



## Is frailty associated with short-term outcomes for elderly patients with acute coronary syndrome?

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### Abstract

**Background** Frailty is a new prognostic factor in cardiovascular medicine due to the aging and increasingly complex nature of elderly patients. It is useful and meaningful to prospectively analyze the manner in which frailty predicts short-term outcomes for elderly patients with acute coronary syndrome (ACS). **Methods** Patients aged  $\geq 65$  years, with diagnosis of ACS from cardiology department and geriatrics department were included from single-center. Clinical data including geriatrics syndromes were collected using Comprehensive Geriatrics Assessment. Frailty was defined according to the Clinical Frailty Scale and the impact of the co-morbidities on risk was quantified by the coronary artery disease (CAD)—specific index. Patients were followed up by clinical visit or telephone consultation and the median follow-up time is 120 days. Following-up items included all-cause mortality, unscheduled return visit, in-hospital and recurrent major adverse cardiovascular events. Multivariable regression survival analysis was performed using Cox regression. **Results** Of the 352 patients, 152 (43.18%) were considered frail according to the study instrument (5–7 on the scale), and 93 (26.42%) were considered moderately or severely frail (6–7 on the scale). Geriatrics syndromes including incontinence, fall history, visual impairment, hearing impairment, constipation, chronic pain, sleeping disorder, dental problems, anxiety or depression, and delirium were more frequently in frail patients than in non-frail patients ( $P = 0.000, 0.031, 0.009, 0.014, 0.000, 0.003, 0.022, 0.000, 0.074, \text{ and } 0.432$ , respectively). Adjusted for sex, age, severity of coronary artery diseases (left main coronary artery lesion or not) and co-morbidities (CAD specific index) by Cox survival analysis, frailty was found to be strongly and independently associated with risk for the primary composite outcomes: all-cause mortality [Hazard Ratio (HR) = 5.393; 95% CI: 1.477–19.692,  $P = 0.011$ ] and unscheduled return visit (HR = 2.832; 95% CI: 1.140–7.037,  $P = 0.025$ ). **Conclusions** Comprehensive Geriatrics Assessment and Clinical Frail Scale were useful in evaluation of elderly patients with ACS. Frailty was strongly and independently associated with short-term outcomes for elderly patients with ACS.

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**Keywords:** Acute coronary syndrome; Comprehensive Geriatrics Assessment; Frailty; Survival analysis; Unscheduled return visit

## 1 Introduction

Acute coronary syndrome (ACS) is one of the most common causes of death for elderly patients. With prolonged life expectancy and development of the interventional treatment, more and more new problems such as geriatrics syndromes are developing and getting attention from cardiologists and geriatricians. Due to the under-represen-

tation of ACS patients over 65 years of age in clinical trials, the evidence for managing elderly ACS patients is especially limited. Recently, frailty has become a high-priority theme in cardiovascular medicine due to the aging and increasingly complex nature of elderly patients.<sup>[1]</sup> China is a rapidly aging society with persistent high prevalence of cardiovascular disease (CVD) in the elderly population, the health care system and doctors are facing increasing challenges to effectively care for these patients having their own physiology characteristic.<sup>[2]</sup> However, frailty is seldom used in evaluation of cardiovascular treatment and prognosis. Our study will focus on: (1) to figure out the prevalence of frailty and situation of geriatrics syndromes in ACS patients in China; (2) will frailty be an independent risk factor of the prognosis (defined as unscheduled returned visit, or all-

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cause mortality) of these patients? (3) If so, does this index remain significant after controlling for co-morbidities?

## 2 Methods

### 2.1 Study population

This was a prospective cohort study. Three hundred and fifty-two patients from cardiology department and Geriatrics department of Peking Union Medical College Hospital were included from December 2014 to May 2015. Inclusion criteria were: (1) If the patients were  $\geq 65$  years; (2) with diagnosed ACS according to their attending physicians. ACS was defined as a spectrum of conditions with non-ST-elevation acute coronary syndromes (NSTEMI) and ST-elevation myocardial infarction (STEMI) according to the American College of Cardiology Foundation and American Heart Association.<sup>[3,4]</sup> There were two exclusion criteria: (1) If the patient was not willing to participate; (2) if the patient was not able to be evaluated because of communication problems or insufficient clinical information to be judged of frailty. Each participant provided written informed consent.

### 2.2 Clinical data collection

Electronic database was built and all the demographic and clinical characteristics were recorded as following: chronological age, sex, body mass index, co-morbidities, geriatrics syndromes and laboratory indicators.

Supposed impact of the co-morbidities on risk was quantified by the coronary artery disease (CAD)-specific index (Table 1).<sup>[5]</sup> Current smokers were defined as patients who were smoking up to admission. Hypertension was defined as patients with a pre-hospital diagnosis of high blood pressure either on or off medications. Cerebro-vascular accident/transient ischemic attack (CVA/TIA) was defined as patients with a history of transient ischemic attack or permanent neurological deficit due to either an ischemic or hemorrhagic cause. Diabetes mellitus (DM) was defined as patients with a pre-hospital diagnosis of type 2 DM (on oral/insulin medications or diet control). New onset DM at the time of the ACS would be defined based on fasting blood sugars and HbA1c which were performed after admission. DM with complications included diabetic retinopathy, diabetic peripheral neuropathy or diabetic nephropathy.

### 2.3 Assessment of frailty and geriatrics syndromes

Frailty was evaluated using a global clinical measure of 7-category Clinical Frail Index (Table 2), which has been proved to be an effective measure of frailty and provided

predictive information similar to that of other established tools about death or prognosis.<sup>[6]</sup> The advantage over the tools previously developed is that Clinical Frailty Scale was easy to use and may readily be administered in a clinical setting.<sup>[6]</sup>

Comprehensive Geriatrics Assessment was used to evaluate geriatrics syndromes such as incontinence,<sup>[7]</sup> constipation, fall history, visual impairment, hearing impairment, chronic pain, sleeping disorder, dental problems, anxiety or depression and delirium.

### 2.4 Clinical outcomes

The primary outcomes were the composite of all-cause

**Table 1. CAD-specific index.**

Risk factors	Integer coefficient
Current smoker	1
Hypertension	1
History of CVA/TIA	1
DM	2
DM with complications	3
COPD	2
PVD	2
Tumor/lymphoma/leukemia	2
Moderate to severe renal disease*	7
Metastatic cancer	5

The integer coefficients are summed, and the resulting score denotes risk group, as follows: 0 to 1, low risk; 2 to 3, moderate risk; and 4, high risk. \*Defined as creatinine  $> 3$  mg/dL. CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; CVA: cerebro-vascular accident; DM: diabetes mellitus; PVD: peripheral vascular disease; TIA: transient ischemic attack.

**Table 2. Clinical frail scale.**

Scale	Index	Symptoms
1	Very fit	Robust, active, energetic, well motivated and fit; these people commonly exercise regularly and are in the most fit group for their age
2	Well	Without active disease, but less fit than people in category 1
3	Well, with treated co-morbid disease	Disease symptoms are well controlled compared with those in category 4
4	Apparently vulnerable	Although not frankly dependent, these people commonly complain of being "slowed up" or have disease symptoms
5	Mildly frail	With limited dependence on others for instrumental activities of daily living
6	Moderately frail	Help is needed with both instrumental and non-instrumental activities of daily living
7	Severely frail	Completely dependent on others for the activities of daily living, or terminally ill

mortality and unscheduled returned visit within the following period. The secondary outcomes were in-hospital major adverse cardiovascular events (MACE): composite of in-hospital death, stroke/transient ischemic attack, infection, major bleeding defined as intracranial bleeding, retroperitoneal bleeding, blood transfusion, hemoglobin decrease > 3 g/dL with overt cause, or hemoglobin decrease > 4 g/dL without overt source and recurrent cardiovascular events during follow-up.

## 2.5 Statistical analysis

Statistical analysis was performed via SPSS 22.0. Categorical data were analyzed by use of the  $\chi^2$  test or the Fisher exact test, and continuous variables were expressed as median compared with the student *t* test and inter quartile range (IQR) due to the non-parametric distribution. The association of frailty with the primary composite outcome was examined by Cox regression test adjusted for relevant prognostic variables [age, sex, severity of coronary artery diseases (left main coronary artery lesion or not) and co-morbidities (the score according to the CAD index)]. A two-sided  $P < 0.05$  was considered significant.

## 3 Results

### 3.1 Baseline characteristics

Between December 2014 and May 2015, 352 evaluable patients aged  $\geq 65$  years with diagnosed ACS were included at Peking Union Medical College Hospital. Of the 352 patients, 203 (57.7%) were male and 149 (42.3%) were female, the median age was 74 and the oldest patient was 90 years old. Among them, 190 (54.0%) were in their early elderly (65–74 years), 143 (40.6%) were in their middle elderly (75–84 years) and 19 (5.4%) were the oldest ( $\geq 85$  years). Of the 352 patients, 152 (43.2%) were considered frail according to the study instrument (5–7 on the scale), and 93 (26.4%) were considered moderately or severely frail (6–7 on the scale).

The baseline characteristics were presented in Table 3. Frail patients were slightly older than non-frail patients, with a mean age of 76 years versus 73 years ( $P < 0.0001$ ). Frail patients presented with a greater burden of co-morbidities, including higher rates of hypertension, chronic obstructive pulmonary disease, congestive heart failure, moderate to severe renal impairment, cerebro-vascular disease, malignant tumor, anemia and osteoporosis. They also had higher CAD index (all  $P < 0.05$  as showed in Table 3).

### 3.2 Geriatrics syndromes

Geriatrics syndromes were also more frequent in frail pa-

tients, including incontinence, constipation, fall history, visual impairment, hearing impairment, chronic pain, sleeping disorder, dental problems (all  $P < 0.05$  as showed in Table 4), which influence the patients quality of life as evaluated using SF-36 form. SF-36 mental component scale (MCS) was 48.00 (37.13, 61.50) in frail patients and 67.59 (48.37, 82.50) in non-frail patients respectively ( $P < 0.0001$ ).

### 3.3 Laboratory indicators

In ACS patients with frailty, nutrition indicators [data are presented as median (IQR)] such as hemoglobin (HGB):

**Table 3. Baseline patients characteristics.**

Variable	Non-frail (n, %) (n = 200)	Frail (n, %) (n = 152)	P
Male	170 (59.86)	123 (55.66)	0.342
65–74 yrs	130 (65.00)	60 (39.47)	< 0.0001*
75–84 yrs	66 (33.00)	77 (50.66)	< 0.0001*
$\geq 85$ yrs	4 (2.00)	15 (9.89)	< 0.0001*
Hypertension	146 (73.00)	130 (85.53)	0.005*
DM	77 (38.50)	72 (47.37)	0.095
COPD	7 (3.50)	23 (15.13)	< 0.0001*
Congestive heart failure	11 (5.50)	26 (17.11)	< 0.0001*
Moderate to severe renal impairment*	3 (1.50)	16 (10.53)	< 0.0001*
Peripheral vascular disease	93 (46.50)	68 (44.74)	0.742
Cerebro-vascular disease	29 (14.50)	45 (29.61)	< 0.0001*
Malignant tumor	14 (7.00)	26 (17.11)	0.003*
Peptic ulcer	19 (9.50)	14 (9.21)	0.921
Anemia	29 (14.50)	61 (40.13)	< 0.0001*
Hyperuricemia /Gout	20 (10.00)	16 (10.53)	0.872
Osteoporosis	21 (10.50)	30 (19.74)	0.015*
High CAD index score <sup>#</sup>	74 (37.00)	93 (61.18)	< 0.0001*

\* $P < 0.05$ , \*Ccr: endogenous creatinine clearance rate < 50 mL/min, <sup>#</sup>CAD index score  $\geq 4$ . CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus.

**Table 4. Geriatrics syndromes.**

Variable	Non-frail (n, %) (n = 200)	Frail (n, %) (n = 152)	P
Incontinence	62 (31.00)	78 (51.32)	< 0.0001*
Fall history	36 (18.00)	42 (27.63)	0.031*
Visual impairment	60 (30.00)	66 (43.42)	0.009*
Hearing impairment	65 (32.50)	69 (45.39)	0.014*
Constipation	68 (34.00)	95 (62.50)	< 0.0001*
Chronic pain	89 (44.50)	92 (60.53)	0.003*
Sleeping disorder	68 (34.00)	70 (46.05)	0.022*
Dental problems	113 (56.50)	123 (80.92)	< 0.0001*
Anxiety or depression	8 (4.00)	13 (8.55)	0.074
Delirium	0 (0)	1 (0.66)	0.432

\* $P < 0.05$ .

127.00 (112.00, 136.00) g/L, serum albumin (Alb): 39.00 (36.00, 42.00) g/L, pre-albumin (PA): 203.00 (149.00, 238.00) mg/L were all significantly lower than non-frail group with HGB: 135.00 (125.75, 143.00) g/L, serum Alb: 42.00 (39.00, 44.00) g/L, PA: 223.00 (191.75, 256.00) mg/L ( $P < 0.05$ ), respectively, (Table 5). Inflammation index like high-sensitivity C-reactive protein (hs-CRP): 3.87 (1.47, 14.51) and interleukin 6 (IL-6): 8.50 (4.90, 18.00) were significantly higher in frail patients than in non-frail group [hs-CRP: 1.82 (0.88, 5.20) and IL-6: 6.45 (3.45, 13.60)], ( $P < 0.05$ ). In multiple linear regression models that adjusted for underlying diseases like anemia, moderate to severe renal impairment and co-morbidities (CAD specific index), frailty was still closely related to the above parameters ( $P < 0.05$ ).

### 3.4 Outcomes

Frail patients were more likely to be treated in intensive cardiac care units than non-frail patients [frail,  $n = 50/152$  (32.89%); non-frail,  $n = 41/200$  (20.50%);  $P = 0.009$ ]. Whereas, frail patients were less likely to undergo coronary angiography than non-frail patients [frail,  $n = 115/152$  (75.66%); non-frail,  $n = 170/200$  (85.00%);  $P = 0.027$ ]. Patients with severe co-morbidities were less likely to undergo coronary angiography and submitted to invasive treatment.

Patients were followed up by clinical visit or telephone consultation. The median follow-up time is 120 days, the longest follow-up time is 190 days, two were lost. Within the follow-up time, 18 patients (5.1%) were died, 73 (20.7%) had unscheduled returned visit (URV). Frailty was associated with increased in-hospital mortality [non-frail,  $n = 0$  (0); frail,  $n = 7$  (2.0%);  $P = 0.002$ ]. Among them, one was

died of ventricular fibrillation; two were died of cardiac shock; one was died of cardiac rupture; three were died of heart failure caused by infection; no statistical difference was showed at in-hospital MACE {major bleeding, [non-frail,  $n = 1$  (0.5%); frail,  $n = 2$  (1.3%);  $P = 0.41$ ]; infection [non-frail,  $n = 2$  (1.0%); frail,  $n = 5$  (3.3%);  $P = 0.13$ ]}

Frailty was associated with increased all-cause mortality during follow-up. Two patients (1.0%) in the non-frail group died (including sudden death = 1, reinfarction = 1) vs. nine (5.9%) in the frail group (including sudden death = 1, heart failure = 2, lung infection = 3, malignant arrhythmias = 1, multiple organ failure = 1, pulmonary embolism = 1;  $P = 0.009$ ). Furthermore, frailty was also associated with increased URV as showed in Table 6, [non-frail = 24 (12.0%), frail = 49 (32.2%),  $P < 0.0001$ ].

In multivariable Cox regression models that adjusted for age, sex, severity of coronary artery diseases [left main (LM) lesion or not] and co-morbidities (CAD specific index) (Figure 1), each 1-category increment of Clinical Frailty

**Table 6. Unscheduled return visit.**

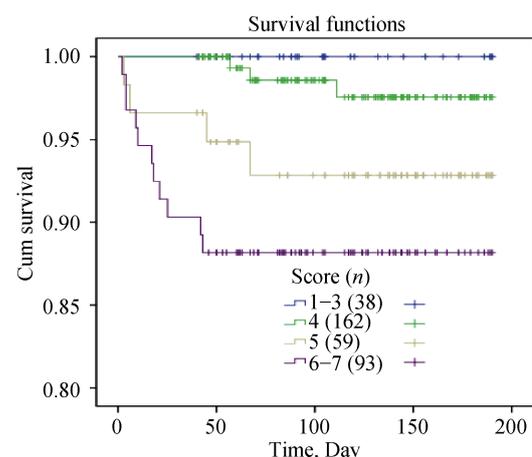
Variable	Non-frail ( $n = 200$ )	Frail ( $n = 152$ )	$P$
Unscheduled return visit	24	49	$< 0.0001^*$
Angina/re-infarction/need PCI	4	7	0.164
Peripheral vascular disease	0	6	0.005*
Major bleeding	2	8	0.017*
Inappropriate pharmacy	1	2	0.409
Dizziness/Headache/TIA	8	6	0.980
Infection	5	6	0.439
Congestive heart failure	2	4	0.241
Malignant tumor	1	2	0.410
Fall/Fracture	0	3	0.046*
URV to other departments	1	5	0.045*

\* $P < 0.05$ . PCI: percutaneous coronary intervention; TIA: transient ischemic attack; URV: unscheduled return visit.

**Table 5. Laboratory indicators.**

Variable	Non-frail [M (Q <sub>1</sub> , Q <sub>3</sub> ) ( $n = 200$ )	Frail [M (Q <sub>1</sub> , Q <sub>3</sub> ) ( $n = 152$ )	$P$
HGB	135.00 (125.75, 143.00)	127.00 (112.00, 136.00)	$< 0.0001^*$
HCT	39.90 (37.38, 42.53)	37.30 (33.60, 40.50)	$< 0.0001^*$
TC	3.77 (3.19, 4.47)	3.83 (3.33, 4.32)	0.893
TG	1.17 (0.83, 1.55)	1.13 (0.88, 1.78)	0.505
LDL-C	2.10 (1.72, 2.69)	2.07 (1.75, 2.48)	0.460
HDL-C	0.99 (0.82, 1.18)	0.95 (0.81, 1.17)	0.405
HbA1C	6.00 (5.63, 6.70)	6.00 (5.53, 6.88)	0.992
Alb	42.00 (39.00, 44.00)	39.00 (36.00, 42.00)	$< 0.0001^*$
PA	223.00 (191.75, 256.00)	203.00 (149.00, 238.00)	0.005*
UA	343.00 (283.00, 388.00)	372.00 (282.25, 443.25)	0.083
hs-CRP	1.82 (0.88, 5.20)	3.87 (1.47, 14.51)	0.001*
IL-6	6.45(3.45, 13.60)	8.50(4.90, 18.00)	0.011*

\* $P < 0.05$ . HbA1C: hemoglobinA1C; HCT: hematocrit; HDL-C: high density Lipoprotein; HGB: hemoglobin; hs-CRP: high-sensitivity C-reactive protein; IL-6: Interleukin 6; LDL-C: low density lipoprotein; Q1: Quartile 1, 25%; Q3: Quartile 3, 75%; TC: total cholesterol; TG: triglyceride; PA: prealbumin; UA: uric acid.



**Figure 1. Kaplan-Meier curves.** Adjusted for age and sex, for study participants ( $n$ ) over the medium term (120 days), according to their scores on the Clinical Frailty Scale. Some scores were grouped.

Scale significantly increased the short-term risks of all-cause mortality, HR = 5.393 (95% CI: 1.477–19.692,  $P = 0.011$ ) and unscheduled return visit, HR = 2.832 (95% CI: 1.140–7.037,  $P = 0.025$ ).

#### 4 Discussion

From the results above, the prevalence of frailty and geriatrics syndrome were high in elderly patients with ACS and frailty was independently associated with the short-term outcomes for elderly patients with ACS.

Frailty is defined as a geriatric syndrome of five components including unintentional weight loss, low physical activity, low strength, slow motor performance, and low energy. It can also be easily remembered as the abbreviation of FRAIL [Fatigue, Resistance (can you walk up one flight of stairs?), Aerobic (Can you walk more than a block?), Illness (more than five), Loss of weight (more than 5% in six months)].<sup>[8]</sup> It's an age-related, biological vulnerability to adverse outcomes that stems from alterations in multiple physiological systems. Data from US shows that 7.0% of cardiovascular health study cohort met frailty criteria.<sup>[9]</sup> Patients with frailty will have higher risk for poor outcomes, slower recovery rate, more iatrogenic complications, higher mortality rate.<sup>[10–12]</sup> Frail status also predicted early mortality, increased hospitalization, increased falls, decline in function.<sup>[13–15]</sup> Upward of 20 frailty assessment tools have been developed, with most tools revolving around the core phenotypic domains of frailty measured by physical performance tests and questionnaires. Study shows, simple assessment scales can also play a good role in the assessment, diagnosis and prediction as complex multi-project.<sup>[16]</sup> So we chose the internationally recognized, efficient and easily used Clinical Frail Scale as the assessment tool of frailty in our study.

With the aging population and improvement of diagnosis and treatment of CVD, cancer and renal insufficiency disease, epidemiological data of CVD also changed. A large cohort study in US shows,<sup>[17]</sup> after interventional treatment, five years cardiovascular mortality decreased by 33%, while non-cardiovascular mortality increased by 57%. So attention should be paid from another aspect. In our study, 167 (44.47%) patients had high coronary heart disease specific index (CAD specific index  $\geq 4$ ) and patients with severe renal impairment and malignant tumor were also included, which were always excluded in previous studies. Therefore, our study of selected objects was closer to the real world experience of clinical work. Our study showed, the proportion of frailty was increasing with age rising. In the early elderly (65–74 years), middle elderly (75–84 years) and the oldest ( $\geq 85$  years), the proportion of frail was 31.58%,

53.85% and 78.95%, respectively. While in previous study, the prevalence of frailty ranges from 10% to 60%, depending on the CAD burden, as well as the tool and cutoff chosen to define frailty.<sup>[18,19]</sup>

Comprehensive Geriatrics Assessment is a powerful tool during the diagnosis and treatment in elderly patients, the geriatrics syndromes can be found and appropriate interventions can be given.<sup>[20]</sup> Our study showed that during Comprehensive Geriatrics Assessment in frail group, 51.32% elderly patients had different degrees of incontinence, 27.63% had fall history, 46.05% had different kinds of sleeping disorders, 80.92% had dental problems, 62.50% had constipation, while all these would affect functional status and quality of life in elderly populations. As defecation caused by constipation was an important risk factor of inducing myocardial ischemia, so geriatrics syndromes should be recognized in the treatment of elderly ACS patients. SF-36 MCS score also showed, quality of life in frail patients were significantly lower than non-frail patients. Besides somatic diseases, psychological problems also existed in ACS patients. Previous study showed, depression and anxiety can be found in 20% of patients with CAD,<sup>[21]</sup> and mental disorder itself was an independent risk factor of worsen of the coronary artery disease. Watkins *et al.*,<sup>[22]</sup> anxiety and depression could increase all-cause mortality in individuals with coronary heart disease by 1.6 times. In our study, 8.55% and 4.00% patients were diagnosed anxiety and/or depression in frail and non-frail group respectively, both treatment for somatic atherosclerosis diseases and care for mental disease were needed in these patients.

Among frail ACS patients, nutrition indicators like HGB, Alb, PA were significantly lower than non-frail group while inflammatory cytokines like hs-CRP and IL-6 were significantly higher. Adjusted for underlying diseases like anemia, moderate to severe renal impairment and co-morbidities, frailty was still closely related to the above parameters, indicating these parameters may be the future laboratory parameters in diagnosis and assessment models for Chinese population. Recent studies had already shown that protein intake increase and anti-resistance exercise can improve physical fitness of patients.<sup>[23]</sup> Therefore, malnutrition, lack of exercise could both be as intervention targets in future frailty studies.

Epidemiological studies have consistently demonstrated that frailty carries a relative risk of  $> 2$  for morbidity and mortality across a spectrum of stable CAD, ACS, heart failure, and trans-catheter or surgical interventions.<sup>[18]</sup> Besides, frailty is also a strong independent predictor of emergency department visits and hospitalization rates for community patients with heart failure.<sup>[24]</sup> URV rates are used as an indicator of quality performance and have been implemented by

a number of healthcare systems. Our study also indicated, Clinical Frailty Scale is a strong independent predictor of all-cause mortality and URV in ACS patients. Therefore, frailty could contribute valuable prognostic insights incremental to existed risk models and assist clinicians in defining optimal care pathways for their patients.

ACCF 2012 Health Policy Statement on Patient-Centered Care in Cardiovascular Medicine stated that six characteristics of an effective healthcare system were identified: the system should be safe, effective, patient-centered, timely, efficient, and equitable. “Biological age” is not the only determining factors of prognosis.<sup>[18]</sup> Frailty could be helpful to predict adverse outcomes in elderly ACS patients. Comprehensive Geriatrics Assessment could be helpful to a more comprehensive grasp of the patients’ underlying disease condition and individualized treatment decisions. Our observational study also laid the initial foundation for subsequent randomized controlled intervention study. “One-stop” multidisciplinary team mode including physician, cardiac rehabilitation, nutritional support and psychological intervention will be a useful attempt for future holistic management and individual therapy. Ultimately, frailty should not be viewed as a reason to withhold care but rather as a means of delivering care in a more patient-centered model.

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