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The impact of frailty on short- and long-term mortality in hospitalized elderly patients with community-acquired pneumonia: a prospective observational study

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Abstract

Objectives: This study aimed to examine the impact of frailty on short- and long-term mortality among elderly patients with community-acquired pneumonia (CAP). The major hypothesis was that frailty, a clinical state of increased vulnerability, is a good predictor of prognosis in elderly CAP patients.

Design: Prospective, observational, follow-up cohort study.

Setting: One 2000-bed tertiary care hospital in Beijing, China.

Participants: Consecutive CAP patients aged ≥65 years that admitted to the geriatric department between September 2017 and February 2019.

Main outcome measures: The primary outcomes were all-cause mortality at 30 days and 1 year after admission to the hospital. Multivariable Cox regression models were used to examine the independent association between frailty (defined by Fried Frailty Phenotype) and 30-day and 1-year mortality of pneumonia.

Results: The cohort included 256 patients, with a median age of 86 years (IQR: 81, 90), 66.8% (171/256) of the patients were frail. All-cause mortality was 5.5% (14/256) at 30 days and 16.8% (43/256) at 1 year. A higher percentage of patients in the frail group than in the non-frail group was classified as severe CAP (28.65% vs 9.41%, P<0.001). Frailty was independently associated with an increased risk of 1-year mortality (multivariable-adjusted HR 2.70, 95% CI 1.69-4.39) after adjustment for age, sex, disability, malnutrition, comorbidities, and the severity of CAP. The 30-day

mortality did not differ between patients with and without frailty by multivariable Cox regression analysis (P=0.108). Severe CAP was associated with increased risks of 30-day and 1-year mortality (multivariable-adjusted HR 30.60, 95% CI 3.77-248.06 and HR 7.68; 95% CI: 3.79-15.58, respectively).

Conclusions: Frail patients are prone to develop severe CAP, and frailty is strongly related to prognosis of 1-year mortality. Our findings suggest that frailty is strongly related to prognosis and should be considered in routine clinical practice and post-discharge management.

Key words: Community-acquired pneumonia; Frailty; Elderly; Prognosis.

Strengths and limitations of this study

1. This study addresses the paucity of knowledge on frailty in elderly patients with community-acquired pneumonia.

2. This study summarized and analyzed well known prognosis variables (such as age, disability, malnutrition, comorbidities, the severity of CAP) and frailty, and proved the significance of frailty to prognosis by multivariate analysis.

3. Frailty defined by the Fried Frailty Phenotype, which is well validated and simple to use.

4.This a single institution and a relatively small sample prospective study, lack of comparison with data from other hospitals and regions.

Introduction

Community-acquired pneumonia (CAP) is the leading cause of infectious disease in the elderly and is associated with high rates of mortality, morbidity and high costs worldwide.[1, 2, 3, 4] In the United States, the incidence of CAP in adults between 65 and 79 years old is 63 cases per 10,000 adults and increases to 164.3 cases per 10,000 adults in the over-80 age group.[5] In China, the incidence of mortality due to pneumonia is 23.55 cases per 100,000 adults aged between 65 and 69 years old and nearly 36 times greater in persons over 85 years.

Well known risk factors for mortality, such as age, functional status, comorbidities, and others, have already been incorporated into the assessment of the severity of CAP,[6,7,8,9] but increasing mortality in elderly CAP patients indicates the need for the identification of novel, ideally modifiable, risk factors for poor outcomes. Particular attention has recently been directed to the concept of the ‘‘frail elderly patient’’.[4] Although frailty has been considered synonymous with disability, comorbidity or advanced old age, it is defined as a cumulative decline and loss of physiological reserves in multiple organs and systems and causes increased vulnerability to adverse outcomes.[10] Frailty has been confirmed to be an independent risk factor for mortality in patients with acute and chronic diseases.[11,12] A European multicenter study that included 5021 patients assessed the impact of frailty on intensive care unit (ICU) admission and 30-day mortality in elderly patients. The results indicated that frailty (measured by the Clinical Frailty Scale) was found in 43% of patients and was independently related to 30-day survival (hazard ratio (HR) 1.54; 95% confidence

interval (CI) 1.38-1.73 for frail versus non-frail patients).[13] However, few studies have investigated the association of frailty with the prognosis of CAP.[14,15] Therefore, we hypothesized that frailty was related to the prognosis of elderly CAP patients, and it may have significant predictive value. The objective of this study was to prospectively evaluate the impact of frailty on the outcome of elderly patients with CAP. This information will be helpful for the early stratification of high-risk patients and the implementation of the hierarchical management of modifiable factors to improve the prognosis of elderly patients with CAP.

Methods

1. Study design

We prospectively enrolled consecutive elderly patients (age ≥65 years) diagnosed with CAP in the geriatric department from September 2017 to February 2019. The exclusion criteria were as follows: 1) Complicated with acute myocardial infarction, acute cerebrovascular disease, gastrointestinal bleeding, or acute renal failure. 2) Surgical history within 3 months. 3) Terminal stage of a malignant tumor.

CAP was defined as pneumonia acquired outside the hospital by an immune-competent individual. The specific criteria for the diagnosis of CAP were as follows: (1) community onset and (2) the presence of new infiltrate on chest X-ray or a computed tomography scan together with at least one of the following: (i) new or increased cough (productive, nonproductive or with a change in sputum characteristics) with or without dyspnea, chest pain or hemoptysis; (ii) fever; (iii) rales and/or signs of consolidation;

(iv) peripheral WBC count > 10,000 cells mm^{-3} or < 4000 cells mm^{-3}, with or without a leftward shift toward immature forms. The exclusion of tuberculosis, lung cancer, noninfectious pulmonary interstitial disease, pulmonary edema, atelectasis, pulmonary embolism, pulmonary eosinophilic infiltration, and pulmonary vasculitis can establish a clinical diagnosis.[16]

2. Baseline assessment

The following parameters were evaluated within 24 hours of admission: age, sex, body mass index (BMI), smoking history, procalcitonin (PCT), high-sensitivity C-reactive protein (hs-CRP), white blood count (WBC), hemoglobin (HGB), alanine aminotransferase (ALT), albumin (ALB), prealbumin (PA), serum creatinine (Scr) and blood urea nitrogen (BUN).

3. Severity of CAP

The diagnostic criteria for severe CAP (SCAP) from the Infectious Diseases Society of America (IDSA) / American Thoracic Society (ATS) were used.[17] For the diagnosis of SCAP, at least 1 major or 3 minor criteria must be satisfied. The major criteria are the need for mechanical ventilation or septic shock. The minor criteria are as follows: respiratory rate >130 breaths/min; arterial oxygen pressure/fraction of inspired oxygen (PaO_2/FiO_2) ratio<250; multilobar infiltrate; confusion; blood urea nitrogen level >120 mg/dL; leukopenia resulting from infection; thrombocytopenia; hypothermia; or hypotension requiring aggressive fluid resuscitation.

4. Frailty assessment

Frailty was assessed by the Fried Frailty Phenotype (FFP) (unintentional weight loss, self-reported exhaustion, weakness, slow walking speed, and low physical activity) [18] within 24 hours of admission. Each construct is assigned "1" if present or "0" if absent, and the score is standardized for sex, height, and weight. The FFP ranges from 0–5; consistent with established definitions, we defined frailty as the FFP score of ≥3, non-frail as the FFP score of 0-2.

5. Covariates

Comorbidity was evaluated with the Charlson Comorbidity Index (CCI).[19] The CCI is the sum of the weighted measures of the following 17 chronic medical conditions: ischemic heart disease, congestive heart failure, cerebrovascular accident, peripheral vascular diseases, chronic lung diseases, diabetes, dementia, connective tissue diseases, renal diseases, liver diseases, hemiplegia, solid or hematological malignancy, and acquired immunodeficiency disease. A score of 1, 2, 3 or 6 is assigned to each disease, depending on the severity.

Functional status assessments were carried out with the Barthel Index (BI) to evaluate the activities of daily living.

The nutritional status assessment was conducted by a professional with the unified Mini Nutritional Assessment-Short Form (MNA-SF) questionnaire.[20] The questionnaire consists of BMI, weight loss in the past 3 months, dietary changes, stress or acute illness, activity and neuropsychiatric diseases. The total score is 14 points. Scores of 0-7 indicated malnutrition.

5. Follow-up and outcomes

All patients were followed for 1 year after admission. The primary outcomes were all-cause mortality at 30 days and 1 year after admission to the hospital.

6. Statistical analysis

Statistical analyses were performed with IBM SPSS software 23.0 (Chicago, USA). Continuous variables were expressed as the means ± standard deviation (SD) or interquartile range (IQR) and compared using Student's t-test or the Mann–Whitney U test. Categorical variables were compared using the chi-squared test or Fisher's exact test. Univariable and multivariable Cox proportional hazards regression models were used to calculate hazard ratio (HR) with 95% confidence interval (CI) for the analysis of the association between frailty status at baseline and 30-day and 1-year all-cause mortality. In all analyses, two-tailed p values < 0.05 were considered to indicate significance.

Patient and public involvement

The research questions and outcome measures were developed based on some most common problems that are widely recognized among elder patients. Patients or the public did not involve in the design of the study, recruitment or conduction of the study. The results of the study would be disseminated to patients once he or she requests so and aggregated data would be reported in project reports and research publications and conferences.

Results

In total, 393 patients with CAP were admitted to our hospital during the study period, 119 patients with the concomitant diseases before admission were excluded (Figure.1), and 18 were excluded due to loss to follow-up. In total of 256 patients (range, 65-99 years) were included for the final statistical analysis. Demographic patient characteristics are shown in Table 1. The median age was 86 years ((IQR: 81, 90), and 207 (80.9%) patients were very old (age ≥80 years). At baseline, 180 (70.3%) patients were male, 71 (27.7%) were malnourished, 171 (66.8%) were frail, and 57 (22.3%) had SCAP. All-cause mortality for the 256 patients with CAP was 5.5% at 30 days and 16.8% at 1 year.

The impact of frailty on the prognosis of CAP

According to the FFP, we classified patients with scores 0-2 as the non-frail group (N=85) and patients with scores ≥3 as the frail group (N=171). Table 2 summarizes the demographics, clinical characteristics and mortality of the CAP patients stratified by the presence or absence of frailty. Compared to the non-frail group, the frail group was more likely to be older (P<0.001) and female (34.50% vs 20.00%, P=0.017). In addition, compared with the non-frail group, the frail group had decreased activities abilities of daily living (P<0.001) and increased CCI scores (P<0.001). Both a lower MNA-SF score (P<0.001) and nutritional indicators such as BMI (22.25±4.40 vs 24.17±3.80, P=0.001), ALB (31.50±4.16 vs 34.38±4.22, P<0.001) and PA (15.98±5.88 vs 18.74±6.41, P=0.001) indicated that the frail group had a worse nutritional status

than the non-frail group. However, there were no significant differences between the two groups with regard to PCT, hs-CRP, ALT, or Scr. A higher percentage of patients in the frail group were classified as SCAP (28.65% vs 9.41%, P<0.001), and experienced higher 30-day mortality (8.19% vs 0.00%, P=0.015) and 1-year mortality (25.15% vs 0.00%, P<0.001) compared with the non-frail group.

Factors associated with 30-day and 1-year mortality in patients with CAP

Table 3 shows the significant risk factors for 30-day mortality in patients with CAP identified in the Cox proportional hazards regression analyses. The univariate Cox regression analyses identified several variables (SCAP, frailty, malnutrition, CCI score) that were significantly associated with 30-day mortality in elderly patients with CAP. In multivariable analysis, SCAP was the only independent risk factor for 30-day mortality (multivariable-adjusted HR 30.60, 95% CI 3.77-248.06), while frailty was not significantly associated with 30-day mortality (adjusted HR 1.83, 95% CI 0.88-3.81, P=0.108).

Table 4 shows the hazard ratios (95% confidence intervals) for 1-year all-cause mortality. The univariate Cox regression analyses identified several variables (SCAP, frailty, malnutrition, CCI score, BI, and BMI) that were significantly associated with 1-year mortality in elderly patients with CAP. In multivariable analysis, SCAP (adjusted HR 7.68; 95% CI: 3.79-15.58), frailty (adjusted HR 2.70, 95% CI 1.69-4.39), and CCI score (adjusted HR 1.19, 95% CI 1.05-1.34) were independent risk factors for 1-year mortality.

Discussion

Our study focused on evaluated the impact of frailty on short- and long-term outcomes in elderly CAP patients. The key points of this study are as follows: 1, Compared to non-frail patients, frail elderly CAP patients were more likely to develop severe pneumonia and had significantly increased short-term and long-term mortality; 2. Frailty was the independent risk factor correlated with 1-year mortality even after adjustment for age, sex, disability, malnutrition, comorbidities, and severity of CAP, but it was not the independent risk factor for the 30-day mortality.

The incidence of CAP increases with increasing age and results in higher risks of morbidity and mortality. Different independent prognostic factors related to mortality have been well described, including age, comorbidities, functional status, microbial etiology and early adequate antibiotic treatment.[8,9,21,22] Several international guidelines explicitly recommend the assessment of pneumonia severity, such as with the PSI or CURB-65, of them age and comorbidities accounted for a significant proportion of the score. An analysis of a prospective cohort study including 987 patients demonstrated that both the PSI and CURB-65 have decreased discriminative power with advancing age.[23] Significantly, however, most authors noted that in the elderly population, age *per se* is not an independent predictor of mortality.[24] Although frailty is considered to be synonymous with disability, comorbidity, or advanced age, Fried LP *et al* defined it as a diminishment in the physiological reserves for a consequence of aging and thus of the accumulation of diseases over time, which leads to a loss in the capacity of response to situations of stress.[18,25] This vulnerability

results in an increased risk of adverse health outcomes including falls, disability, hospitalisation, institutionalisation and death. Various conditions, including malnutrition, sarcopenia, gait impairment, chronic inflammation, polypharmacy, cardiovascular changes and morbidity, were found to be associated with and potentially causes of frailty. [26,27,28]

Consistent with the findings of other studies,[26] we found that the frail group of patients were characterized by older age, a higher percentage of females, more comorbidities, a higher incidence of malnutrition, lower functional status and lower activities of daily life scores. Poor nutritional status, which in different studies encompassed hypoalbuminemia, hypoproteinemia, malnourishment, or a low nutritional score, was a strong predictor of mortality in CAP patients. However, in our study, nutrition status was correlated with mortality by univariate analysis, but it was not a significant independent risk factor after multivariate analysis. At present, it has been validated that malnutrition is an important biological mechanism underlying the occurrence and development of frailty.[27] Recent studies have shown that frailty and malnutrition are intrinsically interrelated in terms of structure, identification tools and treatment.[28,29] The treatment strategies are generally similar for frailty and malnutrition, and these conditions have the potential to exacerbate each other and other comorbid conditions.[26] Frailty and malnutrition can interact with each other, which leads to the further deterioration of the prognosis of patients. The presence of pathological conditions, including undernutrition and chronic diseases, creates a vicious cycle, with a decrease in physiological reserves and the accumulation of deficits.[30] Acute

infectious diseases, such as CAP, may result in hospitalization, disability, institutionalization and death. The whole process of events is summarized in the frailty cascade.[31] In our study, frailty was represented by the Fried Phenotype, which mixes items of functional status (slow walking speed and low levels of physical activity) and nutrition risk (unintentional weight loss). This explains why frailty, but not malnutrition and disability, was associated with higher mortality in multivariate analysis. Our study also confirmed that higher percentage of patients in the frail group than in the non-frail group was classified as SCAP (28.65% vs 9.41%, P<0.001), and the frail group had higher 30-day (8.19% vs 0.00%, P=0.015) and 1-year (25.15% vs 0.00%, P<0.001) mortality compared with the non-frail group. Many authors have evaluated longer-term patient outcomes, either at 90 days or 1 year after CAP.[32] In all cases, the mortality risk was associated with the patient characteristics, i.e., underlying diseases, more than with the characteristics of the acute episode.[22] Unfortunately, in these studies, the basic status assessment of patients only included variables such as age, malnutrition, daily living ability and comorbidities, but few of them considered about frailty. We also found that frailty was independently associated with 1-year mortality after adjusting for the variables mentioned earlier, which implies that frailty can effectively predict the occurrence of severe pneumonia and adverse outcomes.

Many biomarkers of infection, such as the WBC, CRP, and PCT, have been found to play roles in the early diagnosis and prognosis of CAP, [33,34] but their applicability in geriatric patients has not yet been clearly established. The CRP level and the WBC count, like clinical signs and symptoms, are not always reliable parameters in geriatric

patients because they may occasionally fall in the normal range (especially in the elderly).[35] An analysis of a retrospective cohort of 438 CAP patients aged ≥65 years did not reveal any association between CRP or WBC and mortality, or between CRP or WBC and pneumonia severity.[36] Our results suggested that more patients in the frail group developed severe pneumonia, both hs-CRP and PCT were higher in the frail group, but there were no significant differences between the two groups. Neither of the inflammatory biomarkers were associated with short- or long-term mortality in elderly patients with CAP by Cox proportional hazards regression analyses. Immunosenescence, defined as immunological changes that occur with age, is known to be responsible for the increased susceptibility of elderly persons to infectious diseases and for their limited response to vaccines.[37] Elderly patients have an inadequate inflammatory response to infection, which can lead to an underestimation of the severity of pneumonia and, consequently, a delay in the initiation of anti-infective therapy.[38]

Our finding suggested that frail patients are prone to develop severe CAP, and frailty is strongly related to prognosis of 1-year mortality. Since the clinical presentation of pneumonia in the elderly may be atypical, clinicians should suspect pneumonia presenting with symptoms such as falls, altered mental status, fatigue, delirium, and anorexia to avoid the complications associated with delayed diagnosis and therapy.[39] With respect to clinical decision making and the planning of health care, it is important to identify frailty in elderly CAP patients to better stratify their risk of adverse outcomes and plan more specific care tailored to the needs of each patient, such as invasive

diagnostic and therapeutic procedures and the final placement of the patient. In a Korean study, frailty was independently associated with do-not-resuscitate orders and different healthcare transitions, even after adjustment for sepsis and pneumonia severity.[40] An international multidisciplinary group studying geriatric patients proposed an integral geriatric assessment (IGA)[41] adapted to the emergency department (ED) context to assess frailty in elderly patients.[13,42] Even if many physicians and intensivists do not currently undertake the performance of a specific geriatric assessment in critically ill, geriatric patients with infectious diseases, ongoing demographic shifts toward the elderly population will likely force the consideration of this issue in the near future. Our study suggests that frailty should be measured in routine clinical practice to improve the management of elderly patients with CAP and that the postdischarge management of frail patients with CAP is also important.

Finally, we need to note that as a single-center prospective study, there is a lack of comparison with data from other hospitals and regions; the numbers of patients and terminal events were relatively small, and there were many restrictive factors, so the results have certain limitations. This study summarized and analyzed age, comorbidities, frailty and other factors, as well as various prognostic factors selected by multivariate analysis. The findings are still valuable for guiding the treatment and determining the prognosis of CAP in the elderly population. We expect to obtain multicenter and large-sample data in future studies to confirm our research hypothesis.

Conclusions

In summary, frailty was very common in elderly patients with CAP, and frail patients were more likely to suffer from severe disease and a had higher 1-year mortality rate compared with non-frail patients. Our findings suggest that frailty should be considered in routine clinical practice and the postdischarge management of patients with CAP.

Contributors Jia Luo, Wen Tang, Ying Sun and Chun-Yan Jiang contributed to conception and design of this study. Jia Luo and Wen Tang contributed to data collection. Wen Tang, Ying Sun and Chun-Yan Jiang contributed to analyses and interpretation. Jia Luo and Wen Tang contributed to preparation of the manuscript. The final version of the article was approved by all the authors.

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Competing interests: None declared.

Ethical approval: This study was approved by the ethics committee of Beijing Friendship Hospital, Capital Medical University and conducted according to the principles of the Declaration of Helsinki (project number: 2018-P2-138-01). All patients provided informed consent before the commencement of the study.

Data sharing statement: Data could be shared after consultation with author, E-mail: ann11121112@sina.com.

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Table 1. Baseline characteristics of the study patients.

Characteristics	Whole population
Age (years), median (IQR)	86 (81, 90)
65-79 years, n (%)	49(19.1)
≥80 years, n (%)	207 (80.9)
Male, n (%)	180 (70.3)
Smoking status, n (%)	
Current-smoker	29 (11.3)
Ex-smoker	71 (27.7)
Non-smoker	156 (60.9)
Comorbidity, n (%)	
Congestive heart failure	102 (39.8)
Myocardial infarction	33 (12.9)
Cerebrovascular disease	143 (55.9)
Diabetes mellitus	103 (40.2)
Chronic pulmonary disease*	110 (43.0)
Renal disease	32 (12.5)
Hematological malignance	6 (2.4)
Solid malignancy	45 (17.6)
Malnutrition, n (%)†	71 (27.7)
Frailty, n (%)‡	
Non-frail	85 (33.2)
Frail	171 (66.8)
SCAP, n (%)§	57 (22.3)

Mortality	
30-day mortality, n (%)	14 (5.5)
1-year mortality, n (%)	43 (16.8)

Abbreviations: IQR, inter-quartile range; SCAP, severe community acquired pneumonia.

* Chronic lung disease includes chronic obstructive pulmonary disease, asthma, bronchiectasis, and interstitial lung disease.

† Malnutrition: defined by MNA-SF scores ≤ 7.

‡ Frail: defined by Fried Phenotype score ≥ 3.

§ SCAP: defined by IDSA/ATS criteria (2007).

Table 2. Analysis of CAP-related risk factors and prognosis stratified by frailty status

Characteristics	Non-frail	Frail*	P values
N	85	171	
Age median (IQR)	83 (75, 87)	88 (84, 91)	<0.001
Sex, n (%)			
Female	17(20.00)	59(34.50)	0.017
Male	68(80.00)	112(65.50)	
Smoking status			
Current-smoker	11	18	0.288
Ex-smoker	28	43	
Non-smoker	46	110	
BMI (kg/m^2) mean ± SD	24.17±3.80	22.25±4.40	0.001
Barthel Index median (IQR)	95 (85, 100)	50 (20, 70)	<0.001
CCI median (IQR)	3 (2, 4)	4 (3, 6)	<0.001
MNA-SF median (IQR)	12 (11, 14)	9 (7, 11)	<0.001
SCAP†, n（%）	8(9.41)	49(28.65)	<0.001
PCT (ng/ml) median (IQR)	0.27 (0.20, 0.37)	0.29 (0.21, 0.55)	0.149
hs-CRP (mg/L) median (IQR)	19.63 (4.19, 54.29)	27.08 (7.56, 62.43)	0.129
WBC (*10^9/L) median (IQR)	7.02 (5.64,9.01)	8.02 (5.51, 12.33)	0.043
HGB (g/L) median (IQR)	127 (120, 136)	115 (100,128)	<0.001
Scr (umol/L) median (IQR)	78.6 (67.4, 90.5)	75.2 (59.5, 101.6)	0.720
BUN (mmol/L) median (IQR)	5.99 (4.30, 7.01)	5.98 (4.79, 8.65)	0.039
ALT (U/L) median (IQR)	15 (11, 22)	13 (10, 21)	0.058
ALB (g/L) mean ± SD	34.38±4.22	31.50±4.16	<0.001

PA (g/L) mean ± SD	18.74±6.41	15.98±5.88	0.001
30-day mortality, n (%)	0(0)	14(8.19)	0.015
1-year mortality, n (%)	0(0)	43(25.15)	<0.001

Abbreviations: SD, standard deviation; IQR, inter-quartile range; BMI, Body Mass Index; CCI, Charlson's Comorbidity Index; MNA-SF, Mini Nutritional Assessment-Short Form; SCAP, severe community acquired pneumonia; PCT, procalcitonin; hs-CRP, high sensitivity C-reactive protein; WBC, the leukocyte count; HGB, hemoglobin; BUN, blood urea nitrogen; Scr, serum creatinine; ALT, alanine aminotransferase; ALB, albumin; PA, prealbumin.

⁎ Frail: defined by Fried Phenotype score ≥ 3.

† SCAP: defined by the IDSA/ATS criteria (2007).

Table 3. Significant risk factors for 30-day mortality in patients with CAP in COX proportional hazards regression analyses (n =256)

	Univariate			Multivariable		
Variable	HR	95%CI	*P*-Value	HR	95%CI	*P*-Value
SCAP	52.01	6.80-398.09	<0.001	30.60	3.77-248.06	0.001
Malnutrition	0.84	0.73-0.97	0.015	1.11	0.90-1.35	0.330
Frail	2.58	1.42-4.69	0.002	1.83	0.88-3.81	0.108
CCI	1.41	1.19-1.67	<0.001	1.19	0.99-1.43	0.069

Data are shown as estimated HR (95% CIs) of the explanatory variables in the 30-day mortality group.

Abbreviations: HR, hazards ratio; CI, confidence interval; CCI, Charlson's Comorbidity Index; SCAP, severe community acquired pneumonia.

Table 4. Significant risk factors for 1-year mortality in patients with CAP in COX proportional hazards regression analyses (n =256)

	Univariate			Multivariable		
Variable	HR	95%CI	*P*-Value	HR	95%CI	*P*-Value
SCAP	13.32	6.81-26.04	<0.001	7.68	3.79-15.58	<0.001
BI	0.98	0.97-0.99	<0.001	1.01	0.99-1.02	0.352
BMI	0.93	0.87-1.00	0.038	1.07	0.98-1.16	0.128
Malnutrition	0.78	0.72-0.85	<0.001	0.94	0.81-1.10	0.424
Frail	3.41	2.32-5.03	<0.001	2.70	1.69-4.39	<0.001
CCI	1.40	1.26-1.55	<0.001	1.19	1.05-1.34	<0.001

Data are shown as estimated HR (95% CIs) of the explanatory variables in the 1-year mortality group.

Abbreviations: HR, hazards ratio; CI, confidence interval; SCAP, severe community acquired pneumonia; BI, Barthel Index; BMI, Body Mass Index; CCI, Charlson's Comorbidity Index.

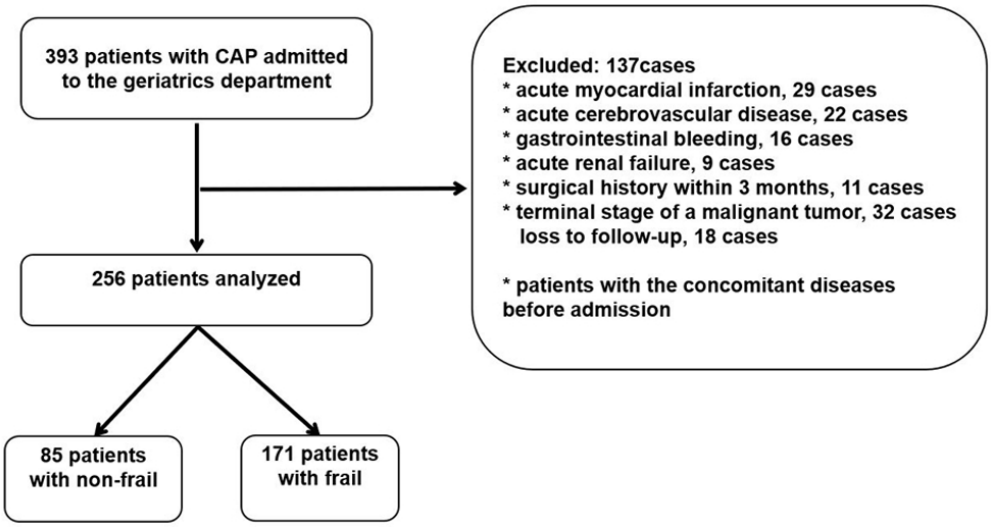

Figure 1.Flow chart of the study population

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The impact of frailty on 30-day and 1-year mortality in hospitalized elderly patients with community-acquired pneumonia: a prospective observational study

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Abstract

Objectives: This study aimed to evaluate the impact of frailty on 30-day and 1-year mortality among elderly patients with community-acquired pneumonia (CAP). The major hypothesis was that frailty, a clinical state of increased vulnerability, is a good predictor of prognosis in elderly CAP patients.

Design: Prospective, observational, follow-up cohort study.

Setting: One 2000-bed tertiary care hospital in Beijing, China.

Participants: Consecutive CAP patients aged ≥65 years admitted to the geriatric department between September 2017 and February 2019.

Main outcome measures: The primary outcomes were all-cause mortality at 30 days and 1 year after admission to the hospital. Cox regression was used to assess the impact of frailty (defined by Frailty Phenotype) on 30-day and 1-year mortality of elderly patients with CAP.

Results: The cohort included 256 patients. Median (IQR) age was 86 (81, 90) with 180 (70.3%) males. 171/256 (66.8%) patients were frail. The prevalence of frailty was significantly associated with older age, female, lower BMI, comorbidity, worse activities of daily living, and poorer nutritional status. Compared to non-frail patients, the frail patients were more likely present with severe CAP (28.65% vs. 9.41%, P<0.001) and with higher 30-day mortality (8.19% vs. 0%, P=0.034) and 1-year mortality (25.15% vs. 0%, P<0.001). In multivariate Cox regression analysis, frailty was independently

associated with an increased risk of 1-year mortality (multivariate-adjusted HR 2.70, 95% CI 1.69-4.39) after adjustment for age, sex, disability, malnutrition, comorbidities, and the severity of CAP. The association between frailty and 30-day mortality was not significant.

Conclusions: The current findings suggest that frailty is strongly associated with severe CAP and higher 1-year mortality in elderly CAP patients, and it should be considered in the management of CAP in elderly patients.

Keywords: Community-acquired pneumonia; Frailty; Elderly; Prognosis.

Strengths and limitations of this study

1. This study addresses the paucity of knowledge on frailty in elderly patients with community-acquired pneumonia.

2. This study summarized and analyzed well-known prognosis variables (such as age, disability, malnutrition, comorbidities, the severity of CAP) and frailty, and proved the significance of frailty to prognosis by multivariate analysis.

3. Frailty was defined by the Fried Frailty Phenotype, which is well validated and simple to use.

4. This was a small sample, single-center study, with relatively few end-point events.

5. The impact of frailty on the outpatients with CAP unproven.

Introduction

Community-acquired pneumonia (CAP) is the leading cause of infectious disease in the elderly and is associated with high rates of mortality, morbidity, and high costs worldwide.[1, 2, 3, 4] In the United States, the incidence of CAP in adults between 65 and 79 years old is 63 cases per 10,000 adults and increases to 164.3 cases per 10,000 adults in the over-80 age group.[5] In China, the reported mortality due to pneumonia is 23.55 cases per 100,000 adults aged between 65 and 69 years old and nearly 36 times greater in persons over 85 years.[6]

Well-known risk factors for mortality, such as age, functional status, comorbidities, and others, have already been incorporated into the assessment of the severity of CAP,[4,6,7,8,9,10] but increasing mortality in elderly CAP patients indicates the need for the identification of novel, ideally modifiable, risk factors for poor outcomes. Particular attention has recently been directed to the concept of the ‘‘frail elderly patient’’. Although frailty has been considered synonymous with disability, comorbidity, or advanced old age, it is defined as a cumulative decline and loss of physiological reserves in multiple organs and systems and causes increased vulnerability to adverse outcomes, including falls, hospitalization, and mortality.[11,12,13] Moreover, frailty has been confirmed to be an independent risk factor for mortality in patients with acute and chronic diseases.[14,15] A European multicenter study that included 5021 patients assessed the impact of frailty on intensive care unit (ICU) admission and 30-day mortality in elderly patients. The results indicated that frailty (measured by the Clinical Frailty Scale) was found in 43% of patients and was independently related to 30-day

survival (hazard ratio (HR) 1.54; 95% confidence interval (CI) 1.38-1.73 for frail versus non-frail patients).[16] The few reported studies focused on frailty and CAP have indicated that frailty factors contributed to increasing post-CAP hospitalizations,[17] and frailty significantly predicted 1-month mortality in older patients.[18] Therefore, we hypothesized that frailty was related to the prognosis of CAP, especially the presence of frailty was associated with negative predictive value in elderly CAP patients (in terms of CAP prognosis and mortality).

In this study, we aimed to assess the prevalence of frailty in older patients admitted with CAP, the association of frailty with CAP severity, the mortality within 30-day and 1-year after admission. This information will be helpful for the early stratification of high-risk patients and the implementation of the hierarchical management of modifiable factors to improve the prognosis of elderly patients with CAP.

Methods

1. Study design

We prospectively enrolled consecutive elderly patients (age ≥65 years) diagnosed with CAP in the geriatric department from September 2017 to February 2019. The exclusion criteria were as follows: 1) Complicated with acute myocardial infarction, acute cerebrovascular disease, gastrointestinal bleeding, or acute renal failure. 2) Surgical history within 3 months. 3) Terminal stage of a malignant tumor.

CAP was defined as pneumonia acquired outside the hospital by an immune-competent individual. The specific criteria for the diagnosis of CAP were as follows: (1)

community-onset and (2) the presence of new infiltrate on chest X-ray or a computed tomography scan together with at least one of the following: (i) new or increased cough (productive, nonproductive or with a change in sputum characteristics) with or without dyspnea, chest pain or hemoptysis; (ii) fever; (iii) rales and/or signs of consolidation; (iv) peripheral WBC count > 10,000 cells mm^{-3} or < 4000 cells mm^{-3}, with or without a leftward shift toward immature forms. The exclusion of tuberculosis, lung cancer, noninfectious pulmonary interstitial disease, pulmonary edema, atelectasis, pulmonary embolism, pulmonary eosinophilic infiltration, and pulmonary vasculitis can establish a clinical diagnosis.[6]

2. Baseline assessment

The following parameters were evaluated within 24 hours of admission: age, sex, body mass index (BMI), smoking history, procalcitonin (PCT), high-sensitivity C-reactive protein (hs-CRP), white blood count (WBC), hemoglobin (HGB), alanine aminotransferase (ALT), albumin (ALB), prealbumin (PA), serum creatinine (Scr) and blood urea nitrogen (BUN). All the Comprehensive Geriatric Assessment including frailty, comorbidity, function, and nutrition status conducted by trained evaluators within 24 hours of admission.

3. Severity of CAP

The diagnostic criteria for severe CAP (SCAP) from the Infectious Diseases Society of America (IDSA) / American Thoracic Society (ATS) were used.[19] For the diagnosis of SCAP, at least 1 major or 3 minor criteria must be satisfied. The major criteria are

the need for mechanical ventilation or septic shock. The minor criteria are as follows: respiratory rate >130 breaths/min; arterial oxygen pressure/fraction of inspired oxygen (PaO_2/FiO_2) ratio<250; multilobar infiltrate; confusion; blood urea nitrogen level >120 mg/dL; leukopenia resulting from infection; thrombocytopenia; hypothermia; or hypotension requiring aggressive fluid resuscitation.

4. Frailty assessment

Frailty was assessed by the Frailty Phenotype (FP): unintentional weight loss, self-reported exhaustion, weakness, slow gait speed, and low physical activity.[20] Each construct is assigned “1” if present or “0” if absent. The FP ranges from 0–5; consistent with established definitions, in this study we defined frailty as the FP score of ≥3, non-frail as the FP score of 0-2.

5. Covariates

Comorbidity was evaluated with the Charlson Comorbidity Index (CCI).[21] The CCI is the sum of the weighted measures of the following 17 chronic medical conditions: ischemic heart disease, congestive heart failure, cerebrovascular accident, peripheral vascular diseases, chronic lung diseases, diabetes, dementia, connective tissue diseases, renal diseases, liver diseases, hemiplegia, solid or hematological malignancy, and acquired immunodeficiency disease. A score of 1, 2, 3, or 6 is assigned to each disease, depending on the severity.

Functional status assessments were carried out with the Barthel Index (BI) to evaluate the activities of daily living.[22]

The nutritional status assessment was conducted with the unified Mini Nutritional Assessment-Short Form (MNA-SF) questionnaire.[23] The questionnaire consists of BMI, weight loss in the past 3 months, dietary changes, stress or acute illness, activity, and neuropsychiatric diseases. The total score is 14 points. Scores of 0-7 indicated malnutrition.

5. Follow-up and outcomes

All patients were followed for 1 year after admission. Deaths were confirmed through surveillance or matched to official death records. The primary outcomes were all-cause mortality at 30 days and 1 year after admission to the hospital.

6. Statistical analysis

Statistical analyses were performed with IBM SPSS software 23.0 (Chicago, USA). Continuous variables were expressed as the means ± standard deviation (SD) or interquartile range (IQR) and compared using Student's t-test or the Mann–Whitney U test. Categorical variables were compared using the chi-squared test or Fisher's exact test. Univariate and multivariate Cox proportional hazards regression models were used to calculate the hazard ratio (HR) with 95% confidence interval (CI) for the analysis of the association between frailty status at baseline and 30-day and 1-year all-cause mortality. In all analyses, two-tailed p values < 0.05 were considered to indicate significance.

Patient and public involvement

Patients or the public did not involve in the design of the study, recruitment or conduction of the study. There are no plans to involve participants in dissemination of results.The results of the study would be disseminated to patients once he or she requests so and aggregated data would be reported in project reports and research publications and conferences.

Results

In total, 393 patients with CAP were admitted to our department during the study period, 119 patients with the concomitant diseases before admission were excluded (Figure.1), and 18 were excluded due to loss to follow-up. A total of 256 patients (range, 65-99 years) were included for the final statistical analysis. Demographic patient characteristics are presented in Table 1. Median (IQR) population age was 86 (81, 90) with 180 (70.3%) males. The frail and malnutrition status were reported in 171 (66.8%) and 71 (27.7%), respectively. Fifty-seven (22.3%) of the patients had SCAP. All-cause mortality for the 256 patients with CAP was 5.5% at 30 days and 16.8% at 1 year.

In the analysis 85 (33.2%) non-frail subjects were compared to the frail group of 171 (66.8%) patients. Frailty was significantly associated with older age, female, lower BMI, worse activity ability of daily living function, comorbidity, and poorer nutritional status. The proportion of SCAP in the frail group is higher (28.65% vs 9.41%, P<0.001), and frail patients experienced higher 30-day mortality (P=0.015) and 1-year mortality (P<0.001). The results of Cox proportional hazards regression are presented in Table 2 and Table 3. Several variables were significantly associated with 30-day mortality in

univariate, including SCAP, frailty, malnutrition, CCI. In a multivariate analysis (Table 2) only SCAP (multivariate-adjusted HR 30.60, 95% CI 3.77-248.06) remained significant. To determine the significant risk factors for 1-year mortality in patients with CAP (Table 3), in a multivariate analysis, SCAP (adjusted HR 7.68; 95% CI: 3.79-15.58), frailty (adjusted HR 2.70, 95% CI 1.69-4.39), and CCI (adjusted HR 1.19, 95% CI 1.05-1.34) were independent risk factors for 1-year mortality.

Furthermore, we conducted a subgroup analysis only enrolled severe CAP patients. In all SCAP subjects (n=57), eight patients (14%) were non-frail and forty-nine patients (86%) were frail. The frail group with SCAP reported worse activity ability of daily living function and nutritional status, higher 30-day and 1-year mortality (Table 4). Several variables were significantly associated with 1-year mortality of SCAP in univariate, including frailty, malnutrition, function status, CCI. In a multivariate analysis (Table 5) only frailty (adjusted HR 2.87, 95% CI 1.58-4.96) and CCI (adjusted HR 1.16, 95% CI 1.01-1.34) remained significant. There was no significant risk factor correlated with the 30-day mortality after the multivariate analysis.

Discussion

The key points of this study are as follows: 1. Our study identified that frail CAP patients were significantly more likely to present with severe pneumonia and had significantly increased 30-day and 1-year mortality; 2. Frailty was an independent risk factor correlated with 1-year mortality even after adjustment for age, sex, disability, malnutrition, comorbidities, and severity of CAP, but it was not the independent risk

factor for the 30-day mortality.

The incidence of CAP increases with increasing age and results in higher risks of morbidity and mortality. Mortality in elderly patients with CAP maybe 25% higher than in the general population (10%).[4,9] Our study demonstrated that all-cause mortality for elderly patients with CAP was 5.5% at 30 days and 16.8% at 1 year. Different independent prognostic factors related to mortality have been well described, including age, comorbidities, functional status, microbial etiology, and early adequate antibiotic treatment.[9,10,24,25] Recently, most authors noted that in the elderly population, age *per se* is not an independent predictor of mortality.[26,27] Interestingly, We found that all patients who died were in the frail-group, whether in 30-day or 1-year followed-up. Although frailty is considered to be synonymous with disability, comorbidity, or advanced age, Fried LP *et al* defined it as a complex age-related clinical condition characterized by a decline in physiological capacity across several organ systems, with a resultant increased susceptibility to stressors.[20,28,29] This vulnerability results in an increased risk of adverse health outcomes including falls, disability, hospitalization, institutionalization, and death. Various conditions, including malnutrition, sarcopenia, gait impairment, chronic inflammation, polypharmacy, cardiovascular changes, and morbidity, were found to be associated with and potential causes of frailty. [30,31,32]

Consistent with the findings of other studies,[30] we found that frail group patients characterized with older age, more females, more comorbidities, worse nutrition status, poorer functional status, and lower activities of daily life abilities. Poor nutritional status, which in different studies encompassed hypoalbuminemia, hypoproteinemia,

malnourishment, or a low nutritional score, was a strong predictor of mortality in CAP patients.[33,34] However, in our study, there was no significant association between the nutrition status and 30 day or 1-year mortality after multivariate analysis (adjust-HR 1.11, 95% CI 0.90-1.35; adjust-HR 0.94, 95% CI 0.81-1.10, respectively). Recent studies have shown that frailty and malnutrition are intrinsically interrelated in terms of structure, identification tools, and treatment.[30,32,35] Malnutrition is also an important biological mechanism underlying the occurrence and development of frailty.[31] In our study, frailty was defined by the Fried Phenotype criterion, in which not only got unintentional weight loss as a criterion but also included functional status such as slow gate speed and low levels of physical activity. This may explain why frailty, but not malnutrition and disability, was significantly associated with higher mortality in multivariate analysis.

Our study also confirmed that frailty was very common in elderly patients with CAP (the prevalence was 66.8%) and significantly associated with the severity of the disease, for 1-year, frailty HR of 2.70 is nearly triple the mortality of non-frail. Many authors have evaluated longer-term patient outcomes, either at 90 days or 1 year after CAP.[36] In all cases, the mortality risk was associated with the patient characteristics, i.e., underlying diseases, more than with the characteristics of the acute episode.[25] Unfortunately, in these studies, the basic status assessment of patients only included variables such as age, malnutrition, daily living ability, and comorbidities, but few of them considered about frailty. The results of the study demonstrated that frailty was independently associated with 1-year mortality after adjusting for the variables

mentioned earlier, which implies that frailty can effectively predict the adverse outcomes.

Many biomarkers of infection, such as the WBC, CRP, and PCT, have been found to play roles in the early diagnosis and prognosis of CAP, [37,38] but their applicability in geriatric patients has not yet been clearly established. The CRP level and the WBC count, like clinical signs and symptoms, are not always reliable parameters in geriatric patients because they may occasionally fall in the normal range (especially in the elderly).[39] An analysis of a retrospective cohort of 438 CAP patients aged ≥65 years did not reveal any association between CRP or WBC and mortality, or between CRP or WBC and pneumonia severity.[40] Our results suggested that more patients in the frail group developed severe pneumonia, both hs-CRP and PCT were no significant differences between the two groups. Immunosenescence, defined as immunological changes that occur with age, is known to be responsible for the increased susceptibility of elderly persons to infectious diseases and for their limited response to vaccines.[41] Elderly patients have an inadequate inflammatory response to infection, which can lead to an underestimation of the severity of pneumonia and, consequently, a delay in the initiation of anti-infective therapy.[42]

Our finding suggested that frail patients are more likely present with severe CAP, and frailty is strongly related to the prognosis of 1-year mortality. Since the clinical presentation of pneumonia in the elderly may be atypical, clinicians should suspect pneumonia presenting with symptoms such as falls, altered mental status, fatigue, delirium, and anorexia to avoid the complications associated with delayed diagnosis

and therapy.[43] With respect to clinical decision making and the planning of health care, it is important to identify frailty in elderly CAP patients to better stratify their risk of adverse outcomes and plan more specific care tailored to the needs of each patient, such as invasive diagnostic and therapeutic procedures and the final placement of the patient. In a Korean study, frailty was independently associated with do-not-resuscitate orders and different healthcare transitions, even after adjustment for sepsis and pneumonia severity.[44] An international multidisciplinary group studying geriatric patients proposed an integral geriatric assessment (IGA)[45] adapted to the emergency department (ED) context to assess frailty in elderly patients.[16,46] Even if many physicians and intensivists do not currently undertake the performance of a specific geriatric assessment in critically ill, geriatric patients with infectious diseases, ongoing demographic shifts toward the elderly population will likely force the consideration of this issue soon. Moreover, we should note that frailty is not an inevitable consequence of aging (even at advanced ages, many people do not become frail) and is a dynamic condition, and individuals can transition in and out of frailty states. The frail prevention is possible, especially during the early stages, and prompt identification is crucial to maximize opportunities for intervention.[11] Therefore, frailty should be measured in routine clinical practice to improve the management of elderly patients with CAP and that the post-discharge management of frail patients with CAP is also important.

Finally, we need to note that as a single-center prospective study, there is a lack of comparison with data from other hospitals and regions; the numbers of patients and end-point events were relatively small, and there were many restrictive factors, so the

results have certain limitations. This study summarized and analyzed age, comorbidities, frailty, and other factors, as well as various prognostic factors selected by multivariate analysis. The findings are still valuable for guiding the treatment and determining the prognosis of CAP in the elderly population. We expect to obtain multicenter and large-sample data in future studies to confirm our research hypothesis.

Conclusions

In summary, frailty was very common in elderly patients with CAP, and frail patients were more likely to suffer from severe disease and with higher 1-year mortality compared with non-frail patients. Our findings suggest that frailty should be considered in routine clinical practice and the post-discharge management of patients with CAP.

Contributors Jia Luo, Wen Tang, Ying Sun, and Chun-Yan Jiang contributed to the conception and design of this study. Jia Luo and Wen Tang contributed to data collection. Wen Tang, Ying Sun, and Chun-Yan Jiang contributed to analyses and interpretation. Jia Luo and Wen Tang contributed to the preparation of the manuscript. The final version of the article was approved by all the authors.

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Competing interests: None declared.

Ethical approval: This study was approved by the ethics committee of Beijing

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Data sharing statement: Data could be shared after consultation with the author, E-mail: ann11121112@sina.com.

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Table 1. Characteristics of the study population by frail group at baseline

Characteristics	Total	Non-frail	Frail†	P values
N (%)	256	85 (33.2)	171 (66.8)	
Age median (IQR)	86 (81, 90)	83 (75, 87)	88 (84, 91)	<0.001 *
Sex, n (%)				
Female	76 (29.7)	17 (20.0)	59 (34.5)	0.017*
Male	180 (70.3)	68 (80.0)	112 (65.5)	
Smoking status				
Current-smoker	29 (11.3)	11 (12.9)	18 (10.5)	0.288
Ex-smoker	71 (27.7)	28 (32.9)	43 (25.1)	
Non-smoker	156 (60.9)	46 (54.1)	110 (64.3)	
BMI (kg/m^2) mean (SD)	22.9 (4.3)	24.2 (3.8)	22.3 (4.4)	0.001*
Barthel Index median (IQR)	65 (40, 95)	95 (85, 100)	50 (20, 70)	<0.001 *
CCI median (IQR)	4 (3, 5)	3 (2, 4)	4 (3, 6)	<0.001 *
MNA-SF median (IQR)	10 (7, 12)	12 (11, 14)	9 (7, 11)	<0.001 *
Malnutrition n(%)§	71 (27.7)	6 (7.1)	65 (38.0)	
SCAP‡, n (%)	57 (22.3)	8 (9.41)	49 (28.65)	<0.001 *
PCT (ng/ml) median (IQR)	0.28 (0.21, 0.44)	0.27 (0.20, 0.37)	0.29 (0.21, 0.55)	0.149
hs-CRP (mg/L) median (IQR)	25.89 (5.79, 61.41)	19.63 (4.19, 54.29)	27.08 (7.56, 62.43)	0.129

WBC (*10^9/L) median (IQR)	7.65 (5.57, 11.06)	7.02 (5.64,9.01)	8.02 (5.51, 12.33)	0.043*
HGB (g/L) median (IQR)	121 (108, 133)	127 (120, 136)	115 (100,128)	<0.001*
Scr (umol/L) median (IQR)	76.9 (61.6, 96.8)	78.6 (67.4, 90.5)	75.2 (59.5, 101.6)	0.720
BUN (mmol/L) median (IQR)	5.98 (4.58, 7.94)	5.99 (4.30, 7.01)	5.98 (4.79, 8.65)	0.039*
ALT (U/L) median (IQR)	14 (10, 22)	15 (11, 22)	13 (10, 21)	0.058
ALB (g/L) mean (SD)	32.46 (4.39)	34.38 (4.22)	31.50 (4.16)	<0.001*
PA (g/L) mean (SD)	16.92 (6.19)	18.74 (6.41)	15.98 (5.88)	0.001*
30-day mortality, n (%)	14 (5.5)	0 (0)	14 (8.19)	0.015*
1-year mortality, n (%)	43 (16.8)	0 (0)	43 (25.15)	<0.001*

Abbreviations: SD, standard deviation; IQR, inter-quartile range; BMI, Body Mass Index; CCI, Charlson's Comorbidity Index; MNA-SF, Mini Nutritional Assessment-Short Form; SCAP, severe community acquired pneumonia; PCT, procalcitonin; hs-CRP, high sensitivity C-reactive protein; WBC, the leukocyte count; HGB, hemoglobin; BUN, blood urea nitrogen; Scr, serum creatinine; ALT, alanine aminotransferase; ALB, albumin; PA, prealbumin.

* P values < 0.05.

† Frail: defined by Fried Phenotype score ≥ 3.

‡ SCAP: defined by the IDSA/ATS criteria (2007).

§ Malnutrition: defined by MNA-SF scores ≤ 7.

Table 2. Significant risk factors for 30-day mortality in patients with CAP in COX proportional hazards regression analyses (n =256)

	Univariate			Multivariate		
Variable	HR	95%CI	*P*-Value	HR	95%CI	*P*-Value
SCAP	52.01	6.80-398.09	<0.001	30.60	3.77-248.06	0.001
Malnutrition	0.84	0.73-0.97	0.015	1.11	0.90-1.35	0.330
Frail	2.58	1.42-4.69	0.002	1.83	0.88-3.81	0.108
CCI	1.41	1.19-1.67	<0.001	1.19	0.99-1.43	0.069

Data are shown as estimated HR (95% CIs) of the explanatory variables in the 30-day mortality group. Adjusted for: age, sex, disability, malnutrition, comorbidities, and the severity of CAP.

Abbreviations: HR, hazards ratio; CI, confidence interval; CCI, Charlson's Comorbidity Index; SCAP, severe community acquired pneumonia.

Table 3. Significant risk factors for 1-year mortality in patients with CAP in COX proportional hazards regression analyses (n =256)

	Univariate			Multivariate		
Variable	HR	95%CI	*P*-Value	HR	95%CI	*P*-Value
SCAP	13.32	6.81-26.04	<0.001	7.68	3.79-15.58	<0.001
BI	0.98	0.97-0.99	<0.001	1.01	0.99-1.02	0.352
BMI	0.93	0.87-1.00	0.038	1.07	0.98-1.16	0.128
Malnutrition	0.78	0.72-0.85	<0.001	0.94	0.81-1.10	0.424
Frail	3.41	2.32-5.03	<0.001	2.70	1.69-4.39	<0.001
CCI	1.40	1.26-1.55	<0.001	1.19	1.05-1.34	<0.001

Data are shown as estimated HR (95% CIs) of the explanatory variables in the 1-year mortality group. Adjusted for: age, sex, disability, malnutrition, comorbidities, and the severity of CAP.

Abbreviations: HR, hazards ratio; CI, confidence interval; SCAP, severe community acquired pneumonia; BI, Barthel Index; BMI, Body Mass Index; CCI, Charlson's Comorbidity Index.

Table 4. Characteristics of SCAP‡ stratified by frail group

Characteristics	Non-frail	Frail†	P values
N, n (%)	8 (14.0)	49 (86.0)	
Age median (IQR)	85 (82, 91)	89 (81, 92)	0.581
Sex, n (%)			
Female	0 (0)	11 (22.5)	0.053
Male	8 (100.0)	38 (77.6)	
BMI (kg/m^2) mean (SD)	22.95 (2.56)	21.59 (4.81)	0.249
Barthel Index median (IQR)	88 (59, 99)	35 (8, 68)	0.001*
CCI median (IQR)	4 (2, 5)	5 (3, 8)	0.129
MNA-SF mean (SD)	11 (3)	7 (3)	0.003*
PCT (ng/ml) median (IQR)	0.30 (0.21, 0.40)	0.31 (0.23, 1.74)	0.477
hs-CRP (mg/L) median (IQR)	33.52 (3.65, 154.94)	34.42 (19.08, 89.78)	0.928
WBC (*10^9/L) mean (SD)	8.45 (2.53)	10.83 (5.27)	0.218
HGB (g/L) median (IQR)	122 (106, 146)	114 (93,123)	0.179
Scr (umol/L) median (IQR)	103.5 (88.5, 121.1)	82.6 (62.1, 114.8)	0.161
BUN (mmol/L) median (IQR)	8.35 (6.86, 9.49)	7.98 (5.67, 12.07)	0.730
ALT (U/L) median (IQR)	16 (10, 27)	13 (10, 20)	0.557
ALB (g/L) median (IQR)	33.10 (31.75, 34.38)	30.00 (27.35, 32.85)	0.039*
PA (g/L) mean (SD)	18.56 (9.60)	14.44 (5.85)	0.118
30-day mortality, n (%)	0(0)	13(26.53)	0.034*
1-year mortality, n (%)	0(0)	31(63.27)	<0.001*

Abbreviations: SD, standard deviation; IQR, inter-quartile range; BMI, Body Mass Index; CCI, Charlson's Comorbidity Index; MNA-SF, Mini Nutritional Assessment-Short Form; SCAP, severe community acquired pneumonia; PCT, procalcitonin; hs-CRP, high sensitivity C-reactive protein; WBC, the leukocyte count; HGB, hemoglobin;

BUN, blood urea nitrogen; Scr, serum creatinine; ALT, alanine aminotransferase; ALB, albumin; PA, prealbumin.

⁎ P values < 0.05.

† Frail: defined by Fried Phenotype score ≥ 3.

‡ SCAP: defined by the IDSA/ATS criteria (2007).

Table 5. Significant risk factors for 1-year mortality in patients with SCAP in COX proportional hazards regression analyses (n =57)

	Univariate			Multivariate		
Variable	HR	95%CI	*P*-Value	HR	95%CI	*P*-Value
BI	0.99	0.98-1.00	0.046	1.00	0.99-1.02	0.875
Malnutrition	0.86	0.77-0.97	0.010	1.05	0.89-1.25	0.545
Frail	2.82	1.70-4.68	<0.001	2.870	1.58-4.96	<0.001
CCI	1.24	1.10-1.40	0.001	1.16	1.01-1.34	0.034

Data are shown as estimated HR (95% CIs) of the explanatory variables in the 1-year mortality group. Adjusted for: age, sex, disability, malnutrition, and comorbidities.

Abbreviations: HR, hazards ratio; CI, confidence interval; SCAP, severe community acquired pneumonia; BI, Barthel Index; CCI, Charlson's Comorbidity Index.

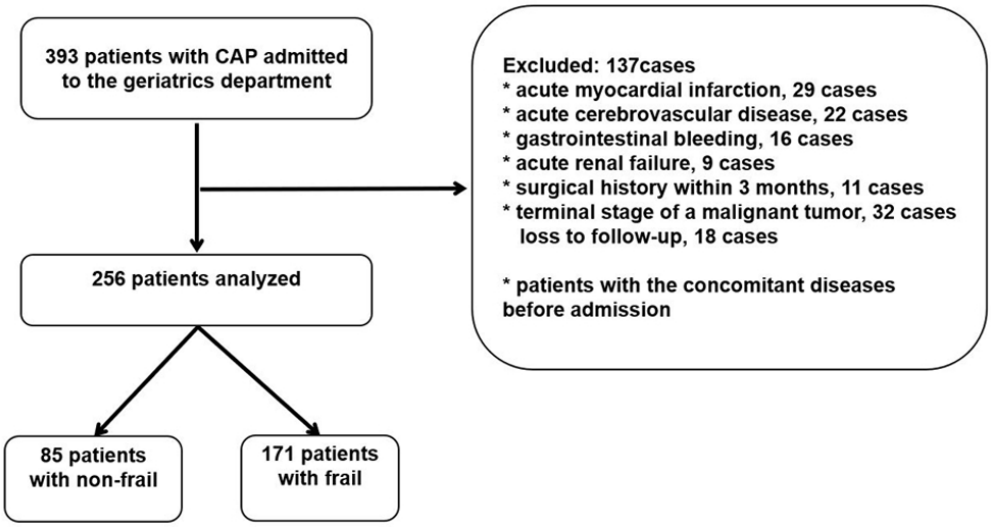

Figure 1.Flow chart of the study population

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Impact of frailty on 30-day and 1-year mortality in hospitalized elderly patients with community-acquired pneumonia: a prospective observational study

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1

Abstract

Objectives: This study evaluates the impact of frailty, which is a state of increased vulnerability to stressors, on 30-day and 1-year mortality among elderly patients with community-acquired pneumonia (CAP). The main hypothesis is that frailty is an independent predictor of prognosis in elderly CAP patients.

Design: Prospective, observational, follow-up cohort study.

Setting: A 2000-bed tertiary care hospital in Beijing, China.

Participants: Consecutive CAP patients aged ≥65 years admitted to the geriatric department of our hospital between September 2017 and February 2019.

Main outcome measures: The primary outcomes were all-cause mortality at 30 days and 1 year after hospital admission. The impact of frailty (defined by Frailty Phenotype) on 30-day and 1-year mortality of elderly patients with CAP was assessed by Cox regression analysis.

Results: The cohort included 256 patients. The median (IQR) age was 86 (81, 90) years, and 180 (70.3%) participants were men. A total of 171/256 (66.8%) patients were frail. The prevalence of frailty was significantly associated with older age, female gender, lower BMI, comorbidities, limitations in activities of daily living, and poor nutritional status. Frail participants were significantly more likely to have severe CAP than non-frail counterparts (28.65% vs. 9.41%, P<0.001). The 1-year mortality risk was approximately three-fold higher in frail patients (adjusted HR, 2.70; 95% CI, 1.69-4.39)

than non-frail patients. Subgroup analysis of patients with severe CAP showed that the 1-year mortality risk was approximately three-fold higher in the frail group (adjusted HR, 2.87; 95% CI, 1.58-4.96) than in the non-frail group. The association between frailty and 30-day mortality was not significant.

Conclusions: These findings suggest that frailty is strongly associated with severe CAP and higher 1-year mortality in elderly patients with CAP, and frailty should be detected early to improve the management of these patients.

Keywords: Community-acquired pneumonia; Frailty; Elderly; Prognosis.

Strengths and limitations of this study

1. This study evaluated frailty in elderly patients with community-acquired pneumonia (CAP).

2. The study analyzed the correlation between prognostic factors (age, disability, malnutrition, comorbidities, and CAP severity) and frailty by multivariate regression analysis and showed that frailty affected the prognosis of CAP.

3. Frailty was defined by Fried's Frailty Phenotype, which is well validated and simple to use.

4. The study was conducted in a single center and evaluated a small number of end-points.

5. The study included a small sample of older patients and did not evaluate the association between frailty and CAP in outpatients.

Introduction

Community-acquired pneumonia (CAP) is the most prevalent infectious disease in the elderly and is associated with high rates of mortality, morbidity, and high costs worldwide.[1, 2, 3, 4] In the United States, the incidence of CAP in the age group 65–79 years is 63 cases per 10,000 adults and increases to 164.3 cases per 10,000 adults in the age group >80 years.[5] Mortality from CAP increases with age. In 2012, the average mortality from pneumonia was 17.46 cases per 100,000 in all age groups in China, 23.55 cases per 100,000 in the age group 65–69 years, and nearly 36 times higher in the age group >85 years.[6]

Studies have shown that age, functional status, comorbidities, and malnutrition are strongly associated with poor prognosis in CAP patients,[4,6,7,8,9,10] and higher mortality in elderly patients with CAP underscores the need to identify novel, modifiable risk factors for poor outcomes. Particular attention has recently been directed to frail elderly patients. Frailty is associated with disabilities, comorbidities, and old age and is defined as a cumulative decline in multiple organ systems and loss of physiological reserves, increasing the vulnerability to adverse outcomes, including falls, hospitalization, and mortality.[11,12,13] Moreover, frailty is an independent risk factor for mortality in patients with acute and chronic diseases.[14,15] A European multicenter study assessed the impact of frailty (measured by the Clinical Frailty Scale) on intensive care unit (ICU) admission and 30-day mortality in 5021 elderly patients and observed that frailty was found in 43% of these patients and was independently related to 30-day survival (hazard ratio [HR], 1.54; 95% confidence interval [CI], 1.38-1.73, frail versus non-frail

patients).[16] A study evaluated the relationship between frailty and CAP in older patients and found that frailty increased hospitalization at 28 days after CAP diagnosis[17] and significantly predicted the risk of 1-month mortality.[18] Therefore, we hypothesized that frailty is positively correlated with CAP severity and mortality in elderly patients.

The objective of this study is to assess the prevalence of frailty in older patients with CAP, the association between frailty and CAP severity, and 30-day and 1-year mortality. This information may be useful for the early stratification of high-risk patients and the hierarchical management of modifiable factors to improve the prognosis of elderly patients with CAP.

Methods

1. Study design

We prospectively and consecutively enrolled elderly patients (aged ≥65 years) diagnosed with CAP in the geriatric department of our institution from September 2017 to February 2019. The exclusion criteria were complications, such as acute myocardial infarction, acute cerebrovascular disease, gastrointestinal bleeding, or acute renal failure; surgical history within 3 months; and terminal stage of a malignant tumor.

CAP was defined as pneumonia acquired outside the hospital by an immunocompetent individual. The criteria for diagnosing CAP were community-onset and the presence of new infiltrates on chest X-ray or computed tomography scan together with at least one of the following conditions: (i) new or increased cough

(productive, nonproductive, or accompanied by a change in sputum characteristics) with or without dyspnea, chest pain, or hemoptysis; (ii) fever; (iii) rales and/or signs of consolidation; (iv) peripheral WBC count >10,000 cells mm^{-3} or <4000 cells mm^{-3} with or without an increase in immature forms. Differential diagnosis included tuberculosis, lung cancer, noninfectious pulmonary interstitial disease, pulmonary edema, atelectasis, pulmonary embolism, pulmonary eosinophilic infiltration, and pulmonary vasculitis. The patients with these diagnoses were excluded.[6]

2. Baseline characteristics

The following parameters were evaluated within 24 hours of admission: age, sex, body mass index (BMI), smoking history, procalcitonin (PCT), high-sensitivity C-reactive protein (hs-CRP), white blood count (WBC), hemoglobin (HGB), alanine aminotransferase (ALT), albumin (ALB), prealbumin (PA), serum creatinine (Scr), and blood urea nitrogen (BUN). A comprehensive geriatric assessment (CGA), including frailty, comorbidities, and functional and nutritional status, was conducted by trained evaluators within 24 hours of admission.

3. Severity of CAP

Severe CAP (SCAP) was diagnosed according to criteria established by the Infectious Diseases Society of America and the American Thoracic Society,[19] and at least one major criterion or three minor criteria should be satisfied. The major criteria were the need for mechanical ventilation or the diagnosis of septic shock. The minor criteria were respiratory rate >130 breaths/min, arterial oxygen pressure/fraction of

inspired oxygen ratio <250 mmHg, multilobar infiltrates, confusion, BUN level >120 mg/dL, leukopenia resulting from infection, thrombocytopenia, hypothermia, or hypotension requiring aggressive fluid resuscitation.

4. Assessment of frailty

Frailty was assessed using the following Frailty Phenotype (FP) criteria: unintentional weight loss (10 lbs in the past 12 months), self-reported exhaustion, weakness (reduced grip strength), slow walking speed, and low physical activity.[20] The cut-off values were consistent with the original criteria. Each construct was considered present (score of 1) or absent (score of 0). The total score ranged from 0 to 5. As established previously, the presence and absence of frailty were defined as a score of $\geqslant$3 and $\leq$2, respectively.

5. Covariates

Comorbidity was evaluated with the Charlson Comorbidity Index (CCI).[21] The CCI is the sum of the weighted scores of the following chronic medical conditions: ischemic heart disease, congestive heart failure, cerebrovascular accident, peripheral vascular diseases, chronic lung diseases, diabetes, dementia, connective tissue diseases, renal diseases, liver diseases, hemiplegia, solid or hematological malignancy, and acquired immunodeficiency disease. A score of 1, 2, 3, or 6 is assigned to each disease, depending on severity.

Functional status was assessed by evaluating patients' ability to perform activities of daily living (ADLs) using the Barthel Index (BI).[22]

The nutritional status was assessed using the Mini Nutritional Assessment-Short Form questionnaire.[23] This questionnaire evaluates BMI, weight loss in the past 3 months, dietary changes, stress or acute illness, degree of mobility, and neuropsychiatric diseases. The total score is 14 points, and scores of 0-7 indicate malnutrition.

5. Follow-up and outcomes

All patients were followed for 1 year after hospital admission. Deaths were confirmed through surveillance or official death records. The primary outcomes were all-cause mortality at 30 days and 1 year after admission.

6. Statistical analysis

Statistical analyses were performed using IBM SPSS software version 23.0 (Chicago, USA). Continuous variables were expressed as the means ± standard deviation (SD) or interquartile range (IQR) and compared using Student's t-test or the Mann–Whitney U test. Categorical variables were compared using the chi-squared test or Fisher's exact test. The association between baseline frailty status and 30-day and 1-year all-cause mortality was analyzed using univariate and multivariate Cox proportional hazards regression models, and the results were expressed as hazard ratio (HR) and 95% confidence interval (CI). A two-tailed p-value of less than 0.05 was considered to indicate a statistically significant difference.

Patient and public involvement

Patients and the public were not involved in the study design, recruitment, or execution, and the participants were not be involved in disseminating the results. The study results will be provided to patients upon request, and aggregated data will be reported in project reports and research publications and meetings.

Results

In our cohort, 393 older patients with CAP were admitted to our department during the study period. Of these, 119 patients were excluded because of concomitant diseases, and 18 were lost to follow-up (Figure 1). A total of 256 patients with CAP aged 65-99 years were included in the final analysis. Demographic characteristics are presented in Table 1. The median age of the cohort was 86 (IQR, 81–90) years, and 180 (70.3%) patients were men. A total of 171 (66.8%) participants were frail, 71 (27.7%) patients were malnourished, and 57 (22.3%) participants had SCAP. All-cause mortality at 30 days and 1 year was 5.5% and 16.8%, respectively.

Frailty was significantly associated with older age, female gender, lower BMI, limitations in ADLs, comorbidities, and poor nutritional status. Frail participants were significantly more likely to have SCAP than non-frail counterparts (28.65% vs. 9.41%, P<0.001). Thirty-day and 1-year mortality was significantly higher in frail patients (0 vs. 8.19%, P=0.015; and 0 vs. 25.25%, P<0.001, respectively). The results of Cox proportional hazards regression are presented in Table 2. SCAP, frailty, malnutrition, and CCI were significantly associated with 30-day mortality in the univariate analysis, but only SCAP remained significant in the multivariate analysis (adjusted HR, 30.60;

95% CI, 3.77-248.06). The factors associated with 1-year mortality in the multivariable analysis were SCAP (adjusted HR, 7.68; 95% CI, 3.79-15.58), frailty (adjusted HR, 2.70; 95% CI, 1.69-4.39), and CCI (adjusted HR, 1.19; 95% CI, 1.05-1.34).

Subgroup analysis by frailty status showed that eight (14%) patients were non-frail and 49 patients (86%) were frail. The frail group presented worse functional and nutritional status and higher 30-day and 1-year mortality (Supplementary Table). In the multivariate analysis of patients with SCAP, 1-year mortality risk was approximately three-fold higher in the frail group (adjusted HR, 2.87; 95% CI, 1.58-4.96) than in the non-frail group, and 1-year mortality risk was 16% higher among those with more comorbidities (adjusted HR, 1.16; 95% CI, 1.01-1.34) (Table 3). Only CCI was significantly correlated with 30-day mortality in the univariate analysis, and none of the study variables were associated with 30-day mortality in the multivariate analysis.

Discussion

The results showed that frail older patients with CAP were significantly more likely to have SCAP and had a significantly higher 30-day and 1-year mortality risk than non-frail patients. In addition, frailty was an independent risk factor for 1-year mortality after adjusting for age, sex, disability, malnutrition, comorbidities, and CAP severity but was not an independent risk factor for 30-day mortality.

The incidence of CAP increases with age, and CAP increases the risk of morbidity and mortality. Mortality is significantly higher in elderly patients with CAP than in the general population.[4,9] All-cause mortality at 30 days and 1 year among elderly patients

with CAP in our cohort was 5.5% and 16.8%, respectively. Known independent prognostic factors for CAP mortality are age, comorbidities, functional status, microbial etiology, and early antibiotic treatment.[9,10,24,25] However, some studies reported that age *per se* was not an independent predictor of CAP mortality in the elderly population with pneumonia.[26,27] Frailty is an age-related disease associated with disabilities, comorbidities, and advanced age, and is characterized by a decline in physiological functions across multiple organ systems and increased vulnerability to stressors,[20,28,29] which increases the risk of adverse health outcomes, including falls, disability, hospitalization, institutionalization, and death. Various conditions, including malnutrition, sarcopenia, gait impairment, chronic inflammation, polypharmacy, cardiovascular changes, and morbidity, may cause frailty. [30,31,32] Accordingly, in our sample, all patients who died within 30 days or 1 year were frail.

Frailty was more prevalent in women, which is consistent with a previous study.[30] In addition, frail patients had older age, more comorbidities, poor nutritional and functional status, and limited ability to perform ADLs. Poor nutritional status, including hypoalbuminemia, hypoproteinemia, malnourishment, and a low nutritional score, is a strong predictor of mortality in CAP patients.[33,34] However, in our cohort, there was no significant association between nutritional status and 30-day or 1-year mortality in the multivariate analysis (adjusted HR, 1.11; 95% CI, 0.90-1.35; adjusted HR, 0.94; 95% CI, 0.81-1.10, respectively). Some studies have shown that the definition, diagnosis, and treatment of frailty and malnutrition overlap.[30,32,35] Malnutrition is a physiological condition that predisposes to the occurrence and development of frailty.[31] In our study,

frailty was defined as a syndrome that affects multiple organ systems and was a strong predictor of long-term mortality, and this multidimensional nature may explain why frailty, but not malnutrition and disability, was significantly associated with higher mortality in the multivariate analysis.

Our results indicated that frailty was common in elderly patients with CAP (prevalence of 66.8%) and was closely linked to disease severity; furthermore, frailty increased 1-year mortality risk nearly three-fold compared with the absence of frailty (adjusted HR, 2.70; 95% CI, 1.69-4.39). A study evaluated patient outcomes at 1 year after the diagnosis of CAP and showed that age ⩾65 years, nursing home residency, and comorbidity were positively associated with 1-year mortality.[36] Another study found that the risk of CAP mortality was more strongly correlated with underlying diseases than with CAP severity.[25] However, these studies did not assess the effect of frailty on CAP prognosis. The results of our study demonstrated that frailty was independently associated with 1-year mortality after adjusting for risk factors, suggesting that frailty could accurately predict adverse outcomes.

Our findings suggest that frail patients are more likely to have SCAP, and frailty is positively correlated to the risk of 1-year mortality. Since the clinical presentation of pneumonia may be atypical in the elderly, clinicians should suspect pneumonia in the presence of symptoms such as falls, altered mental status, fatigue, delirium, and anorexia to avoid complications associated with delayed diagnosis and therapy.[37] With respect to clinical decision-making and planning of health services, it is important to identify frailty in elderly CAP patients to better stratify the risk of adverse outcomes

and implement treatments tailored to individual needs, including invasive diagnostic procedures and therapies and the type of care at the late stage of the disease. A Korean study found that frailty was independently associated with do-not-resuscitate orders and healthcare transitions, even after adjusting for sepsis and pneumonia severity.[38] An international multidisciplinary group proposed a CGA[39] adapted to the emergency department context to assess frailty in elderly patients.[16,40] Although many physicians and intensivists do not currently perform CGAs in critically ill patients with infectious diseases, demographic shifts may require addressing this issue promptly. Moreover, frailty is a dynamic state and can be reversed.[41] Preventing frailty is possible, especially during onset, and the early diagnosis of this condition is crucial to improve therapeutic efficacy and the post-discharge management of elderly patients with CAP.[11]

This study has limitations. First, the results were not compared with data from other hospitals and regions. Second, the number of patients and end-point events was small. Third, the study did not evaluate the association between frailty and CAP in outpatients; therefore, the results cannot be generalized to other patient groups.

This study adjusted for confounding factors and demonstrated that frailty strongly affected the long-term prognosis of CAP patients. These data can contribute to the long-term management of frailty in CAP patients.

Conclusions

Frailty is very common in elderly patients with CAP and increases the risk of 1-year

mortality from CAP and SCAP. Our findings suggest that frailty should be evaluated in routine clinical practice to improve the post-discharge management of older patients with CAP.

Contributors Jia Luo, Wen Tang, Ying Sun, and Chun-Yan Jiang conceived and designed the study. Jia Luo and Wen Tang collected data. Wen Tang, Ying Sun, and Chun-Yan Jiang analyzed and interpreted data. Jia Luo and Wen Tang wrote the manuscript. All authors approved the final manuscript.

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Ethical approval: This study was approved by the research ethics committee of Beijing Friendship Hospital and Capital Medical University and conformed to the ethical guidelines of the Declaration of Helsinki (Project No. 2018-P2-138-01). All patients provided informed consent before the commencement of the study.

Data sharing: Data are available with the first author (e-mail: ann11121112@sina.com).

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Table 1. Baseline characteristics of the study population according to frailty status.

Characteristics	Total cohort	Non-frail	Frail†	P-values
N (%)	256	85 (33.2)	171 (66.8)	
Age, median (IQR)	86 (81, 90)	83 (75, 87)	88 (84, 91)	<0.001*
Sex, n (%)				
Female	76 (29.7)	17 (20.0)	59 (34.5)	0.017*
Male	180 (70.3)	68 (80.0)	112 (65.5)	
Smoking status, n (%)				
Current	29 (11.3)	11 (12.9)	18 (10.5)	0.288
Previous	71 (27.7)	28 (32.9)	43 (25.1)	
Never	156 (60.9)	46 (54.1)	110 (64.3)	
BMI (kg/m^2), mean (SD)	22.9 (4.3)	24.2 (3.8)	22.3 (4.4)	0.001*
Barthel Index, median (IQR)	65 (40, 95)	95 (85, 100)	50 (20, 70)	<0.001*
CCI, median (IQR)	4 (3, 5)	3 (2, 4)	4 (3, 6)	<0.001*
MNA-SF, median (IQR)	10 (7, 12)	12 (11, 14)	9 (7, 11)	<0.001*
Malnutrition, n (%)§	71 (27.7)	6 (7.1)	65 (38.0)	
SCAP‡, n (%)	57 (22.3)	8 (9.41)	49 (28.65)	<0.001*
PCT (ng/mL), median (IQR)	0.28 (0.21, 0.44)	0.27 (0.20, 0.37)	0.29 (0.21, 0.55)	0.149
hs-CRP (mg/L), median (IQR)	25.89 (5.79, 61.41)	19.63 (4.19, 54.29)	27.08 (7.56, 62.43)	0.129
WBC (*10^9/L), median (IQR)	7.65 (5.57, 11.06)	7.02 (5.64,9.01)	8.02 (5.51, 12.33)	0.043*
HGB (g/L), median (IQR)	121 (108, 133)	127 (120, 136)	115 (100,128)	<0.001*

Scr (μmol/L), median (IQR)	76.9 (61.6, 96.8)	78.6 (67.4, 90.5)	75.2 (59.5, 101.6)	0.720
BUN (mmol/L), median (IQR)	5.98 (4.58, 7.94)	5.99 (4.30, 7.01)	5.98 (4.79, 8.65)	0.039*
ALT (U/L), median (IQR)	14 (10, 22)	15 (11, 22)	13 (10, 21)	0.058
ALB (g/L), mean (SD)	32.46 (4.39)	34.38 (4.22)	31.50 (4.16)	<0.001*
PA (g/L), mean (SD)	16.92 (6.19)	18.74 (6.41)	15.98 (5.88)	0.001*
30-day mortality, n (%)	14 (5.5)	0 (0)	14 (8.19)	0.015*
1-year mortality, n (%)	43 (16.8)	0 (0)	43 (25.15)	<0.001*

Abbreviations: SD, standard deviation; IQR, inter-quartile range; BMI, body mass index; CCI, Charlson's Comorbidity Index; MNA-SF, Mini Nutritional Assessment-Short Form; SCAP, severe community-acquired pneumonia; PCT, procalcitonin; hs-CRP, high sensitivity C-reactive protein; WBC, white blood cell count; HGB, hemoglobin; BUN, blood urea nitrogen; Scr, serum creatinine; ALT, alanine aminotransferase; ALB, albumin; PA, prealbumin.

* P < 0.05.

† Frailty was defined as Fried Phenotype scores ≥ 3.

‡ SCAP was defined by IDSA/ATS criteria (2007).

§ Malnutrition was defined as MNA-SF scores ≤ 7.

Table 2. Significant risk factors for 30-day and 1-year mortality in patients with community-acquired pneumonia in COX proportional hazards regression analyses (n=256).

	Univariate			Multivariate		
Variable	HR	95% CI	P-Value	HR	95% CI	P-Value
30-day mortality						
SCAP	52.01	6.80-398.09	<0.001	30.60	3.77-248.06	0.001
Malnutrition	0.84	0.73-0.97	0.015	1.11	0.90-1.35	0.330
Frailty	2.58	1.42-4.69	0.002	1.83	0.88-3.81	0.108
CCI	1.41	1.19-1.67	<0.001	1.19	0.99-1.43	0.069
1-year mortality						
SCAP	13.32	6.81-26.04	<0.001	7.68	3.79-15.58	<0.001
BI	0.98	0.97-0.99	<0.001	1.01	0.99-1.02	0.352
BMI	0.93	0.87-1.00	0.038	1.07	0.98-1.16	0.128
Malnutrition	0.78	0.72-0.85	<0.001	0.94	0.81-1.10	0.424
Frailty	3.41	2.32-5.03	<0.001	2.70	1.69-4.39	<0.001
CCI	1.40	1.26-1.55	<0.001	1.19	1.05-1.34	<0.001

Data are estimated hazard ratios and 95% confidence intervals of the explanatory variables in the 30-day and 1-year mortality group. Data were adjusted for age, sex, disability, malnutrition, comorbidities, and the severity of CAP.

Abbreviations: HR, hazards ratio; CI, confidence interval; SCAP, severe community-acquired pneumonia; BI, Barthel Index; BMI, body mass index; CCI, Charlson's Comorbidity Index.

Table 3. Significant risk factors for 1-year mortality in patients with severe community-acquired pneumonia in COX proportional hazards regression analyses (n=57).

	Univariate			Multivariate		
Variable	HR	95% CI	P-value	HR	95% CI	P-value
BI	0.99	0.98–1.00	0.046	1.00	0.99–1.02	0.875
Malnutrition	0.86	0.77–0.97	0.010	1.05	0.89–1.25	0.545
Frailty	2.82	1.70–4.68	<0.001	2.87	1.58–4.96	<0.001
CCI	1.24	1.10–1.40	0.001	1.16	1.01–1.34	0.034

Data are estimated hazard ratios and 95% confidence intervals of the explanatory variables in the 1-year mortality group. Data were adjusted for age, sex, disability, malnutrition, and comorbidities.

Abbreviations: HR, hazards ratio; CI, confidence interval; SCAP, severe community-acquired pneumonia; BI, Barthel Index; CCI, Charlson's Comorbidity Index.

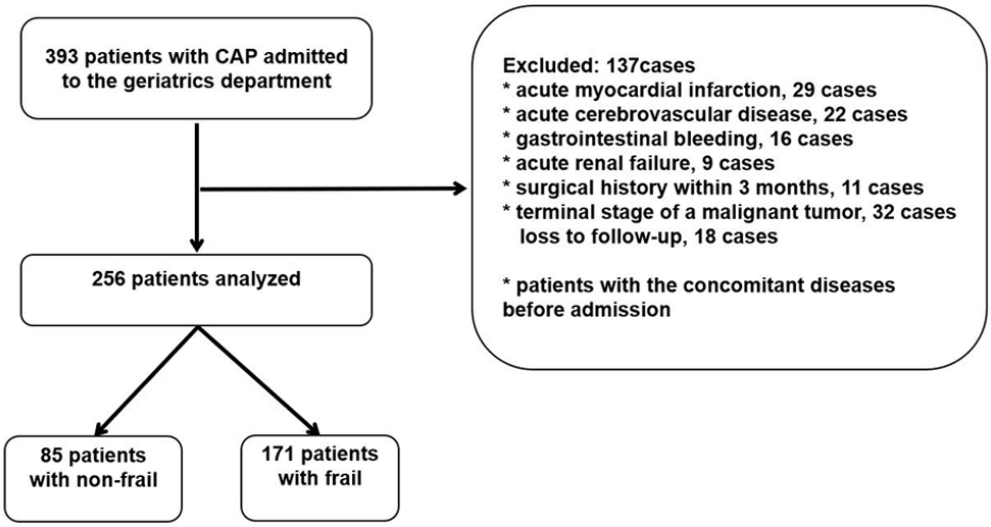

Figure 1.Flow chart of the study population

Supplementary Table. Characteristics of severe community-acquired pneumonia‡ stratified by frailty status.

Characteristics	Non-frail	Frail†	P-values
N, n (%)	8 (14.0)	49 (86.0)	
Age, median (IQR)	85 (82–91)	89 (81–92)	0.581
Sex, n (%)			
Female	0 (0)	11 (22.5)	0.053
Male	8 (100)	38 (77.6)	
BMI (kg/m^2), mean (SD)	22.95 (2.56)	21.59 (4.81)	0.249
Barthel Index, median (IQR)	88 (59–99)	35 (8–68)	0.001*
CCI, median (IQR)	4 (2–5)	5 (3–8)	0.129
MNA-SF, mean (SD)	11 (3)	7 (3)	0.003*
PCT (ng/mL), median (IQR)	0.30 (0.21–0.40)	0.31 (0.23–1.74)	0.477
hs-CRP (mg/L), median (IQR)	33.52 (3.65–154.94)	34.42 (19.08–89.78)	0.928
WBC (*10^9/L), mean (SD)	8.45 (2.53)	10.83 (5.27)	0.218
HGB (g/L), median (IQR)	122 (106–146)	114 (93–123)	0.179
Scr (μmol/L), median (IQR)	103.5 (88.5–121.1)	82.6 (62.1–114.8)	0.161
BUN (mmol/L), median (IQR)	8.35 (6.86–9.49)	7.98 (5.67–12.07)	0.730
ALT (U/L), median (IQR)	16 (10–27)	13 (10–20)	0.557
ALB (g/L), median (IQR)	33.10 (31.75–34.38)	30.00 (27.35–32.85)	0.039*
PA (g/L), mean (SD)	18.56 (9.60)	14.44 (5.85)	0.118
30-day mortality, n (%)	0 (0)	13 (26.53)	0.034*
1-year mortality, n (%)	0 (0)	31 (63.27)	<0.001*

Abbreviations: SD, standard deviation; IQR, inter-quartile range; BMI, body mass index; CCI, Charlson's Comorbidity Index; MNA-SF, Mini Nutritional Assessment-Short Form; PCT, procalcitonin; hs-CRP, high-sensitivity C-reactive

protein; WBC, white blood cell count; HGB, hemoglobin; BUN, blood urea nitrogen; Scr, serum creatinine; ALT, alanine aminotransferase; ALB, albumin; PA, prealbumin.

$\ast$ $P < 0.05$.

† Frailty was defined as Fried Phenotype scores ≥ 3.

‡ Defined by IDSA/ATS criteria (2007).

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Impact of frailty on 30-day and 1-year mortality in hospitalized elderly patients with community-acquired pneumonia: a prospective observational study

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Abstract

Objectives: This study evaluates the impact of frailty, which is a state of increased vulnerability to stressors, on 30-day and 1-year mortality among elderly patients with community-acquired pneumonia (CAP). The main hypothesis is that frailty is an independent predictor of prognosis in elderly CAP patients.

Design: Prospective, observational, follow-up cohort study.

Setting: A 2000-bed tertiary care hospital in Beijing, China.

Participants: Consecutive CAP patients aged ≥65 years admitted to the geriatric department of our hospital between September 2017 and February 2019.

Main outcome measures: The primary outcomes were all-cause mortality at 30 days and 1 year after hospital admission. The impact of frailty (defined by Frailty Phenotype) on 30-day and 1-year mortality of elderly patients with CAP was assessed by Cox regression analysis.

Results: The cohort included 256 patients. The median (IQR) age was 86 (81, 90) years, and 180 (70.3%) participants were men. A total of 171/256 (66.8%) patients were frail. The prevalence of frailty was significantly associated with older age, female gender, lower BMI, comorbidities, limitations in activities of daily living, and poor nutritional status. Frail participants were significantly more likely to have severe CAP than non-frail counterparts (28.65% vs. 9.41%, P<0.001). The 1-year mortality risk was approximately three-fold higher in frail patients (adjusted HR, 2.70; 95% CI, 1.69-4.39) than non-frail patients. Subgroup analysis of patients with severe CAP showed that the

1-year mortality risk was approximately three-fold higher in the frail group (adjusted HR, 2.87; 95% CI, 1.58-4.96) than in the non-frail group. The association between frailty and 30-day mortality was not significant.

Conclusions: These findings suggest that frailty is strongly associated with severe CAP and higher 1-year mortality in elderly patients with CAP, and frailty should be detected early to improve the management of these patients.

Keywords: Community-acquired pneumonia; Frailty; Elderly; Prognosis.

Strengths and limitations of this study

1. This study evaluated frailty in elderly patients with community-acquired pneumonia (CAP).

2. The study analyzed the correlation between prognostic factors (age, disability, malnutrition, comorbidities, and CAP severity) and frailty by multivariate regression analysis and showed that frailty affected the prognosis of CAP.

3. Frailty was defined by Fried's Frailty Phenotype, which is well validated and simple to use.

4. The study was conducted in a single center and evaluated a small number of end-points.

5. The study included a small sample of older patients and did not evaluate the association between frailty and CAP in outpatients.

Introduction

Community-acquired pneumonia (CAP) is the most prevalent infectious disease in the elderly and is associated with high rates of mortality, morbidity, and high costs worldwide.[1, 2, 3, 4] In the United States, the incidence of CAP in the age group 65–79 years is 63 cases per 10,000 adults and increases to 164.3 cases per 10,000 adults in the age group >80 years.[5] Mortality from CAP increases with age. In 2012, the average mortality from pneumonia was 17.46 cases per 100,000 in all age groups in China, 23.55 cases per 100,000 in the age group 65–69 years, and nearly 36 times higher in the age group >85 years.[6]

Studies have shown that age, functional status, comorbidities, and malnutrition are strongly associated with poor prognosis in CAP patients,[4,6,7,8,9,10] and higher mortality in elderly patients with CAP underscores the need to identify novel, modifiable risk factors for poor outcomes. Particular attention has recently been directed to frail elderly patients. Frailty is associated with disabilities, comorbidities, and old age and is defined as a cumulative decline in multiple organ systems and loss of physiological reserves, increasing the vulnerability to adverse outcomes, including falls, hospitalization, and mortality.[11,12,13] Moreover, frailty is an independent risk factor for mortality in patients with acute and chronic diseases.[14,15] A European multicenter study assessed the impact of frailty (measured by the Clinical Frailty Scale) on intensive care unit (ICU) admission and 30-day mortality in 5021 elderly patients and observed that frailty was found in 43% of these patients and was independently related to 30-day survival (hazard ratio [HR], 1.54; 95% confidence interval [CI], 1.38-1.73, frail versus non-frail

patients).[16] A study evaluated the relationship between frailty and CAP in older patients and found that frailty was associated with increased hospitalization at 28 days after CAP diagnosis[17] and significantly predicted the risk of 1-month mortality.[18] Therefore, we hypothesized that frailty is positively correlated with CAP severity and mortality in elderly patients.

The objective of this study was to assess the prevalence of frailty in older patients with CAP, the association between frailty and CAP severity, and 30-day and 1-year mortality. This information may be useful for the early stratification of high-risk patients and the hierarchical management of modifiable factors to improve the prognosis of elderly patients with CAP.

Methods

1. Study design

We prospectively and consecutively enrolled elderly patients (aged ≥65 years) diagnosed with CAP in the geriatric department of our institution from September 2017 to February 2019. The exclusion criteria were complications, such as acute myocardial infarction, acute cerebrovascular disease, gastrointestinal bleeding, or acute renal failure; surgical history within 3 months; and terminal stage of a malignant tumor (Figure 1).

CAP was defined as pneumonia acquired outside the hospital by an immunocompetent individual. The criteria for diagnosing CAP were community-onset and the presence of new infiltrates on chest X-ray or computed tomography scan

together with at least one of the following conditions: (i) new or increased cough (productive, nonproductive, or accompanied by a change in sputum characteristics) with or without dyspnea, chest pain, or hemoptysis; (ii) fever; (iii) rales and/or signs of consolidation; (iv) peripheral WBC count >10,000 cells mm^{-3} or <4000 cells mm^{-3} with or without an increase in immature forms. Differential diagnosis included tuberculosis, lung cancer, noninfectious pulmonary interstitial disease, pulmonary edema, atelectasis, pulmonary embolism, pulmonary eosinophilic infiltration, and pulmonary vasculitis. The patients with these diagnoses were excluded.[6]

2. Baseline characteristics

The following parameters were evaluated within 24 hours of admission: age, sex, body mass index (BMI), smoking history, procalcitonin (PCT), high-sensitivity C-reactive protein (hs-CRP), white blood count (WBC), hemoglobin (HGB), alanine aminotransferase (ALT), albumin (ALB), prealbumin (PA), serum creatinine (Scr), and blood urea nitrogen (BUN). A comprehensive geriatric assessment (CGA), including frailty, comorbidities, and functional and nutritional status, was conducted by trained evaluators within 24 hours of admission.

3. Severity of CAP

Severe CAP (SCAP) was diagnosed according to criteria established by the Infectious Diseases Society of America and the American Thoracic Society,[19] and at least one major criterion or three minor criteria should be satisfied. The major criteria were the need for mechanical ventilation or the diagnosis of septic shock. The minor

criteria were respiratory rate >130 breaths/min, arterial oxygen pressure/fraction of inspired oxygen ratio <250 mmHg, multilobar infiltrates, confusion, BUN level >120 mg/dL, leukopenia resulting from infection, thrombocytopenia, hypothermia, or hypotension requiring aggressive fluid resuscitation.

4. Assessment of frailty

Frailty was assessed using the following Frailty Phenotype (FP) criteria: unintentional weight loss (4.5kg in the past 12 months), self-reported exhaustion, weakness (reduced grip strength), slow walking speed, and low physical activity.[20] The cut-off values were consistent with the original criteria. Each construct was considered present (score of 1) or absent (score of 0). The total score ranged from 0 to 5. As established previously, the presence and absence of frailty were defined as a score of $\geqslant$3 and $\leq$2, respectively.

5. Covariates

Comorbidity was evaluated with the Charlson Comorbidity Index (CCI).[21] The CCI is the sum of the weighted scores of the following chronic medical conditions: ischemic heart disease, congestive heart failure, cerebrovascular accident, peripheral vascular diseases, chronic lung diseases, diabetes, dementia, connective tissue diseases, renal diseases, liver diseases, hemiplegia, solid or hematological malignancy, and acquired immunodeficiency disease. A score of 1, 2, 3, or 6 is assigned to each disease, depending on severity.

Functional status was assessed by evaluating patients' ability to perform activities

of daily living (ADLs) using the Barthel Index (BI).[22]

Nutritional status was assessed using the Mini Nutritional Assessment-Short Form questionnaire.[23] This questionnaire evaluates BMI, weight loss in the past 3 months, dietary changes, stress or acute illness, degree of mobility, and neuropsychiatric diseases. The total score is 14 points, and scores of 0-7 indicate malnutrition.

5. Follow-up and outcomes

All patients were followed for 1 year after hospital admission. Deaths were confirmed through surveillance or official death records. The primary outcomes were all-cause mortality at 30 days and 1 year after admission.

6. Statistical analysis

Statistical analyses were performed using IBM SPSS software version 23.0 (Chicago, USA). Continuous variables were expressed as the means ± standard deviation (SD) or interquartile range (IQR) and compared using Student's t-test or the Mann–Whitney U test. Categorical variables were compared using the chi-squared test or Fisher's exact test. The association between baseline frailty status and 30-day and 1-year all-cause mortality was analyzed using univariate and multivariate Cox proportional hazards regression models, and the results were expressed as hazard ratio (HR) and 95% confidence interval (CI). A two-tailed p-value of less than 0.05 was considered to indicate a statistically significant difference.

Patient and public involvement

Patients and the public were not involved in the study design, recruitment, or execution, and the participants were not be involved in disseminating the results. The study results will be provided to patients upon request, and aggregated data will be reported in project reports and research publications and meetings.

Results

In our cohort, 393 older patients with CAP were admitted to our department during the study period. Of these, 119 patients were excluded because of concomitant diseases, and 18 were lost to follow-up (Figure 1). A total of 256 patients with CAP aged 65-99 years were included in the final analysis. Demographic characteristics are presented in Table 1. The median age of the cohort was 86 (IQR, 81–90) years, and 180 (70.3%) patients were men. A total of 171 (66.8%) participants were frail, 71 (27.7%) patients were malnourished, and 57 (22.3%) participants had SCAP. All-cause mortality at 30 days and 1 year was 5.5% and 16.8%, respectively.

Frailty was significantly associated with older age, female gender, lower BMI, limitations in ADLs, comorbidities, and poor nutritional status. Frail participants were significantly more likely to have SCAP than non-frail counterparts (28.65% vs. 9.41%, P<0.001). Thirty-day and 1-year mortality was significantly higher in frail patients (0 vs. 8.19%, P=0.015; and 0 vs. 25.25%, P<0.001, respectively). The results of Cox proportional hazards regression are presented in Table 2. SCAP, frailty, malnutrition, and CCI were significantly associated with 30-day mortality in the univariate analysis, but only SCAP remained significant in the multivariate analysis (adjusted HR, 30.60;

95% CI, 3.77-248.06). The factors associated with 1-year mortality in the multivariable analysis were SCAP (adjusted HR, 7.68; 95% CI, 3.79-15.58), frailty (adjusted HR, 2.70; 95% CI, 1.69-4.39), and CCI (adjusted HR, 1.19; 95% CI, 1.05-1.34).

Subgroup analysis of patients with SCAP by frailty status showed that eight (14%) patients were non-frail and 49 patients (86%) were frail. The frail group presented significantly worse functional and nutritional status and higher 30-day and 1-year mortality (Supplementary Table). In the multivariate analysis of patients with SCAP, 1-year mortality risk was approximately three-fold higher in the frail group (adjusted HR, 2.87; 95% CI, 1.58-4.96) than in the non-frail group, and 1-year mortality risk was 16% higher among those with more comorbidities (adjusted HR, 1.16; 95% CI, 1.01-1.34) (Table 3). Only CCI was significantly correlated with 30-day mortality (HR, 1.21; 95% CI, 1.02-1.43).

Discussion

The results showed that frail older patients with CAP were significantly more likely to have SCAP and had a significantly higher 30-day and 1-year mortality risk than non-frail patients. In addition, frailty was an independent risk factor for 1-year mortality after adjusting for age, sex, disability, malnutrition, comorbidities, and CAP severity but was not an independent risk factor for 30-day mortality.

The incidence of CAP increases with age, and CAP increases the risk of morbidity and mortality. Mortality is significantly higher in elderly patients with CAP than in the general population.[4,9] All-cause mortality at 30 days and 1 year among elderly patients

with CAP in our cohort was 5.5% and 16.8%, respectively. Known independent prognostic factors for CAP mortality are age, comorbidities, functional status, microbial etiology, and early antibiotic treatment.[9,10,24,25] However, some studies reported that age *per se* was not an independent predictor of CAP mortality in the elderly population with pneumonia.[26,27] Frailty is an age-related disease associated with disabilities, comorbidities, and advanced age, and is characterized by a decline in physiological functions across multiple organ systems and increased vulnerability to stressors,[20,28,29] which increases the risk of adverse health outcomes, including falls, disability, hospitalization, institutionalization, and death. Various conditions, including malnutrition, sarcopenia, gait impairment, chronic inflammation, polypharmacy, cardiovascular changes, and morbidity, may cause frailty. [30,31,32] Accordingly, in our sample, all patients who died within 30 days or 1 year were frail.

Frailty was more prevalent in women in our study, which is consistent with a previous study.[30] In addition, frail patients had significantly older age, more comorbidities, poor nutritional and functional status, and limited ability to perform ADLs. Poor nutritional status, including hypoalbuminemia, hypoproteinemia, malnourishment, and a low nutritional score, is a strong predictor of mortality in CAP patients.[33,34] However, in our cohort, there was no significant association between nutritional status and 30-day or 1-year mortality in the multivariate analysis (adjusted HR, 1.11; 95% CI, 0.90-1.35; adjusted HR, 0.94; 95% CI, 0.81-1.10, respectively). Some studies have shown that the definition, diagnosis, and treatment of frailty and malnutrition overlap.[30,32,35] Malnutrition is a physiological condition that predisposes to the occurrence and

development of frailty.[31] In our study, frailty was defined as a syndrome that affects multiple organ systems and was a strong predictor of long-term mortality, and this multidimensional nature may explain why frailty, but not malnutrition and disability, was significantly associated with higher mortality in the multivariate analysis.

Our results indicated that frailty was common in elderly patients with CAP (prevalence of 66.8%) and was closely linked to pneumonia severity; furthermore, frailty increased 1-year mortality risk nearly three-fold compared with the absence of frailty (adjusted HR, 2.70; 95% CI, 1.69-4.39). A study evaluated patient outcomes at 1 year after the diagnosis of CAP and showed that age ⩾65 years, nursing home residency, and comorbidity were positively associated with 1-year mortality.[36] Another study found that the risk of CAP mortality was more strongly correlated with underlying diseases than with CAP severity.[25] However, these studies did not assess the effect of frailty on CAP prognosis. The results of our study demonstrated that frailty was independently associated with 1-year mortality after adjusting for risk factors, suggesting that frailty could accurately predict adverse outcomes.

Our findings suggest that frail patients are more likely to have SCAP, and frailty is positively correlated to the risk of 1-year mortality. Since the clinical presentation of pneumonia may be atypical in the elderly, clinicians should suspect pneumonia in the presence of symptoms such as falls, altered mental status, fatigue, delirium, and anorexia to avoid complications associated with delayed diagnosis and therapy.[37] With respect to clinical decision-making and planning of health services, it is important to identify frailty in elderly CAP patients to better stratify the risk of adverse outcomes

and implement treatments tailored to individual needs, weighing up the risks and benefits of invasive diagnostic procedures and therapies, as well as taking into account end of life care needs for individuals with advanced frailty. A Korean study found that frailty was independently associated with do-not-resuscitate orders and healthcare transitions, even after adjusting for sepsis and pneumonia severity.[38] An international multidisciplinary group proposed a CGA[39] adapted to the emergency department context to assess frailty in elderly patients.[16,40] Although many physicians and intensivists do not currently perform CGAs in critically ill patients with infectious diseases, demographic shifts may require addressing this issue promptly. Moreover, frailty is a dynamic state and can be reversed.[41] Preventing frailty is possible, especially during onset, and the early diagnosis of this condition is crucial to improve therapeutic efficacy and the post-discharge management of elderly patients with CAP.[11]

This study has limitations. First, the results were not compared with data from other hospitals and regions. Second, the number of patients and end-point events was small. Third, the study did not evaluate the association between frailty and CAP in outpatients; therefore, the results cannot be generalized to other patient groups.

This study adjusted for confounding factors and demonstrated that frailty strongly affected the long-term prognosis of CAP patients. These data can contribute to the long-term management of frailty in CAP patients.

Conclusions

Frailty is very common in elderly patients with CAP and increases the risk of 1-year mortality from CAP and SCAP. Our findings suggest that frailty should be evaluated in routine clinical practice to improve the post-discharge management of older patients with CAP.

Contributors Jia Luo, Wen Tang, Ying Sun, and Chun-Yan Jiang conceived and designed the study. Jia Luo and Wen Tang collected data. Wen Tang, Ying Sun, and Chun-Yan Jiang analyzed and interpreted data. Jia Luo and Wen Tang wrote the manuscript. All authors approved the final manuscript.

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Competing interests: None declared.

Ethical approval: This study was approved by the research ethics committee of Beijing Friendship Hospital and Capital Medical University and conformed to the ethical guidelines of the Declaration of Helsinki (Project No. 2018-P2-138-01). All patients provided informed consent before the commencement of the study.

Data sharing: Data are available with the first author (e-mail: ann11121112@sina.com).

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Table 1. Baseline characteristics of the study population according to frailty status.

Characteristics	Total cohort	Non-frail	Frail†	P-values
N (%)	256	85 (33.2)	171 (66.8)	
Age, median (IQR)	86 (81, 90)	83 (75, 87)	88 (84, 91)	<0.001*
Sex, n (%)				
Female	76 (29.7)	17 (20.0)	59 (34.5)	0.017*
Male	180 (70.3)	68 (80.0)	112 (65.5)	
Smoking status, n (%)				
Current	29 (11.3)	11 (12.9)	18 (10.5)	0.288
Previous	71 (27.7)	28 (32.9)	43 (25.1)	
Never	156 (60.9)	46 (54.1)	110 (64.3)	
BMI (kg/m^2), mean (SD)	22.9 (4.3)	24.2 (3.8)	22.3 (4.4)	0.001*
Barthel Index, median (IQR)	65 (40, 95)	95 (85, 100)	50 (20, 70)	<0.001*
CCI, median (IQR)	4 (3, 5)	3 (2, 4)	4 (3, 6)	<0.001*
MNA-SF, median (IQR)	10 (7, 12)	12 (11, 14)	9 (7, 11)	<0.001*
Malnutrition, n (%)§	71 (27.7)	6 (7.1)	65 (38.0)	
SCAP‡, n (%)	57 (22.3)	8 (9.41)	49 (28.65)	<0.001*
PCT (ng/mL), median (IQR)	0.28 (0.21, 0.44)	0.27 (0.20, 0.37)	0.29 (0.21, 0.55)	0.149
hs-CRP (mg/L), median (IQR)	25.89 (5.79, 61.41)	19.63 (4.19, 54.29)	27.08 (7.56, 62.43)	0.129

WBC (*10^9/L), median (IQR)	7.65 (5.57, 11.06)	7.02 (5.64,9.01)	8.02 (5.51, 12.33)	0.043*
HGB (g/L), median (IQR)	121 (108, 133)	127 (120, 136)	115 (100,128)	<0.001*
Scr (μmol/L), median (IQR)	76.9 (61.6, 96.8)	78.6 (67.4, 90.5)	75.2 (59.5, 101.6)	0.720
BUN (mmol/L), median (IQR)	5.98 (4.58, 7.94)	5.99 (4.30, 7.01)	5.98 (4.79, 8.65)	0.039*
ALT (U/L), median (IQR)	14 (10, 22)	15 (11, 22)	13 (10, 21)	0.058
ALB (g/L), mean (SD)	32.46 (4.39)	34.38 (4.22)	31.50 (4.16)	<0.001*
PA (g/L), mean (SD)	16.92 (6.19)	18.74 (6.41)	15.98 (5.88)	0.001*
30-day mortality, n (%)	14 (5.5)	0 (0)	14 (8.19)	0.015*
1-year mortality, n (%)	43 (16.8)	0 (0)	43 (25.15)	<0.001*

Abbreviations: SD, standard deviation; IQR, inter-quartile range; BMI, body mass index; CCI, Charlson's Comorbidity Index; MNA-SF, Mini Nutritional Assessment-Short Form; SCAP, severe community-acquired pneumonia; PCT, procalcitonin; hs-CRP, high sensitivity C-reactive protein; WBC, white blood cell count; HGB, hemoglobin; BUN, blood urea nitrogen; Scr, serum creatinine; ALT, alanine aminotransferase; ALB, albumin; PA, prealbumin.

* P < 0.05.

† Frailty was defined as Fried Phenotype scores ≥ 3.

‡ SCAP was defined by IDSA/ATS criteria (2007).

§ Malnutrition was defined as MNA-SF scores ≤ 7.

Table 2. Factors associate with 30-day and 1-year mortality in patients with community-acquired pneumonia in COX proportional hazards regression analyses (n=256).

	Univariate			Multivariate		
Variable	HR	95% CI	P-Value	HR	95% CI	P-Value
30-day mortality						
SCAP	52.01	6.80-398.09	<0.001	30.60	3.77-248.06	0.001*
BI	0.99	0.97-1.00	0.101	_	_	_
BMI	0.97	0.86-1.09	0.609	_	_	_
Malnutrition	0.84	0.73-0.97	0.015	1.11	0.90-1.35	0.330
Frailty	2.58	1.42-4.69	0.002	1.83	0.88-3.81	0.108
CCI	1.41	1.19-1.67	<0.001	1.19	0.99-1.43	0.069
1-year mortality						
SCAP	13.32	6.81-26.04	<0.001	7.68	3.79-15.58	<0.001*
BI	0.98	0.97-0.99	<0.001	1.01	0.99-1.02	0.352
BMI	0.93	0.87-1.00	0.038	1.07	0.98-1.16	0.128
Malnutrition	0.78	0.72-0.85	<0.001	0.94	0.81-1.10	0.424
Frailty	3.41	2.32-5.03	<0.001	2.70	1.69-4.39	<0.001*
CCI	1.40	1.26-1.55	<0.001	1.19	1.05-1.34	<0.001*

Data are estimated hazard ratios and 95% confidence intervals of the explanatory variables in the 30-day and 1-year mortality group. Data were adjusted for age, sex, disability, malnutrition, comorbidities, and the severity of CAP.

Abbreviations: HR, hazards ratio; CI, confidence interval; SCAP, severe community-acquired pneumonia; BI, Barthel Index; BMI, body mass index; CCI, Charlson's Comorbidity Index.

* $P < 0.05$.

Table 3. Factors associate with 30-day and 1-year mortality in patients with severe community-acquired pneumonia in COX proportional hazards regression analyses (n=57).

	Univariate			Multivariate		
Variable	HR	95% CI	P-Value	HR	95% CI	P-Value
30-day mortality						
BI	1.00	0.99-1.02	0.899	_	_	_
BMI	1.04	0.92-1.18	0.507	_	_	_
Malnutrition	0.73	0.24-2.23	0.581	_	_	_
Frailty	26.61	0.04-16017.0	0.315	_	_	_
CCI	1.21	1.02–1.43	0.028	1.21	1.02-1.43	0.028*
1-year mortality						
BI	0.99	0.98–1.00	0.046	1.00	0.99–1.02	0.875
BMI	0.99	0.92-1.08	0.854	_	_	_
Malnutrition	0.86	0.77–0.97	0.010	1.05	0.89–1.25	0.545
Frailty	2.82	1.70–4.68	<0.001	2.87	1.58–4.96	<0.001*
CCI	1.24	1.10–1.40	0.001	1.16	1.01–1.34	0.034*

Data are estimated hazard ratios and 95% confidence intervals of the explanatory variables in the 1-year mortality group. Data were adjusted for age, sex, disability, malnutrition, and comorbidities.

Abbreviations: HR, hazards ratio; CI, confidence interval; SCAP, severe community-acquired pneumonia; BI, Barthel Index; CCI, Charlson's Comorbidity Index.

* P < 0.05.

Figure legend:

Figure1: Flowchart of patients excluded/included for the frailty assessment analyses in community-acquired pneumonia cohort.

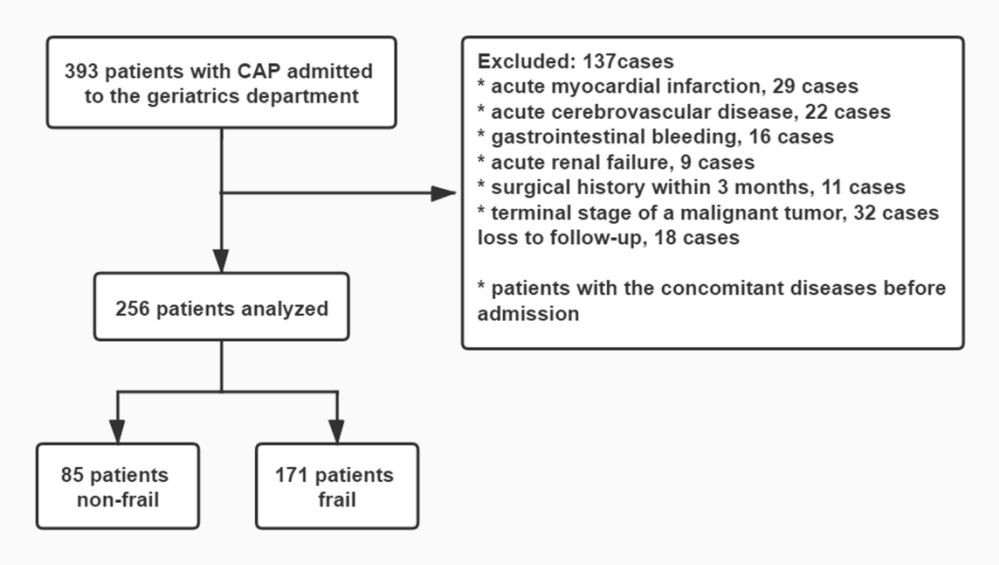

Figure1: Flowchart of patients excluded/included for the frailty assessment analyses in community-acquired pneumonia cohort.

Supplementary Table. Characteristics of severe community-acquired pneumonia‡ stratified by frailty status.

Characteristics	Non-frail	Frail†	P-values
N, n (%)	8 (14.0)	49 (86.0)	
Age, median (IQR)	85 (82–91)	89 (81–92)	0.581
Sex, n (%)			
Female	0 (0)	11 (22.5)	0.053
Male	8 (100)	38 (77.6)	
BMI (kg/m^2), mean (SD)	22.95 (2.56)	21.59 (4.81)	0.249
Barthel Index, median (IQR)	88 (59–99)	35 (8–68)	0.001*
CCI, median (IQR)	4 (2–5)	5 (3–8)	0.129
MNA-SF, mean (SD)	11 (3)	7 (3)	0.003*
PCT (ng/mL), median (IQR)	0.30 (0.21–0.40)	0.31 (0.23–1.74)	0.477
hs-CRP (mg/L), median (IQR)	33.52 (3.65–154.94)	34.42 (19.08–89.78)	0.928
WBC (*10^9/L), mean (SD)	8.45 (2.53)	10.83 (5.27)	0.218
HGB (g/L), median (IQR)	122 (106–146)	114 (93–123)	0.179
Scr (μmol/L), median (IQR)	103.5 (88.5–121.1)	82.6 (62.1–114.8)	0.161
BUN (mmol/L), median (IQR)	8.35 (6.86–9.49)	7.98 (5.67–12.07)	0.730
ALT (U/L), median (IQR)	16 (10–27)	13 (10–20)	0.557
ALB (g/L), median (IQR)	33.10 (31.75–34.38)	30.00 (27.35–32.85)	0.039*
PA (g/L), mean (SD)	18.56 (9.60)	14.44 (5.85)	0.118
30-day mortality, n (%)	0 (0)	13 (26.53)	0.034*
1-year mortality, n (%)	0 (0)	31 (63.27)	<0.001*

Abbreviations: SD, standard deviation; IQR, inter-quartile range; BMI, body mass index; CCI, Charlson's Comorbidity Index; MNA-SF, Mini Nutritional Assessment-Short Form; PCT, procalcitonin; hs-CRP, high-sensitivity C-reactive

protein; WBC, white blood cell count; HGB, hemoglobin; BUN, blood urea nitrogen; Scr, serum creatinine; ALT, alanine aminotransferase; ALB, albumin; PA, prealbumin.

$\ast$ $P < 0.05$.

† Frailty was defined as Fried Phenotype scores ≥ 3.

‡ Defined by IDSA/ATS criteria (2007).

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Impact of frailty on 30-day and 1-year mortality in hospitalized elderly patients with community-acquired pneumonia: a prospective observational study

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Abstract

Objectives: This study evaluates the impact of frailty, which is a state of increased vulnerability to stressors, on 30-day and 1-year mortality among elderly patients with community-acquired pneumonia (CAP). The main hypothesis is that frailty is an independent predictor of prognosis in elderly CAP patients.

Design: Prospective, observational, follow-up cohort study.

Setting: A 2000-bed tertiary care hospital in Beijing, China.

Participants: Consecutive CAP patients aged ≥65 years admitted to the geriatric department of our hospital between September 2017 and February 2019.

Main outcome measures: The primary outcomes were all-cause mortality at 30 days and 1 year after hospital admission. The impact of frailty (defined by Frailty Phenotype) on 30-day and 1-year mortality of elderly patients with CAP was assessed by Cox regression analysis.

Results: The cohort included 256 patients. The median (IQR) age was 86 (81, 90) years, and 180 (70.3%) participants were men. A total of 171/256 (66.8%) patients were frail. The prevalence of frailty was significantly associated with older age, female gender, lower BMI, comorbidities, limitations in activities of daily living, and poor nutritional status. Frail participants were significantly more likely to have severe CAP than non-frail counterparts (28.65% vs. 9.41%, P<0.001). The 1-year mortality risk was approximately three-fold higher in frail patients (adjusted HR, 2.70; 95% CI, 1.69-4.39) than non-frail patients. Subgroup analysis of patients with severe CAP showed that the

1-year mortality risk was approximately three-fold higher in the frail group (adjusted HR, 2.87; 95% CI, 1.58-4.96) than in the non-frail group. The association between frailty and 30-day mortality was not significant.

Conclusions: These findings suggest that frailty is strongly associated with severe CAP and higher 1-year mortality in elderly patients with CAP, and frailty should be detected early to improve the management of these patients.

Keywords: Community-acquired pneumonia; Frailty; Elderly; Prognosis.

Strengths and limitations of this study

1. This is a prospective cohort study, included the comprehensive scope of prognostic factors (frailty, age, disability, undernutrition, comorbidities, and disease severity) for patients with community-acquired pneumonia (CAP).

2. Results of this study may contribute to a better understanding of the risk profile of frail older adults hospitalized with CAP.

3. Frailty was defined by Fried's Frailty Phenotype, which is well validated and simple to use.

4. The study was conducted in a single center and evaluated a small number of end-points.

5. The study included a small sample of older patients and did not evaluate the association between frailty and CAP in outpatients.

Introduction

Community-acquired pneumonia (CAP) is the most prevalent infectious disease in the elderly and is associated with high rates of mortality, morbidity, and high costs worldwide.[1, 2, 3, 4] In the United States, the incidence of CAP in the age group 65–79 years is 63 cases per 10,000 adults and increases to 164.3 cases per 10,000 adults in the age group >80 years.[5] Mortality from CAP increases with age. In 2012, the average mortality from pneumonia was 17.46 cases per 100,000 in all age groups in China, 23.55 cases per 100,000 in the age group 65–69 years, and nearly 36 times higher in the age group >85 years.[6]

Studies have shown that age, functional status, comorbidities, and malnutrition are strongly associated with poor prognosis in CAP patients,[4,6,7,8,9,10] and higher mortality in elderly patients with CAP underscores the need to identify novel, modifiable risk factors for poor outcomes. Particular attention has recently been directed to frail elderly patients. Frailty is associated with disabilities, comorbidities, and old age and is defined as a cumulative decline in multiple organ systems and loss of physiological reserves, increasing the vulnerability to adverse outcomes, including falls, hospitalization, and mortality.[11,12,13] Moreover, frailty is an independent risk factor for mortality in patients with acute and chronic diseases.[14,15] A European multicenter study assessed the impact of frailty (measured by the Clinical Frailty Scale) on intensive care unit (ICU) admission and 30-day mortality in 5021 elderly patients and observed that frailty was found in 43% of these patients and was independently related to 30-day survival (hazard ratio [HR], 1.54; 95% confidence interval [CI], 1.38-1.73, frail versus non-frail

patients).[16] A study evaluated the relationship between frailty and CAP in older patients and found that frailty was associated with increased hospitalization at 28 days after CAP diagnosis[17] and significantly predicted the risk of 1-month mortality.[18] Therefore, we hypothesized that frailty is positively correlated with CAP severity and mortality in elderly patients.

The objective of this study was to assess the prevalence of frailty in older patients with CAP, the association between frailty and CAP severity, and 30-day and 1-year mortality. This information may be useful for the early stratification of high-risk patients and the hierarchical management of modifiable factors to improve the prognosis of elderly patients with CAP.

Methods

1. Study design

We prospectively and consecutively enrolled elderly patients (aged ≥65 years) diagnosed with CAP in the geriatric department of our institution from September 2017 to February 2019. The exclusion criteria were complications, such as acute myocardial infarction, acute cerebrovascular disease, gastrointestinal bleeding, or acute renal failure; surgical history within 3 months; and terminal stage of a malignant tumor (Figure 1).

CAP was defined as pneumonia acquired outside the hospital by an immunocompetent individual. The criteria for diagnosing CAP were community-onset and the presence of new infiltrates on chest X-ray or computed tomography scan

together with at least one of the following conditions: (i) new or increased cough (productive, nonproductive, or accompanied by a change in sputum characteristics) with or without dyspnea, chest pain, or hemoptysis; (ii) fever; (iii) rales and/or signs of consolidation; (iv) peripheral WBC count >10,000 cells mm^{-3} or <4000 cells mm^{-3} with or without an increase in immature forms. Differential diagnosis included tuberculosis, lung cancer, noninfectious pulmonary interstitial disease, pulmonary edema, atelectasis, pulmonary embolism, pulmonary eosinophilic infiltration, and pulmonary vasculitis. The patients with these diagnoses were excluded.[6]

2. Baseline characteristics

The following parameters were evaluated within 24 hours of admission: age, sex, body mass index (BMI), smoking history, procalcitonin (PCT), high-sensitivity C-reactive protein (hs-CRP), white blood count (WBC), hemoglobin (HGB), alanine aminotransferase (ALT), albumin (ALB), prealbumin (PA), serum creatinine (Scr), and blood urea nitrogen (BUN). A comprehensive geriatric assessment (CGA), including frailty, comorbidities, and functional and nutritional status, was conducted by trained evaluators within 24 hours of admission.

3. Severity of CAP

Severe CAP (SCAP) was diagnosed according to criteria established by the Infectious Diseases Society of America and the American Thoracic Society,[19] and at least one major criterion or three minor criteria should be satisfied. The major criteria were the need for mechanical ventilation or the diagnosis of septic shock. The minor

criteria were respiratory rate >130 breaths/min, arterial oxygen pressure/fraction of inspired oxygen ratio <250 mmHg, multilobar infiltrates, confusion, BUN level >120 mg/dL, leukopenia resulting from infection, thrombocytopenia, hypothermia, or hypotension requiring aggressive fluid resuscitation.

4. Assessment of frailty

Frailty was assessed using the following Frailty Phenotype (FP) criteria: unintentional weight loss (4.5kg in the past 12 months), self-reported exhaustion, weakness (reduced grip strength), slow walking speed, and low physical activity.[20] The cut-off values were consistent with the original criteria. Each construct was considered present (score of 1) or absent (score of 0). The total score ranged from 0 to 5. As established previously, the presence and absence of frailty were defined as a score of $\geqslant$3 and $\leq$2, respectively.

5. Covariates

Comorbidity was evaluated with the Charlson Comorbidity Index (CCI).[21] The CCI is the sum of the weighted scores of the following chronic medical conditions: ischemic heart disease, congestive heart failure, cerebrovascular accident, peripheral vascular diseases, chronic lung diseases, diabetes, dementia, connective tissue diseases, renal diseases, liver diseases, hemiplegia, solid or hematological malignancy, and acquired immunodeficiency disease. A score of 1, 2, 3, or 6 is assigned to each disease, depending on severity.

Functional status was assessed by evaluating patients' ability to perform activities

of daily living (ADLs) using the Barthel Index (BI).[22]

Nutritional status was assessed using the Mini Nutritional Assessment-Short Form questionnaire.[23] This questionnaire evaluates BMI, weight loss in the past 3 months, dietary changes, stress or acute illness, degree of mobility, and neuropsychiatric diseases. The total score is 14 points, and scores of 0-7 indicate malnutrition.

5. Follow-up and outcomes

All patients were followed for 1 year after hospital admission. Deaths were confirmed through surveillance or official death records. The primary outcomes were all-cause mortality at 30 days and 1 year after admission.

6. Statistical analysis

Statistical analyses were performed using IBM SPSS software version 23.0 (Chicago, USA). Continuous variables were expressed as the means ± standard deviation (SD) or interquartile range (IQR) and compared using Student's t-test or the Mann–Whitney U test. Categorical variables were compared using the chi-squared test or Fisher's exact test. The association between baseline frailty status and 30-day and 1-year all-cause mortality was analyzed using univariate and multivariate Cox proportional hazards regression models, and the results were expressed as hazard ratio (HR) and 95% confidence interval (CI). A two-tailed p-value of less than 0.05 was considered to indicate a statistically significant difference.

Patient and public involvement

Patients and the public were not involved in the study design, recruitment, or execution, and the participants were not be involved in disseminating the results. The study results will be provided to patients upon request, and aggregated data will be reported in project reports and research publications and meetings.

Results

In our cohort, 393 older patients with CAP were admitted to our department during the study period. Of these, 119 patients were excluded because of concomitant diseases, and 18 were lost to follow-up (Figure 1). A total of 256 patients with CAP aged 65-99 years were included in the final analysis. Demographic characteristics are presented in Table 1. The median age of the cohort was 86 (IQR, 81–90) years, and 180 (70.3%) patients were men. A total of 171 (66.8%) participants were frail, 71 (27.7%) patients were malnourished, and 57 (22.3%) participants had SCAP. All-cause mortality at 30 days and 1 year was 5.5% and 16.8%, respectively.

Frailty was significantly associated with older age, female gender, lower BMI, limitations in ADLs, comorbidities, and poor nutritional status. Frail participants were significantly more likely to have SCAP than non-frail counterparts (28.65% vs. 9.41%, P<0.001). Thirty-day and 1-year mortality was significantly higher in frail patients (0 vs. 8.19%, P=0.015; and 0 vs. 25.25%, P<0.001, respectively). The results of Cox proportional hazards regression are presented in Table 2. SCAP, frailty, malnutrition, and CCI were significantly associated with 30-day mortality in the univariate analysis, but only SCAP remained significant in the multivariate analysis (adjusted HR, 30.60;

95% CI, 3.77-248.06). The factors associated with 1-year mortality in the multivariable analysis were SCAP (adjusted HR, 7.68; 95% CI, 3.79-15.58), frailty (adjusted HR, 2.70; 95% CI, 1.69-4.39), and CCI (adjusted HR, 1.19; 95% CI, 1.05-1.34).

Subgroup analysis of patients with SCAP by frailty status showed that eight (14%) patients were non-frail and 49 patients (86%) were frail. The frail group presented significantly worse functional and nutritional status and higher 30-day and 1-year mortality (Supplementary Table). In the multivariate analysis of patients with SCAP, 1-year mortality risk was approximately three-fold higher in the frail group (adjusted HR, 2.87; 95% CI, 1.58-4.96) than in the non-frail group, and 1-year mortality risk was 16% higher among those with more comorbidities (adjusted HR, 1.16; 95% CI, 1.01-1.34) (Table 3). Only CCI was significantly correlated with 30-day mortality (HR, 1.21; 95% CI, 1.02-1.43).

Discussion

The results showed that frail older patients with CAP were significantly more likely to have SCAP and had a significantly higher 30-day and 1-year mortality risk than non-frail patients. In addition, frailty was an independent risk factor for 1-year mortality after adjusting for age, sex, disability, malnutrition, comorbidities, and CAP severity but was not an independent risk factor for 30-day mortality.

The incidence of CAP increases with age, and CAP increases the risk of morbidity and mortality. Mortality is significantly higher in elderly patients with CAP than in the general population.[4,9] All-cause mortality at 30 days and 1 year among elderly patients

with CAP in our cohort was 5.5% and 16.8%, respectively. Known independent prognostic factors for CAP mortality are age, comorbidities, functional status, microbial etiology, and early antibiotic treatment.[9,10,24,25] However, some studies reported that age *per se* was not an independent predictor of CAP mortality in the elderly population with pneumonia.[26,27] Frailty is an age-related disease associated with disabilities, comorbidities, and advanced age, and is characterized by a decline in physiological functions across multiple organ systems and increased vulnerability to stressors,[20,28,29] which increases the risk of adverse health outcomes, including falls, disability, hospitalization, institutionalization, and death. Various conditions, including malnutrition, sarcopenia, gait impairment, chronic inflammation, polypharmacy, cardiovascular changes, and morbidity, may cause frailty. [30,31,32] Accordingly, in our sample, all patients who died within 30 days or 1 year were frail.

Frailty was more prevalent in women in our study, which is consistent with a previous study.[30] In addition, frail patients had significantly older age, more comorbidities, poor nutritional and functional status, and limited ability to perform ADLs. Poor nutritional status, including hypoalbuminemia, hypoproteinemia, malnourishment, and a low nutritional score, is a strong predictor of mortality in CAP patients.[33,34] However, in our cohort, there was no significant association between nutritional status and 30-day or 1-year mortality in the multivariate analysis (adjusted HR, 1.11; 95% CI, 0.90-1.35; adjusted HR, 0.94; 95% CI, 0.81-1.10, respectively). Some studies have shown that the definition, diagnosis, and treatment of frailty and malnutrition overlap.[30,32,35] Malnutrition is a physiological condition that predisposes to the occurrence and

development of frailty.[31] In our study, frailty was defined as a syndrome that affects multiple organ systems and was a strong predictor of long-term mortality, and this multidimensional nature may explain why frailty, but not malnutrition and disability, was significantly associated with higher mortality in the multivariate analysis.

Our results indicated that frailty was common in elderly patients with CAP (prevalence of 66.8%) and was closely linked to pneumonia severity; furthermore, frailty increased 1-year mortality risk nearly three-fold compared with the absence of frailty (adjusted HR, 2.70; 95% CI, 1.69-4.39). A study evaluated patient outcomes at 1 year after the diagnosis of CAP and showed that age ⩾65 years, nursing home residency, and comorbidity were positively associated with 1-year mortality.[36] Another study found that the risk of CAP mortality was more strongly correlated with underlying diseases than with CAP severity.[25] However, these studies did not assess the effect of frailty on CAP prognosis. The results of our study demonstrated that frailty was independently associated with 1-year mortality after adjusting for risk factors, suggesting that frailty could accurately predict adverse outcomes.

Our findings suggest that frail patients are more likely to have SCAP, and frailty is positively correlated to the risk of 1-year mortality. Since the clinical presentation of pneumonia may be atypical in the elderly, clinicians should suspect pneumonia in the presence of symptoms such as falls, altered mental status, fatigue, delirium, and anorexia to avoid complications associated with delayed diagnosis and therapy.[37] With respect to clinical decision-making and planning of health services, it is important to identify frailty in elderly CAP patients to better stratify the risk of adverse outcomes

and implement treatments tailored to individual needs, weighing up the risks and benefits of invasive diagnostic procedures and therapies, as well as taking into account end of life care needs for individuals with advanced frailty. A Korean study found that frailty was independently associated with do-not-resuscitate orders and healthcare transitions, even after adjusting for sepsis and pneumonia severity.[38] An international multidisciplinary group proposed a CGA[39] adapted to the emergency department context to assess frailty in elderly patients.[16,40] Although many physicians and intensivists do not currently perform CGAs in critically ill patients with infectious diseases, demographic shifts may require addressing this issue promptly. Moreover, frailty is a dynamic state and can be reversed.[41] Preventing frailty is possible, especially during onset, and the early diagnosis of this condition is crucial to improve therapeutic efficacy and the post-discharge management of elderly patients with CAP.[11]

This study has limitations. First, the results were not compared with data from other hospitals and regions. Second, the number of patients and end-point events was small. Third, the study did not evaluate the association between frailty and CAP in outpatients; therefore, the results cannot be generalized to other patient groups.

This study adjusted for confounding factors and demonstrated that frailty strongly affected the long-term prognosis of CAP patients. These data can contribute to the long-term management of frailty in CAP patients.

Conclusions

Frailty is very common in elderly patients with CAP and increases the risk of 1-year mortality from CAP and SCAP. Our findings suggest that frailty should be evaluated in routine clinical practice to improve the post-discharge management of older patients with CAP.

Contributors Jia Luo, Wen Tang, Ying Sun, and Chun-Yan Jiang conceived and designed the study. Jia Luo and Wen Tang collected data. Wen Tang, Ying Sun, and Chun-Yan Jiang analyzed and interpreted data. Jia Luo and Wen Tang wrote the manuscript. All authors approved the final manuscript.

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Data sharing: Data are available with the first author (e-mail: ann11121112@sina.com).

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Table 1. Baseline characteristics of the study population according to frailty status.

Characteristics	Total cohort	Non-frail	Frail†	P-values
N (%)	256	85 (33.2)	171 (66.8)	
Age, median (IQR)	86 (81, 90)	83 (75, 87)	88 (84, 91)	<0.001*
Sex, n (%)				
Female	76 (29.7)	17 (20.0)	59 (34.5)	0.017*
Male	180 (70.3)	68 (80.0)	112 (65.5)	
Smoking status, n (%)				
Current	29 (11.3)	11 (12.9)	18 (10.5)	0.288
Previous	71 (27.7)	28 (32.9)	43 (25.1)	
Never	156 (60.9)	46 (54.1)	110 (64.3)	
BMI (kg/m^2), mean (SD)	22.9 (4.3)	24.2 (3.8)	22.3 (4.4)	0.001*
Barthel Index, median (IQR)	65 (40, 95)	95 (85, 100)	50 (20, 70)	<0.001*
CCI, median (IQR)	4 (3, 5)	3 (2, 4)	4 (3, 6)	<0.001*
MNA-SF, median (IQR)	10 (7, 12)	12 (11, 14)	9 (7, 11)	<0.001*
Malnutrition, n (%)§	71 (27.7)	6 (7.1)	65 (38.0)	
SCAP‡, n (%)	57 (22.3)	8 (9.41)	49 (28.65)	<0.001*
PCT (ng/mL), median (IQR)	0.28 (0.21, 0.44)	0.27 (0.20, 0.37)	0.29 (0.21, 0.55)	0.149
hs-CRP (mg/L), median (IQR)	25.89 (5.79, 61.41)	19.63 (4.19, 54.29)	27.08 (7.56, 62.43)	0.129
WBC (*10^9/L), median (IQR)	7.65 (5.57, 11.06)	7.02 (5.64,9.01)	8.02 (5.51, 12.33)	0.043*
HGB (g/L), median (IQR)	121 (108, 133)	127 (120, 136)	115 (100,128)	<0.001*

Scr (μmol/L), median (IQR)	76.9 (61.6, 96.8)	78.6 (67.4, 90.5)	75.2 (59.5, 101.6)	0.720
BUN (mmol/L), median (IQR)	5.98 (4.58, 7.94)	5.99 (4.30, 7.01)	5.98 (4.79, 8.65)	0.039*
ALT (U/L), median (IQR)	14 (10, 22)	15 (11, 22)	13 (10, 21)	0.058
ALB (g/L), mean (SD)	32.46 (4.39)	34.38 (4.22)	31.50 (4.16)	<0.001*
PA (g/L), mean (SD)	16.92 (6.19)	18.74 (6.41)	15.98 (5.88)	0.001*
30-day mortality, n (%)	14 (5.5)	0 (0)	14 (8.19)	0.015*
1-year mortality, n (%)	43 (16.8)	0 (0)	43 (25.15)	<0.001*

Abbreviations: SD, standard deviation; IQR, inter-quartile range; BMI, body mass index; CCI, Charlson's Comorbidity Index; MNA-SF, Mini Nutritional Assessment-Short Form; SCAP, severe community-acquired pneumonia; PCT, procalcitonin; hs-CRP, high sensitivity C-reactive protein; WBC, white blood cell count; HGB, hemoglobin; BUN, blood urea nitrogen; Scr, serum creatinine; ALT, alanine aminotransferase; ALB, albumin; PA, prealbumin.

* P < 0.05.

† Frailty was defined as Fried Phenotype scores ≥ 3.

‡ SCAP was defined by IDSA/ATS criteria (2007).

§ Malnutrition was defined as MNA-SF scores ≤ 7.

Table 2. Factors associated with 30-day and 1-year mortality in patients with community-acquired pneumonia in Cox proportional hazards regression analyses (n=256).

	Univariate			Multivariate		
Variable	HR	95% CI	P-Value	HR	95% CI	P-Value
30-day mortality						
SCAP	52.01	6.80-398.09	<0.001	30.60	3.77-248.06	0.001*
BI	0.99	0.97-1.00	0.101	_	_	_
BMI	0.97	0.86-1.09	0.609	_	_	_
Malnutrition	0.84	0.73-0.97	0.015	1.11	0.90-1.35	0.330
Frailty	2.58	1.42-4.69	0.002	1.83	0.88-3.81	0.108
CCI	1.41	1.19-1.67	<0.001	1.19	0.99-1.43	0.069
1-year mortality						
SCAP	13.32	6.81-26.04	<0.001	7.68	3.79-15.58	<0.001*
BI	0.98	0.97-0.99	<0.001	1.01	0.99-1.02	0.352
BMI	0.93	0.87-1.00	0.038	1.07	0.98-1.16	0.128
Malnutrition	0.78	0.72-0.85	<0.001	0.94	0.81-1.10	0.424
Frailty	3.41	2.32-5.03	<0.001	2.70	1.69-4.39	<0.001*
CCI	1.40	1.26-1.55	<0.001	1.19	1.05-1.34	<0.001*

Data are estimated hazard ratios and 95% confidence intervals of the explanatory variables in the 30-day and 1-year mortality group. Data were adjusted for age, sex, disability, malnutrition, comorbidities, and the severity of CAP.

Abbreviations: HR, hazards ratio; CI, confidence interval; SCAP, severe community-acquired pneumonia; BI, Barthel Index; BMI, body mass index; CCI, Charlson's Comorbidity Index.

* $P < 0.05$.

Table 3. Factors associated with 30-day and 1-year mortality in patients with severe community-acquired pneumonia in Cox proportional hazards regression analyses (n=57).

	Univariate			Multivariate		
Variable	HR	95% CI	P-Value	HR	95% CI	P-Value
30-day mortality						
BI	1.00	0.99-1.02	0.899	_	_	_
BMI	1.04	0.92-1.18	0.507	_	_	_
Malnutrition	0.73	0.24-2.23	0.581	_	_	_
Frailty	26.61	0.04-16017.0	0.315	_	_	_
CCI	1.21	1.02–1.43	0.028	1.21	1.02-1.43	0.028*
1-year mortality						
BI	0.99	0.98–1.00	0.046	1.00	0.99–1.02	0.875
BMI	0.99	0.92-1.08	0.854	_	_	_
Malnutrition	0.86	0.77–0.97	0.010	1.05	0.89–1.25	0.545
Frailty	2.82	1.70–4.68	<0.001	2.87	1.58–4.96	<0.001*
CCI	1.24	1.10–1.40	0.001	1.16	1.01–1.34	0.034*

Data are estimated hazard ratios and 95% confidence intervals of the explanatory variables in the 1-year mortality group. Data were adjusted for age, sex, disability, malnutrition, and comorbidities.

Abbreviations: HR, hazards ratio; CI, confidence interval; SCAP, severe community-acquired pneumonia; BI, Barthel Index; CCI, Charlson's Comorbidity Index.

＊P < 0.05.

Figure legend:

Figure1: Flowchart of patients excluded/included for the frailty assessment analyses in community-acquired pneumonia cohort.

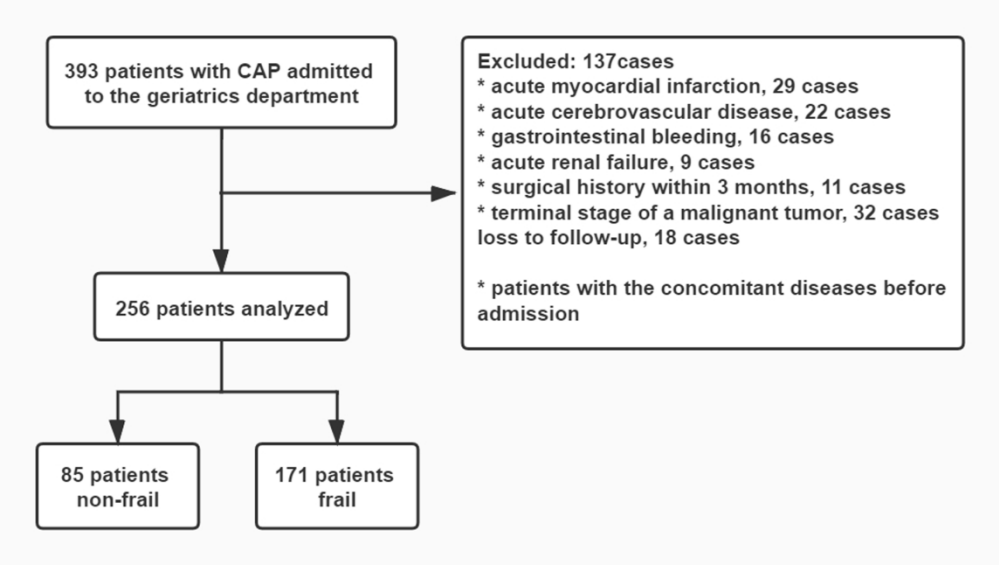

Figure1: Flowchart of patients excluded/included for the frailty assessment analyses in community-acquired pneumonia cohort.

Supplementary Table. Characteristics of patients with severe community-acquired pneumonia‡ stratified by frailty status.

Characteristics	Non-frail	Frail†	P-values
N, n (%)	8 (14.0)	49 (86.0)	
Age, median (IQR)	85 (82–91)	89 (81–92)	0.581
Sex, n (%)			
Female	0 (0)	11 (22.5)	0.053
Male	8 (100)	38 (77.6)	
BMI (kg/m^2), mean (SD)	22.95 (2.56)	21.59 (4.81)	0.249
Barthel Index, median (IQR)	88 (59–99)	35 (8–68)	0.001*
CCI, median (IQR)	4 (2–5)	5 (3–8)	0.129
MNA-SF, mean (SD)	11 (3)	7 (3)	0.003*
PCT (ng/mL), median (IQR)	0.30 (0.21–0.40)	0.31 (0.23–1.74)	0.477
hs-CRP (mg/L), median (IQR)	33.52 (3.65–154.94)	34.42 (19.08–89.78)	0.928
WBC (*10^9/L), mean (SD)	8.45 (2.53)	10.83 (5.27)	0.218
HGB (g/L), median (IQR)	122 (106–146)	114 (93–123)	0.179
Scr (μmol/L), median (IQR)	103.5 (88.5–121.1)	82.6 (62.1–114.8)	0.161
BUN (mmol/L), median (IQR)	8.35 (6.86–9.49)	7.98 (5.67–12.07)	0.730
ALT (U/L), median (IQR)	16 (10–27)	13 (10–20)	0.557
ALB (g/L), median (IQR)	33.10 (31.75–34.38)	30.00 (27.35–32.85)	0.039*
PA (g/L), mean (SD)	18.56 (9.60)	14.44 (5.85)	0.118
30-day mortality, n (%)	0 (0)	13 (26.53)	0.034*
1-year mortality, n (%)	0 (0)	31 (63.27)	<0.001*

Abbreviations: SD, standard deviation; IQR, inter-quartile range; BMI, body mass index; CCI, Charlson's Comorbidity Index; MNA-SF, Mini Nutritional

Assessment-Short Form; PCT, procalcitonin; hs-CRP, high-sensitivity C-reactive protein; WBC, white blood cell count; HGB, hemoglobin; BUN, blood urea nitrogen; Scr, serum creatinine; ALT, alanine aminotransferase; ALB, albumin; PA, prealbumin.

$\ast$ $P < 0.05$.

† Frailty was defined as Fried Phenotype scores ≥ 3.

‡ Defined by IDSA/ATS criteria (2007).