

A Frailty Assessment Tool to Predict In-Hospital Mortality in Patients with Acute Exacerbations of Chronic Obstructive Pulmonary Disease

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Background: The exacerbation of chronic obstructive pulmonary disease (AECOPD) is a chronic, frequent, and life-threatening lung disease. In 2014, a frailty index (FI) based on deficits in commonly used laboratory tests (FI-Lab) was suggested to identify older adults at increased risk of death.

Objective: We aim to study the prognostic value of the FI-Lab in older Chinese patients who were admitted because of AECOPD.

Methods: We screened 1932 older patients hospitalized with AECOPD from September 2016 to June 2019 at Zhenjiang First People's Hospital, China. A multivariate logistic regression analysis was used to identify prognostic factors for in-hospital mortality.

Results: A total of 77 survivors and 77 non-survivors were finally included in the study. Both the mean DECAF (including dyspnea, eosinopenia, consolidation, acidemia, and atrial fibrillation) score and the mean FI-Lab value of non-survivors were statistically higher than those of survivors (4.45 ± 0.80 versus 3.03 ± 0.90 , $P=0.000$; 0.51 ± 0.13 versus 0.29 ± 0.10 , $P=0.000$, respectively). Logistic regression analysis suggested that DECAF Rank and FI-Lab Rank were strongly related factors of death in AECOPD patients. The areas under the receiver-operating characteristic (ROC) curves were 0.906 for FI-Lab and 0.870 for DECAF ($P=0.2991$).

Conclusion: FI-Lab is a simple, efficient, and objective tool to stratify the risk of in-hospital mortality of AECOPD.

Keywords: frailty index, FI-Lab, DECAF, AECOPD, prognosis

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic, frequent, and life-threatening lung disease. The acute exacerbation of chronic obstructive pulmonary disease (AECOPD) suggests decreased physical activity and pulmonary function.¹ A simple prognosis tool can contribute to clinical management, early risk stratification, and prevention of poor outcomes, as well as monitoring during treatment. Clinicians are constantly seeking predictors of mortality for patients with AECOPD. Current prognostic markers for AECOPD include two main categories: inflammation-related markers²⁻⁴ and dyspnea, eosinopenia, consolidation, acidemia, and atrial fibrillation (DECAF) score.⁵⁻⁷

Inflammatory mediators can destroy lung structure and promote neutrophil inflammation, which can worsen illness and cause death. Inflammation-related markers such as C-reactive protein (CRP) and interleukin,^{2,4} red blood cell

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distribution (RDW) widths,^{8,9} eosinophil counts,¹⁰ and neutrophil and lymphocyte ratio (NLR)¹¹ are often associated with mortality or readmission of AECOPD patients. DECAF^{5,7,12} (including dyspnea, eosinopenia, pulmonary consolidation, acidemia, and atrial fibrillation) is also a commonly used predictor of in-hospital mortality in AECOPD patients.

However, most of the inflammation-related markers can only suggest significant differences between patients with AECOPD and patients with stable COPD, while the accuracy of their prognoses is relatively low. The DECAF scoring system requires five indicators: clinical presentation, electrocardiogram, imaging (chest x-ray or computed tomography), blood gas analysis, and routine blood work. DECAF scoring requires relatively specialized knowledge. First, it is a little difficult to evaluate dyspnea and changes in lung consolidation. Moreover, DECAF scoring is not practical for repeated evaluations of patients because imaging changes are relatively slow. Therefore, no generally accepted indicator exists. We need objective predictions that are easy to obtain, to be able to provide more accurate prognoses regarding AECOPD patients, and perhaps we could try interdisciplinary indexes as well.

Frailty is a clinical condition characterized by a decline in reserves and resistance to stressors. It pervades older adults and causes them to be more vulnerable to numerous health problems, as well as at greater risk of dying.^{13,14} Older patients are now recommended for frailty assessments.¹⁵ In addition, people with COPD are more likely to coexist with frailty. Indeed, they share the same risk factors as do seniors and those who smoke. Common pathogenesis, including inflammatory lesions and endocrine dysfunction, could affect both COPD and frailty.^{16,17} Can an objective and easily measurable frailty index be found for predicting mortality in AECOPD patients?

The frailty index based on routine laboratory tests (FI-Lab) is a comprehensive, objective, and readily detectable index for quantifying frailty. The FI-Lab consists of 21 common blood tests (complete blood count, kidney function, thyroid function, liver function, electrolyte, etc.) plus systolic and diastolic blood pressures.¹⁸ An FI-Lab value is calculated by counting the number of deficits in a patient and dividing by the total number of deficits measured to produce a score between 0 and 1. A higher score indicates greater frailty. Although studies by Rockwood et al¹⁹ and Howlett et al²⁰ have confirmed that the FI-Lab can quantify health and point to adverse

outcomes including death, most of the pre-existing prognostic studies using the FI-Lab only focused on long-term care nursing homes.^{13,20,21} Therefore, what is the correlation between the FI-Lab and prognosis in older AECOPD inpatients? Our objective is to study the prognostic value of the FI-Lab in older Chinese patients who were admitted because of AECOPD.

Methods

Study Design and Study Participants

A retrospective observational study was conducted at Zhenjiang First People's Hospital, China, between September 2016 and June 2019. This is a tertiary teaching hospital in China. The study protocol was approved by the hospital ethics committee. All data were collected retrospectively from the hospital database. Because of the retrospective characteristic of the study design, the patient consent to review their medical records was waived by the ethics committee. The authors complied strictly with the Declaration of Helsinki and covered patient data confidentiality.

The primary clinical diagnosis of AECOPD patients was at least 60 years of age. In total, 1932 patients (1824 survived and 108 died in hospital) were screened for this study. We excluded inpatients with secondary causes such as lung cancer, bronchiectasis, asthma, interstitial lung disease and active pulmonary tuberculosis. Each patient was admitted to the study only once during his or her initial hospitalization. Patients with incomplete data (clinical data, auxiliary examination, hematologic examination, etc.) were excluded. A total of 285 were excluded due to missing data, of which 61 were excluded due to missing data on FI-Lab tool. We also excluded patients who were automatically discharged or moved to another hospital.

After that exclusion, there were 426 survivors and 98 non-survivors. Previous differences in the characteristics of survivors and non-survivors may lead to biased estimates. To reduce this bias, we used propensity score matching (PSM) techniques.²² A logistical regression model was used to estimate the propensity to participate in both groups according to a set of observed covariates. PSM matching (1:1 matching) covariates included: age, gender, the number of smokers, the number of drinkers, history of comorbid diseases (including type 2 diabetes, hypertension, myocardial infarction, or stroke). Finally, 77 survivors and 77 non-survivors were included in the study. The flow chart of subject inclusion is summarized in Figure 1.

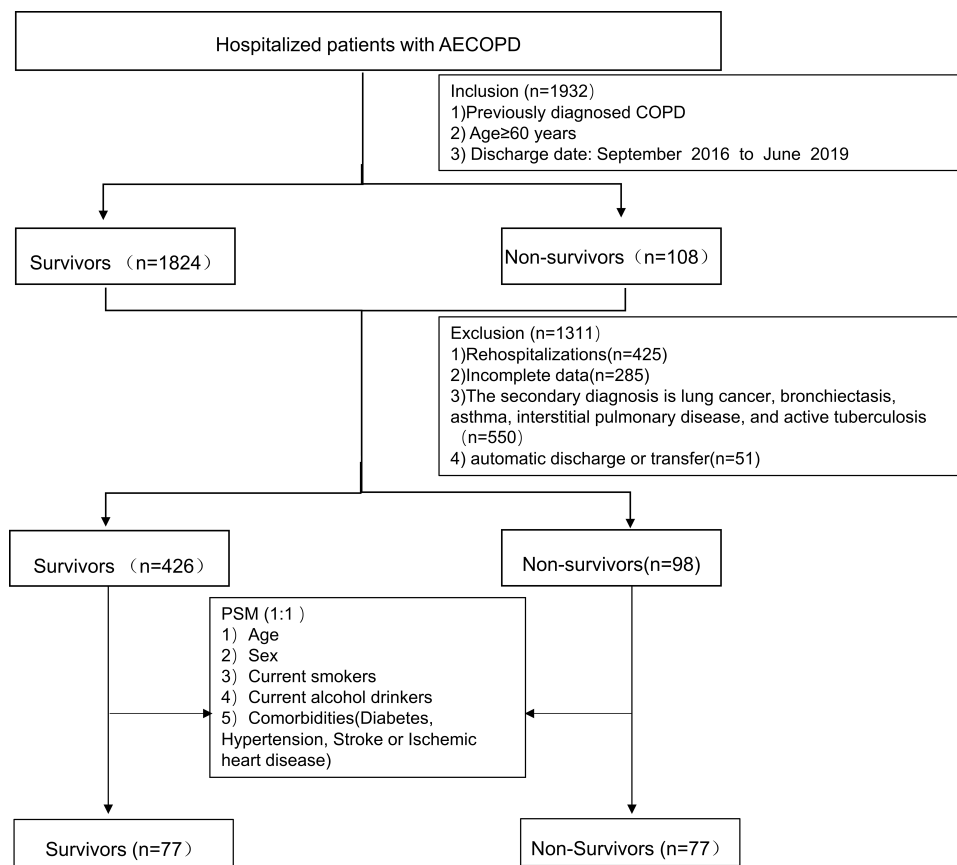


Figure 1 Flow chart of patient admission.

Definitions

COPD and AECOPD

The COPD diagnosis was established by a consistent air-flow obstruction on spirometry (FEV1/forced vital capacity <0.70).²³ The exacerbation of COPD (AECOPD) was defined as an acute change in a patient's respiratory symptoms that is beyond normal variability and is sufficient to warrant a change in therapy.²³

FI-Lab

Rockwood et al¹⁹ and Howlett et al²⁰ developed an FI (the FI-Lab) of up to 23 variables based on 21 routine blood tests plus measured systolic and diastolic blood pressure based on deficit accumulation (Supplementary Table 1). The FI-Lab can meet several criteria of ideal biomarkers (influential to the pathogenesis, easy to measure, sensitive to changes, improved to an intervention, prognostic to outcome) provided by Mcshane et al²⁴ and Gruttola et al.²⁵ FI-Lab has been built by evaluating each variable as 0 or 1. '0' indicates that values are within the normal cut-offs but '1' indicates that values are outside the normal cut-offs as deficits. An FI-Lab score is built by counting the number of deficits and

dividing by the total number of items tested for a score between 0 and 1. For example, a patient with deficits in six variables of the 23-item FI-Lab would have an FI-Lab value of 0.26 (6 divided by 23). A higher score indicates greater frailty.

An FI-Lab score was calculated only if over 70% of the variables (items 16 to 23) were available. We treated the FI-Lab score as a continuous variable based on previous studies and ranked participants based on the FI-Lab value in four categories: < 0.2, 0.2–0.4, 0.4–0.6, and >0.6. We have also tried to find an optimal threshold for FI-Lab to predict mortality.

DECAF Score

DECAF consists of five parameters: dyspnea (D), eosinopenia (E), consolidation (C), acidemia (A), and atrial fibrillation (F). Evaluating DECAF in AECOPD patients can help to predict mortality. DECAF is a predictor of AECOPD with a score range between 1 and 6. A higher score indicates the poorer condition. A recent study found that patients with a DECAF score of four or more are at

high risk of mortality.⁶ Based on the DECAF score, we ranked participants at four levels: ≤ 2 , 3, 4, and ≥ 5 .

Measurements

Electronic Data were collected from the inpatient hospital database. Patients characteristics such as gender, age, current smokers, current alcohol drinkers, comorbid diseases (diabetes, hypertension, myocardial infarction or stroke), length of stay, and rehospitalization were documented. Initial blood results and systolic pressure, diastolic pressure were extracted on admission.

Blood tests include complete blood count (total leukocyte, neutrophil, eosinophil, lymphocyte, platelet counts, mean platelet volume, red cell distribution width, hemoglobin); blood biochemical (total protein, albumin, aspartate aminotransferase, calcium, creatinine, urea, fasting blood glucose, alkaline phosphatase, phosphorus, potassium, sodium); thyroid function (thyroid-stimulating hormone, thyroxine, free thyroxine); syphilis; hematopoietic raw materials (serum folate, vitamin B12); inflammatory markers including C-reactive protein-(CRP), neutrophil-to-lymphocyte ratio(NLR), platelet-to-lymphocyte ratio(PLR); blood gas analysis.

Statistical Analysis

Data were analyzed using IBM SPSS for Windows, Version 23.0 (IBM Corp, Armonk, NY). The survivors were compared to the non-survivors. The baseline difference between the groups was matched by PSM. The median with interquartile range was employed for nonparametric continuous variables, and the mean \pm standard deviation was used for

parametric continuous variables. Count and percentage were used when applicable. Mann–Whitney *U*-tests for nonparametric continuous variables or Student's *t*-tests for parametric continuous variables. Chi-square tests were employed for dichotomous variables. A multivariate logistic regression analysis was used to identify prognostic factors for hospital mortality. The area under the receiver operator characteristic curve (AUCs) was used to assess the performance of FI-Lab and DECAF in hospital mortality prediction. The comparison of the AUCs was performed using the DeLong method.²⁶ The Youden Index method was used to determine the optimal thresholds of FI-Lab or DECAF to predict mortality. A two-tailed *p*-value of 0.05 was considered statistically significant.

Results

General Characteristics of Survivors and Non-Survivors on Admission

We reviewed the case records for 34 months. Finally, according to the strict inclusion and exclusion criteria and PSM matching method, a total of 154 patients were enrolled, including 77 survivors and 77 non-survivors independently (Figure 1). The general characteristics in two groups were shown in Table 1. The mean age of these 154 patients was 79.73 ± 8.38 years. Men were more common in both groups. 85 patients (55.19%) were current smokers while only 21 patients (13.64%) were current alcohol drinkers. Among the comorbidities, hypertension is the most common (56.49%). There were no statistically significant difference in blood pressure between the two groups.

Table 1 The Balanced General Characteristics of Survivors and Non-Survivors on Admission

Indexes	Survivors (n=77)	Non-Survivors (n=77)	P-value
Age (years)	79.38 \pm 8.14	80.09 \pm 8.65	0.207
Men (%)	57 (74.0)	52 (67.5)	0.376
Current smokers (%)	45(58.4)	40(51.9)	0.418
Current alcohol drinkers (%)	11(14.3)	10(13)	0.814
Length of hospital days	10.06 \pm 4.53	10.26 \pm 8.70	0.862
Comorbidities (%)			
Diabetes	12(15.6)	16(20.8)	0.664
Hypertension	41(53.2)	46(59.7)	0.416
Stroke or Ischemic heart disease	17(22.1)	26(33.8)	0.106
Blood pressure			
Systolic blood pressure (mmHg)	136.65 \pm 22.63	131.18 \pm 22.64	0.136
Diastolic blood pressure (mmHg)	77.92 \pm 11.52	75.61 \pm 15.00	0.285

Some Laboratory Findings of Survivors and Non-Survivors

According to previous researches, complete blood count results, inflammatory indicators, partial pressure of carbon dioxide (PaCO₂) are always associated with AECOPD. The above laboratory findings of survivors and non-survivors are shown in Table 2. In the non-survivors, lymphocyte counts, eosinophil counts, hemoglobin, platelet count level were significantly lower, whereas leukocyte counts, neutrophil counts, red blood cell distribution (RDW) level were significantly higher compared with the survivors (all $P < 0.05$). There were no significant differences in other parameters. We also found non-survivors had higher partial pressure of carbon dioxide (PaCO₂) and inflammatory markers (NLR, PLR, CRP).

FI-Lab and DECAF of Survivors and Non-Survivors

We calculated FI-Lab for all patients. FI-Lab values were divided into four categories: < 0.2 , $0.2-0.4$, $0.4-0.6$, and >0.6 and the FI-Lab of $0.2-0.39$ was most common ($n=64$; 41.56%). Among survivors, 68 patients (88.3%) had FI-Lab values of <0.4 and the most common were 0.2 to 0.39 ($n=32$; 41.56%). In non-survives, 58 patients (75.3%) had FI-Lab values of >0.4 and the most common values were $0.4-0.6$ ($n=39$; 50.65%). The mean FI-Lab of

non-survives was statistically higher to that of survivors (0.51 ± 0.13 versus 0.29 ± 0.10 , $P=0.000$) (Table 3).

We also calculated DECAF scores for all patients. DECAF scores were ranked in four categories: ≤ 2 , 3, 4, and ≥ 5 . A DECAF score of 4 was most prevalent ($n=53$; 34.41%). The most common DECAF scores in non-survivors were ≥ 4 ($n=71$, 92.21%) while the scores were <4 in survivors ($n=56$; 72.73%). The mean DECAF score of non-survivors was statistically higher than that of survivors (4.45 ± 0.80 versus 3.03 ± 0.90 , $P=0.000$), as shown in Table 3.

Multivariate Logistic Regression Analysis

Some complete blood count parameters (leukocytes, neutrophils, hemoglobin, et al) were already included in the blood parameters of 21 FI-Lab items and were no longer included in the logistic regression equation. Variables (age, gender, blood pressure, comorbidities, platelet count, et al) not statistically significant were also not included in the logistic regression equation. Finally, eight statistically significant parameters (all $P < 0.05$) were included in the logistic regression model, including CRP, NLR, PLR, DECAF rank, FI-Lab rank, PaCO₂, RDW, eosinophil count in the logistic regression model. The results showed that the DECAF and FI-Lab ranks correlated with hospital mortality in AECOPD patients ($P=0.000$), as shown in Table 4.

Table 2 Some Laboratory Findings of Survivors and Non-Survivors

Parameters	Survivors (n=77)	Non-Survivors (n=77)	P-value
Complete blood count results			
Leukocyte count ($\times 10^9/L$)	7.66 ± 3.87	10.70 ± 7.40	0.002 *
Neutrophil count ($\times 10^9/L$)	6.14 ± 3.59	9.36 ± 7.08	0.001 *
Lymphocyte count ($\times 10^9/L$)	1.14 ± 0.78	0.84 ± 0.72	0.016 *
Eosinophil count ($\times 10^9/L$)	0.02(0.00, 0.10)	0(0, 0.01)	0.003 *
Platelet count ($\times 10^9/L$)	197.58 ± 73.24	185.27 ± 86.34	0.341
MPV (fl)	10.31 ± 1.32	10.29 ± 1.26	0.906
RDW (%)	13.74 ± 1.06	15.36 ± 2.89	0.000 *
Hemoglobin (g/l)	125.19 ± 16.90	107.90 ± 23.46	0.000 *
Inflammatory markers			
NLR	5.36(3.27, 10.29)	11.60(6.20, 19.35)	0.000 *
PLR	191.25(132.20, 288.27)	245.0(147.9, 406.65)	0.047 *
CRP (mg/l)	13.17(4.08, 59.35)	25.24(9.90, 79.45)	0.011 *
Blood gas analysis			
PaCO ₂ (mmHg)	51.13 ± 13.48	64.49 ± 21.63	0.000 *

Note: *P-value < 0.05 .

Abbreviations: NLR, neutrophil and lymphocyte ratio; RDW, red blood cell distribution; MPV, mean platelet volume; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PaCO₂, partial pressure of carbon dioxide.

Table 3 FI-Lab and DECAF of Survivors and Non-Survivors at the Time of Admission

Values	Survivors (n=77)	Non-Survivors (n=77)	P-value
DECAF Rank (n, %)			
≤2	24	1	0.000*
3	32	5	0.000*
4	17	36	0.000*
≥5	4	35	0.000*
Mean DECAF score	3.03 ± 0.90	4.45 ± 0.80	0.000*
FI-Lab Rank (n, %)			
<0.2	20 (25.97)	0	0.000*
0.20–0.39	48 (62.34)	18	0.000*
0.40–0.6	9 (11.68)	39	0.000*
≥0.60	1	19	0.000*
Mean FI-Lab	0.29 ± 0.10	0.51 ± 0.13	0.000*

Note: *P-value <0.05.

ROC Analysis

ROC curves were calculated to estimate FI-Lab and DECAF concerning mortality (Figure 2). The AUCs were 0.906 for FI-Lab and 0.870 for DECAF ($P=0.2991$). When the FI-Lab was 0.4388, the sensitivity, specificity, and Youden index were 70.1%, 96.1%, and 0.675 respectively. When the DECAF score was 3.5, sensitivity, specificity, and Youden index were 92.2%, 72.7%, and 0.649. FI-Lab has a slightly stronger screening ability than DECAF.

Discussion

We explored the prognostic value of the FI-Lab in AECOPD inpatients in China. Rather than using the traditional respiratory indices to predict mortality in AECOPD, we used the interdisciplinary FI-Lab to predict risk among patients with AECOPD. Our study demonstrated that the mean FI-Lab values and mean DECAF scores in non-survivors were much higher than those of survivors. Inpatient mortality increased in accordance with increases

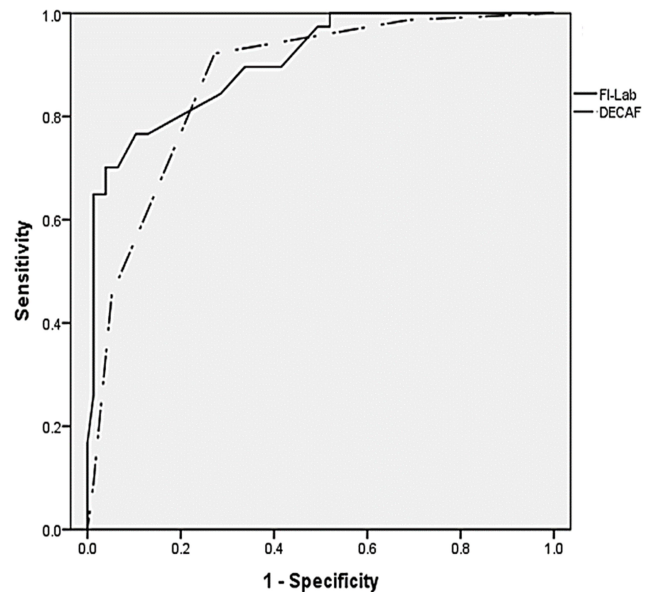


Figure 2 ROC curves for FI-Lab and DECAF.

in the FI-Lab or DECAF scores. Therefore, both the FI-Lab and DECAF scores can be successfully applied to predict in-hospital mortality.

This study found that single indexes, including RDW, CRP, and partial pressure of carbon dioxide (PaCO_2), in non-survivors were significantly higher than those of survivors. Moreover, eosinophil counts in non-survivors were significantly lower than those of survivors. However, after logistic regression analysis, only the FI-Lab rank and DECAF rank were risk factors for death. This suggests that single indexes show low prognostic value. Gu et al²⁷ pointed out that no single biomarkers can be effectively applied to the quantitative diagnosis and prognosis of AECOPD. Therefore, we should seek new comprehensive biomarkers such as FI-Lab and DECAF scoring.

Nafae et al²⁸ reported that DECAF scores were significant predictors of hospital mortality, with areas under the curve (AUCs) of 0.870. The AUCs of the DECAF scores in our study were occasionally 0.870. Many studies^{5,12} have shown that the value of DECAF scores in predicting mortality in AECOPD patients is superior to other respiratory scoring systems, including the acute physiology and

Table 4 Results of Multivariate Logistic Analysis (Forward Stepwise)

Variables	β	Sb	Wald χ^2	Odds Ratio	95% CI: Lower–Upper Limit	P-value
FI-Lab Rank	2.164	0.444	23.753	8.705	3.646–20.782	0.000*
DECAF Rank	1.726	0.354	24.748	5.620	2.811–11.236	0.000*

Note: *P-value <0.05.

chronic health evaluation (APACHE) score, the community-acquired pneumonias (CAPS) score, the confusion, urea nitrogen, respiratory rate, and blood pressure, 65 years of age and older (CURB-65) score, and the blood urea nitrogen, altered mental status, and pulse, 65 years of age and older (BAP-65) score. However, the DECAF scoring has some weaknesses. First, our study suggested that DECAF scores had high sensitivity but low specificity (when the DECAF cutoff score was 3.5, the sensitivity and specificity were 92.2% and 72.7%, respectively, and the Youden index was 0.649). One study even showed that the sensitivity of the DECAF score for predicting mortality in AECOPD patients was 100%, but the specificity was poor (34.1%).²⁹ Second, the DECAF score consists of five parameters and covers clinical, serological, radiological, and electrocardiography scales. Therefore, this score is difficult to assess and inconvenient for repeated testing, because imaging changes are relatively slow in patients. Finally, pulmonary consolidation of imaging tests often suggests pneumonia, and there is a debate with regard to judging whether AECOPD includes AECOPD with pneumonia.

The association between frailty and mortality has been well established,¹⁵ based on the fact that COPD and frailty share a common pathogenesis and that co-morbidity is more prevalent in older patients.^{30,31} The FI-Lab used in this paper is a 23-item indicator (21 hematological indices plus systolic and diastolic blood pressures) that was proposed by Howlett et al.^{19,20,32} The FI-Lab has been widely used for objective assessments of the degrees of frailty. FI-Lab values were found to be significantly higher in non-survivors than in survivors. The FI-Lab was significantly correlated with mortality, with an AUC area of 0.906, suggesting that the predictive value of the FI-Lab is slightly more reliable than that of the DECAF scoring (AUCs of 0.870). FI-Lab assessments are objective, easy to apply at the bedside, and convenient to repeat. When the FI-Lab was 0.4388, the specificity for predicting mortality was 96.1%, which was much higher than with the DECAF scores. However, although the specificity of the FI-Lab reached 96.1%, its sensitivity was relatively poor (only 70.1%). Therefore, we still need to find a better predictor through future research.

Limitations

This study has some limitations. First, this was a retrospective study, we need a prospective cohort study to confirm the conclusion. Second, although we screened

numerous cases (total cases were 1932), the final sample size was relatively small (n=154). Strict exclusion criteria and excluded patients with missing data may lead to selection bias and reporting bias independently. Third, because this was a retrospective study, it was not able to analyze some critical outcomes in detail including causes of death, falls during hospitalization, quality of life, the incidence of acute cardiovascular events, and social support. Finally, it may take time to determine abnormalities in the 23 elements. If the FI-Lab can be coded into a program (or an App) and integrated into hospital information systems (HIS), it can be calculated automatically.

Conclusion

This study demonstrates that an FI constructed from routinely collected laboratory and clinical data identifies older AECOPD adults at increased risk of death. FI-Lab is a simple, effective, and objective indicator that can quickly help clinicians stratify AECOPD patients. FI-Lab dynamic monitoring can be of great clinical value in understanding patient progress and predicting risk of death for AECOPD patients.

Acknowledgments

The project was supported by a research grant by the Hospital-level Scientific Fund of Zhenjiang First People's Hospital (Y2019006).

Disclosure

All the authors declare no conflicts of interest in this work.

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