International Journal of Chronic Obstructive Pulmonary Disease Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Frailty and Exacerbation of Chronic Obstructive Pulmonary Disease: Is There Any Association?

Koichi Nishimura[1,2], Masaaki Kusunose[3], Ryo Sanda[3], Ayumi Shibayama[4], Kazuhito Nakayasu[5]

[1]National Center for Geriatrics and Gerontology, Obu, Aichi, Japan; [2]Clinic Nishimura, Ayabe, Kyoto, Japan; [3]Department of Respiratory Medicine, National Center for Geriatrics and Gerontology, Obu, Aichi, Japan; [4]Department of Nursing, National Center for Geriatrics and Gerontology, Obu, Aichi, Japan; [5]Data Research Section, Kondo P.P. Inc., Osaka, Japan

Correspondence: Koichi Nishimura, Clinic Nishimura, 4-3. Kohigashi, Kuri-cho, Ayabe, Kyoto, 623-0222, Japan, Tel +81-773-47-0321, Fax +81-773-47-0201, Email koichinishimura1@gmail.com

Purpose: This study investigated if individuals with chronic obstructive pulmonary disease (COPD) and frailty are more likely to have acute exacerbations of COPD or require hospitalization for exacerbation than those without frailty.

Patients and Methods: Data on 135 outpatients with stable COPD were analyzed with the Cox proportional hazards model to assess the risk of future events. The Kihon Checklist was administered at baseline to classify the participants as robust, pre-frail, or frail. The follow-up period was a maximum of six and a half years.

Results: In all, 76 patients (56.3%) experienced an exacerbation and 46 (34.1%) were hospitalized due to it. Multivariate Cox proportional hazards analysis that accounted for FEV_1 and sex showed that the frail group was more likely to face future risks of COPD exacerbations [Hazard ratio 1.762 (95% CI 1.011–3.070), p=0.046] and hospitalizations for exacerbation [2.238 (1.073–4.667), p=0.032] than the robust group. No significant differences were observed when comparing robust patients to those who were pre-frail or pre-frail to frail either in exacerbations or hospitalizations. When comparing the C-indices for frailty and FEV_1, the former index (exacerbation 0.591 and hospitalization 0.663) did not exceed the latter (0.663 and 0.769) in either analysis.

Conclusion: Frail COPD patients have a more unfavorable future risk of acute exacerbations of COPD and hospitalizations for exacerbation than robust patients. However, no significant differences were observed when comparing robust patients to those who were pre-frail or pre-frail to frail, suggesting that the future risk for COPD patients with frailty is only higher compared to those who are considered robust. Additionally, FEV_1 was found to be a more reliable predictor of future events than measures of frailty.

Keywords: COPD, acute exacerbations of COPD, hospitalization, future risk, Kihon Checklist

Introduction

All clinical indicators should be evaluated from three perspectives: their ability to discriminate between subjects, detect change, and predict future outcomes. As for discriminative properties in patients with chronic obstructive pulmonary disease (COPD), forced expiratory volume in one second (FEV_1) remains a key indicator for the diagnosis of COPD, with FEV_1/forced vital capacity (FVC) less than 0.70 being a well-established criterion for diagnosis, although other indices have been proposed. In terms of predictive characteristics, FEV_1 was also considered the best prognostic tool and marker of treatment response in the twentieth century,[1] but physical activity and exercise capacity are now considered to be better predictive indicators.[2,3] As an example of evaluative predispositions, the primary endpoint of previous clinical trials was mostly FEV_1, but this is now often replaced by a reduction in the frequency of acute exacerbations of COPD. As such, although FEV_1 may have been supplanted by other indices, it remains the most accessible and convenient indicator and still plays a central role in the management of COPD.

Although the relationship between aging and COPD has long been discussed, research on the relationship between frailty and COPD has received more attention since frailty is linked to aging. A number of cross-sectional studies have demonstrated the discriminative property of frailty in subjects with COPD.[4–7] A previous study noted that COPD patient with frailty may respond well to pulmonary rehabilitation, one of the standard treatments for COPD, but subsequently

Received: 19 December 2023
Accepted: 14 May 2024
Published: 24 May 2024

experience rapid deterioration of their disease, especially after the end of rehabilitation.[8–11] Therefore, the predictive property of frailty is still an important research question. The long-term mortality of COPD patients with and without frailty has been investigated,[12–20] and the predominant conclusions are that those who are frail have a poorer prognosis than their non-frail counterparts, and that frailty is one of the predictors of mortality for COPD patients.[12,14,16–18,20] In the daily care of COPD patients, acute exacerbation of COPD and hospitalizations or readmissions are more frequent problems that often concern both patients and practitioners, so whether or not frailty can predict these events is an important question.

The first study comparing the prediction of exacerbation between COPD patients with and without frailty was reported in 2019 by a post hoc analysis of data from the National Emphysema Treatment Trial (NETT), a large multicenter clinical trial conducted by the National Heart, Lung, and Blood Institute in the United States.[13] In their study, frail participants had a significantly increased rate of hospitalization compared with those who were non-frail. These results were supported by those from research groups in Beijing and the UK, the latter by Hanlon et al using data from the UK Biobank.[14,16,17] Although there are several factors that have been reported as predictors of acute exacerbations in subjects with COPD, including severity of airflow limitation,[21–24] COPD-specific health status measured by patient-reported outcomes (PROs) such as the COPD Assessment Test (CAT),[25–29] symptoms of chronic bronchitis,[30] blood eosinophilia[31] and a history of exacerbations that may reflect an independent susceptibility phenotype,[24] the severity of airflow limitation or FEV_1 may be the most common characteristic of patients who subsequently develop acute exacerbations, especially from the standpoint of COPD patient care. This study sought to answer the following research questions:

1. Are frail COPD patients more likely to develop acute exacerbations of COPD than those without frailty?
2. Are frail COPD patients more likely to undergo hospitalization due to exacerbation than those without frailty?
3. Which is a better predictor of exacerbation and hospitalization, airflow limitation or frailty?

Materials and Methods

From 2013 to 2023, the Respiratory Medicine Outpatient Clinic at the National Center for Geriatrics and Gerontology collected data for a longitudinal study on individuals diagnosed with COPD.[25,32] Participants who met the inclusion criteria and provided informed consent were assessed every 6 months, including postbronchodilating pulmonary function tests and the collection of PROs measurements. Previous study results have examined the predictive properties of PROs using information obtained at the first visit as a baseline.[25] In 2015, we added the Kihon Checklist to our cohort survey, allowing for an alternative diagnosis of frailty.[32] Thus, for the present analysis, the baseline was defined as the time the Kihon Checklist was first administered, to examine whether the information at that time was related to the time of the first exacerbation or hospitalization due to exacerbation.

We studied 141 clinically stable COPD patients aged 50 years and older with a smoking history of 10 or more pack-years, a post-bronchodilator FEV_1/FVC ratio of less than 0.7, no abnormal shadows on chest radiographs, no active lung disease, no uncontrolled comorbidity, and no change in treatment regimen in the preceding four weeks. Exclusion criteria included history of asthma (self-reported) and exacerbations of COPD in the preceding three months. All participants had at least six months of previous outpatient treatment to avoid subsequent changes due to new medical interventions. The study was approved by the Ethics Committee of the National Center for Geriatrics and Gerontology (No. 1138–3) (updated on 12 July 2020). It was conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained from all participants. As we have reported on the association between frailty and mortality using an almost identical dataset,[33] this paper is the result of a second analysis of the same study participants who were consecutively recruited from February 2015 to February 2022.

Subjects were instructed to arrive at the study site at least 12 hours after cessation of bronchodilator use. Spirometry was performed with a CHESTAC-8800 spirometer (Chest, Tokyo, Japan) more than 60 minutes after inhalation of a dry powder formula of long-acting bronchodilators and was monitored by a physician. The highest values from three tests were used and residual volume (RV) was calculated using the closed-circuit helium method. All measurements were performed by laboratory technicians according to the guidelines of the American Thoracic Society and the European Respiratory Society.[34] The predicted values for lung function were calculated according to the guidelines of the Japanese Respiratory Society.[35]

The Kihon Checklist is a self-administered 25-item questionnaire covering activities of daily living, physical strength, nutritional status, oral condition, cognitive status and risk of depression.[36] The Total score of the Kihon Checklist ranges

from 0 (no frailty) to 25 (severe frailty), and the frailty status of the participants was classified as robust (0–3), pre-frail (4–7), or frail (8–25).[37] Notably, the BMI score was calculated using values obtained from measurements taken at the same time as the pulmonary function test, rather than self-reported.[32] The health status of individuals with COPD was evaluated using previously validated Japanese versions of the CAT.[38,39] The CAT consists of eight items, each of which is scored from 0 to 5 in relation to cough, phlegm, chest tightness, breathlessness, activity limitation, confident to leave home, sleep and energy. The total score of the CAT ranges from 0 to 40, with a score of zero indicating no impairment.[38]

All participants were followed and evaluated for a maximum of six and a half years until January 2023. The time from enrolment to the last involvement or event was documented for examination. Acute exacerbation of COPD was defined as a worsening of respiratory symptoms requiring treatment with systemic corticosteroids or antibiotics, or both.[24] However, six cases in which the presence or absence of acute exacerbations could not be determined due to insufficient data caused by a limited follow-up period were excluded from the analysis.

Study results are expressed as mean ± standard deviation and p-values less than 0.05 were considered to be statistically significant. Kruskal–Wallis and Fisher's exact tests were used to compare differences between groups. Univariate and multivariate Cox proportional hazards analyses were performed to assess the associations between measurements and subsequent events, with results presented as hazard ratios (HR) and 95% confidence intervals (CI). The C-index of an event prediction model was used to compare different models, with a higher value close to 1.0 indicating better risk prediction. Kaplan-Meier curves and Log rank tests were also used for time-to-event outcomes.

Results

A total of 135 patients (126 males) with varying degrees of airflow limitation, ranging from mild to very severe, were included. The mean age and FEV_1 were 75.1 ± 6.8 years and 1.75 ± 0.54 L (69.5 ± 20.3% predicted), respectively. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification of airflow limitation, 40 (29.6%) were classified as GOLD 1 (FEV_1 ≥80% predicted), 71 (52.6%) as GOLD 2 (50% ≤ FEV_1 < 80% predicted), 19 (14.1%) as GOLD 3 (30% ≤ FEV_1 < 50% predicted), and 5 (3.7%) as GOLD 4 (FEV_1 < 30% predicted). This study differed slightly from many others in this area in that it included many older patients and had a relatively small number of participants with severe and very severe COPD. Because the number of patients classified as GOLD 3 and GOLD 4 was relatively small, the 24 patients classified in these categories were treated as one group for subsequent analyses.

Based on the Kihon Checklist Total score, 64 (47.4%), 36 (26.7%), and 35 (25.9%) subjects were classified as robust, pre-frail, and frail, respectively. Table 1 shows the patient characteristics and pulmonary function test results between the

Table 1 Comparison of Patient Characteristics at the Baseline Assessment Between Robust, Pre-Frail and Frail Groups Classified by the Kihon Checklist Total Score in 135 Subjects with COPD

		Robust (N=64)	Pre-frail (N=36)	Frail (N=35)	Comparison Between 3 Groups
		mean SD	mean SD	mean SD	p value
Age	years	73.0 ± 6.6	76.0 ± 5.3	78.0 ± 7.4	0.004†
BMI	kg/m^2	23.1 ± 3.5	21.9 ± 2.8	23.1 ± 3.3	0.133†
Cumulative Smoking	pack-years	56.2 ± 31.0	64.0 ± 36.7	61.4 ± 27.5	0.368†
FEV_1	Liters	1.91 ± 0.51	1.69 ± 0.56	1.51 ± 0.49	0.002†
FEV_1	%pred	72.6 ± 20.1	69.3 ± 22.3	64.0 ± 17.9	0.169†
FEV_1/FVC	%	57.4 ± 9.9	54.6 ± 11.6	53.8 ± 11.1	0.236†
RV/TLC	%	43.0 ± 8.8	44.4 ± 12.2	48.9 ± 13.3	0.043†
CAT score	(0–40)	6.0 ± 5.2	8.5 ± 6.3	13.9 ± 8.0	<0.001†
Sex	Male / Female	61 / 3	32 / 4	33 / 2	0.453§
GOLD stage	GOLD1/GOLD2 / GOLD3+4	23 / 35 / 6	12 / 15 / 9	5 / 21 / 9	0.031§

Notes: The numbers in parentheses denote possible score range. †Kruskal–Wallis test, §Fisher's exact test.
Abbreviations: CAT, the COPD Assessment Test; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

three groups. Statistically significant differences were observed between the groups for FEV_1 (L) and RV/TLC (%) ($p<0.05$). However, no significant differences were found for FEV_1 (% pred) and FEV_1/FVC (%). We also found statistically significant differences in the CAT score and the stage of airflow limitation as defined by the GOLD document.

Of the 135 included subjects, 76 (56.3%) had an episode of exacerbation. The mean time from enrolment to the first exacerbation or last information was 28.3 ± 25.9 months ranging from 0.2 to 96.5 months (847.6 ± 775.9 days with a range of 5 to 2896 days). In addition, 46 subjects (34.1%) were hospitalized at least once for an exacerbation, with a mean of 41.3 ± 29.4 months ranging from 1.6 to 96.5 months (1237.5 ± 882.9 days with a range of 48 to 2896 days).

Regarding the first exacerbation of COPD, univariate Cox proportional hazards analysis of the first episode of acute exacerbation of COPD showed that the frail group was more likely to experience an acute exacerbation than the robust group, but this was not observed in the pre-frail group (Table 2). The C-index of the frail-related categorization did not exceed that of FEV_1. To account for the expected influence of FEV_1 at the baseline assessment, a multivariate Cox proportional hazards analysis was performed, adjusting for FEV_1 and sex. This analysis confirmed that the frail group was significantly more likely to develop an acute exacerbation than the robust group. Such differences were not evident upon comparing the pre-frail with the robust group through both univariate and multivariate Cox regression analyses (Table 2). The Log rank test revealed a statistically significant difference between the frail and robust groups (p=0.002). However, no statistically significant differences emerged in comparisons between the pre-frail group and either the robust or frail groups (Log rank test, pre-frail vs robust, p=0.209; pre-frail vs frail, p=0.146). The Kaplan-Meier survival analysis, utilized to evaluate the first exacerbation across the frail, pre-frail, and robust groups, is depicted in Figure 1.

In relation to the first hospitalization attributable to exacerbation, univariate Cox regression analysis detected significant disparities both between the pre-frail and robust groups and between the frail and robust groups. However, when adjusting for FEV_1 and sex through multivariate Cox proportional hazards analysis, only the frail group exhibited a significant association with the first hospitalization due to exacerbation. This association was not observed between the pre-frail and robust groups under the multivariate Cox regression model (Table 3). The Log rank test highlighted a significant difference between the frail and robust groups (p=0.001), as well as between the pre-frail and robust groups (p=0.019). Figure 2 presents the findings of the Kaplan-Meier analysis for the first hospitalization.

Discussion

The present study assessed the feasibility of assessing frailty to predict exacerbations and hospitalizations due to exacerbation in COPD patients. The results showed that exacerbations and hospitalizations due to exacerbation were more likely to occur in frail COPD patients than their robust counterparts. However, no significant differences were

Table 2 Univariate and Multivariate Cox Proportional Hazards Analyses on the Relationship Between the Baseline Measurements and Acute Exacerbation of COPD

	Univariate Cox Proportional Hazards Analyses			Multivariate Cox Proportional Hazards Analyses		
	Hazard Ratio (95% CI)	**p value**	**c-index**	**Hazard Ratio (95% CI)**	**p value**	**c-index**
Frail (Ref. Robust)			0.591			0.682
Pre-frail	1.418 (0.813–2.471)	0.218		1.092 (0.610–1.955)	0.767	
Frail	2.275 (1.325–3.907)	0.003		1.762 (1.011–3.070)	0.046	
Sex (Ref. Male)	2.009 (0.917–4.400)	0.081	0.519	1.834 (0.811–4.149)	0.145	
FEV_1 (L)	0.329 (0.209–0.517)	<0.001	0.673	0.364 (0.227–0.584)	<0.001	

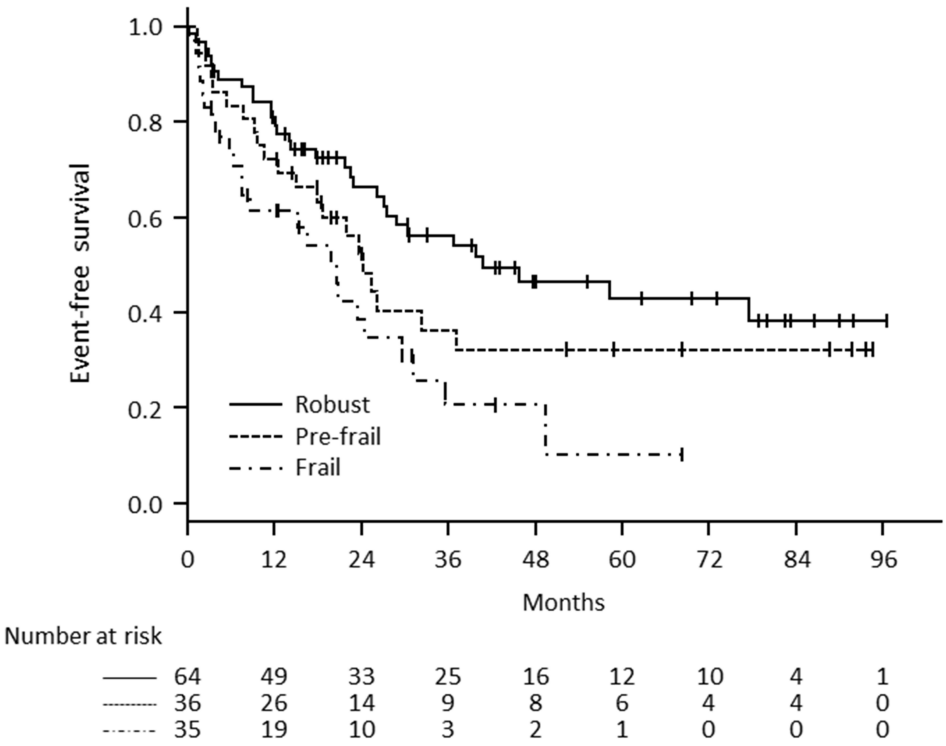

Figure 1 Kaplan–Meier curves of cumulative incidence of acute exacerbation of COPD based on three strata (frail, pre-frail and robust) defined by the Kihon Checklist Total score.

observed between pre-frail and either frail or robust participants. In addition, FEV_1, which is easily obtained in clinical practice, was also evaluated and showed a higher C-index for predicting exacerbations and hospitalizations due to exacerbation. Thus, while frailty is a statistically significant predictor independent of FEV_1, the latter appears to be more effective in predicting future exacerbations.

Previous reports examining the association between frailty and outcomes in subjects with COPD have often considered the question of whether the results may vary depending on how frailty is defined.[16–18] Fried et al defined frailty as a condition meeting three out of five criteria comprising unintentional weight loss, self-reported exhaustion, low grip strength, slow walking speed and low physical activity.[40] Alternative tools such as the Frailty Index and Clinical Frailty Scale using the cumulative deficit approach have also been validated.[41–43] The present study assessed frailty using the Kihon Checklist, a multidomain tool that is validated and widely used in Japan.[32,36,37] Although we screened frailty status using the Kihon Checklist, there might be inconsistencies in frailty classification between different screening tools. However, the prevalence of frailty was 25.9% in our patients, which is comparable with other studies, although direct

Table 3 Univariate and Multivariate Cox Proportional Hazards Analyses on the Relationship Between the Baseline Measurements and First Hospitalization Due to Exacerbation of COPD

	Univariate Cox Proportional Hazards Analyses			Multivariate Cox Proportional Hazards Analyses		
	Hazard Ratio (95% CI)	p value	c-index	Hazard Ratio (95% CI)	p value	c-index
Frail (Ref. Robust)			0.663			0.785
Pre-frail	2.368 (1.154–4.857)	0.019		1.569 (0.746–3.298)	0.235	
Frail	3.456 (1.688–7.075)	0.001		2.238 (1.073–4.667)	0.032	
Sex (Ref. Male)	1.275 (0.394–4.129)	0.686	0.510	1.107 (0.338–3.623)	0.867	
FEV_1 (L)	0.155 (0.082–0.294)	<0.001	0.769	0.181 (0.093–0.352)	<0.001	

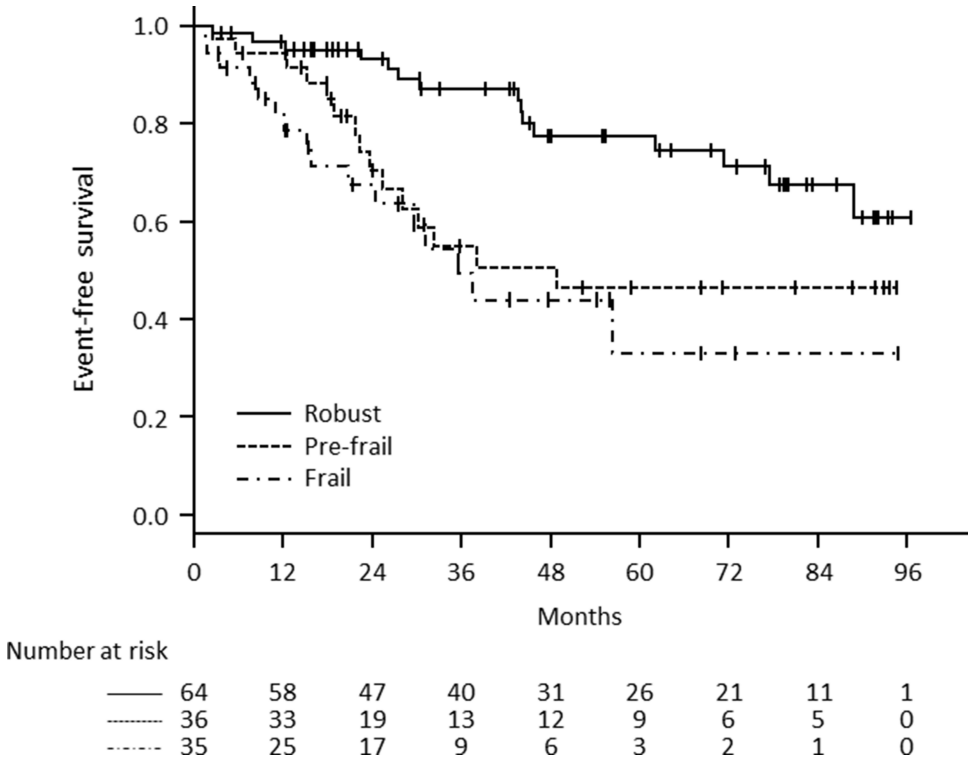

Figure 2 Kaplan–Meier curves of cumulative incidence of hospitalization due to exacerbation of COPD based on three strata (frail, pre-frail and robust) defined by the Kihon Checklist Total score.

comparisons are difficult due to the differences in both the criteria used and the populations or settings studied. This may be a limitation of the current study.

COPD is currently considered to be a respiratory disease with systemic manifestations, and a multidimensional approach in addition to airflow limitation is recommended to assess an individual's disease severity.[44] When a large number of patients are assessed cross-sectionally, some patient indicators show strong correlations. Dyspnea, the most common disease-specific symptom in patients, is thought to result from dynamic hyperinflation, but physiological airflow limitation and hyperinflation are strongly correlated, and it is often difficult to determine which is more important.[45] Frailty, which is considered to be the strongest expression of aging, is strongly correlated with PRO measures such as health status, as we have previously reported.[32] For this reason, it is important to select the appropriate variables for analysis. Therefore, in the present study, the analysis of frailty was adjusted for FEV_1 and sex. Although poor health status measured by the CAT and a history of repeated exacerbations have been reported to be the best predictors of exacerbation over the last two decades,[24–26,28,29] our findings showed that FEV_1 may be confirmed as the best predictor of future exacerbations, in line with established literature.[23]

Some discussion of the relationship between CAT scores and frailty in terms of exacerbation prediction is warranted here. Comparing the baseline findings in the frail, pre-frail, and robust groups in the present study, there was a significant difference in CAT scores among the three groups (Table 1). Although few reports have studied the association between frailty and COPD-specific health status in COPD patients, it has been reported that the St. George's Respiratory Questionnaire (SGRQ) Total score and frailty are significantly correlated.[32] Much of the literature suggests a close association between CAT and acute exacerbations, including reports that higher CAT scores are more likely to predict exacerbations.[25,26,28,29] The findings of the current study that frail patients are more prone to acute exacerbations are in agreement with these findings. Whether a lower CAT score, ie, impaired COPD-specific health status, or the presence of frailty is more strongly associated with the development of acute exacerbations cannot be determined from the present study, and further research is needed.

This study found a significant difference in the occurrence of acute exacerbations in COPD patients with frailty compared to those without frailty. The exact mechanism behind this difference has yet to be identified, but it is speculated that frail

COPD patients may experience progressive muscle weakness, reduced physical activity, social isolation, and deteriorating health, all of which could contribute to an increased risk of acute exacerbations.[46] These exacerbations are often triggered by factors such as respiratory infections, and it is possible that frail COPD patients are more susceptible to these triggers or have a lower threshold for experiencing exacerbations. Further research is needed to confirm this hypothesis. However, there have been reports indicating a rise in inflammatory markers in frail patients,[47,48] although there have been no direct studies on COPD. This indicates that chronic inflammation is present in these patients and that unmanifested inflammation may contribute to the development of acute exacerbations. This indicates that chronic inflammation is present in these individuals, which is also observed in COPD cases that are frequently linked to systemic comorbidities and may contribute to the onset of acute exacerbations.

Some limitations of the present study should be mentioned. First, this single-center study was limited by the number of patients with COPD admitted to the study site, but it included all patients with stable COPD seen at this hospital during the study period. Given the small sample size, it is possible that there was insufficient power to assess any association. Second, the study design may have been subject to selection bias because we only recruited patients who could regularly attend our outpatient clinic. It is likely that we did not include sufficient numbers of those patients without any subjective symptoms who were unaware of having COPD, or patients who could not regularly attend our clinic due to the heavy physical burden. A small proportion of patients with severe or very severe COPD could lead to bias. Lastly, because our study included predominantly men, generalizing these results to women with COPD may be unwarranted. However, as the number of women with COPD in Japan is quite low, the study reflects the reality of clinical COPD in our population.

One of our previous studies also examined the ability of some patient-reported outcome (PRO) measurement tools to predict three future events: death, acute exacerbation, and resulting hospitalization, and found that different PRO measurement tools gave quite different results for different events.[25] Thus, we hypothesized that different future events to be predicted would result in different prognostic abilities for frailty. Therefore, from the viewpoint of the prognostic ability of frailty, we decided to analyze the predictive ability of mortality first, and published a separate paper on our study of mortality and frailty as defined by the Kihon Checklist in the same cohort using an almost identical sample to that used in the current study.[33] The previous study focused on mortality, whereas the current one focused on acute exacerbations and hospitalizations resulting from exacerbations. From the perspective of the predictive value of frailty, whether the event to be predicted was death or acute exacerbation and resulting hospitalization, the results were significantly different only between frail and robust patients, and the results were similar between the events to be predicted. This suggests that differences in events may be less important from the perspective of predicting outcomes. However, we cannot rule out the possibility that different data sets might give different results, and we hope that further research will be conducted in this area.

Conclusion

This study examined the predictive properties of frailty for both acute exacerbations of COPD and hospitalizations due to exacerbation in patients with COPD and sought to determine which was more strongly associated with future events, airflow limitation or frailty. We found that both acute exacerbations of COPD and hospitalizations for exacerbation were higher in frail COPD patients than in robust COPD patients. However, no significant differences were observed when comparing robust patients to those who were pre-frail or pre-frail to frail, suggesting that the future risk of COPD patients with frailty is only higher compared to those who are considered robust. Therefore, these findings can be considered a narrow result, as frail COPD patients only have a worse future risk compared to the robust patient group. However, the C-index did not reach the level of the most commonly used FEV_1, suggesting that FEV_1 is a better predictor of these future events than frailty.

Acknowledgments

This study was partly supported by the Research Funding for Longevity Sciences (22-7) from the National Center for Geriatrics and Gerontology, Japan.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no competing interests in this work.

References

1. Anthonisen NR, Wright EC, Hodgkin JE. Prognosis in chronic obstructive pulmonary disease. *Am Rev Respir Dis*. 1986;133(1):14–20. doi:10.1164/arrd.1986.133.1.14
2. Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T. Analysis of the factors related to mortality in chronic obstructive pulmonary disease: role of exercise capacity and health status. *Am J Respir Crit Care Med*. 2003;167(4):544–549. doi:10.1164/rccm.200206-583OC
3. Waschki B, Kirsten A, Holz O, et al. Physical activity is the strongest predictor of all-cause mortality in patients with COPD: a prospective cohort study. *Chest*. 2011;140(2):331–342. doi:10.1378/chest.10-2521
4. Yan LC, Lu HY, Wang XY, et al. Prevalence and risk factors of frailty in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis. *Eur Geriatr Med*. 2023;14(4):789–802. doi:10.1007/s41999-023-00800-2
5. Wang L, Zhang X, Liu X. Prevalence and clinical impact of frailty in COPD: a systematic review and meta-analysis. *BMC Pulm Med*. 2023;23(1):164. doi:10.1186/s12890-023-02454-z
6. Antoniu SA, Boiculese LV, Prunoiu V. Frailty, a dimension of impaired functional status in advanced COPD: utility and clinical applicability. *Medicina*. 2021;57(5):474. doi:10.3390/medicina57050474
7. Guan C, Niu H. Frailty assessment in older adults with chronic obstructive respiratory diseases. *Clin Interv Aging*. 2018;13:1513–1524. doi:10.2147/CIA.S173239
8. Finamore P, Scarlata S, Delussu AS, Traballesi M, Incalzi RA, Laudisio A. Frailty Impact during and after Pulmonary Rehabilitation. *COPD*. 2021;18(5):518–524. doi:10.1080/15412555.2021.1967915
9. Wang Z, Hu X, Dai Q. Is it possible to reverse frailty in patients with chronic obstructive pulmonary disease? *Clinics*. 2020;75:e1778. doi:10.6061/clinics/2020/e1778
10. Bernabeu-Mora R, Oliveira-Sousa SL, Sanchez-Martinez MP, Garcia-Vidal JA, Gacto-Sanchez M, Medina-Mirapeix F. Frailty transitions and associated clinical outcomes in patients with stable COPD: a longitudinal study. *PLoS One*. 2020;15(4):e0230116. doi:10.1371/journal.pone.0230116
11. Maddocks M, Kon SS, Canavan JL, et al. Physical frailty and pulmonary rehabilitation in COPD: a prospective cohort study. *Thorax*. 2016;71(11):988–995. doi:10.1136/thoraxjnl-2016-208460
12. Galizia G, Cacciatore F, Testa G, et al. Role of clinical frailty on long-term mortality of elderly subjects with and without chronic obstructive pulmonary disease. *Aging Clin Exp Res*. 2011;23(2):118–125. doi:10.1007/BF03351076
13. Kennedy CC, Novotny PJ, LeBrasseur NK, Wise RA, Sciurba FC, Benzo RP. Frailty and clinical outcomes in chronic obstructive pulmonary disease. *Ann Am Thorac Soc*. 2019;16(2):217–224. doi:10.1513/AnnalsATS.201803-175OC
14. Luo J, Zhang D, Tang W, Dou LY, Sun Y. Impact of frailty on the risk of exacerbations and all-cause mortality in elderly patients with stable chronic obstructive pulmonary disease. *Clin Interv Aging*. 2021;16:593–601. doi:10.2147/CIA.S303852
15. Scarlata S, Finamore P, Laudisio A, et al. Association between frailty index, lung function, and major clinical determinants in chronic obstructive pulmonary disease. *Aging Clin Exp Res*. 2021;33(8):2165–2173. doi:10.1007/s40520-021-01878-z
16. Hanlon P, Lewsey J, Quint JK, et al. Frailty in COPD: an analysis of prevalence and clinical impact using UK Biobank. *BMJ Open Respir Res*. 2022;9(1). doi:10.1136/bmjresp-2022-001314
17. Zhang D, Tang W, Dou LY, Luo J, Sun Y. Four different frailty models predict health outcomes in older patients with stable chronic obstructive pulmonary disease. *BMC Geriatr*. 2022;22(1):57. doi:10.1186/s12877-022-02750-z
18. Brighton LJ, Nolan CM, Barker RE, et al. Frailty and mortality risk in COPD: a cohort study comparing the fried frailty phenotype and short physical performance battery. *Int J Chron Obstruct Pulmon Dis*. 2023;18:57–67. doi:10.2147/COPD.S375142
19. Tsai CL, Chang WP, Lin YK, Ho SC, Lin YH. Physical frailty related to cognitive impairment and COPD exacerbation: a cross-sectional study. *Respir Med*. 2023;208:107129. doi:10.1016/j.rmed.2023.107129
20. Verduri A, Carter B, Laraman J, et al. Frailty and its influence on mortality and morbidity in COPD: a systematic review and meta-analysis. *Intern Emerg Med*. 2023;18(8):2423–2434. doi:10.1007/s11739-023-03405-6
21. Chai CS, Ng DL, Bt Mos S, et al. COPD exacerbations and patient-reported outcomes according to post-bronchodilator FEV(1) - a post-hoc analysis of pooled data. *BMC Pulm Med*. 2023;23(1):150. doi:10.1186/s12890-023-02436-1
22. Montes de Oca M, Talamo C, Halbert RJ, et al. Frequency of self-reported COPD exacerbation and airflow obstruction in five Latin American cities: the Proyecto Latinoamericano de Investigacion en Obstruccion Pulmonar (PLATINO) study. *Chest*. 2009;136(1):71–78. doi:10.1378/chest.08-2081
23. Jones PW, Willits LR, Burge PS, Calverley PM; Inhaled Steroids in Obstructive Lung Disease in Europe study i. Disease severity and the effect of fluticasone propionate on chronic obstructive pulmonary disease exacerbations. *Eur Respir J*. 2003;21(1):68–73. doi:10.1183/09031936.03.00013303
24. Hurst JR, Vestbo J, Anzueto A, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med*. 2010;363(12):1128–1138. doi:10.1056/NEJMoa0909883
25. Nishimura K, Kusunose M, Sanda R, Mori M, Shibayama A, Nakayasu K. Comparison of predictive properties between tools of patient-reported outcomes: risk prediction for three future events in subjects with COPD. *Diagnostics*. 2023;13(13):2269. doi:10.3390/diagnostics13132269

26. Jo YS, Yoon HI, Kim DK, Yoo CG, Lee CH. Comparison of COPD assessment test and clinical COPD questionnaire to predict the risk of exacerbation. *Int J Chron Obstruct Pulmon Dis*. 2018;13:101–107. doi:10.2147/COPD.S149805
27. Sloots JM, Barton CA, Buckman J, et al. The predictive value of an adjusted COPD assessment test score on the risk of respiratory-related hospitalizations in severe COPD patients. *Chron Respir Dis*. 2017;14(1):72–84. doi:10.1177/1479972316687099
28. Garcia-Sidro P, Naval E, Martinez Rivera C, et al. The CAT (COPD Assessment Test) questionnaire as a predictor of the evolution of severe COPD exacerbations. *Respir Med*. 2015;109(12):1546–1552. doi:10.1016/j.rmed.2015.10.011
29. Lee SD, Huang MS, Kang J, et al. The COPD assessment test (CAT) assists prediction of COPD exacerbations in high-risk patients. *Respir Med*. 2014;108(4):600–608. doi:10.1016/j.rmed.2013.12.014
30. Kim V, Han MK, Vance GB, et al. The chronic bronchitic phenotype of COPD: an analysis of the COPDGene Study. *Chest*. 2011;140(3):626–633. doi:10.1378/chest.10-2948
31. Singh D, Agusti A, Martinez FJ, et al. Blood eosinophils and chronic obstructive pulmonary disease: a global initiative for chronic obstructive lung disease science committee 2022 review. *Am J Respir Crit Care Med*. 2022;206(1):17–24. doi:10.1164/rccm.202201-0209PP
32. Kusunose M, Oga T, Nakamura S, Hasegawa Y, Nishimura K. Frailty and patient-reported outcomes in subjects with chronic obstructive pulmonary disease: are they independent entities? *BMJ Open Respir Res*. 2017;4(1):e000196. doi:10.1136/bmjresp-2017-000196
33. Nishimura K, Kusunose M, Shibayama A, Nakayasu K. Is frailty a mortality predictor in subjects with chronic obstructive pulmonary disease? *Int J Chronic Obstr*. 2023;Volume 18:2955–2960. doi:10.2147/COPD.S439966
34. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26(2):319–338. doi:10.1183/09031936.05.00034805
35. Sasaki H, Nakamura M, Kida K, Kambe M, Takahashi K, Fujimura M. Reference values for spirogram and blood gas analysis in Japanese adults. *J Jpn Respir Soc*. 2001;39(5):S1–S17.
36. Arai H, Satake S. English translation of the Kihon Checklist. *Geriatr Gerontol Int*. 2015;15(4):518–519. doi:10.1111/ggi.12397
37. Satake S, Senda K, Hong YJ, et al. Validity of the Kihon Checklist for assessing frailty status. *Geriatr Gerontol Int*. 2016;16(6):709–715. doi:10.1111/ggi.12543
38. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD assessment test. *Eur Respir J*. 2009;34(3):648–654. doi:10.1183/09031936.00102509
39. Tsuda T, Suematsu R, Kamohara K, et al. Development of the Japanese version of the COPD assessment test. *Respir Investig*. 2012;50(2):34–39. doi:10.1016/j.resinv.2012.05.003
40. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol a Biol Sci Med Sci*. 2001;56(3):M146–156. doi:10.1093/gerona/56.3.M146
41. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. *ScientificWorldJournal*. 2001;1:323–336. doi:10.1100/tsw.2001.58
42. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ*. 2005;173(5):489–495. doi:10.1503/cmaj.050051
43. Brummel NE, Bell SP, Girard TD, et al. Frailty and Subsequent Disability and Mortality Among Patients With Critical Illness. *Am J Respir Crit Care Med*. 2016;196(1):64–72.
44. Oga T, Tsukino M, Hajiro T, Ikeda A, Nishimura K. Predictive properties of different multidimensional staging systems in patients with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2011;6:521–526. doi:10.2147/COPD.S24420
45. Nishimura K, Yasui M, Nishimura T, Oga T. Airflow limitation or static hyperinflation: which is more closely related to dyspnea with activities of daily living in patients with COPD? *Respir Res*. 2011;12(1):135. doi:10.1186/1465-9921-12-135
46. Osadnik CR, Brighton LJ, Burtin C, et al. European Respiratory Society statement on frailty in adults with chronic lung disease. *Eur Respir J*. 2023;62(2):2300442. doi:10.1183/13993003.00442-2023
47. Soysal P, Stubbs B, Lucato P, et al. Inflammation and frailty in the elderly: a systematic review and meta-analysis. *Ageing Res Rev*. 2016;31:1–8. doi:10.1016/j.arr.2016.08.006
48. Pansarasa O, Mimmi MC, Davin A, Giannini M, Guaita A, Cereda C. Inflammation and cell-to-cell communication, two related aspects in frailty. *Immunity Ageing*. 2022;19(1):49. doi:10.1186/s12979-022-00306-8