represent the BMI's piece of the regression equation. Potentially confounding variables adjusted for were age, race, sex, history of cancer, history of congestive heart failure, history of stroke, history of renal disease, history of liver disease, history of chronic obstructive pulmonary disease, smoking history, nursing home residence, presence of pleural effusion on chest x-ray or CT scan, altered mental status at admission, and heart rate, respiratory rate, temperature, systolic blood pressure, blood urea nitrogen, serum sodium, serum glucose, and hematocrit on admission. P-values < 0.05 were considered statistically significant.

RESULTS

Patient Characteristics

Our study included 7449 patients. Of these, 46.2% were male; 7% were underweight, 32% were normal weight, 26% were overweight, and 35.1% were obese. The obese patients were further stratified into class I (17%), II (9%), and III (10%) based on definitions established by WHO [21]. Patient characteristic results for demographics, comorbidities, physical exam findings, and disease severity can be seen in table 1. Interestingly, frequency of the need for intensive care was highest in the class III obesity group (20%) and lowest in the underweight (16%), overweight (16%) and class II obesity groups (16%). Furthermore, frequency of the need for ventilatory support was highest in the class III obesity group (19%) and lowest in both the normal weight and overweight groups (12%).

Time to Clinical Stability

The median days to clinical stability was 2 days, which was the same amongst all classes. The percentage of patients with time to clinical stability ≤ 3 days was similar between all groups (see table 2). Using BMI as a continuous predictor and adjusted for confounders, BMI was not significantly associated with time to clinical stability ≤ 3 days (χ^2=1.18, EDF=1.00, p=0.278). See figure 1 and supplementary tables S1a and S1b.

Length of Stay

The median length of stay was 5 days in all groups except for the class II obesity group, which was 4 days. These differences, however, were not deemed clinically significant (see table 2). The percentage of patients whose length of stay was <5 days was lowest in the underweight group and highest in the class II obesity group. Using BMI as a continuous predictor and adjusted for confounders, BMI was not associated with length of stay <5 days (χ^2=1.83, EDF=2.74, p=0.608), due to significant overlap in the smoothed curve of log odds and confidence interval on both above and below 0 (see figure 2 and tables S2a and S2b).

Clinical Failure

The percentage of patients who were deemed a clinical failure was highest in the class III obesity group and lowest in the normal weight group (see table 2). Using BMI as a continuous predictor and adjusted for confounders, higher BMI was significantly associated with higher odds of clinical failure (χ^2=28.08, EDF=1.00, p<0.001, see figure 3 and tables S3a and S3b). Based on the smoothed curve and 95% confidence interval, BMI was protective at BMI ≤27.78 as the curve and confidence interval corresponded to a log odds of clinical failure entirely below 0. Also based on the smoothed curve, BMI becomes a risk factor at BMI ≥28.59 as the smoothed curve and confidence interval are entirely above 0.

Mortality

The percentage of CAP patients who died was highest in the underweight group and lowest in the class II and III obesity groups for all time points (see table 2). After adjusting for confounding variables, BMI as a continuous predictor was not significantly associated with in-hospital mortality (see tables S4a and 4Sb) but was significantly associated with 30-day (χ^2=39.97, EDF=3.07, p<0.001, see tables S5a and S5b), 6-month (χ^2=89.42, EDF=3.44, p<0.001, see tables S6a and S6b) and 1-year (χ^2=83.97, EDF=2.89, p<0.001, see tables S7a and S7b) mortalities. For mortality at 30 days, BMI ≤22.93 was a risk factor as the smoothed curve and 95% confidence interval for the log odds remain entirely above 0. BMI was protective between 26.57 and 38.69, as the smoothed curve and 95% confidence interval for the log odds are entirely below 0. For mortality at 6 months, BMI ≤23.74 was similarly a risk factor for mortality and BMI between 26.97 and 49.19 was protective. For mortality at 1 year, BMI ≤24.14 was a risk factor for mortality and BMI ≥26.97 was protective. See figure 4.

DISCUSSION

Our study demonstrates that obesity is associated with decreased mortality in patients with CAP. Our comprehensive analysis of obesity adds to the literature the fact that after patients reach class II obesity, there is no incremental benefit of increasing BMI. The degree of the observed benefit is not linear as the magnitude of the protective benefit of an increased BMI plateaus at a BMI of 35 (end spectrum of class I obesity). In other words, class II/III obesity would not confer additional benefit compared to class I, but class I/II/III would confer a benefit compared to a normal BMI. Another important aspect of this study is the long-term follow-up. In fact, obesity did not have a statistically significant benefit on in-hospital mortality; however, mortality benefits of increased BMI were observed at all other follow-up periods. We found no relationship between obesity and time to clinical stability or length of stay. Interestingly, obesity was associated with an increased risk of clinical failure, although this did not translate into increased in-hospital mortality.

Our findings support Nie et al's metanalysis who found that obese individuals with CAP have lower mortality risk despite increased risk of infection [11]. Chen performed a similar study looking at CAP patients followed over periods of 30-day, 6 months and 1 year. They also found a mortality benefit in obese patients, particularly at 1 year follow up [22]. Braun showed a similar mortality benefit of obesity in 763 CAP patients followed over 6 years[18]. Taken together, these studies indicate that obesity is associated with better outcomes in patients with CAP and point to the same direction as out study. The generalized additive model with smooth curves provided by our study allows for a nuanced assessment of this association, which is not linear.

Theories have attempted to explain the obesity paradox; however, no clear explanation has been proven to explain the counterintuitive benefits obesity may have on mortality in certain populations. It has been proposed that a link between the effects of obesity on the body's immune system and inflammatory state may provide a benefit on long-term prognosis during acute infection [7, 8]. Obesity represents a chronic state of inflammation, which affects both pro and anti-inflammatory biomarkers that may provide some survival benefit. For example, tumor necrosis factor α (TNFα), a proinflammatory cytokine and marker of pneumonia severity, is believed to be dampened by the increased number of TNFα receptors produced by adipose tissue [9, 10]. Other adipokines, inflammatory cytokines released by adipocytes, have also shown to play a role in the immune-regulatory response to infections. One such adipokine, leptin, modulates the T-cell response and is a protective component of the immune system. Also,

adiponectin has anti-inflammatory properties and may possibly decrease inflammation in the lungs [11, 12]. Our study suggests that the possible beneficial effects are obtained once patients reach class I obesity.

Another theory attempting to explain the obesity paradox involves the amount of lean muscle mass. Obese individuals have more lean muscle mass in addition to increased adiposity and thus have decreased mortality. Marquis postulates that loss of body mass is indicative of poorer prognosis and higher mortality. Individuals with higher degree of protein degradation, as in that seen in systemic inflammation, may lead to a depletion of essential amino acids necessary for immune defense and tissue regeneration [23]. In addition, muscle mass is found to be inversely proportional to risk of death. Abramowitz et al found that the effect of BMI on mortality is attenuated after adjusting for muscle mass [24]. Expanding on this argument, individuals with central adiposity but a normal BMI are found to have higher mortality [25, 26]. Considering this data, we can speculate that individuals with obesity class I may have decreased mortality due to an increase in muscle mass. Moving from class I to increasing obesity classes may not increase muscle mass further, hence may not offer additional survival benefit.

In our study, patients with obesity were younger and presented with lower severity illness as demonstrated by lower proportion of pneumonia severity index classes IV and V. These findings could also explain why patients with obesity had decreased long-term mortality. This association was present after adjustment for age and other variables that reflect severity of illness. However, residual confounding can remain even after adjustment in regression models. Interestingly, Singanayagam et al performed a cohort study in 1079 patients with CAP. In their cohort, there was no difference in severity of illness upon admission and in the immediate need for mechanical ventilation or vasopressor support between patients with obesity and non-obese patients with CAP. Despite that, obesity was associated with decreased 30-day mortality in multivariate analysis.[27]

Our study has several strengths and limitations. One main strength of our study, as previously mentioned, was that we were able to study the effects of obesity on mortality in a large cohort of CAP patients. We were also able to investigate this population over time from in hospital to 1-year post discharge. Most studies to date are limited to 30 days. Thirdly, the prevalence of obesity in the studied population (35.1%) is similar to that seen in the United States, (39.8%) adding to the generalizability of the study's findings across the US population[28]. Our study was able to demonstrate the mortality effect of increased BMI in patients affected by CAP over different classes of obesity, which had not been done with previous studies to date. One limitation is the lack of patients in the extremes of BMI. Furthermore, we did not specify causes of mortality over the 1 year follow- up. Thirdly, despite the patient

obesity demographics reflecting that of the United States, our study is limited only to the city of Louisville, Kentucky. A fourth limitation is that we did not measure muscle mass.

The results of our study suggest that future studies that evaluate obesity and mortality need to stratify obesity in different classes. It further suggests that the definition of a "healthy" weight may need to be reevaluated. Though the mortality benefit of obesity in CAP is observed in the medical literature, the actual physiologic mechanism remains in question. Future studies evaluating the actual physiologic mechanisms should focus on specific obesity classes. Though unknown, factors such as lean body mass and distribution of adiposity may contribute to the physiologic mechanisms involved in the obesity paradox. The differential impact of obesity on outcomes according to different etiologies of pneumonia should also be further explored, particularly in view of the COVID-19 pandemic. In conclusion, we found a protective benefit of obesity on mortality in CAP patients. However, we uniquely demonstrate that the association between BMI and mortality is not linear, and no incremental benefit of increasing BMI levels is observed in those with obesity classes II and III.

REFERENCES

1. Hainer V, Aldhoon-Hainerova I. Obesity paradox does exist. *Diabetes Care* 2013: 36 Suppl 2: S276-281.

2. Mazimba S, Holland E, Nagarajan V, Mihalek AD, Kennedy JLW, Bilchick KC. Obesity paradox in group 1 pulmonary hypertension: analysis of the NIH-Pulmonary Hypertension registry. *Int J Obes (Lond)* 2017: 41(8): 1164-1168.

3. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA* 2013: 309(1): 71-82.

4. Prospective Studies C, Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, Qizilbash N, Collins R, Peto R. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet* 2009: 373(9669): 1083-1096.

5. Frasca D, McElhaney J. Influence of Obesity on Pneumococcus Infection Risk in the Elderly. *Front Endocrinol (Lausanne)* 2019: 10: 71.

6. Vaillant L, La Ruche G, Tarantola A, Barboza P, InVS fteita. Epidemiology of fatal cases associated with pandemic H1N1 influenza 2009. *Eurosurveillance* 2009: 14(33): 19309.

7. Fezeu L, Julia C, Henegar A, Bitu J, Hu FB, Grobbee DE, Kengne A-P, Hercberg S, Czernichow S. Obesity is associated with higher risk of intensive care unit admission and death in influenza A (H1N1) patients: a systematic review and meta-analysis. *Obesity Reviews* 2011: 12(8): 653-659.

8. Fisher-Hoch SP, Mathews CE, McCormick JB. Obesity, diabetes and pneumonia: the menacing interface of non-communicable and infectious diseases. *Tropical Medicine & International Health* 2013: 18(12): 1510-1519.

9. Investigators AI, Webb SA, Pettila V, Seppelt I, Bellomo R, Bailey M, Cooper DJ, Cretikos M, Davies AR, Finfer S, Harrigan PW, Hart GK, Howe B, Iredell JR, McArthur C, Mitchell I, Morrison S, Nichol AD, Paterson DL, Peake S, Richards B, Stephens D, Turner A, Yung M. Critical care services and 2009 H1N1 influenza in Australia and New Zealand. *The New England journal of medicine* 2009: 361(20): 1925-1934.

10. Seidu S, Gillies C, Zaccardi F, Kunutsor SK, Hartmann-Boyce J, Yates T, Singh AK, Davies MJ, Khunti K. The impact of obesity on severe disease and mortality in people with SARS-CoV-2: A systematic review and meta-analysis. *Endocrinol Diabetes Metab* 2020: e00176.

11. Nie W, Zhang Y, Jee SH, Jung KJ, Li B, Xiu Q. Obesity survival paradox in pneumonia: a meta-analysis. *BMC Med* 2014: 12: 61.

12. Corrales-Medina VF, Valayam J, Serpa JA, Rueda AM, Musher DM. The obesity paradox in community-acquired bacterial pneumonia. *Int J Infect Dis* 2011: 15(1): e54-57.

13. Lee J, Kim K, Jo YH, Lee JH, Kim J, Chung H, Hwang JE. Severe thinness is associated with mortality in patients with community-acquired pneumonia: a prospective observational study. *Am J Emerg Med* 2015: 33(2): 209-213.

14. Torres A, Peetermans WE, Viegi G, Blasi F. Risk factors for community-acquired pneumonia in adults in Europe: a literature review. *Thorax* 2013: 68(11): 1057-1065.

15. Atamna A, Elis A, Gilady E, Gitter-Azulay L, Bishara J. How obesity impacts outcomes of infectious diseases. *Eur J Clin Microbiol Infect Dis* 2017: 36(3): 585-591.

16. Chalmers JD, Mandal P, Singanayagam A, Akram AR, Choudhury G, Short PM, Hill AT. Severity assessment tools to guide ICU admission in community-acquired pneumonia: systematic review and meta-analysis. *Intensive care medicine* 2011: 37(9): 1409-1420.

17. Kahlon S, Eurich DT, Padwal RS, Malhotra A, Minhas-Sandhu JK, Marrie TJ, Majumdar SR. Obesity and outcomes in patients hospitalized with pneumonia. *Clin Microbiol Infect* 2013: 19(8): 709-716.

18. Braun N, Hoess C, Kutz A, Christ-Crain M, Thomann R, Henzen C, Zimmerli W, Mueller B, Schuetz P. Obesity paradox in patients with community-acquired pneumonia: Is inflammation the missing link? *Nutrition* 2017: 33: 304-310.

19. Ramirez JA, Wiemken TL, Peyrani P, Arnold FW, Kelley R, Mattingly WA, Nakamatsu R, Pena S, Guinn BE, Furmanek SP, Persaud AK, Raghuram A, Fernandez F, Beavin L, Bosson R, Fernandez-Botran R, Cavallazzi R, Bordon J, Valdivieso C, Schulte J, Carrico RM, University of Louisville Pneumonia Study G. Adults Hospitalized With Pneumonia in the United States: Incidence, Epidemiology, and Mortality. *Clin Infect Dis* 2017: 65(11): 1806-1812.

20. Peyrani P, Arnold FW, Bordon J, Furmanek S, Luna CM, Cavallazzi R, Ramirez J. Incidence and Mortality of Adults Hospitalized With Community-Acquired Pneumonia According to Clinical Course. *Chest* 2020: 157(1): 34-41.

21. WHO. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. WHO Technical Report Series 854. Geneva: World Health Organization. [cited; Available from:

22. Chen J, Wang J, Jiang H, Li MC, He SY, Li XP, Shen D. Lower long-term mortality in obese patients with community-acquired pneumonia: possible role of CRP. *Clinics (Sao Paulo)* 2019: 74: e608.

23. Marquis K, Debigare R, Lacasse Y, LeBlanc P, Jobin J, Carrier G, Maltais F. Midthigh muscle cross-sectional area is a better predictor of mortality than body mass index in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2002: 166(6): 809-813.

24. Abramowitz MK, Hall CB, Amodu A, Sharma D, Androga L, Hawkins M. Muscle mass, BMI, and mortality among adults in the United States: A population-based cohort study. *PLoS One* 2018: 13(4): e0194697.

25. Sahakyan KR, Somers VK, Rodriguez-Escudero JP, Hodge DO, Carter RE, Sochor O, Coutinho T, Jensen MD, Roger VL, Singh P, Lopez-Jimenez F. Normal-Weight Central Obesity: Implications for Total and Cardiovascular Mortality. *Ann Intern Med* 2015: 163(11): 827-835.

26. Braun N, Gomes F, Schutz P. "The obesity paradox" in disease--is the protective effect of obesity true? *Swiss Med Wkly* 2015: 145: w14265.

27. Singanayagam A, Singanayagam A, Chalmers JD. Obesity is associated with improved survival in community-acquired pneumonia. *Eur Respir J* 2013: 42(1): 180-187.

28. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity and severe obesity among adults: United States, 2017–2018. 2020.

ROLE OF THE FUNDING SOURCE

Study was supported primarily by the Division of Infectious Diseases, University of Louisville, Kentucky. The parent study was given partial support by Pfizer Inc.

CONFLICT OF INTEREST

All authors declared no conflict of interest in relation to the main objective of this work.

AUTHOR CONTRIBUTIONS

Design of the study – Julio Ramirez

Statistical Analysis – Stephen Furmanek and Connor Glick

Writing – Richard Y Kim, Julio Ramirez, Connor Glick, Stephen Furmanek, and Rodrigo Cavallazzi

Critical Review – Rodrigo Cavallazzi

All authors have reviewed and approved the final version of the manuscript.

Table 1: Patient characteristics on hospital admission

Variable	Underweight BMI < 18.5	Normal weight 18.5 ≤ BMI < 25	Overweight 25 ≤ BMI < 30	Obese class I 30 ≤ BMI < 35	Obese class II 35 ≤ BMI < 40	Obese class III 40 ≤ BMI
Total Study Population						
Pneumonia, Frequency(%)	545 (7)	2357 (32)	1932 (26)	1250 (17)	654 (9)	711 (10)
Demographics						
Age, Median(IQR)*	75 [62,85]	72 [58,84]	70 [57,80]	67 [56,77]	62 [52,73]	58 [47,67]
Male sex, Frequency(%)	213 (39)	1199 (51)	1004 (52)	566 (45)	255 (39)	206 (29)
Race, Frequency(%)						
Black	107 (20)	374 (16)	326 (17)	277 (22)	161 (25)	230 (32)
White	434 (80)	1940 (82)	1574 (82)	965 (77)	482 (74)	477 (67)
Other	4 (1)	43 (2)	32 (2)	8 (1)	11 (2)	4 (1)
Social and Medical History			**Frequency (%)**			
Smoking history						
Current smoker	198 (36)	774 (33)	584 (30)	390 (31)	201 (31)	196 (28)
History of smoking	182 (33)	867 (37)	759 (39)	468 (37)	245 (38)	239 (34)
Non-smoking history	165 (30)	716 (30)	589 (31)	392 (31)	208 (32)	276 (39)
Chronic obstructive pulmonary disease	318 (58)	1068 (45)	857 (44)	574 (46)	311 (48)	347 (49)
Renal disease	114 (21)	699 (30)	564 (29)	396 (32)	194 (30)	218 (31)
Congestive heart failure	125 (23)	594 (25)	540 (28)	408 (33)	208 (32)	249 (35)
Neoplastic disease	105 (19)	390 (17)	242 (13)	130 (10)	67 (10)	56 (8)
Nursing home resident	98 (18)	385 (16)	248 (13)	125 (10)	58 (9)	73 (10)
Stroke	67 (12)	312 (13)	277 (14)	153 (12)	72 (11)	75 (11)
Liver disease	33 (6)	188 (8)	126 (7)	87 (7)	49 (8)	45 (6)
Physical Exam Findings			**Median (IQR)**			
Heart rate (Beats/Minute)	109 [93,122]	106 [92,120]	105 [91,119]	105 [90,119]	105 [93,117]	104 [90,118]
Respiratory rate (Breaths/Minute)	22 [20,28]	22 [20,27]	22 [20,27]	22 [20,27]	22 [20,26]	23 [20,27]
Systolic blood pressure (mmHg)	110 [95,132]	112 [96,130]	115 [99,133]	119 [102,138]	120 [105,141]	122 [105,141]
Temperature (Degrees Fahrenheit)	98.8 [98.2,99.7]	98.9 [98.2,100.2]	99.0 [98.2,100.6]	99.0 [98.4,100.4]	99.0 [98.4,100.2]	99.0 [98.3,100.0]
Hematocrit (percent)	34 [30,39]	35 [31,39]	36 [32,40]	36 [32,40]	37 [33,41]	37 [33,40]
Serum sodium (mEq/L)	136 [133,140]	137 [134,140]	137 [134,140]	137 [134,140]	137 [135,140]	138 [135,140]
Blood urea nitrogen (mg/dL)	19 [13,30]	20 [14,31]	19.5 [14,29]	19 [13,28]	18 [13,28]	17 [12,28]
Serum glucose (mg/dl)	130 [107,168]	134 [110,177]	142 [114,193]	153 [119,211]	156 [119,227]	159 [121,237]
Severity of Disease			**Frequency (%)**			
Pneumonia severity index risk class IV/V	379 (70)	1578 (67)	1193 (62)	710 (57)	333 (51)	323 (45)
Altered mental status	125 (23)	500 (21)	380 (20)	190 (15)	111 (17)	101 (14)
Pleural effusion	187 (34)	849 (36)	624 (32)	383 (31)	180 (28)	184 (26)
Need for intensive care	86 (16)	420 (18)	314 (16)	211 (17)	104 (16)	140 (20)
Need for vasopressors	14 (3)	71 (3)	61 (3)	34 (3)	12 (2)	21 (3)
Need for ventilatory support	69 (13)	282 (12)	232 (12)	170 (14)	97 (15)	137 (19)

*IQR: Interquartile range

Table 2: Study outcomes according to weight classes

Variable	Underweight BMI < 18.5	Normal weight 18.5 ≤ BMI < 25	Overweight 25 ≤ BMI < 30	Obese class I 30 ≤ BMI < 35	Obese class II 35 ≤ BMI < 40	Obese class III 40 ≤ BMI
Total Study Population						
Pneumonia, Frequency(%)	545 (7)	2357 (32)	1932 (26)	1250 (17)	654 (9)	711 (10)
Outcomes			**Median (IQR)**			
Time to clinical stability	2 [1,4]	2 [1,4]	2 [1,4]	2 [1,3]	2 [1,4]	2 [1,4]
< 4 days, Frequency(%)	371 (68.1)	1714 (72.7)	1411 (73.0)	947 (75.8)	468 (71.6)	531 (74.7)
Length of stay	5 [3,9]	5 [3,8]	5 [3,8]	5 [3,8]	4 [3,7]	5 [3,8]
< 5 days, Frequency(%)	222 (40.7)	1072 (45.5)	852 (44.1)	598 (47.8)	328 (50.2)	343 (48.2)
Clinical failure, Frequency(%)	127 (23.3)	516 (21.9)	433 (22.4)	290 (23.2)	155 (23.7)	196 (27.6)
Mortality, Frequency(%)						
In-Hospital	46 (8.4)	170 (7.2)	104 (5.4)	52 (4.2)	28 (4.3)	29 (4.1)
30-Day	116 (21.8)	375 (16.2)	204 (10.7)	105 (8.6)	50 (7.7)	50 (7.1)
6-Month	218 (41.2)	667 (28.8)	404 (21.2)	204 (16.6)	89 (13.8)	91 (12.9)
1-Year	260 (49.3)	859 (37.3)	526 (27.7)	280 (22.9)	113 (17.6)	135 (19.1)

*IQR: Interquartile range

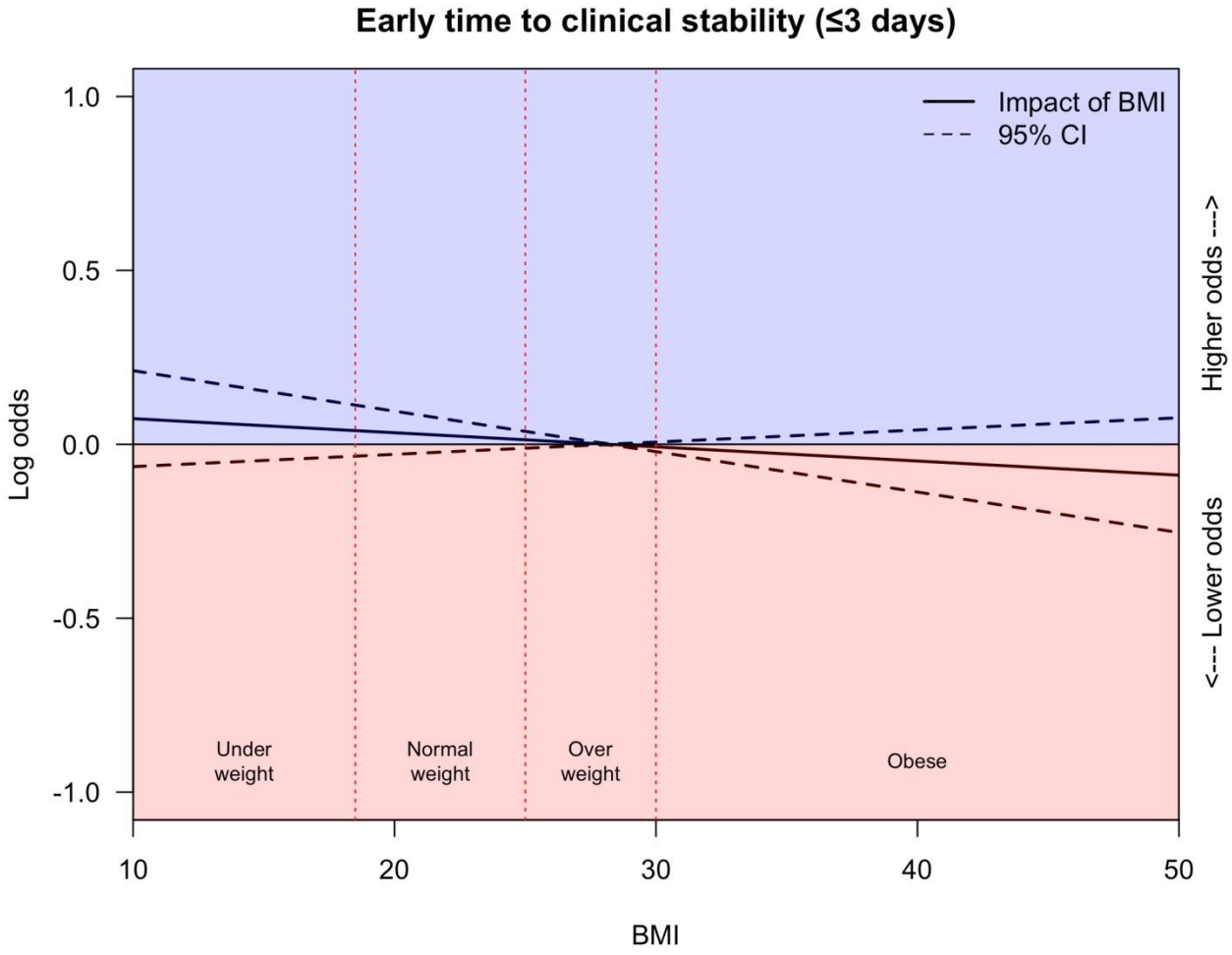
Legends for figures:

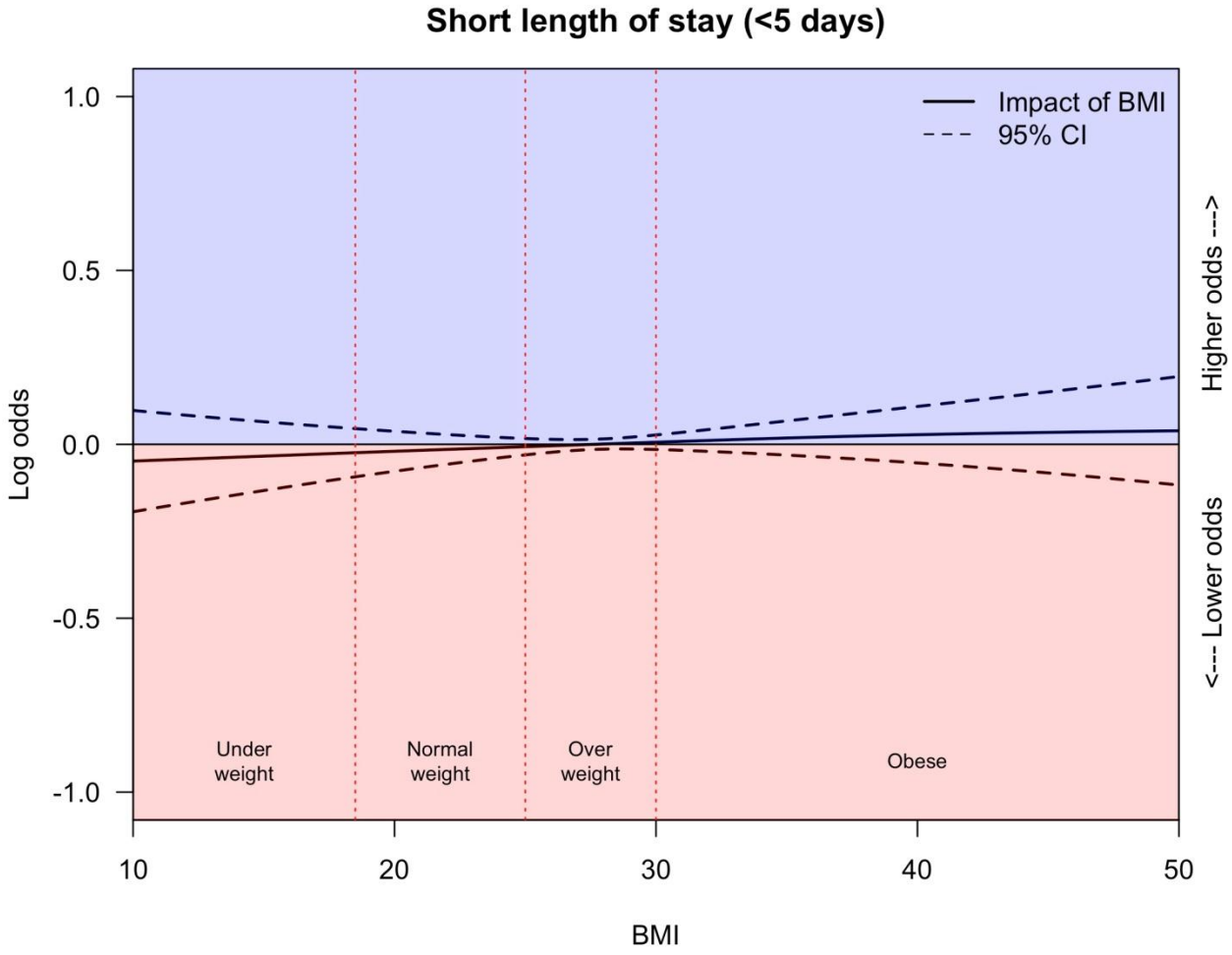
Figure 1. Early time to clinical stability (≤ 3 days) according to body mass index in hospitalized patients with community-acquired pneumonia.

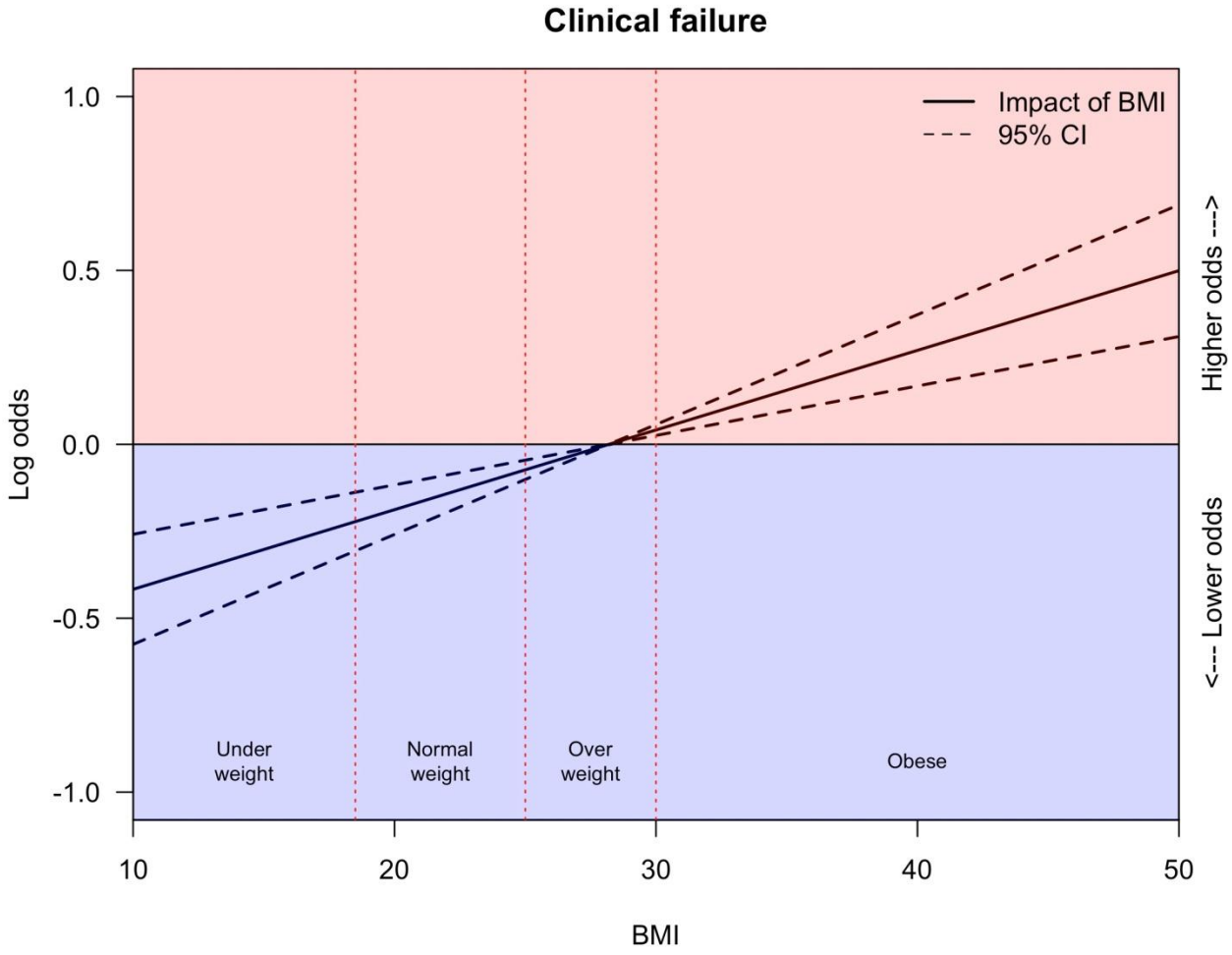
Figure 2. Short length of stay (< 5 days) according to body mass index in hospitalized patients with community-acquired pneumonia.

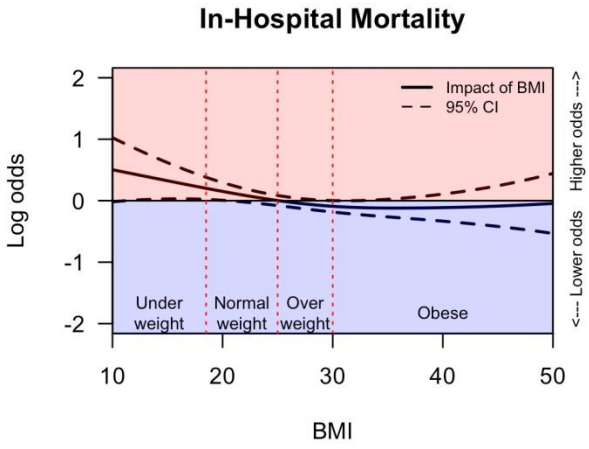
Figure 3. Clinical failure according to body mass index in hospitalized patients with community-acquired pneumonia.

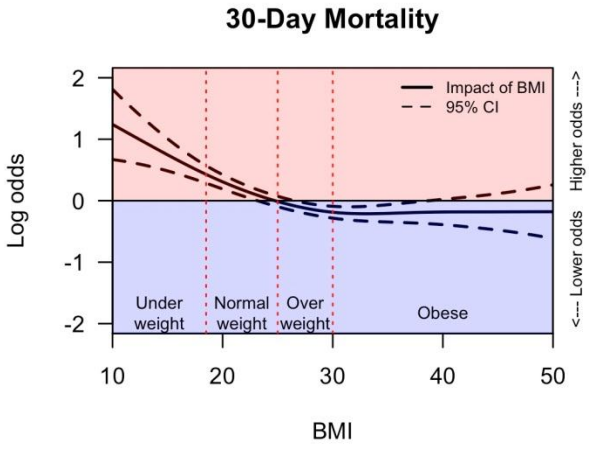
Figure 4. Mortality according to body mass index in hospitalized patients with community-acquired pneumonia.

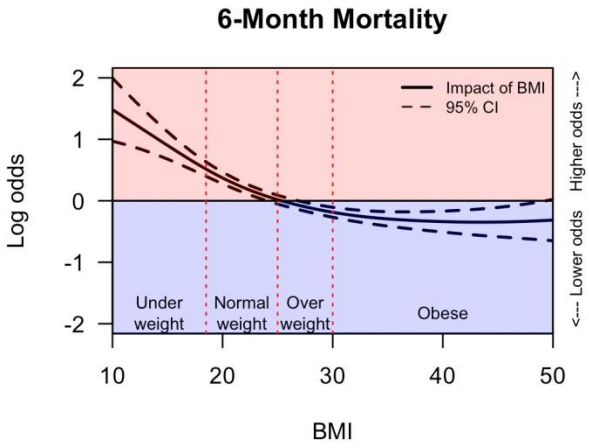

Early time to clinical stability (≤3 days)
Impact of BMI
95% CI
Higher odds --->
<--- Lower odds
Log odds
1.0
0.5
0.0
-0.5
-1.0
Under weight
Normal weight
Over weight
Obese
10
20
30
40
50
BMI

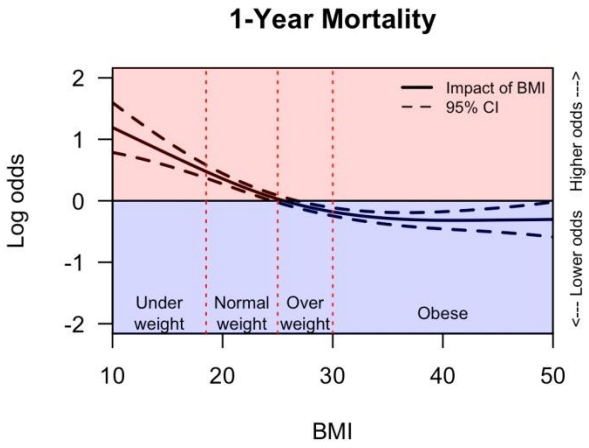

Short length of stay (<5 days)
Impact of BMI
95% CI
Higher odds --->
<--- Lower odds
Log odds
1.0
0.5
0.0
-0.5
-1.0
Under weight
Normal weight
Over weight
Obese
10
20
30
40
50
BMI


Clinical failure
Impact of BMI
95% CI
Higher odds --->
<--- Lower odds
Log odds
1.0
0.5
0.0
-0.5
-1.0
Under weight
Normal weight
Over weight
Obese
10
20
30
40
50
BMI


In-Hospital Mortality
Log odds
BMI
Impact of BMI
95% CI
Higher odds --->
<--- Lower odds
Under weight
Normal weight
Over weight
Obese
2
1
0
-1
-2
10
20
30
40
50


30-Day Mortality
Log odds
BMI
Impact of BMI
95% CI
Higher odds --->
<--- Lower odds
Under weight
Normal weight
Over weight
Obese
2
1
0
-1
-2
10
20
30
40
50


6-Month Mortality
Log odds
BMI
Impact of BMI
95% CI
Higher odds --->
<--- Lower odds
Under weight
Normal weight
Over weight
Obese
2
1
0
-1
-2
10
20
30
40
50


1-Year Mortality
Log odds
BMI
Impact of BMI
95% CI
Higher odds --->
<--- Lower odds
Under weight
Normal weight
Over weight
Obese
2
1
0
-1
-2
10
20
30
40
50

Supplementary material

Table of Contents

Title: Survival Incremental Benefit Does Not Extend Beyond Class I Obesity in Hospitalized Patients with Community-Acquired Pneumonia

Authors: Richard Y. Kim, Connor Glick, Stephen Furmanek, Julio A. Ramirez, Rodrigo Cavallazzi

Abbreviations and definitions

GAM – Generalized additive model

Beta – the slope estimate from the parametric portion of the GAM; the change in log-odds of receiving the outcome given a change in the variable

OR – the odds ratio, or exponentiated slope term

95% CI LB – Lower bound of the 95% confidence interval of the OR

95% CI UB – Upper bound of the 95% confidence interval of the OR

Edf – Effective degrees of freedom of the smoothed function for the variables in the GAM. Degrees of freedom are penalized in a GAM based on the smoothed function

χ^2 – The Chi-Squared statistic associated with each smoothed function

Tables S1a and S1b. Generalized additive model assessing the effect of variables on time to clinical stability (≤ 3 days) in hospitalized patients with community-acquired pneumonia.

Table S1a.

	Beta	OR	95% CI LB	95% CI UB	p-value
Sex	0.08	1.08	0.96	1.21	0.185
White	-0.21	0.81	0.70	0.94	**0.005**
Other race	-0.14	0.87	0.54	1.42	0.582
Altered mental status	-0.55	0.58	0.50	0.66	**<0.001**
Cancer	-0.18	0.84	0.71	0.98	**0.027**
CHF	-0.05	0.95	0.84	1.08	0.463
Stroke	-0.01	0.99	0.84	1.17	0.914
Renal disease	-0.01	0.99	0.86	1.14	0.919
Liver disease	-0.01	0.99	0.80	1.23	0.946
COPD	-0.19	0.82	0.73	0.93	**0.002**
Nursing home resident	-0.31	0.73	0.62	0.86	**<0.001**
Smoking history	0.02	1.02	0.88	1.18	0.804
Non-smoking history	0.00	1.00	0.85	1.17	0.952
Glucose	0.00	1.00	1.00	1.00	0.745
Pleural effusion	-0.15	0.86	0.76	0.97	**0.013**

Table S1b.

	Edf	χ^2	p-value
Age	1.60	1.20	0.553
Heart rate	3.80	27.24	**<0.001**
Respiratory rate	6.83	82.85	**<0.001**
Systolic blood pressure	6.52	45.92	**<0.001**
Temperature	5.66	11.46	0.116
BMI	1.00	1.18	0.278
Blood urea nitrogen	2.75	27.34	**<0.001**
Sodium	2.89	8.66	**0.048**
Hematocrit	2.54	10.02	**0.024**

Tables S2a and S2b. Generalized additive model assessing the effect of variables on length of stay (< 5 days) in hospitalized patients with community-acquired pneumonia.

Table S2a.

	Beta	OR	95% CI LB	95% CI UB	p-value
Sex	0.18	1.2	1.08	1.32	**0.001**
White	-0.01	0.99	0.87	1.13	0.875
Other race	0.28	1.32	0.86	2.04	0.205
Altered mental status	-0.24	0.79	0.69	0.9	**0.001**
Heart rate	-0.01	0.99	0.99	1	0
Cancer	-0.08	0.92	0.79	1.06	0.26
CHF	-0.34	0.71	0.63	0.8	0
Stroke	-0.28	0.75	0.65	0.88	0
Renal disease	-0.15	0.86	0.76	0.98	**0.02**
Liver disease	-0.1	0.91	0.75	1.1	0.309
COPD	-0.3	0.74	0.67	0.83	0
Nursing home resident	-0.43	0.65	0.55	0.77	0
History of smoking	-0.1	0.91	0.8	1.03	0.139
Non-smoking history	-0.11	0.89	0.78	1.03	0.112
Pleural effusion	-0.3	0.74	0.67	0.83	0

Table S2b.

	Edf	χ^2	p-value
Age	1.62	9.07	**0.011**
Respiratory rate	6.68	84.27	**0.000**
Systolic blood pressure	5.71	27.07	**0.000**
Temperature	2.31	2.84	0.405
BMI	2.74	1.83	0.608
Blood Urea Nitrogen	2.27	7.13	0.068
Sodium	6.91	18.38	**0.014**
Glucose	1.89	2.86	0.370
Hematocrit	2.91	27.67	**0.000**

Tables S3a and S3b. Generalized additive model assessing the effect of variables on clinical failure in hospitalized patients with community-acquired pneumonia.

Table S3a.

	Beta	OR	95% CI LB	95% CI UB	p-value
Age	-0.01	0.99	0.99	1.00	**0.046**
Sex	0.00	1.00	0.88	1.15	0.976
White	0.19	1.21	1.02	1.44	**0.030**
Other race	0.05	1.05	0.59	1.89	0.865
Altered mental status	1.10	2.99	2.55	3.50	**<0.001**
Cancer	0.14	1.15	0.95	1.39	0.153
CHF	0.43	1.53	1.33	1.77	**<0.001**
Stroke	-0.14	0.87	0.72	1.06	0.167
Renal disease	-0.07	0.93	0.79	1.10	0.394
Liver disease	-0.03	0.97	0.76	1.25	0.833
COPD	0.33	1.39	1.20	1.60	**<0.001**
Nursing home resident	0.26	1.30	1.07	1.57	**0.007**
Smoking history	-0.13	0.88	0.74	1.04	0.135
Non-smoking history	-0.18	0.84	0.69	1.01	0.064
Pleural effusion	0.29	1.34	1.17	1.54	**<0.001**

Table S3b.

	Edf	χ^2	p-value
Heart rate	1.88	30.94	**<0.001**
Respiratory rate	7.50	387.74	**<0.001**
Systolic blood pressure	6.23	182.61	**<0.001**
Temperature	8.34	35.95	**<0.001**
BMI	1.00	28.08	**<0.001**
Blood urea nitrogen	4.42	60.38	**<0.001**
Sodium	3.84	21.59	**0.001**
Glucose	3.99	33.60	**<0.001**
Hematocrit	2.15	3.06	0.315

Tables S4a and S4b. Generalized additive model assessing the effect of variables on in-hospital mortality in hospitalized patients with community-acquired pneumonia.

Table S4a.

	Beta	OR	95% CI LB	95% CI UB	p-value
Age	0.02	1.02	1.01	1.03	**<0.001**
Sex	0.14	1.14	0.92	1.43	0.236
White	0.53	1.71	1.23	2.37	**0.002**
Other race	-0.57	0.56	0.13	2.45	0.444
Altered mental status	0.53	1.70	1.34	2.17	**<0.001**
Temperature	-0.09	0.91	0.86	0.96	**<0.001**
Cancer	0.90	2.45	1.89	3.18	**<0.001**
CHF	0.16	1.17	0.92	1.49	0.191
Stroke	-0.05	0.95	0.71	1.29	0.752
Renal disease	0.23	1.26	0.98	1.61	0.074
Liver disease	0.67	1.95	1.32	2.89	**0.001**
COPD	-0.14	0.87	0.69	1.09	0.225
Nursing home resident	0.68	1.97	1.51	2.56	**<0.001**
Smoking history	0.34	1.41	1.03	1.93	**0.031**
Non-smoking history	0.29	1.33	0.94	1.88	0.104
Sodium	-0.01	0.99	0.97	1.01	0.228
Glucose	0.00	1.00	1.00	1.00	0.432
Pleural effusion	0.39	1.47	1.18	1.84	**0.001**

Table S4b.

	Edf	χ^2	p-value
Heart rate	1.01	12.14	**0.001**
Respiratory rate	8.62	98.39	**<0.001**
Systolic blood pressure	2.39	32.65	**<0.001**
BMI	1.99	6.14	0.088
Blood urea nitrogren	3.01	46.66	**<0.001**
Hematocrit	1.78	1.87	0.463

Tables S5a and S5b. Generalized additive model assessing the effect of variables on 30-day mortality in hospitalized patients with community-acquired pneumonia.

Table S5a.

	Beta	OR	95% CI LB	95% CI UB	p-value
Age	0.03	1.03	1.02	1.04	**<0.001**
Sex	0.19	1.21	1.02	1.43	**0.026**
White	0.43	1.54	1.21	1.96	**0.001**
Other race	-0.03	0.97	0.42	2.24	0.947
Altered mental status	0.69	2.00	1.66	2.41	**<0.001**
Systolic blood pressure	-0.01	0.99	0.99	1.00	**<0.001**
Cancer	1.20	3.33	2.74	4.04	**<0.001**
CHF	0.13	1.14	0.96	1.37	0.144
Stroke	0.05	1.05	0.84	1.31	0.685
Renal disease	0.14	1.15	0.95	1.40	0.140
Liver disease	0.41	1.51	1.10	2.05	**0.010**
COPD	-0.19	0.83	0.69	0.99	0.033
Nursing home resident	0.70	2.01	1.64	2.46	**<0.001**
Smoking history	0.18	1.20	0.96	1.51	0.115
Non-smoking history	0.19	1.21	0.94	1.55	0.142
Pleural effusion	0.46	1.58	1.34	1.86	**<0.001**

Table S5b.

	Edf	χ^2	p-value
Heart rate	3.70	22.11	**<0.001**
Respiratory rate	8.31	81.70	**<0.001**
Temperature	1.58	28.51	**<0.001**
BMI	3.07	39.97	**<0.001**
Blood urea nitrogen	2.53	53.72	**<0.001**
Sodium	6.22	24.95	**0.001**
Glucose	6.60	9.56	0.237
Hematocrit	3.73	17.48	**0.003**

Tables S6a and S6b. Generalized additive model assessing the effect of variables on 6-month mortality in hospitalized patients with community-acquired pneumonia.

Table S6a.

	Beta	OR	95% CI LB	95% CI UB	p-value
Age	0.03	1.03	1.02	1.03	**<0.001**
Sex	0.25	1.28	1.12	1.46	**<0.001**
White	0.21	1.23	1.03	1.47	**0.025**
Other race	-0.42	0.66	0.34	1.29	0.223
Altered mental status	0.54	1.71	1.46	2.00	**<0.001**
Cancer	1.35	3.87	3.28	4.56	**<0.001**
CHF	0.31	1.36	1.18	1.57	**<0.001**
Stroke	-0.02	0.98	0.82	1.18	0.849
Renal disease	0.16	1.17	1.00	1.36	**0.049**
Liver disease	0.35	1.42	1.11	1.82	**0.006**
COPD	0.05	1.05	0.91	1.21	0.489
Nursing home resident	0.89	2.43	2.04	2.89	**<0.001**
Smoking history	0.14	1.15	0.97	1.36	0.119
Non-smoking history	0.16	1.18	0.97	1.43	0.098
Glucose	0.00	1.00	1.00	1.00	0.907
Pleural effusion	0.49	1.63	1.43	1.86	**<0.001**

Table S6b.

	Edf	χ^2	p-value
Heart rate	4.03	24.74	**<0.001**
Respiratory rate	6.02	62.90	**<0.001**
Systolic blood pressure	3.85	17.33	**0.003**
Temperature	3.70	68.14	**<0.001**
BMI	3.44	89.42	**<0.001**
Blood urea nitrogen	2.48	27.37	**<0.001**
Sodium	4.26	19.27	**0.002**
Hematocrit	3.88	39.70	**<0.001**

Tables S7a and S7b. Generalized additive model assessing the effect of variables on 1-year mortality in hospitalized patients with community-acquired pneumonia.

Table S7a.

	Beta	OR	95% CI LB	95% CI UB	p-value
Sex	0.32	1.37	1.21	1.55	**<0.001**
White	0.15	1.16	0.99	1.37	0.070
Other race	-0.36	0.70	0.38	1.27	0.236
Altered mental status	0.52	1.69	1.45	1.96	**<0.001**
Cancer	1.40	4.07	3.46	4.79	**<0.001**
CHF	0.40	1.49	1.30	1.70	**<0.001**
Stroke	0.05	1.05	0.89	1.25	0.561
Renal disease	0.10	1.10	0.95	1.28	0.197
Liver disease	0.27	1.31	1.04	1.65	**0.023**
COPD	0.22	1.25	1.10	1.43	**0.001**
Nursing home resident	0.90	2.45	2.06	2.90	**<0.001**
Smoking history	0.06	1.07	0.91	1.25	0.433
Non-smoking history	0.13	1.13	0.95	1.35	0.167
Pleural effusion	0.48	1.62	1.43	1.83	**<0.001**

Table S7b.

	Edf	χ^2	p-value
Age	2.36	117.39	**<0.001**
Heart rate	3.76	20.44	**0.001**
Respiratory rate	5.55	46.36	**<0.001**
Systolic blood pressure	1.85	12.56	**0.003**
Temperature	3.49	68.34	**<0.001**
BMI	2.89	83.97	**<0.001**
Blood urea nitrogen	2.79	22.96	**<0.001**
Sodium	7.33	22.68	**0.005**
Glucose	5.91	8.40	0.302
Hematocrit	3.55	60.88	**<0.001**