

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

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**To cite:** Luo J, Tang W, Sun Y, *et al.* Impact of frailty on 30-day and 1-year mortality in hospitalised elderly patients with community-acquired pneumonia: a prospective observational study. *BMJ Open* 2020;**10**:e038370. doi:10.1136/bmjopen-2020-038370

► Prepublication history and additional materials for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2020-038370>).

Received 10 March 2020  
Revised 03 September 2020  
Accepted 11 September 2020



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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  $\geq 65$  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 body mass index, comorbidities, limitations in activities of daily living (ADLs) and poor nutritional status. Frail participants were significantly more likely to have severe CAP (SCAP) than non-frail counterparts (28.65% vs 9.41%,  $p < 0.001$ ). The 1-year mortality risk was approximately threefold higher in frail patients (adjusted HR, 2.70; 95% CI, 1.69 to 4.39) than non-frail patients. Subgroup analysis of patients with SCAP showed that the 1-year mortality risk was approximately threefold higher in the frail group (adjusted HR, 2.87; 95% CI, 1.58 to 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 SCAP and higher 1-year mortality in elderly patients with CAP, and frailty should be detected early to improve the management of these patients.

## INTRODUCTION

Community-acquired pneumonia (CAP) is the most prevalent infectious disease in the

## Strengths and limitations of this study

- This is a prospective cohort study, included the comprehensive scope of prognostic factors (frailty, age, disability, malnutrition, comorbidities and disease severity) for patients with community-acquired pneumonia (CAP).
- Results of this study may contribute to a better understanding of the risk profile of frail older adults hospitalised with CAP.
- Frailty was defined by Fried's frailty phenotype, which is well validated and simple to use.
- The study was conducted in a single centre and evaluated a small number of endpoints.
- The study included a small sample of older patients and did not evaluate the association between frailty and CAP in outpatients.

elderly and is associated with high rates of mortality, morbidity and high costs worldwide.<sup>1–4</sup> In the USA, 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.<sup>5</sup> 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.<sup>6</sup>

Studies have shown that age, functional status, comorbidities and malnutrition are strongly associated with poor prognosis in CAP patients,<sup>4 6–10</sup> 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, hospitalisation and mortality.<sup>11–13</sup> Moreover, frailty is an independent risk factor for mortality in patients with acute and chronic diseases.<sup>14 15</sup> A European multicenter study assessed the impact of frailty (measured by the Clinical Frailty Scale) on intensive care unit 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 (HR, 1.54; 95% CI, 1.38–1.73, frail vs non-frail patients).<sup>16</sup> A study evaluated the relationship between frailty and CAP in older patients and found that frailty was associated with increased hospitalisation at 28 days after CAP diagnosis<sup>17</sup> and significantly predicted the risk of 1-month mortality.<sup>18</sup> Therefore, we hypothesised 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

### Study design

We prospectively and consecutively enrolled elderly patients (aged  $\geq 65$  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 tumour (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 CT scan together with at least one of the following conditions: (1) new or increased cough (productive, non-productive or

accompanied by a change in sputum characteristics) with or without dyspnoea, chest pain or haemoptysis; (2) fever; (3) rales and/or signs of consolidation and (4) peripheral white blood count (WBC) count  $>10 \times 10^9/L$  or  $<4 \times 10^9/L$  with or without an increase in immature forms. Differential diagnosis included tuberculosis, lung cancer, non-infectious pulmonary interstitial disease, pulmonary oedema, atelectasis, pulmonary embolism, pulmonary eosinophilic infiltration and pulmonary vasculitis. The patients with these diagnoses were excluded.<sup>6</sup>

### Baseline characteristics

The following parameters were evaluated within 24 hours of admission: age, sex, body mass index (BMI), smoking history, procalcitonin, high-sensitivity C reactive protein, WBC, haemoglobin, alanine aminotransferase, albumin, prealbumin, serum creatinine 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.

### Severity of CAP

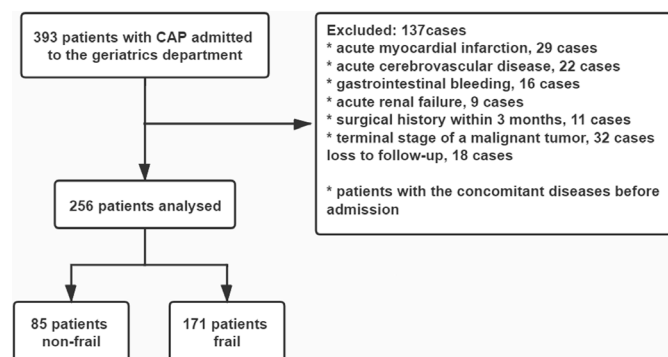
Severe CAP (SCAP) was diagnosed according to criteria established by the Infectious Diseases Society of America and the American Thoracic Society,<sup>19</sup> and at least one major criterion or three minor criteria should be satisfied. The major criteria were the need for mechanical ventilation or the diagnosis of septic shock. The minor criteria were respiratory rate  $>130$  breaths/min, arterial oxygen pressure/fraction of inspired oxygen ratio  $<250$  mm Hg, multilobar infiltrates, confusion, BUN level  $>120$  mg/dL, leucopenia resulting from infection, thrombocytopenia, hypothermia or hypotension requiring aggressive fluid resuscitation.

### Assessment of frailty

Frailty was assessed using the following frailty phenotype criteria: unintentional weight loss (4.5 kg in the past 12 months), self-reported exhaustion, weakness (reduced grip strength), slow walking speed and low physical activity.<sup>20</sup> 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  $\geq 3$  and  $\leq 2$ , respectively.

### Covariates

Comorbidity was evaluated with the Charlson Comorbidity Index (CCI).<sup>21</sup> The CCI is the sum of the weighted scores of the following chronic medical conditions: ischaemic 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 haematological malignancy and acquired immunodeficiency disease. A score of 1, 2, 3 or 6 is assigned to each disease, depending on severity.



**Figure 1** Flowchart of patients excluded/included for the frailty assessment analyses in community-acquired pneumonia (CAP) cohort.

Functional status was assessed by evaluating patients' ability to perform ADLs using the Barthel Index.<sup>22</sup>

Nutritional status was assessed using the Mini Nutritional Assessment-Short Form questionnaire.<sup>23</sup> 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.

### 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.

### Statistical analysis

Statistical analyses were performed using IBM SPSS software V.23.0. Continuous variables were expressed as the means±SD or IQR and compared using Student's t-test or the Mann-Whitney U test. Categorical variables were compared using the  $\chi^2$  test or Fisher's exact test. The association between baseline frailty status and 30-day and 1-year all-cause mortality was analysed using univariate and multivariate Cox proportional hazards regression models, and the results were expressed as HR and 95% 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 to be involved in disseminating the results. The study results will be provided to patients on 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 one-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 to 248.06). The factors associated with 1-year mortality in the multivariable analysis were SCAP (adjusted HR, 7.68; 95% CI, 3.79 to 15.58), frailty (adjusted HR, 2.70; 95% CI, 1.69 to 4.39) and CCI (adjusted HR, 1.19; 95% CI, 1.05 to 1.34).

Subgroup analysis of patients with SCAP by frailty status showed that 8 (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 (see online supplemental table). In the multivariate analysis of patients with SCAP, 1-year mortality risk was approximately threefold higher in the frail group (adjusted HR, 2.87; 95% CI, 1.58 to 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 to 1.34) (table 3). Only CCI was significantly correlated with 30-day mortality (HR, 1.21; 95% CI, 1.02 to 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.<sup>4–9</sup> 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 aetiology and early antibiotic treatment.<sup>9 10 24 25</sup> However, some studies reported that age per se was not an independent predictor of CAP mortality in the elderly population with pneumonia.<sup>26 27</sup> Frailty is an age-related disease associated with disabilities, comorbidities and advanced age, and is characterised by a decline in physiological functions across multiple organ systems and increased vulnerability to stressors,<sup>20 28 29</sup> which increases the 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, may cause frailty.<sup>30–32</sup> 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.<sup>30</sup> In addition, frail patients had significantly older age, more comorbidities,

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

Characteristics	Total cohort	Non-frail	Frail†	P value
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 <sup>2</sup> ), 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 <sup>9</sup> /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)	0.72
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*

\*P&lt;0.05.

†Frailty was defined as Fried phenotype scores ≥3.

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

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

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

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.<sup>33 34</sup> 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 to 1.35; adjusted HR, 0.94; 95% CI, 0.81 to 1.10, respectively). Some studies have shown that the definition, diagnosis and treatment of frailty and malnutrition overlap.<sup>30 32 35</sup> Malnutrition is a physiological condition that predisposes to the occurrence and development of frailty.<sup>31</sup> 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 threefold compared with the absence of frailty (adjusted HR, 2.70; 95% CI, 1.69 to 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.<sup>36</sup> Another study found that the risk of CAP mortality was more strongly correlated with underlying diseases than with CAP severity.<sup>25</sup> 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

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

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

Data are estimated HR and 95% CIs 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.

\*P<0.05.

BI, Barthel Index; BMI, body mass index; CAP, community-acquired pneumonia; CCI, Charlson's Comorbidity Index; SCAP, severe community-acquired pneumonia.

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.<sup>37</sup> With respect to clinical decision-making and

**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)

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

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

\*P<0.05.

BI, Barthel Index; BMI, body mass index; CCI, Charlson's Comorbidity Index.

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 health-care transitions, even after adjusting for sepsis and pneumonia severity.<sup>38</sup> An international multidisciplinary group proposed a CGA<sup>39</sup> adapted to the emergency department context to assess frailty in elderly patients.<sup>16–40</sup> 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.<sup>41</sup> Preventing frailty is possible, especially during onset, and the early diagnosis of this condition is crucial to improve therapeutic efficacy and the postdischarge management of elderly patients with CAP.<sup>11</sup>

This study has limitations. First, the results were not compared with data from other hospitals and regions. Second, the number of patients and endpoint events was small. Third, the study did not evaluate the association between frailty and CAP in outpatients; therefore, the results cannot be generalised 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 postdischarge management of older patients with CAP.

**Contributors** JL, WT, YS and CJ conceived and designed the study. JL and WT collected data. WT, YS and CJ analysed and interpreted data. JL and WT wrote the manuscript. All authors approved the final manuscript.

**Funding** This work was supported by the Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding Support (Process No. ZYLX201838) and the Beijing Friendship Hospital of Capital Medical University Hospital Startup Funding (Process No. yyqdk2017-37).

**Competing interests** None declared.

**Patient consent for publication** Parental/guardian consent obtained.

**Ethics 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.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available upon reasonable request to corresponding author (e-mail: twybz@163.com).

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