Influence of overweight and obesity on the mortality of hospitalized patients with community-acquired pneumonia

Ning Wang, Bo-Wei Liu, Chun-Ming Ma, Ying Yan, Quan-Wei Su, Fu-Zai Yin

Abstract

BACKGROUND
Obesity is associated with a better prognosis in patients with community-acquired pneumonia (the so-called obesity survival paradox), but conflicting results have been found.

AIM
To investigate the relationship between all-cause mortality and body mass index in patients with community-acquired pneumonia.

METHODS
This retrospective study included patients with community-acquired pneumonia hospitalized in the First Hospital of Qinhuangdao from June 2013 to November 2018. The patients were grouped as underweight (< 18.5 kg/m²), normal weight (18.5-23.9 kg/m²), and overweight/obesity (≥ 24 kg/m²). The primary outcome was all-cause hospital mortality.

RESULTS
Among 2327 patients, 297 (12.8%) were underweight, 1013 (43.5%) normal weight, and 1017 (43.7%) overweight/obesity. The all-cause hospital mortality was 4.6% (106/2327). Mortality was lowest in the overweight/obesity group and highest in the underweight group (2.8%, vs 5.0%, vs 9.1%, P < 0.001). All-cause mortality of overweight/obesity patients was lower than normal-weight patients [odds ratio (OR) = 0.535, 95% confidence interval (CI) = 0.334-0.855, P = 0.009], while the all-cause mortality of underweight patients was higher than that of normal-weight patients.
patients (OR = 1.886, 95%CI: 1.161-3.066, P = 0.010). Multivariable analysis showed that abnormal neutrophil counts (OR = 2.38, 95%CI: 1.55-3.65, P < 0.001), abnormal albumin levels (OR = 0.20, 95%CI: 0.06-0.72, P = 0.014), high-risk Confusion-Urea-Respiration-Blood pressure-65 score (OR = 2.89, 95%CI: 1.48-5.64, P = 0.002), and intensive care unit admission (OR = 3.11, 95%CI: 1.77-5.49, P < 0.001) were independently associated with mortality.

CONCLUSION
All-cause mortality of normal-weight patients was higher than overweight/obesity patients, lower than that of underweight patients. Neutrophil counts, albumin levels, Confusion-Urea-Respiration-Blood pressure-65 score, and intensive care unit admission were independently associated with mortality in patients with community-acquired pneumonia.

Key Words: Body mass index; Overweight; Community-acquired pneumonia; Mortality; Prognosis; Obesity

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: This study found that the all-cause mortality of community-acquired pneumonia in overweight or obese patients was lower than that in normal-weight patients, and the infection index was lower than that in normal-weight patients. The sample size in this study was large, and it breaks the traditional body mass index grouping method. The grouping method in this study is consistent with the traditional grouping method.

INTRODUCTION
Community-acquired pneumonia (CAP) is a lower respiratory tract infection due to one or more pathogens acquired outside of a hospital setting[1]. This contrasts with pneumonia acquired within the hospital setting, including nosocomial pneumonia and ventilator-associated pneumonia[1]. The incidence of CAP ranges from 10.6 to 44.8 cases per 1000 person-years and increases with age[2]. CAP risk factors include age, smoking, chronic comorbidities (such as diabetes mellitus and chronic lung, renal, heart, or liver disease), oral/oral/dental/periodontal disease, treatment with proton pump inhibitors, prescription opioids, and high alcohol consumption[3-5]. Pathogens that cause CAP include respiratory viruses, Streptococcus pneumoniae (S. pneumoniae), Mycoplasma pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Chlamydia pneumoniae, Legionella species, Staphylococcus aureus, and Gram-negative rods[6,7]. Complications of pneumonia include parapneumonic effusion, empyema, lung abscess, sepsis, and cardiac complications, such as heart failure, cardiac arrhythmias, and acute coronary syndromes[8,9]. Lower respiratory tract infections are among the top 4 causes of death, and the most common infectious cause of death, worldwide[10]. The mortality rate is highly variable, ranging from < 1% to > 30%, depending on comorbidities and findings at presentation[11-13].

The prognostic factors for CAP include sex, cognitive symptoms, high urea levels, high respiratory rate, low blood pressure, age ≥ 65 years, comorbidities (cancer, chronic liver disease, heart failure, cerebrovascular disease, and chronic renal disease), and low or higher body temperature[14,15]. Obesity is associated with increased morbidity and mortality, including increased risk of cardiovascular events and increased risk of certain cancers[16-18].

Nevertheless, several studies have shown that the mortality of obese individuals is reduced in various diseases, a phenomenon that is referred to as the “obesity survival
paradox"[19]. Lacroix et al.[20] found a negative correlation between body mass index (BMI) and pneumonia mortality in an observational study of 2600 middle-aged American men. In a cohort study of 110000 Japanese adults, BMI (≥ 25 kg/m²) had a protective effect on pneumonia mortality [odds ratio (OR) = 0.7, 95% confidence interval (CI): 0.5-0.8][21]. Thus, in some diseases, obesity has emerged as a protective factor that could improve prognosis and reduce mortality[22-24]. Nevertheless, conflicting results are found in the literature[25,26]. In pneumonia caused by severe acute respiratory syndrome coronavirus 2, obesity is associated with worse outcomes[27], but the present study investigated “classical” CAP, not coronavirus disease 2019.

This study aimed to investigate the relationship between BMI and all-cause mortality of CAP and to examine the mechanism of overweight/obesity as a protective factor in CAP prognosis. The results could help our understanding and management of CAP.

**MATERIALS AND METHODS**

**Study design and patients**

This study was approved by the Ethics Committee of the First Hospital of Qinhuangdao, and all participants provided written informed consent. This retrospective study included patients with CAP hospitalized in the First Hospital of Qinhuangdao from June 2013 to November 2018.

All patients were diagnosed with CAP according to the clinical guidelines developed by the Respiratory Society of the Chinese Medical Association[28]. The exclusion criteria were: (1) Hospital-acquired pneumonia (HAP; i.e., pneumonia at 48 h after admission); (2) Pulmonary tuberculosis, pulmonary tumors, non-infectious pulmonary interstitial disease, pulmonary edema, atelectasis, pulmonary embolism, pulmonary eosinophilic infiltration, and pulmonary vasculitis caused by other factors, < 18 years of age; or (3) Immunosuppression, which was defined as current, 28-d use of oral prednisolone at any dose, or other immunosuppressive drugs (e.g., methotrexate, azathioprine, cyclosporine, and anti-TNF-α agents), or patients known to have received solid organ transplantation.

**Assessment of BMI**

All patients had their weight and height measured on admission as part of a nutritional risk assessment score. BMI was calculated as height/weight². Patients were classified into BMI subgroups: (1) Underweight (BMI < 18.5 kg/m²); (2) Normal weight (BMI 18.5-23.9 kg/m²); and (3) Overweight/obesity (BMI ≥ 24 kg/m²)[29].

**Patient assessment**

Severity assessment scores on admission included the CURB-65 score (i.e., disturbance of consciousness, urea > 7 mmol/L, respiratory rate ≥ 30 breaths/min, systolic blood pressure (SBP) < 90 mmHg and/or diastolic blood pressure (DBP) ≤ 60 mmHg, age ≥ 65 years old)[30]. One point was allocated for each item, five points in total. A score of 0-1 points indicated low risk, 2 points indicate moderate risk, and 3-5 points indicated high risk[30].

**Outcome**

The primary outcome was all-cause hospital mortality, defined as the ratio of the total number of deaths from all causes during the study period to the total number of people included in the study.

**Data collection and definitions**

The demographic and clinical characteristics, laboratory biochemical indicators measured for the first time after admission, and other risk factors [including a history of diabetes, use of a ventilator during the disease, and transfer to intensive care unit (ICU)] were collected from the hospital medical record database, and whether the patient terminated hospitalization due to death—an event that was duly recorded. The normal value of white blood cells (WBC) was 3.5-9.5 × 10⁹/L. The normal value of neutrophils (NEUT) was 1.8-6.3 × 10⁹/L. The normal value of C-reactive protein (CRP) was 0-10 mg/L. The normal value of blood urea nitrogen (BUN) was 2.86-8.20 mmol/L. The normal value of albumin (ALB) was 35.0-55.0 g/L. Death of the patient was queried through the medical record system. If the patient’s discharge order was death, then the patient was considered an in-hospital death. Death was judged based
on respiratory and cardiac arrest, not including brain death.

Statistical analysis
All data were analyzed using SPSS 21 (IBM, Armonk, NY, United States). Data are expressed as medians (interquartile range) or a numerical value with percentage. When data were not normally distributed, the values were log-transformed for analysis. Categorical variables were analyzed using the chi-square test. Continuous variables were analyzed using Student’s t-test (two groups) or analysis of variance (ANOVA) with the least significant difference post hoc test (more than two groups). Multiple logistic regression analyses were used to examine the association between the survival state and the observation index. Statistical significance was established at \( P < 0.05 \).

RESULTS

Characteristics of the patients according to BMI
This study identified 2500 patients with CAP, of which 2327 patients had available BMI data (173 patients were excluded due to a lack of BMI data). There were 297 (12.8%) underweight patients, 1013 (43.5%) with a normal weight, and 1017 (43.7%) overweight/obesity (Table 1). There were statistically significant differences among the three groups in terms of age, sex, diabetes history, consciousness, SBP, DBP, NEUT, CRP, BUN, ALB, use of a ventilator, CURB-65 score, ICU admission, and death (all \( P < 0.05 \)). Mortality was lowest in the overweight/obesity group and highest in the underweight group (overweight/obesity: 2.8%, vs normal: 5.0%, vs underweight: 9.1%, \( P < 0.001 \)). According to the CURB-65 class, the number of low-risk CAP cases was highest in the overweight/obesity group (overweight/obesity: 73.2%, vs normal: 66.6%, vs underweight: 52.5%, \( P < 0.001 \)). Accordingly, the proportion of patients admitted to the ICU was lowest in the overweight/obesity group (overweight: 12.1%, vs normal: 18.0%, vs underweight: 20.5%, \( P < 0.001 \)).

Some infection indicators, such as WBC, NEUT, CRP, and BUN, were higher in the underweight group than in the overweight group. The ALB levels in the underweight group were lower than in the overweight/obesity group (median, 33.0 vs 36.9 g/L, \( P < 0.001 \)). The proportion of patients with confusion was higher in the underweight group than in the overweight/obesity group (16.8% vs 6.7%, \( P < 0.001 \)). The history of diabetes in the overweight/obesity group was higher than in the underweight group (25.7% vs 12.6%, \( P < 0.001 \)).

Characteristics of the patients according to survival
Table 2 shows the clinical and laboratory characteristics of the 2327 patients with CAP and according to mortality. The < 65-year-old patients represented 43.0% of the survivors, compared with 57.0% for those > 65 years old (\( P < 0.001 \)). The overweight/obesity group’s survival rate was higher than that of the underweight group (44.5% vs 12.2%, \( P < 0.001 \)). The patients with a history of diabetes represented 37.9% of the deaths. According to the CURB-65 score, the high-risk group had the lowest survival rate, while the low-risk group had the highest survival rate (\( P < 0.001 \)).

Compared with the non-survival group, the survival group was less likely to spend time in the ICU (14.0% vs 52.8%, \( P < 0.001 \)). In addition, the hospital days and the frequency of ventilator use in the non-survival group were higher than in the survival group (both \( P < 0.05 \)). The levels of WBC, NEUT, CRP, and BUN in the death group were higher than in the survival group (all \( P < 0.001 \)). Finally, ALB levels in the survival group were higher than in the mortality group (\( P < 0.001 \)).

Multivariable analysis
Table 3 shows univariable and multivariable logistic regression analyses for in-hospital mortality of 2327 patients with CAP. The univariable analyses showed that diabetes history, WBC, NET, CRP, ALB, CURB-65 risk stratification, BMI, and ICU admission were significantly associated with all-cause mortality (all \( P < 0.05 \)). In the univariable analyses, the all-cause mortality of overweight/obesity patients was lower than that of normal-weight patients (OR = 0.54, 95%CI: 0.33-0.86, \( P = 0.009 \)), while the all-cause mortality of underweight patients was higher than that of normal-weight patients (OR = 1.89, 95%CI: 1.16-3.07, \( P = 0.010 \)). The multivariable analysis showed that abnormal NEUT counts (OR = 2.38, 95%CI: 1.55-3.65, \( P < 0.001 \)), abnormal ALB levels (OR = 0.20, 95%CI: 0.06-0.72, \( P = 0.014 \)), high-risk CURB-65 score (OR = 2.89, 95%CI: 1.44-5.70, \( P = 0.001 \)).
| Characteristics          | BMI categories (kg/m²) |  |  |  | P value |
|-------------------------|-----------------------|---|---|---|--------|
| Age (yr), (median, IQR), n (%) | < 18.5 (n = 297) | 18.5-23.9 (n = 1013) | ≥ 24 (n = 1017) |  |
| < 65                    | 77 (63, 84)          | 68 (56, 79)⁺       | 65 (53, 77)⁺     | < 0.001 |
| ≥ 65                    | 80 (26.9)           | 416 (41.4)⁺       | 476 (46.8)⁻      | < 0.001 |
| Sex, n (%)              | 217 (73.1)           | 597 (58.9)⁺       | 541 (53.2)⁻      |  |
| Male                    | 156 (52.5)           | 617 (60.9)⁺       | 581 (57.2)       |  |
| Female                  | 141 (47.5)           | 396 (39.1)⁺       | 436 (42.8)       |  |
| Diabetes history, n (%) | No                   | 260 (87.4)         | 995 (81.3)⁺      |  |
|                        | Yes                  | 37 (12.6)          | 185 (18.7)       |  |
| Consciousness, n (%)    | No                   | 247 (83.2)         | 919 (90.7)⁺      |  |
|                        | Yes                  | 50 (16.8)          | 94 (9.3)⁺        |  |
| RR (breaths/min), (median, IQR), n (%) | < 18.5 (n = 297) | 18.5-23.9 (n = 1013) | ≥ 24 (n = 1017) |  |
| < 30                    | 282 (94.9)           | 975 (96.2)         | 974 (95.8)       | 0.597 |
| ≥ 30                    | 15 (5.1)             | 38 (3.8)           | 43 (4.2)         |  |
| SBP (mmHg), (median, IQR), n (%) | < 60 (n = 121.5) | ≥ 90 (n = 280) | > 90 (n = 17) |  |
| < 90                    | 121.5 (110.0, 142.0) | 127.0 (113.0, 140.0) | 130.0 (120.0, 145.0) | < 0.001 |
| ≥ 90                    | 280 (94.3)           | 990 (97.7)         | 1002 (98.5)      | < 0.001 |
| < 90                    | 17 (5.7)             | 23 (2.3)           | 15 (1.5)         |  |
| DBP (mmHg), (median, IQR), n (%) | < 60 (n = 73.0) | ≥ 60 (n = 49.1) | ≤ 60 (n = 8.56) |  |
| < 90                    | 73.0 (65.0, 81.0)    | 77.0 (70.0, 84.0)  | 80.0 (70.0, 88.0) | < 0.001 |
| ≥ 90                    | 49.1 (63.5)          | 890 (87.9)         | 933 (91.7)⁺      | < 0.001 |
| < 60                    | 125 (42.1)           | 478 (47.2)⁺       | 516 (50.7)⁺      | 0.025 |
| ≥ 60                    | 138 (46.5)           | 459 (45.3)         | 441 (43.3)       |  |
| WBC (10⁹/L), (median, IQR), n (%) | Normal (n = 159) | Abnormal (n = 138) | CRP (mg/L), (median, IQR), n (%) |  |
| Normal                  | 159 (53.5)           | 554 (54.7)         | 6.75 (4.28, 10.64) | 0.039 |
| Abnormal                | 138 (46.5)           | 459 (45.3)         | 6.03 (3.78, 9.49)⁺ | 0.025 |
| CRP (mg/L), (median, IQR), n (%) | Normal (n = 58) | Abnormal (n = 239) | Normal (n = 6.30) | 0.001 |
| Normal                  | 58 (19.5)            | 266 (26.3)         | 5.60 (4.20, 8.10)⁺ |  |
| Abnormal                | 239 (80.5)           | 747 (73.7)         | 5.50 (4.10, 7.38)⁺ | 0.001 |
| BUN (mmol/L), (median, IQR), n (%) | Normal (n = 177) | Abnormal (n = 120) | Normal (n = 3.30) |  |
| Normal                  | 177 (59.6)           | 656 (64.8)⁺       | 34.7 (31.0, 38.5)⁺ | 0.001 |
| Abnormal                | 120 (40.4)           | 357 (35.2)⁺       | 37 (31.0, 38.5)⁺ |  |
| ALB (g/L), (median, IQR), n (%) | Normal (n = 98) | Abnormal (n = 199) | Normal (n = 3.30) | 0.001 |
| Normal                  | 98 (33.0)            | 461 (45.5)⁺       | 34.7 (31.0, 38.5)⁺ |  |
| Abnormal                | 199 (67.0)           | 552 (54.5)⁺       | 461 (45.5)⁺      |  |
| HOD (d), (median, IQR), n (%) | Normal (n = 10) | Abnormal (n = 19) | Normal (n = 10) |  |
| Normal                  | 10 (7, 15)           | 10 (7, 14)         | 10 (7, 14)       | 0.599 |
| Abnormal                | 19 (67.0)            | 552 (54.5)⁺       | 396 (38.9)⁺      |  |
| Ventilator use          | 47 (16.0)            | 108 (10.7)⁺       | 95 (9.4)⁺        | 0.006 |
Table 1

| Category       | BMI (kg/m²) | CURB-65 Score, Median (IQR) | ΔCI | p-value |
|----------------|-------------|-----------------------------|-----|---------|
| Low risk       | 18.5-23.9   | 1 (0, 2)                    | 1   | <0.001  |
| Moderate risk  | 24          | 2 (1, 5)                    | 2   | <0.001  |
| High risk      | 24          | 2 (1, 5)                    | 2   | <0.001  |
| Death, n (%)   | 18.5-23.9   | 1 (0, 2)                    | 1   | <0.001  |

*P < 0.05, body mass index (BMI) 18.5-23.9 kg/m² group vs BMI <18.5 kg/m² group.

**P < 0.05, BMI ≥ 24 kg/m² group vs BMI 18.5-23.9 kg/m² group.

***P < 0.05, BMI ≥ 24 kg/m² group vs BMI ≥ 24 kg/m² group.

Data are expressed as median with interquartile ranges or n with percentiles (%). When data were not normally distributed, they were Log-n transformed for analysis. The CURB-65 score is a tool for assessing the severity of patients with community-acquired pneumonia, including new onset confusion; urea > 7 mmol/L; respiratory rate ≥ 30 breaths/min, systolic blood pressure < 90 mmHg and/or diastolic blood pressure ≤ 60 mmHg; and age ≥ 65 years. BMI: Body mass index; IQR: Interquartile range; ALB: Albumin; BUN: Blood urea nitrogen; CRP: C-reactive protein; DBP: Diastolic blood pressure; HOD: Hospital day; ICU: Intensive care unit; NEUT: Neutrophil granulocyte; RR: Respiratory rate; SBP: Systolic blood pressure; WBC: White blood cell.

95% CI: 1.48-5.64, P = 0.002, and ICU admission (OR = 3.11, 95% CI: 1.77-5.49, P < 0.001) were independently associated with mortality in patients with CAP.

**DISCUSSION**

Although obesity is associated with increased mortality due to multiple causes[16-18], it is associated with a better prognosis in patients with CAP (the so-called obesity survival paradox)[19-24]. However, conflicting results have been found[25,26], especially regarding the categories of patients at risk of higher mortality. Therefore, this study aimed to investigate the relationship between all-cause mortality and BMI in patients with CAP. The results strongly suggested that overweight/obesity patients accounted for the largest proportion of CURB-65 low-risk patients with CAP. The all-cause mortality of overweight/obesity patients was lower than that of normal-weight patients and NEUT counts, ALB levels, CURB-65 score, and ICU admission were independently associated with mortality in patients with CAP.

This study showed that abnormal NEUT counts were independently associated with a poor prognosis of CAP, which is already well-known[31-34]. Hypoalbuminemia is a well-known marker of adverse prognosis in a number of conditions and can be the result of various underlying conditions such as sepsis, cirrhosis, nephrotic syndrome, protein-losing enteropathy, malnutrition, and frailty[35]. Hypoalbuminemia is also associated with a poor prognosis in hospitalized patients[35,36] and in those with CAP[37,38]. The CURB-65 score is a well-known scoring system for the prognosis of pneumonia in the ICU setting[39,40]. It is based on confusion, uremia, respiratory rate, blood pressure, and age, and it can be used to guide management[41]. Finally, of course, ICU admission indicates a severe condition with a higher likelihood of a poor outcome[42-44].

As a general rule, obesity is associated with a higher risk of surgical-site infections, nosocomial infections, periodontitis, skin infections, and acute pancreatitis[45,46]. In overweight patients, there are recognized changes that include hypoxia, oxidative stress, and insulin resistance. Immune cells adapt to an altered tissue microenvironment by adapting their metabolism, eventually leading to an immune response imbalance, chemotaxis damage, and immune cell differentiation[47]. The relationship between obesity and chronic respiratory diseases, including obstructive sleep apnea and obesity hypopnea syndrome, has also been well described[48]. Obese patients show lung function changes, including decreased lung volume, reduced respiratory compliance, reduced gas exchange, impaired respiratory muscle function, and increased airway resistance[49]. Given that these clinical manifestations collectively indicate an increased risk of infection with bacterial and viral pathogens and drive potential changes in lung function, it is logical to theorize that obese patients would be at increased risk for both the development of pneumonia and for much worse clinical outcomes. It can be intuitively assumed that obese patients are more likely to exhibit adverse clinical outcomes and an increased mortality secondary to pneumonia.

Nevertheless, the risk of developing CAP in obese individuals is lower than in the general population[3,46]. BMI and the prognosis of pneumonia have recently emerged
Table 2 Clinical and laboratory characteristics of 2327 patients admitted to hospital with pneumonia in different survival state groups

| Characteristics                        | Survival (n = 2221) | Death (n = 106) | P value |
|----------------------------------------|---------------------|-----------------|---------|
| Age (yr), (median, IQR), n (%)         | 68 (55, 79)         | 78.5 (70, 85.25) | < 0.001 |
| < 65                                   | 955 (43.0)          | 17 (16.0)       | < 0.001 |
| ≥ 65                                   | 1266 (57.0)         | 89 (84.0)       |         |
| Sex, n (%)                             |                     |                 | 0.206   |
| Male                                   | 1287 (57.9)         | 68 (64.2)       |         |
| Female                                 | 934 (42.1)          | 38 (35.8)       |         |
| BMI (kg/m²), (median, IQR), n (%)      | 23.44 (20.57, 25.99)| 21.10 (18.40, 24.08) | < 0.001 |
| Underweight                            | 270 (12.2)          | 27 (25.5)       | < 0.001 |
| Normal weight                          | 962 (43.3)          | 51 (48.1)       |         |
| Overweight/obesity                     | 988 (44.5)          | 28 (26.4)       |         |
| Diabetes history, n (%)                | 442 (20.2)          | 39 (37.9)       | < 0.001 |
| Smoking history (yr), n (%)            | 409 (18.8)          | 10 (9.7)        | 0.020   |
| Consciousness, n (%)                   |                     |                 | < 0.001 |
| Conscious                              | 2038 (91.8)         | 77 (72.6)       |         |
| Confusion                              | 183 (8.2)           | 29 (27.4)       |         |
| RR (breaths/min), (median, IQR), n (%) | 20 (20, 20)         | 20 (19, 24)     | 0.093   |
| < 30                                   | 2135 (96.1)         | 96 (90.6)       | 0.010   |
| ≥ 30                                   | 86 (3.9)            | 10 (9.4)        |         |
| SBP (mmHg), (median, IQR), n (%)       | 130.0 (116.0, 144.0)| 130.0 (104.5, 150.0) | 0.186   |
| ≥ 90                                   | 2178 (98.1)         | 94 (88.7)       | < 0.001 |
| < 90                                   | 43 (1.9)            | 12 (11.3)       |         |
| DBP (mmHg), (median, IQR), n (%)       | 79.0 (70.0, 86.0)   | 77.5 (62.8, 86.0) | 0.078   |
| < 90                                   | 1989 (89.6)         | 82 (77.4)       | < 0.001 |
| ≥ 90                                   | 232 (10.4)          | 24 (22.6)       |         |
| WBC (10⁹/L), (median, IQR), n (%)      | 7.99 (5.80, 11.39)  | 11.65 (8.67, 16.38) | < 0.001 |
| Normal                                 | 1258 (56.6)         | 32 (30.2)       | < 0.001 |
| Abnormal                               | 963 (43.4)          | 74 (69.8)       |         |
| NEUT (10⁹/L), (median, IQR), n (%)     | 5.86 (3.74, 9.00)   | 10.02 (6.88, 14.64) | < 0.001 |
| Normal                                 | 1099 (49.5)         | 20 (18.9)       | < 0.001 |
| Abnormal                               | 1122 (50.5)         | 86 (81.1)       | < 0.001 |
| CRP (mg/L), (median, IQR), n (%)       | 24.96 (4.52, 78.38) | 52.48 (18.27, 139.64) | < 0.001 |
| ≤ 10 mg/L                              | 626 (28.2)          | 11 (10.4)       | < 0.001 |
| > 10 mg/L                              | 1595 (71.8)         | 95 (89.6)       |         |
| BUN (mmol/L), (median, IQR), n (%)     | 5.50 (4.10, 7.70)   | 8.95 (5.65, 14.33) | < 0.001 |
| Normal                                 | 1507 (67.9)         | 48 (45.3)       | < 0.001 |
| Abnormal                               | 714 (32.1)          | 58 (54.7)       |         |
| ALB (g/L), (median, IQR), n (%)        | 35.70 (31.90, 39.20)| 31.20 (28.00, 34.30) | < 0.001 |
| Normal                                 | 1159 (52.2)         | 22 (20.8)       | < 0.001 |
| Abnormal                               | 1062 (47.8)         | 84 (79.2)       |         |
| HOD (days), (median, IQR)              | 9 (7, 14)           | 15 (6, 25)      | 0.014   |
| Ventilator use, n (%)                  | 200 (9.1)           | 50 (47.6)       | < 0.001 |
ICU admission, n (%) | 310 (14.0) | 56 (52.8) | < 0.001
CURB-65 score, (median, IQR), n (%) | 1 (0, 2) | 2 (1, 3) | < 0.001
Low risk | 1542 (69.4) | 34 (32.1) | < 0.001
Medium risk | 491 (22.1) | 36 (34.0)
High risk | 188 (8.5) | 36 (34.0)

Data are expressed as medians with interquartile ranges or n with percentiles %. When data were not normally distributed, they were Log-n transformed for analysis. The CURB-65 score is a tool for assessing the severity of patients with community-acquired pneumonia, including new onset confusion; urea > 7 mmol/L; respiratory rate ≥ 30 breaths/min, systolic blood pressure < 90 mmHg and/or diastolic blood pressure ≥ 60 mmHg; and age ≥ 65 years. Normal weight: 18.5 kg/m² BMI ≤ 23.9 kg/m²; Overweight: BMI ≥ 24 kg/m²; Underweight: BMI < 18.5 kg/m².

Table 3 Univariable and multivariable logistic regression analysis for all-cause mortality of 2327 patients with community-acquired pneumonia

| Characteristics | Univariable | Multivariable |
|-----------------|-------------|---------------|
| | OR | 95%CI | P value | OR | 95%CI | P value |
| Sex (male vs female) | 1.299 | 0.865-1.949 | 0.207 | 1.423 | 0.994-2.037 | 0.054 |
| Diabetes history | 1.718 | 1.205-2.450 | 0.003 | 2.378 | 1.549-3.651 | < 0.001 |
| WBC (abnormal vs normal) | 3.138 | 2.233-4.408 | < 0.001 | 2.378 | 1.549-3.651 | < 0.001 |
| NEUT (abnormal vs normal) | 3.559 | 2.573-4.925 | < 0.001 | 2.378 | 1.549-3.651 | < 0.001 |
| CRP (abnormal vs normal) | 1.321 | 1.136-1.537 | < 0.001 | 1.430 | 0.742-2.753 | 0.285 |
| ALB (abnormal vs normal) | 0.029 | 0.011-0.078 | < 0.001 | 0.201 | 0.056-0.724 | 0.014 |
| CURB-65 score (moderate risk vs low risk) | 3.325 | 2.058-5.372 | < 0.001 | 1.430 | 0.742-2.753 | 0.285 |
| (High risk vs Low risk) | 8.685 | 5.307-14.212 | < 0.001 | 2.885 | 1.476-5.641 | 0.002 |
| BMI (overweight/obesity vs normal weight) | 0.535 | 0.334-0.855 | 0.009 | 1.430 | 0.742-2.753 | 0.285 |
| BMI (underweight vs normal weight) | 1.886 | 1.161-3.066 | 0.010 | 1.430 | 0.742-2.753 | 0.285 |
| ICU admission | 6.904 | 4.629-10.298 | < 0.001 | 3.113 | 1.765-5.488 | < 0.001 |

The CURB-65 score is a tool for assessing the severity of patients with community-acquired pneumonia, including new onset confusion; urea > 7 mmol/L; respiratory rate ≥ 30 breaths/min, systolic blood pressure < 90 mmHg and/or diastolic blood pressure ≥ 60 mmHg; and age ≥ 65 years. Normal weight: 18.5 kg/m² BMI ≤ 23.9 kg/m²; Overweight: BMI ≥ 24 kg/m²; Underweight: BMI < 18.5 kg/m². WBC: White blood cell; NEUT: Neutrophil granulocyte; CRP: C-reactive protein; ALB: Albumin; BMI: Body mass index; ICU: Intensive care unit; OR: Odds ratio; CI: Confidence interval.

The present study confirms that overweight/obesity patients actually have lower all-cause mortality. This is consistent with the fact that the inflammatory indices of overweight/obesity patients were lower than those of underweight patients, and the majority of overweight/obesity patients were at low CURB-65 risk. Similarly, overweight/obesity patients do not have a higher ICU occupancy rate. On the contrary, underweight patients are more likely to be admitted to the ICU.

Previous studies on the relationship between obesity, pneumonia, and mortality have yielded intriguing observations. For example, an early study by Lacroix et al[20] showed a negative correlation between BMI and pneumonia-associated mortality in an observational study of 2600 middle-aged American men. In a prospective study of 110 thousand Japanese adults, it was also found that BMI ≥ 25 kg/m² promoted a protective effect in the context of pneumonia-associated mortality[21], and the trend between BMI and CAP mortality showed a significant inverse relationship (P < 0.001). Braun et al[50] found that in 763 patients, the 64 obese patients (BMI > 30 kg/m²) had a significantly lower 6-year all-cause mortality compared with normal-weight patients (BMI 18.5-25 kg/m²). Other studies also report similar results[22-24], supporting the
Wang N et al. Overweight/obesity on CAP mortality

present study. Nevertheless, some points still remain to be clarified. Indeed, Kornum et al.\(^{25}\) showed that males were at a higher risk of hospitalization than females, which was not observed in the present study. In addition, the relationship between obesity and clinical outcomes appears to be different between children and adults\(^{26}\), but the present study did not include children.

Some hypotheses can be formulated to try to explain these results. One of the protective factors involved in the better prognosis of CAP in obesity might be an increase in the relative number and frequency of circulating M1 macrophages in overweight patients. Indeed, in an animal model, the content of macrophages in adipose tissue was positively correlated with adipocyte volume and the extent of obesity\(^{31}\). Under the regulation of chemokines, inflammatory factors, and free fatty acids in adipose tissue of obese people, IKKS, which is the activator of NF-κB in macrophages, activates the signal pathway via phosphorylation of p65, which stimulates a greater number of macrophages to display the M1 sub-type\(^{52}\). The increased number of M1 macrophages form a coronal aggregate that expands around the necrotic adipocytes to form similar foam cells, opening lysosomes and autophagic pathways, allowing macrophages to absorb and degrade the ectopic accumulation of lipid\(^ {53}\). M1 macrophages can also reduce the acute inflammatory response by increasing PPAR-γ activation, autophagy, and lipid oxidation\(^ {54}\). There is also hyperleptinemia in obese patients, which is involved in innate and acquired immunity and increases the activity of macrophages, chemotaxis of neutrophils, cytotoxicity of natural killer cells, and the production of T and B cells\(^ {55}\). This activation of all immune cells could promote bacterial clearance. In an animal model reported in 2007, Hsu et al.\(^ {56}\) found that ob/ob mice had a leptin deficiency. Using wild-type mice as controls, both the ob/ob and wild-type strains were infected with S. pneumoniae. It was found that the ob/ob mice had higher mortality and lower lung bacterial clearance rate, which was related to an impaired phagocytic function of the alveolar macrophages, decreased pulmonary neutrophil counts, and a decrease in bioactive proinflammatory cytokines. Exogenous leptin increased the survival rate and lung bacterial clearance rate of ob/ob mice.

A systematic analysis of 13 randomized controlled trials \(n = 1954\) of glucocorticoids for adult CAP showed that glucocorticoids significantly reduced mortality [risks ratio (RR): 0.58, 95% CI: 0.40-0.4] and significantly lowered the early clinical failure rate in adults with severe CAP (RR: 0.32, 95% CI: 0.15-0.7)\(^ {57}\). Glucocorticoids shorten the clinical cure time, hospital stay, and ICU stay time and reduce the incidence of pneumonia-associated complications. Glucocorticoids play a key role in anti-viral functions, the immune response, and display anti-inflammatory properties and promote other physiological functions, such that the symptoms of pulmonary parenchyma edema can be relieved in the early stages of inflammation. In the recovery period, glucocorticoids can effectively inhibit the proliferation of capillaries, downregulate collagen, inhibit the proliferation of granulation tissue and scar formation in the lung, and avoid pulmonary fibrosis. In addition, glucocorticoids can combine with lipopolysaccharide, which is the main component of Gram-negative bacterial endotoxins, so that it can effectively reduce the damage caused by endotoxins and relieve the corresponding symptoms. At the same time, it can also improve the microcirculation of patients, effectively avoiding platelet aggregation and thus preventing the formation of thromboses. Studies have shown that glucocorticoids in obese people are higher than in the general population\(^ {58,59}\). The endogenous glucocorticoid axis might be another hypothesis for the results observed in the present study.

In the current study, BMI could not be included in the multivariable analysis because it was the variable that was covariant with the largest number of other variables included in the models. Indeed, being underweight is associated with hypoalbuminemia and an inflammatory condition and with a poor prognosis in a variety of conditions\(^ {60-62}\). Hence, the independent contribution of BMI to CAP mortality could be assessed, as it is an easy-to-determine factor that could be considered in patient management.

This study has limitations. The patients were all from a single hospital. Therefore, when considering the relatively high incidence of CAP, the sample size was relatively small. In addition, it included only hospitalized patients and did not include patients with mild pneumonia and those who returned home with antibiotics. Finally, due to the study’s retrospective nature, only all-cause mortality could be examined, and CAP-specific mortality should be investigated in the future. Additional studies are still necessary to examine the prognostic factors of CAP.
CONCLUSION

The inflammatory index and the severity of pneumonia in overweight/obesity patients with CAP were lower than in the normal-weight group, and the all-cause mortality was lower. NEUT counts, ALB levels, CURB-65 score, and ICU admission were independently associated with mortality in patients with CAP.

ARTICLE HIGHLIGHTS

Research background
Obesity is associated with a better prognosis in patients with community-acquired pneumonia (the so-called obesity survival paradox), but conflicting results have been found.

Research motivation
To investigate the relationship between all-cause mortality and body mass index (BMI) in patients with community-acquired pneumonia.

Research objectives
To investigate the relationship between all-cause mortality and BMI in patients with community-acquired pneumonia.

Research methods
This retrospective study included patients with community-acquired pneumonia hospitalized at the First Hospital of Qinhuangdao from June 2013 to November 2018. The patients were grouped as underweight (< 18.5 kg/m²), normal weight (18.5-23.9 kg/m²), and overweight/obesity (≥ 24 kg/m²). The primary outcome was all-cause hospital mortality.

Research results
Among 2327 patients, 297 (12.8%) were underweight, 1013 (43.5%) normal weight, and 1017 (43.7%) overweight/obesity. The all-cause hospital mortality was 4.6% (2.8% vs 5.0% vs 9.1%, P < 0.001). All-cause mortality of overweight/obesity patients was lower than normal-weight patients [odds ratio (OR) = 0.535, 95% confidence interval (CI): 0.334-0.855, P = 0.009], while the all-cause mortality of underweight patients was higher than that of normal-weight patients (OR = 1.886, 95%CI: 1.161-3.066, P = 0.010). Multivariable analysis showed that abnormal neutrophil counts (OR = 2.38, 95%CI: 1.55-3.65, P < 0.001), abnormal albumin levels (OR = 0.20, 95%CI: 0.06-0.72, P = 0.014), high-risk Confusion-Urea-Respiration-Blood pressure-65 score (OR = 2.89, 95%CI: 1.48-5.64, P = 0.002), and intensive care unit admission (OR = 3.11, 95%CI: 1.77-5.49, P < 0.001) were independently associated with mortality.

Research conclusions
All-cause mortality of normal-weight patients was higher than overweight/obesity patients, and lower than that of underweight patients. Neutrophil counts, albumin levels, Confusion-Urea-Respiration-Blood pressure-65 score, and intensive care unit admission were independently associated with mortality in patients with community-acquired pneumonia.

Research perspectives
This study found that the all-cause mortality of community-acquired pneumonia in overweight or obese patients was lower than that in normal-weight patients, and the infection index was lower than that in normal-weight patients. The sample size in this study was large, and it breaks the traditional BMI grouping method. The grouping method of this study is consistent with the traditional grouping method.

ACKNOWLEDGEMENTS

The authors would like to thank all study participants who were enrolled in this study.
Wang N et al. Overweight/obesity on CAP mortality

REFERENCES

1. Lanks CW, Musani AI, Hsia DW. Community-acquired Pneumonia and Hospital-acquired Pneumonia. Med Clin North Am 2019; 103: 487-501 [PMID: 29055516 DOI: 10.1016/j.mcn.2018.12.008]

2. Yu H, Rubin J, Dunning S, Li S, Sato R. Clinical and economic burden of community-acquired pneumonia in the Medicare fee-for-service population. J Am Geriatr Soc 2012; 60: 2137-2143 [PMID: 23120409 DOI: 10.1111/j.1532-5415.2012.04208.x]

3. Postnikova LB, Klimkin PF, Boldina MV, Gudim AL, Kubysheva NI. [Fatal severe community-acquired pneumonia: risk factors, clinical characteristics and medical errors of hospital patients]. Ter Arkh 2020; 92: 42-49 [PMID: 32598792 DOI: 10.26442/0040-5660.2020.03.000538]

4. Almirall J, Serra-Prat M, Bolibar I, Balasso V. Risk Factors for Community-Acquired Pneumonia in Adults: A Systematic Review of Observational Studies. Respiration 2017; 94: 299-311 [PMID: 28738364 DOI: 10.1159/000479089]

5. Edelman EJ, Gordon KS, Crothers K, Akgün K, Bryant KJ, Becker WC, Gaither JR, Gibert CL, Gordon AJ, Marshall BDL, Rodríguez-Barradas MC, Samet JH, Justice AC, Tate JP, Fiellin DA. Association of Prescribed Opioids With Increased Risk of Community-Acquired Pneumonia Among Patients With and Without HIV. JAMA Intern Med 2019; 179: 297-304 [PMID: 30615036 DOI: 10.1001/jamainternmed.2018.6101]

6. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, Dowell SF, File TM Jr, Musher DM, Niederman MS, Torres A, Whitney CG. Infectious Diseases Society of America; American Thoracic Society. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007; 44 Suppl 2: S27-S72 [PMID: 17278083 DOI: 10.1086/511159]

7. Hider AC, Frazier DW. Community-Acquired Pneumonia. Emerg Med Clin North Am 2018; 36: 665-683 [PMID: 29296998 DOI: 10.1016/j.yemc.2018.07.001]

8. Corrales-Medina VF, Sub KN, Rose G, Chirinos JA, Doucette S, Cameron DW, Fergusson DA. Cardiac complications in patients with community-acquired pneumonia: a systematic review and meta-analysis of observational studies. PLoS Med 2011; 8: e1001048 [PMID: 21738449 DOI: 10.1371/journal.pmed.1001048]

9. Smeeth L, Cook C, Thomas S, Hall AJ, Hubbard R, Vallance P. Risk of deep vein thrombosis and pulmonary embolism after acute infection in a community setting. Lancet 2006; 367: 1075-1079 [PMID: 16581406 DOI: 10.1016/S0140-6736(06)68474-2]

10. Organization WH. The top 10 causes of death. 2014 [DOI: 10.1787/888933823033]

11. Waterer GW, Self WH, Courtney DM, Grijalva CG, Balk RA, Girard TD, Fakhran SS, Trabue C, McNabb P, Anderson EJ, Williams DJ, Bramley AM, Jain S, Edwards KM, Wunderink RG. In-Hospital Deaths Among Adults With Community-Acquired Pneumonia. Chest 2018; 154: 628-635 [PMID: 29859184 DOI: 10.1016/j.chest.2018.05.021]

12. Krumholz HM, Lin Z, Keenan PS, Chen J, Ross JS, Drye EE, Bernheim SM, Wang Y, Bradley EH, Han LF, Normand SL. Relationship between hospital readmission and mortality rates for patients hospitalized with acute myocardial infarction, heart failure, or pneumonia. JAMA 2013; 309: 587-593 [PMID: 23403683 DOI: 10.1001/jama.2013.333]

13. Dharmarajan K, Hsieh AF, Kulkarni VT, Lin Z, Ross JS, Horwitz LI, Kim N, Suter LG, Lin H, Normand SL, Krumholz HM. Trajectories of risk after hospitalization for heart failure, acute myocardial infarction, or pneumonia: retrospective cohort study. BMJ 2015; 350: h411 [PMID: 25656852 DOI: 10.1136/bmj.h411]

14. Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, Lewis SA, Macfarlane JT. Defining community-acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax 2003; 58: 377-382 [PMID: 12728155 DOI: 10.1136/thorax.58.5.377]

15. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, Coley CM, Marrie TJ, Kapoor WN. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med 1997; 336: 243-250 [PMID: 8995086 DOI: 10.1056/NEJM199701233360402]

16. Jensen MD, Ryan DH, Aposian CM, Ard JD, Cornazzie AG, Donato KA, Hu FB, Hubbard VS, Jakicic JM, Kushner RF, Loria CM, Millen BE, Nonas CA, Pi-Sunyer FX, Stevens J, Stevens VJ, Wadden TA, Wolfe BM, Yanovski SZ, Jordan HS, Kendall KA, Lux LJ, Mentor-Marcel R, Morgan LC, Trisolini MG, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC, Jr., Tomasselli GF. American College of Cardiology/American Heart Association Task Force on Practice Guidelines: ACC/AHA/SCAI 2007 guidelines for the management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2007; 49 Suppl 8: 305-47 [PMID: 17494964 DOI: 10.1016/j.jacc.2007.12.065]

17. Garvey WT, Mechanick JI, Brett EM, Garber AJ, Hurley DL, Jastreboff AM, Nadolsky K, Pessah-Pollack R, Poddar K, Ross JS, Horwitz LI, Kim N, Suter LG, Lin H, Normand SL, Krumholz HM. Trajectories of risk after hospitalization for heart failure, acute myocardial infarction, or pneumonia: retrospective cohort study. BMJ 2015; 350: h411 [PMID: 25656852 DOI: 10.1136/bmj.h411]

18. Heymsfield SB, Wadden TA. Mechanisms, Pathophysiology, and Management of Obesity. N Engl J Med 2019; 380: 999-1005 [PMID: 30912501 DOI: 10.1056/NEJMe1812106]
Nie W, Zhang Y, Jee SH, Jung KJ, Li B, Xiu Q. Obesity survival paradox in pneumonia: a meta-analysis. *BMJ Med* 2014; 12: 61 [PMID: 24722122 DOI: 10.1186/1741-7015-12-61]

LaCroix AZ, Lipson S, Miles TP, White L. Prospective study of pneumonia hospitalizations and mortality of U.S. older people: the role of chronic conditions, health behaviors, and nutritional status. *Public Health Rep* 1989; 104: 350-360 [PMID: 25028060]

Inoue Y, Koizumi A, Wada Y, Iso H, Watanabe Y, Date C, Yamamoto A, Kikuchi S, Inaba Y, Toyoshima H, Tamakoshi A. Risk and protective factors related to mortality from pneumonia among middle-aged and elderly community residents: the JACC Study. *J Epidemiol* 2007; 17: 194-202 [PMID: 18904518 DOI: 10.2188/jea17.194]

Zhou B, Zhao S, Tang M, Chen K, Hua W, Su Y, Chen S, Liang Z, Xu W, Li X, Xue X, Sun X, Zhang S. Overweight and obesity as protective factors against mortality in nonischemic cardiomyopathy patients with an implantable cardioverter defibrillator. *Clin Cardiol* 2020; 43: 1435-1442 [PMID: 32936479 DOI: 10.1002/clc.23458]

Kahlson 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: 709-716 [PMID: 22963453 DOI: 10.1111/j.1469-0691.2012.04003.x]

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 [PMID: 31291389 DOI: 10.6061/clinics/2019/e608]

Kornum JB, Norgaard M, Dehlsteen C, Due KM, Thomsen RW, Tjonneland A, Sorensen HT, Overvad K. Obesity and risk of subsequent hospitalisation with pneumonia. *Eur Respir J* 2010; 36: 1330-1336 [PMID: 20551023 DOI: 10.1183/09031936.00142009]

Bramley AM, Reed C, Finelli L, Self WH, Amponsah K, Arnold SR, Williams DJ, Grijalva CG, Anderson JH, Stockmann C, Trabue C, Fakhran S, Balk R, McCullers JA, Pavia AT, Edwards KM, Wunderink RG, Jain S; Centers for Disease Control and Prevention Etiology of Pneumonia in the Community (EPIC) Study Team. Relationship Between Body Mass Index and Outcomes Among Hospitalized Patients With Community-Acquired Pneumonia. *J Infect Dis* 2017; 215: 1873-1882 [PMID: 28520948 DOI: 10.1093/infdis/jix241]

Hammer M, Gale CR, Kivimäki M, Batty GD. Overweight, obesity, and risk of hospitalization for COVID-19: A community-based cohort study of adults in the United Kingdom. *Proc Natl Acad Sci USA* 2020; 117: 21011-21013 [PMID: 32788355 DOI: 10.1073/pnas.2011086117]

Chinese society of respiratory diseases. [Guidelines for diagnosis and treatment of community acquired pneumonia]. *Chin J Pract Riral Doctors* 2006; 20: 158-160

WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004; 363: 157-163 [PMID: 14726171 DOI: 10.1016/S0140-6736(03)15268-3]

Liu JL, Xu F, Zhou H, Wu XJ, Shi LX, Lu RQ, Farcomeni A, Venditti M, Zhao YL, Luo SY, Dong XJ, Falcone M. Expanded CURB-65: a new score system predicts severity of community-acquired pneumonia with superior efficiency. *Sci Rep* 2016; 6: 22991 [PMID: 26957602 DOI: 10.1038/srep22991]

de Jager CP, Wever PC, Gemen EF, Wever PC, Gemen EF, Kusters R, van Gageldonk-Lafeber AB, van der Poll T, Laheij R. The neutrophil-lymphocyte count ratio in patients with community-acquired pneumonia. *PLoS One* 2012; 7: e46561 [PMID: 23049706 DOI: 10.1371/journal.pone.0046561]

Grudzinska FS, Brodlink S, Schoefeld BR, Jackson T, Scott A, Thickett DR, Sapey E. Neutrophils in community-acquired pneumonia: parallels in dysfunction at the extremes of age. *Thorax* 2020; 75: 164-171 [PMID: 31732687 DOI: 10.1136/thoraxjnl-2018-212826]

Pascoe SJ, Papi A, Midwinter D, Lettis S, Barnes N. Circulating neutrophil levels are a predictor of pneumonia risk in chronic obstructive pulmonary disease. *Respir Res* 2019; 20: 195 [PMID: 31443653 DOI: 10.1186/s12931-019-1157-0]

Yang T, Wan C, Wang H, Qin J, Chen L, Y’ S, Wen F. The prognostic and risk-stratified value of neutrophil–lymphocyte count ratio in Chinese patients with community-acquired pneumonia. *Eur J Inflamm* 2017; 15: 22-27 [DOI: 10.1177/1721727x17702150]

Gouden V, Vashishth R, Jalilai I. Hypoalbuminemia. *StatPearls. Treasure Island (FL)* 2021 [DOI: 10.1016/978-0-12-818277-2.00002-9]

Braamskamp MJ, Dolman KM, Tabbers MM. Clinical practice. Protein-losing enteropathy in children. *Eur J Pediatr* 2010; 169: 1179-1185 [PMID: 20571826 DOI: 10.1007/s00431-010-1235-2]

Hedlund JU, Hansson LO, Ortvist AB. Hypoalbuminemia in hospitalized patients with community-acquired pneumonia. *Arch Intern Med 1995; 155*: 1438-1442 [PMID: 7790494]

Damayanti N, Abidin A, Keltan EU. The correlation between albumin levels with 30 days mortality in community acquired pneumonia patients. *Environ Sci 2018; 125*: 012141 [DOI: 10.1088/1755-1315/125/1/012141]

Martí C, Garín N, Grosquín O, Ponce A, Combesque C, Carballo S, Perrier A. Prediction of severe community-acquired pneumonia: a systematic review and meta-analysis. *Crit Care* 2012; 16: R141 [PMID: 22839689 DOI: 10.1186/cc11447]

Jones BE, Jones J, Bewick T, Lim WS, Aronsky D, Brown SM, Boersma WG, van der Eerden MM, Dean NC. CURB-65 pneumonia severity assessment adapted for electronic decision support. *Chest* 2011; 140: 156-163 [PMID: 21163875 DOI: 10.1378/chest.10-1296]

Jain V, Vashishth R, Yilmaz G, Bhardwaj A. Pneumonia Pathology. *StatPearls. Treasure Island (FL)*
Wang N et al. Overweight/obesity on CAP mortality

2021 [DOI: 10.5040/9780571352654.0000004]

42 Rodríguez A, Lisboa T, Blot S, Martín-Loeches I, Solé-Violan J, De Mendoza D, Rello J. Community-Acquired Pneumonia Intensive Care Units (CAPUCI) Study Investigators. Mortality in ICU patients with bacterial community-acquired pneumonia: when antibiotics are not enough. Intensive Care Med 2009; 35: 430-438 [PMID: 19066850 DOI: 10.1007/s00134-008-1363-6]

43 Cillóniz C, Domingo L, Pericás JM, Rodríguez-Hurtado D, Torres A. Community-acquired pneumonia in critically ill very old patients: a growing problem. Eur Respir Rev 2020; 29 [PMID: 32075858 DOI: 10.1183/16000617.0126-2019]

44 Arnold FW, Wiemken TL, Peyrani P, Ramirez JA, Brock GN. CAPU: an influence. Nature Medicine 2020; 807-812 [PMID: 31292615 DOI: 10.1093/jme/dyz129]

45 Gaber T, Streil C, Buttgeireit F. Metabolic regulation of inflammation. Nat Rev Rheumatol 2017; 13: 20-29 [PMID: 28331208 DOI: 10.1038/nrrheum.2017.37]

46 Piper AJ, Grunstein RR. Obesity hypoventilation syndrome: mechanisms and management. Am J Respir Crit Care Med 2011; 183: 292-298 [PMID: 21037018 DOI: 10.1164/rccm.201008-1280CI]

47 Murugan AT, Carr J, Renigunta R, Flaherty KV. Role of corticosteroids in the management of severe community-acquired pneumonia: a systematic review and meta-analysis. Int J Obes (Lond) 2013; 37: 187-200 [PMID: 23660396 DOI: 10.1016/j.ijeo.2013.04.003]

48 Huttenen R, Syrjänen J. Obesity and the risk and outcome of infection. Int J Obes (Lond) 2013; 37: 333-340 [PMID: 22546772 DOI: 10.1038/ijo.2012.62]

49 Ghilotti F, Bellocco R, Ye W, Adamo H, Trolle Lagerros Y. Obesity and risk of infections: results from men and women in the Swedish National March Cohort. Int J Obes (Lond) 2019; 43: 1783-1794 [PMID: 31292615 DOI: 10.1093/ije/dyz129]

50 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 [PMID: 27742103 DOI: 10.1016/j.nut.2016.07.016]

51 Weissberg SP, McCann B, Rosenbaum M, Leibel RL, Ferrante AW Jr. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest 2003; 112: 1762-1769 [PMID: 12767995 DOI: 10.1172/JCI12797]

52 Hill AA, Reid Bolus W, Hasty AH. A decade of progress in adipose tissue macrophage biology. Immunity Rev 2014; 262: 134-152 [PMID: 25319332 DOI: 10.1111/irm.12216]

53 Caspar-Bauguil S, Kolditz C, Lefort C, Viura I, Mouiel S, Beuzelin D, Tavernier G, Marques MA, Zakroff-Girard A, Pecher C, Houssier M, Mir L, Nicolas S, Moro C, Langin D. Fatty acids from fat depot activate an inflammatory response but are stored as triacylglycerols in adipose tissue macrophages. Diabetologia 2015; 58: 2627-2636 [PMID: 26245186 DOI: 10.1007/s00125-015-3719-0]

54 Kratz M, Coats BR, Biess JT, Hagan D, Muts OK, Peris E, Schoenfelt KQ, Kuzman RN, Larson I, Billing PS, Landeholm RW, Crouthamel M, Gozal D, Hwang S, Singh P, Becker L. Metabolic dysfunction drives a mechanistically distinct proinflammatory phenotype in adipose tissue macrophages. Cell Metab 2014; 20: 614-625 [PMID: 25242226 DOI: 10.1016/j.cmet.2014.08.010]

55 King P, Mortensen EM, Bollinger M, Restrepo MI, Skalsky K, Avni T, Carrara E, Leibovici L, Paul M. Corticosteroids for pneumonia. Cochrane Database Syst Rev 2017; 150: 323-339 [PMID: 28331208 DOI: 10.1002/14651858.CD001924.pub3]

56 Stern A, Skalsky K, Avni T, Carrara E, Leibovici L, Paul M. Corticosteroids for pneumonia. Cochrane Database Syst Rev 2017; 12: CD007720 [PMID: 29236286 DOI: 10.1002/14651858.CD007720.pub3]

57 Ma H. Clinical effect observation of small dose glucocorticoid in the treatment of severe community acquired pneumonia. Psychol Monthly 2019; 14: 181 [DOI: 10.26226/morressier.56d5ba2bd462b80296c966ed]

58 Akaletseu E, Genser L, Rutter GA. Glucocorticoid Metabolism in Obesity and Following Weight Loss. Front Endocrinol (Lausanne) 2020; 11: 59 [PMID: 32153504 DOI: 10.3389/fendo.2020.00059]

59 Haga T, Ito K, Ono M, Maruyama Y, Iguchi M, Suzuki H, Hayashi E, Sakashita K, Nagao T, Ikemoto S, Okaniwa A, Kitami M, Inoo E, Tatsumi K. Underweight and hypalbuminaemia as risk indicators for mortality among psychiatric patients with medical comorbidities. Psychiatry Clin Neurosci 2017; 71: 807-812 [PMID: 28715136 DOI: 10.1111/pcn.12553]

60 Hu WH, Eisenstein S, Parry L, Ramamooorthy S. Preoperative malnutrition with mild hypalbuminaemia associated with postoperative mortality and morbidity of colorectal cancer: a propensity score matching study. Nutr J 2019; 18: 33 [PMID: 31253199 DOI: 10.1186/s12977-019-0458-y]

61 Park D, Lee JH, Han S. Underweight: another risk factor for cardiovascular disease? Medicine (Baltimore) 2017; 96: e8769 [PMID: 29310352 DOI: 10.1097/MD.0000000000008769]
