

# Cognitive Frailty and 30-Day Mortality in a National Cohort of Older Chinese Inpatients

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**Purpose:** Studies exploring the association of cognitive frailty and mortality have been mainly based on community settings or nursing home settings. The aim of our study was to explore the association between cognitive frailty and 30-day mortality among older Chinese inpatients.

**Patients and Methods:** A national cohort study was performed in different hospitals in China. A baseline survey was conducted from October 2018 and February 2019. Trained investigators collected the 30-day mortality. Cognitive impairment and frailty were defined by the Mini-Cog and FRAIL scale, respectively. Multivariate regression was used to explore the association between cognitive impairment and frailty status with 30-day mortality.

**Results:** Of these participants, there were 3891 (41.91%) women and 5392 (58.09%) men, with an average age of 72.41 (SD=5.72). The prevalence of cognitive frailty was 5.44%. After adjusting for age, gender, education, depression and activities of daily living (ADL), the odds ratios (ORs) for 30-day mortality among inpatients were 3.43 (95% CI: 1.80–6.55) for cognitive frailty, 1.85 (95% CI: 1.01–3.41) for frailty only, and 1.43 (95% CI: 0.77–2.65) for cognitive impairment only compared to the reference group (neither frailty nor cognitive impairment). In addition, the discrimination of 30-day mortality was higher among patients with cognitive frailty (area under the curve =0.676 [95% CI: 0.621–0.731]) than either frailty (area under the curve =0.644 [95% CI: 0.594–0.694]) or cognitive impairment (area under the curve = 0.606 [95% CI: 0.556–0.655]) separately. Stratified analysis showed that these associations still existed when grouped by gender.

**Conclusion:** Our study found that Chinese inpatients with cognitive frailty had a higher risk of 30-day mortality than those without frailty and cognitive impairment, suggesting that clinicians should be encouraged to perform early screening of patients with frailty and cognitive impairment and carry out effective interventions to reverse cognitive frailty syndrome.

**Keywords:** frailty, cognitive impairment, mortality, older adults, Chinese; inpatients

## Introduction

Population aging is a worldwide demographic issue, corresponding to the increased longevity in older adults. These older adults often suffer from age-related comorbidities, with a higher likelihood of developing frailty and cognitive impairment when coexisting with stressors such as illness, injury and psychosocial stress.<sup>1</sup> Frailty and cognitive impairment are prevalent among older adults.<sup>2,3</sup> Both of these geriatric syndromes are reported in conjunction with an increased risk of mortality and other adverse outcomes, such as hospitalization and disability.<sup>4,5</sup> Therefore, managing and identifying frailty and cognitive impairment is essential for improving health in this population.

Currently, a great number of studies have found a close association between frailty and cognitive impairment, indicating that frailty and cognitive impairment are risk factors for one another.<sup>6,7</sup> Frailty and cognitive impairment seem to have similar pathogenic mechanisms, with chronic inflammation, oxidative stress, and hormonal dysregulation likely playing an important role.<sup>8</sup> In vulnerable older adults, these syndromes often cooccur, with the term “cognitive frailty” recommended by an international consensus group to define an older adult with the characteristics of both frailty and cognitive impairment but an absence of dementia.<sup>9</sup> However, there is no consensus definition of cognitive frailty, and there is also no consensus assessment tool to measure frailty and cognitive function. Some studies have used the Fried frailty phenotype,<sup>10</sup> FRAIL scale,<sup>8</sup> and Clinical Frailty Scale (CFS)<sup>11</sup> to define frailty. There are also various assessment scales to measure cognitive impairment, such as the Mini-Mental State Examination (MMSE)<sup>12</sup> and Montreal Cognitive Assessment (MoCA), which may result in different prevalence of cognitive frailty.

Cognitive frailty has been widely reported to be associated with mortality. Several studies have indicated that older adults suffering from cognitive frailty have the highest risk of mortality compared with those having separate frailty or cognitive impairment or being nonfrail with intact cognitive function.<sup>11,13–21</sup> However, most of the abovementioned studies focused on community-dwelling adults<sup>15,17</sup> or nursing home residents.<sup>22</sup> No study has reported this association among hospitalized older Chinese adults. Given that hospitalized older adults suffer worse health, it is therefore essential to examine the association between cognitive frailty and mortality among these vulnerable older patients in the hospital. Our objectives were to investigate the prevalence of cognitive frailty and to explore the association between cognitive frailty and 30-day mortality among hospitalized Chinese patients. We believe these findings could add new advances to this field.

## Patients and Methods

### Study Design and Population

As other published studies have reported, this study was a national large-scale longitudinal study of frailty among hospitalized older patients at tertiary hospitals<sup>23</sup> in different centers in China. Detailed information on the sampling methods was described in a previous study.<sup>23</sup> Briefly, researchers adopted two stages of cluster sampling

methods to recruit participants from the selected hospital. The baseline survey was performed between October 2018 and February 2019. We collected the data, including demographic, medical, physiological and psychological conditions, via questionnaire interviews and assessments. This study was approved by the Review Board, and all patients signed the informed consent form (S-K540). In addition, protocol number ChiCTR1800017682 was noted in our published study.<sup>23</sup> We included hospitalized participants aged  $\geq 65$  years old, excluding patients that were unconscious, could not communicate with the trained investigators.

### Frailty Assessment

The FRAIL scale was employed by investigators to assess frailty syndrome. The FRAIL scale consists of five simple questions to evaluate five patient domains, including fatigue, ambulation, resistance, weight loss and illness.<sup>24</sup> The questions were as follows: (1) How much of the time did you feel tired during the past four weeks? (all of the time or most of the time was scored as 1, others as 0); (2) Can you walk a couple of blocks by yourself without any aid and without any difficulty? (Yes=0, No=1); (3) Can you walk up 10 steps without having to stop and rest, by yourself, without aid? (Yes=0, No=1); (4) How many illnesses did the doctor tell you that you have? (more than five was recorded as 1, whereas when the number ranged from 0 to 4, it was recorded as 0). Detailed information on the illnesses was reported in a previous study. (5) Did you lose weight, at 5% or more, within the past six months? (Yes=1, No=0). The frailty categories were classified as frailty ( $\geq 3$  points) or nonfrail (0–2 points).

### Cognitive Impairment Assessment

We used a Chinese version of Mini-Cog, with two components that included a three-item recalled words test and one simple scored clock, to assess cognitive function.<sup>25</sup> The total points ranged from 0–5, with a score of less than 3 points indicating cognitive impairment. This assessment was a simple, non-time-consuming screening tool and is widely employed in clinics and hospital wards.

Cognitive frailty was defined when patients met these two geriatric syndromes (frailty and cognitive impairment).

### Other Variables

We also collected other important variables, including socio-demographic (age, gender, education, marital status,

ethnicity), functional covariates (vision, hearing, urinary function), depression, nutritional status and length of hospital stay. Lifestyle variables, which were self-reported, included smoking status and alcohol consumption. Functional covariates were detected based on whether they influenced daily life (dysfunction and normal). Depression symptoms were assessed using the Geriatric Depression Scale (GDS) with the definition score  $\geq 5$  points.<sup>26</sup> Nutritional status was assessed by the Mini-Nutritional Assessment-Short Form (normal nutritional status: 12–14; at risk of malnutrition: 8–11; malnourished: 0–7).<sup>27</sup> The activities of daily living (ADLs) were assessed using the Barthel index.<sup>28</sup>

## Follow-Up for Outcome

After performing a baseline survey, trained investigators attended a standard training program to obtain the necessary skills to conduct telephone interviews for follow-up. Thirty-day mortality was identified and recorded by the trained investigators.

## Statistical Analysis

We performed all statistical analyses using the SAS package, version 9.4, (SAS Institute Inc., Cary, NC, USA), with significant differences identified by a two-sided  $P$ -value  $< 0.05$ . We divided the cohort into the following four groups: cognitive frailty, having only frailty with intact cognitive function, nonfrail with cognitive impairment, and nonfrail with normal cognitive function. All variables are displayed as mean  $\pm$  standard deviation or proportions/frequency when the data are numerical variables and categorical variables, respectively. Student's  $t$ -test, chi square test and one-way ANOVA were conducted to detect the differences between various groups. Multivariate logistic regression analysis was used to identify the odds ratio (OR), as well as the pulsing confidence interval (CI) of association between the aforementioned cognitive frailty groups and 30-day mortality. Based on a previous study, we assume that patients with frailty and cognitive impairment have a higher risk of 30-day mortality than those in the other three groups. Additionally, we listed the raw model and three other adjusted models. Model 1 adjusted for age, gender, and education; Model 2 adjusted for the factors in Model 1 plus depression; Model 3 adjusted for ADL in addition to the factors from Model 2. We also performed subgroup analysis based on gender. Finally, receiver operating characteristic analysis was used to compare the area under the

curve (AUC) among cognitive frailty, frailty alone, and cognitive impairment alone for predicting 30-day mortality.

## Results

### Demographics

The study flowchart is shown in Figure 1. We conducted a baseline survey that recruited 9996 patients from six provinces, resulting in 9283 participants after deleting incomplete data and participants lost to follow-up at 30 days. Overall, the average age was 72.41 (SD=5.72), with 41.91% female. The prevalence of frailty, cognitive impairment and depression was 16.91%, 20.51%, and 16.17%, respectively. Females had a significantly higher proportion of illiterate individuals than men (23.65% versus 9.72%) and had a higher prevalence of frailty, cognitive impairment, and depression than males (18.79% versus 15.56%; 25.49% versus 16.91%; 19.09 versus 14.07%), as shown in Table 1

### Comparisons of Variables According to Frailty and Cognitive Impairment Status

Overall, the prevalence of cognitive frailty was 5.44%. Participants with cognitive frailty were older and more often female. Additionally, a significantly higher percentage were illiterate, suffered from depression, had lower handgrip strength and were malnourished (all  $P < 0.05$ ) compared with the other three groups. Furthermore, patients with cognitive frailty scored significantly lower in ADL and BMI (Table 2).

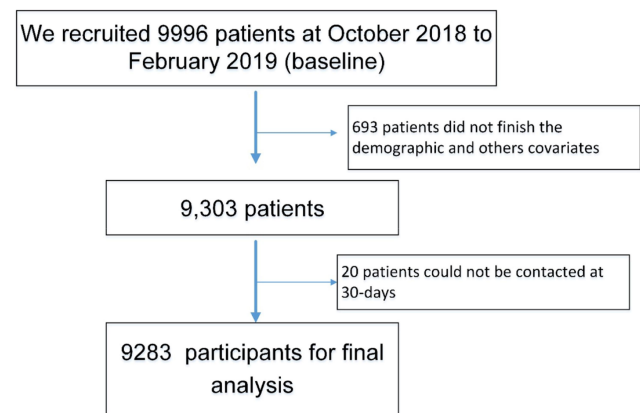


Figure 1 Flowchart of study selection.

**Table 1** Characteristics of the Study Population According to Gender

Variables	Overall	Female	Male	P-value
Sample	9283	3891(41.91)	5392(58.09)	
Age (years) (mean, SD)	72.41±5.72	72.28±5.50	72.51±5.87	0.060
Education (n, %)				<0.001
Illiterate	1444(15.56)	920(23.65)	524(9.72)	
Primary	2666(28.72)	1136(29.20)	1530(28.38)	
Meddle	3787(40.80)	1417(36.43)	2370(43.96)	
University	1384(14.91)	417(10.72)	967(17.94)	
ADL (mean, SD)	27.88±4.23	27.65±4.37	28.04±4.12	<0.0001
BMI (kg/m <sup>2</sup> ) (mean, SD)	23.61±3.49	23.65±3.70	23.57±3.34	0.259
Ethnicity (n, %)				0.299
Other	510(5.49)	225(5.78)	285(5.29)	
Han	8773(94.51)	3666(94.22)	5107(94.71)	
Marital status (n, %)				<0.001
Marriage	8253(89.1)	3206(82.52)	5047(93.69)	
Divorced or widowed	1019(10.9)	679(17.48)	340(6.31)	
Smoking status (n, %)				<0.001
Never smoking	6104(65.75)	3649(93.78)	2455(45.53)	
Current smoking	1042(11.23)	108(2.78)	934(17.32)	
Smoking before	2137(23.02)	134(3.44)	2003(37.15)	
Alcohol consumption (n, %)				<0.001
Never	7071(76.17)	3771(96.92)	3300(61.20)	
Current	1096(11.81)	78(2.00)	1018(18.88)	
Quit	1116(12.02)	42(1.08)	1074(19.92)	
Long-time bedridden (n, %)				0.203
No	9048(97.4)	3783(97.22)	5265(97.64)	
Yes	235(2.6)	108(2.78)	127(2.36)	
Vision (n, %)				0.0002
Yes	1911(20.6)	873(22.44)	1038(19.25)	
No	7372(79.4)	3018(77.56)	4354(80.75)	
Hearing (n, %)				0.317
Yes	1661(17.89)	678(17.42)	983(18.23)	
No	7622(82.11)	3213(82.58)	4409(81.77)	
Urinary function (n, %)				<0.001

(Continued)

**Table 1** (Continued).

Variables	Overall	Female	Male	P-value
Dysfunction	1288(13.87)	347(8.92)	941(17.45)	
Normal	7995(86.12)	3544(91.08)	4451(82.55)	
Frailty (n, %)				<0.001
Yes	1570(16.91)	731(18.79)	839(15.56)	
No	7713(83.08)	3160(81.21)	4553(84.44)	
Cognitive impairment (n, %)				<0.001
No	7379(79.48)	2899(74.51)	4480(83.09)	
Yes	1904(20.51)	992(25.49)	912(16.91)	
Depression (n, %)				<0.0001
No	7707(83.83)	3116(80.91)	4591(85.93)	
Yes	1487(16.17)	735(19.09)	752(14.07)	
MNA-SF (n, %)				0.136
12–14	5081(54.73)	2083(53.53)	2998(55.60)	
8–11	3224(34.73)	1391(35.75)	1833(34.00)	
0–7	978(10.54)	417(10.72)	561(10.40)	
Low Hand grip strength (n, %)				0.034
Yes	4742(51.08)	2038(52.38)	2704(50.15)	
No	4541(48.92)	1853(47.62)	2688(49.85)	
The length of hospital stay (mean, SD)	9.67±7.23	9.45±6.81	9.82±7.51	0.016

**Abbreviations:** MNA-SF, Mini-Nutritional Assessment-Short Form (normal nutritional status:12–14; at risk of malnutrition: 8–11; malnourished:0–7).

## Univariate Analysis for the Variables Associated with 30-Day Mortality

Overall, the average ADL and age in the deceased group was significantly higher than that of the surviving group (28.04±4.12 versus 27.65±4.37,  $P<0.0001$ ; 72.4±5.7 versus 73.8±6.1,  $P=0.014$ ). In addition, the percentage of patients with cognitive frailty, depression and low hand-grip strength in the deceased group was higher than that of the surviving group (all  $P<0.001$ ), as shown in Table 3.

## Association Between Cognitive Frailty Status and 30-Day Mortality

Table 4 indicates the association between 30-day mortality and cognitive frailty status. Overall, the ORs with

95% CIs for 30-day mortality among patients with cognitive frailty, frailty alone, and cognitive impairment alone, compared to patients in the nonfrail and intact cognitive function group, were 6.83 (95% CI: 3.91–11.95), 2.88 (95% CI: 1.63–5.06), and 1.80 (95% CI: 0.99–3.28), respectively in the raw model. Additionally, these associations for 30-day mortality in each category decreased after adjusting for different variables in different models. After adjusting for age, gender, education, depression and ADL, the ORs with 95% CIs for 30-day mortality among patients with cognitive frailty, frailty alone, and cognitive impairment alone, compared to those who were nonfrail and with intact cognitive function, were 3.43 (95% CI: 1.80–6.55), 1.85 (95% CI: 1.01–3.41), and 1.43 (95% CI: 0.77–2.65), respectively.

**Table 2** Characteristics of the Study Population According to Frailty and Cognitive Impairment Status

Variables	Frailty and Cognitive Impairment (505)	Frailty Only (1065)	Cognitive Impairment Only (1399)	Nonfrail and with Normal Cognitive Function (6314)	P-value
Age (years) (mean, SD)	75.10±6.66	73.23±5.99	73.25±6.05	71.87±5.41	<0.0001
ADL (mean, SD)	23.41±6.51	25.21±5.34	27.96±4.16	28.67±3.30	<0.0001
BMI (kg/m <sup>2</sup> ) (mean, SD)	22.61±3.76	23.11±3.94	23.44±3.69	23.80±3.33	<0.0001
Gender (n, %)					<0.0001
Female	267(52.87)	464(43.56)	725(51.82)	2435(38.56)	
Male	238(47.13)	601(56.44)	674(48.18)	3879(61.44)	
Ethnicity (n, %)					<0.0001
Han	433(85.74)	987(92.67)	1290(92.20)	6063(96.02)	
Other	72(14.25)	78(7.33)	109(7.80)	251(3.98)	
Education (n, %)					<0.0001
Illiterate	193(38.21)	159(14.93)	408(29.16)	684(10.83)	
Primary	149(29.51)	322(30.23)	492(35.17)	1703(26.98)	
Middle	126(24.95)	422(39.62)	400(28.60)	2839(44.98)	
University	37(7.34)	162(15.22)	99(7.07)	1086(17.21)	
Marital status (n, %)					<0.0001
Marriage	408(80.95)	932(87.60)	1184(84.75)	5729(90.83)	
Divorced or widowed	96(19.05)	132(12.40)	213(15.25)	578(9.17)	
Smoking status (n, %)					0.0007
Never smoking	352(69.70)	699(65.63)	978(69.91)	4075(64.54)	
Current smoking	42(8.31)	107(10.05)	148(10.57)	745(11.80)	
Smoking before	111(21.99)	259(24.32)	273(19.52)	1494(23.66)	
Alcohol consumption (n, %)					<0.0001
Never	422(83.56)	823(77.28)	1106(79.06)	4720(74.75)	
Current	23(4.55)	94(8.82)	145(10.36)	834(13.21)	
Quit	60(11.89)	148(13.90)	148(10.58)	760(12.04)	
Long-time bedridden (n, %)					
No	446(88.32)	968(90.89)	1379(98.57)	6255(99.06)	
Yes	59(11.68)	97(9.11)	20(1.43)	59(0.94)	
Vision (n, %)					<0.001
Yes	147(29.10)	286(26.85)	306(21.87)	1172(18.56)	

(Continued)



**Table 2** (Continued).

Variables	Frailty and Cognitive Impairment (505)	Frailty Only (1065)	Cognitive Impairment Only (1399)	Nonfrail and with Normal Cognitive Function (6314)	P-value
No	358(70.90)	779(73.14)	1093(78.13)	5142(81.44)	
Hearing (n, %)					<0.0001
Yes	129(25.54)	250(23.47)	259(18.51)	1023(16.20)	
No	376(74.46)	815(76.52)	1140(81.49)	5291(83.80)	
Urinary function (n, %)					<0.0001
Dysfunction	110(21.78)	222(20.85)	166(11.87)	790(12.51)	
Normal	395(78.22)	843(79.15)	1233(88.13)	5524(87.49)	
Depression (n, %)					<0.0001
No	289(58.03)	634(60.21)	1145(82.55)	5639(90.14)	
Yes	209(41.97)	419(39.79)	242(17.45)	617(9.86)	
MNA-SF (n, %)					<0.0001
12–14	70(13.86)	283(26.57)	598(42.74)	4130(65.41)	
8–11	232(45.94)	475(44.60)	656(46.89)	1861(29.47)	
0–7	203(40.20)	307(28.83)	145(10.36)	323(5.12)	
Low Hand grip strength (n, %)					<0.001
Yes	422(83.56)	741(69.58)	856(61.19)	2723(43.13)	
No	83(16.44)	324(30.42)	543(38.81)	3591(56.87)	
The length of hospital stay (mean, SD)	11.02±7.23	11.33±7.99	9.52±6.94	9.31±7.11	<0.0001

**Abbreviations:** MNA-SF, Mini-Nutritional Assessment-Short Form (normal nutritional status: 12–14; at risk of malnutrition: 8–11; malnourished: 0–7); ADL, activities of daily living.

## Stratified Association Between Cognitive Frailty Status and 30-Day Mortality by Gender

This association between cognitive frailty status and 30-day mortality was almost unchanged by gender (female versus male), with a significantly greater risk of 30-day mortality in participants with cognitive frailty in both females and males. Detailed information is shown in [Figure 2](#).

## Prognostic Score Comparison

Our study shows that the identification of 30-day mortality was significantly higher using cognitive frailty (AUC=0.676

[95% CI: 0.621–0.731]) than either frailty (AUC=0.644 [95% CI: 0.594–0.694]) or cognitive impairment (AUC=0.606 [95% CI: 0.556–0.655]) alone. In addition, there was a significant difference when the AUC of cognitive frailty was compared to that of cognitive impairment ( $P=0.001$ ) or frailty ( $P=0.025$ ) alone. However, the difference in AUC between frailty alone and cognitive impairment alone was not significant (0.193). The results are shown in [Figure 3](#).

## Discussion

Our study found that Chinese inpatients with cognitive frailty or frailty had an increased risk of 30-day mortality

**Table 3** Univariate Analysis for the Variables Associated with 30-Day Mortality

Variables	Survivor at 30-Day	Deceased at 30-Day	P-value
Age (years) (mean, SD)	72.4±5.7	73.8±6.1	0.014
Gender (n, %)			
Female	3851(41.93)	40(40.40)	0.759
Male	5333(58.07)	59(59.60)	
Education (n, %)			<0.0001
Illiterate	1423(15.50)	21(21.21)	
Primary	2622(28.56)	44(44.44)	
Meddle	3758(40.93)	29(29.29)	
University	1379(15.02)	5(5.05)	
ADL (mean, SD)	27.65±4.37	28.04±4.12	<0.0001
BMI (kg/m <sup>2</sup> ) (mean, SD)	23.65±3.70	23.57±3.34	0.2596
Frailty cognitive category (n, %)			<0.0001
Cognitive frailty	479(5.22)	26(26.26)	
Only Frailty	1046(11.39)	19(19.19)	
Only cognitive impairment	1384(15.07)	15(15.15)	
No frailty and no cognitive impairment	6275(68.33)	39(39.39)	
Ethnicity (n, %)			0.256
Han	8682(94.53)	91(91.92)	
Other	502(5.47)	8(8.08)	
Marital status (n, %)			0.717
Marriage	8166(89.02)	87(87.88)	
Divorced or widowed	1007(10.98)	12(12.12)	
Smoking status (n, %)			0.204
Never smoking	6046(99.05)	58(58.59)	
Current smoking	1026(98.46)	16(16.16)	
Smoking before	2112(98.83)	25(25.25)	
Alcohol consumption (n, %)			0.444
Never	6999(76.21)	72(72.73)	
Current	1085(11.81)	11(11.11)	
Quit	1100(11.98)	16(16.16)	

(Continued)

**Table 3** (Continued).

Variables	Survivor at 30-Day	Deceased at 30-Day	P-value
Long-time bedridden (n, %)			0.003
No	8957(97.65)	91(91.92)	
Yes	227(2.47)	8(8.08)	
Vision (n, %)			0.06
Yes	1898(20.67)	13(13.13)	
No	7286(79.33)	86(86.87)	
Hearing (n, %)			0.939
Yes	1643(17.89)	18(18.18)	
No	7541(82.11)	81(81.82)	
Urinary function (n, %)			0.340
Dysfunction	1271(13.84)	17(17.17)	
Normal	7913(86.16)	82(82.83)	
Frailty (n, %)			<0.0001
NO	7659(83.40)	54(54.55)	
Yes	1525(16.60)	45(45.45)	
Cognitive impairment (n, %)			<0.0001
No	7321(79.71)	58(58.59)	
Yes	1863(20.29)	41(41.41)	
Depression (n, %)			<0.0001
No	7641(84.00)	66(67.35)	
Yes	1455(16.00)	32(32.65)	
MNA-SF (n, %)			<0.001
12–14	5061(55.11)	20(20.20)	
8–11	3181(34.64)	43(43.43)	
0–7	942(10.26)	36(36.36)	
Low Hand grip strength (n, %)			<0.0001
Yes	4661(50.75)	81(81.82)	
No	4523(49.25)	18(18.18)	
The length of hospital stay (mean, SD)	9.45±6.81	9.82±7.51	0.016

**Abbreviations:** MNA-SF, Mini-Nutritional Assessment-Short Form (normal nutritional status: 12–14; at risk of malnutrition: 8–11; malnourished: 0–7).



**Table 4** Multiple Variable Regression Analysis for 30-Day Mortality According to Status of Cognitive Impairment and Frailty

Exposure	Non-Adjusted (OR,95%, CI)	Adjusted I (OR,95%, CI)	Adjusted II (OR,95%, CI,)	Adjusted III (OR,95%, CI)
Nonfrail and no cognitive	Reference	Reference	Reference	Reference
Cognitive impairment only	1.80(0.99–3.28)	1.54(0.83–2.85)	1.50(0.81–2.78)	1.43(0.77–2.65)
Frailty only	2.88(1.63–5.06)	2.71(1.53–4.78)	2.39(1.32–4.34)	1.85(1.01–3.41)
Frailty and cognitive impairment	6.83(3.91–11.95)	5.73(3.16–10.36)	5.02(2.71–9.33)	3.43(1.80–6.55)

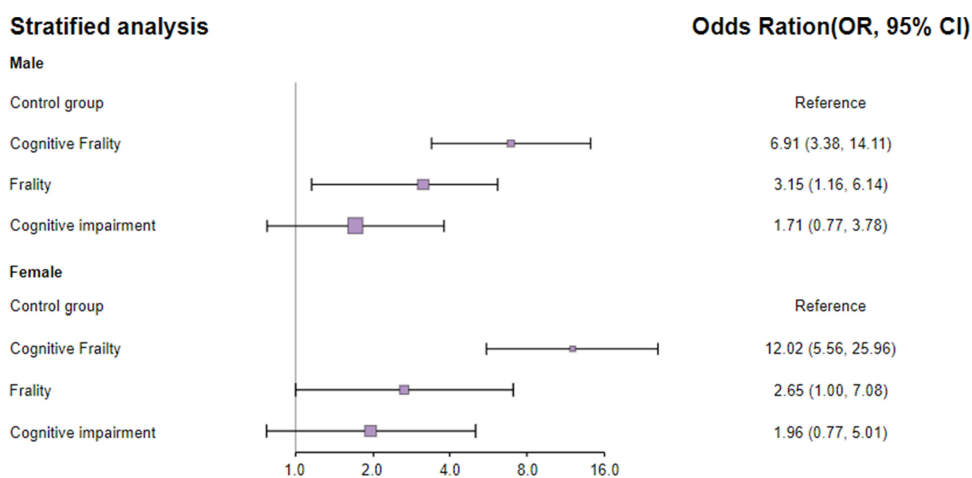
**Notes:** Adjusted I: age gender education. Adjusted II: age gender education, depression. Adjusted III: age gender education, depression, and ADL.

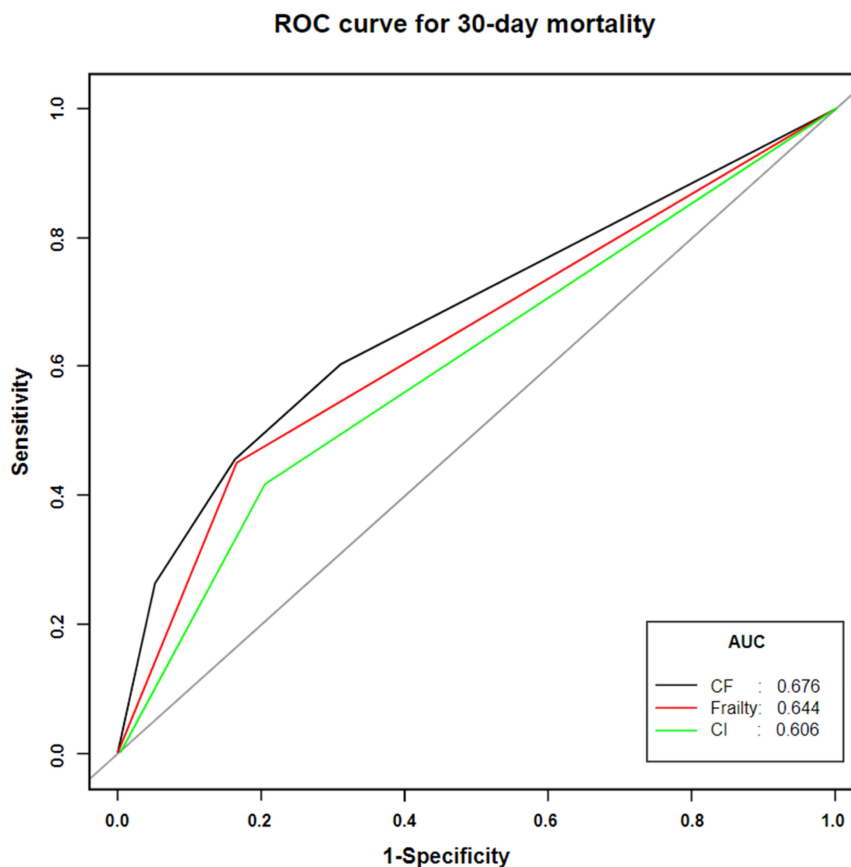
compared to those without frailty and cognitive impairment. However, the association in participants with only cognitive impairment compared to patients without frailty and cognitive impairment was not found to be significant, indicating that the combined effect of frailty and cognitive impairment was more hazardous for patients. Moreover, we found that cognitive frailty had better discrimination performance for 30-day mortality than frailty or cognitive impairment alone. Additionally, stratified analysis based on gender showed similar results. These findings highlight that early screening for frailty coexisting with cognitive impairment for older inpatients is essential. Given that these two geriatric syndromes undergo a dynamic change from prefrailty to frailty, it is crucial to perform effective interventions, such as prescribing exercise and nutritional programs for this vulnerable elderly population.

The prevalence of cognitive frailty was 5.44%, which is slightly higher than that in a previous study conducted in a community setting. In a study reported by Shimada et al with 5104 community-dwelling older adults, the prevalence of cognitive frailty, measured by the Mini-Mental

State Examination (MMSE), and the frailty phenotype was 2.7%.<sup>29</sup> In another study conducted with 8864 older adults, the prevalence of cognitive frailty was 1.2%.<sup>30</sup> Furthermore, in a study that used modified CHS criteria and MMSE to examine frailty and cognitive impairment, the prevalence of cognitive impairment was 4.4%,<sup>31</sup> which was close to our study. However, another study combined prefrailty and frailty to define cognitive frailty, resulting in a higher prevalence of 22%.<sup>32</sup> Similar results were found in a recent study that included prefrailty and frailty, with a prevalence of 22.6%,<sup>8</sup> which was higher than our results. Therefore, different subjects, definitions and measurement tools of frailty and cognitive impairment can lead to divergent prevalence results. Given the different definitions of cognitive frailty, further studies need to define a standard definition that will help to guild clinical staff to prevent and treat cognitive impairment.

A great number of studies have been published exploring this association, with a majority of these studies based on community-dwelling older adults<sup>13,15,33</sup> or nursing home residents.<sup>22</sup> A study from Singapore Longitudinal

**Figure 2** Stratified analysis between cognitive frailty status and 30-day mortality by gender.



CF: Cognitive frailty

CI: Cognitive impairment

**Figure 3** Three prediction models for 30-day mortality based on receiver operation characteristic. Model 1 for cognitive frailty (black); Model 2 for frailty alone; Model 3 for cognitive impairment alone.

Aging (SLA), including 2375 community-dwelling older people, reported that the cognitive frailty group had an approximately 5-fold greater risk of mortality when compared to the robust without cognitive impairment group.<sup>11</sup> In addition, a cohort study with 3677 noninstitutionalized older people reported that the hazard ratio for mortality was 1.69 (95% CI: 1.43–2.01) among cognitive frailty patients compared with robust individuals without cognitive impairment.<sup>8</sup> Our findings indicated that patients with cognitive frailty had the strongest factor associated with 30-day mortality risk (3.43-fold) compared to those without frailty and cognitive impairment, which is consistent with these previously mentioned studies. However, our study focused on older adults in hospitals, and previously mentioned studies were community-dwelling older people.

In fact, older hospitalized patients often suffer from multiple comorbidities, leading to more vulnerability to the detrimental effects of cognitive frailty. Numerous older adults need to access the hospital to get to the root of their health problems. Cognitive frailty will become a serious issue that influences the health of hospitalized patients. A previous meta-analysis reported that older people with cognitive frailty had an increased risk of adverse outcomes, such as mortality, poor quality of life and hospitalization, than robust individuals without cognitive impairment.<sup>34</sup> However, screening cognitive frailty is not routine clinical practice for hospitalized patients, resulting in neglect of the potential risk of cognitive frailty by medical staff. Therefore, our study and previous studies indicate the cumulative effects of combined frailty and

cognitive impairment on adverse outcomes. It is very important that clinicians pay much more attention to these vulnerable patients.

A previous study explored the complicated pathways for cognitive frailty leading to death, indicating that inflammatory, vascular and hormonal factors may play an important role in coexisting frailty and cognitive impairment.<sup>35,36</sup> Given the involvement of these complex mechanisms, more animal experiments and studies are needed to investigate the neurobiological pathways to determine the reason that cognitive frailty increases the risk of death. However, preventive and managerial measures for reversing cognitive impairment are a priority for clinicians and nurses. A previous study found that patients suffering from cognitive impairment who undertook physical activity were associated with a 36% reduction in mortality compared to physically inactive patients.<sup>8</sup> This study has important clinical implications. We speculate that regular physical activity improves muscle strength, which reduces mortality rates. Further evidence-based research is urgently required to understand this mechanism, guiding how to employ this effective intervention in a community- or hospital-based setting.

In our study, we need to be cautious when making recommendations to guide clinical practice. First, we collected data with a 30-day outcome, which is short-term. A longer follow-up is required to validate this association. Second, the design of the observational study was too limited to make a causal reference. Third, we used a simple cognitive tool that was suitable for application in a clinical setting, whereas numerous studies used MMSE ( $\leq 25$  points) to detect cognitive impairment;<sup>8,11</sup> therefore, our results may generate a different prevalence of cognitive frailty that could not reflect multidimensional aspects of inpatients' capacity and function, leading to an underestimation of the risk of mortality. Fourth, other important confounding factors, such as the Charlson comorbidity index score,<sup>37</sup> were not collected in the baseline survey, which may overestimate these results. Although this study has some limitations, several strengths also exist that merit attention. First, we adopted two-stage cluster sampling with a large number of participants from multiple centers, minimizing possible selection bias. Second, we used comprehensive statistical analysis, namely multivariate logistic regression analysis, to adjust for various covariates and we used stratified analysis to calculate all results.

## Conclusions and Implications

In this study, we found that patients with cognitive frailty, a term describing a new concept of coexisting frailty and cognitive impairment, had an increased risk of 30-day mortality compared to older Chinese robust inpatients with intact cognitive function. This is a reminder that clinicians and nurses urgently need to screen for these two geriatric syndromes when older patients are admitted to the hospital. Furthermore, they need to plan for a comprehensive intervention, such as exercise and cognitive training, during hospitalization.

## Abbreviations

ADL, activities of daily living; OR, odds ratio; MNA-SF, Mini-Nutritional Assessment-Short Form; CFS, Clinical Frailty Scale; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; CHS criteria, Cardiovascular Health Study; AUC, area under the curve; GDS, Geriatric Depression Scale GDS.

## Data Sharing Statement

Deidentified data are accessible on reasonable request via e-mail to the corresponding author.

## Ethical Statement

The study was approved by Ethics Committee of Peking Union Medical College Hospital (number S-K540). In addition, participants have provided written informed consent for this project. The authors confirm that this study was conducted in accordance with the Declaration of Helsinki.

## Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare no competing interests in this work.

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