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ORIGINAL RESEARCH

Relationship Between COPD Progression and Frailty Progression: A Five-year Observation in Real Clinical Practice

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Purpose: Although a cross-sectional association between frailty and chronic obstructive pulmonary disease (COPD) has been established, the longitudinal relationship between the progression of both frailty and COPD remains unclear.

Materials and Methods: This longitudinal study followed 87 COPD patients over five years, with evaluations conducted every six months. Participants underwent pulmonary function tests and completed the Kihon Checklist, a tool widely used in Japan to assess frailty. Kihon Checklist scores range from 0 (no frailty) to 25 (severe frailty), categorizing participants as robust (0–3), pre-frail (4–7), or frail (8–25). Annual changes were analyzed using linear mixed models.

Results: A significant association was observed between time and worsening frailty classification, with patients transitioning from robust to pre-frail or from pre-frail to frail (odds ratio: 1.224, $p = 0.004$). However, the GOLD stages (GOLD 1 to GOLD 4) did not exhibit significant progression over five years. The cohort demonstrated significant declines in forced expiratory volume in one second (FEV_1) and increases in Kihon Checklist total scores. FEV_1 decreased by an estimated mean of 28.6 mL per year (95% CI: 18.9–38.4, $p < 0.001$), while the Kihon Checklist total score increased by 0.30 annually (95% CI: 0.09–0.51, $p = 0.006$). Estimated FEV_1 declined significantly from baseline after two years in the baseline frail group ($p < 0.01$), after 3.5 years in the pre-frail group ($p < 0.01$), and after four years in the robust group ($p < 0.05$). Although the GOLD 3+4 group showed a significant increase in Kihon Checklist total scores after 3.5 years ($p < 0.05$), no significant change was observed in the GOLD 1 and GOLD 2 groups.

Conclusion: COPD patients with frailty show a more rapid decline in FEV_1, indicating accelerated COPD progression. These findings suggest frailty is static and only COPD is progressing.

Keywords: disease progression, Kihon Checklist, linear mixed models

Introduction

Lung function progressively declines with age, leading to a gradual reduction in forced expiratory volume in one second (FEV_1) and the FEV_1/forced vital capacity (FVC) ratio.[1,2] The changes observed in the lungs of aging individuals mirror those seen in patients with chronic obstructive pulmonary disease (COPD), as many mechanisms associated with aging are also present in COPD. COPD is recognized as a model disease of aging, with some researchers supporting the hypothesis that it represents a state of accelerated aging.[3,4]

Frailty, characterized by age-related declines in physical and psychological function, cognitive ability, and social interaction, increases vulnerability in both the body and mind. It is closely associated with the concept of aging and may even be considered synonymous with the aging process itself. Studies have reported a high prevalence of frailty among patients with COPD.[5–9] Comparisons between COPD patients with and without frailty have demonstrated that those with frailty experience more severe dyspnea, suffer greater symptom burden, have poorer quality of life, face a higher risk of acute exacerbations,[10–14] and exhibit increased mortality rates.[10–13,15–18]

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There have also been several longitudinal studies published on the progression of frailty and the progression of low lung function and chronic respiratory disorders.[19–24] However, most studies have analyzed general population samples or epidemiological research data similar to this, and it must be said that the results of studies analyzing the relationship between the progression of disease and the progression of frailty in subjects with a diagnosis of COPD are extremely limited. Lee et al reported that COPD was associated with a faster transition from robust to pre-frail or frail status in initially robust women.[21] He et al found that, when compared with subjects with normal spirometry findings, patients with COPD and preserved ratio impaired spirometry (PRISm) findings showed accelerated progression of the frailty index (FI), which is a widely used multidimensional assessment of frailty that incorporates health deficits from multiple organs and systems.[20] Cheng et al showed that frailty was associated with increased risk of COPD and that COPD was identified as a susceptibility factor for frailty, affirming a reciprocal causal relationship between frailty and COPD, using bidirectional two-sample Mendelian randomization analysis.[19]

COPD, characterized by airflow limitation, is widely recognized for its progressive nature, with FEV_1 declining annually as the disease advances.[25] Similarly, the total score on the Kihon Checklist, a tool widely used in Japan to assess frailty,[7,17,26–29] is expected to increase with age. However, how frailty and the Kihon Checklist total score progress in individual cases remains largely unknown. Just as the annual decrease in FEV_1 is utilized to assess COPD progression, an increase in the Kihon Checklist total score over time may lead to the development of frailty. The Kihon Checklist has been used in a cohort study of COPD patients conducted at our facility since 2015, with responses collected from patients every six months. We reanalyzed the data from this cohort study to compare the progression of frailty and COPD. The aim of this study is to describe the longitudinal changes in lung function and frailty in patients with COPD, and to investigate the possible association between baseline frailty and lung function decline.

Materials and Methods

Study Design and Patient Enrollment

Since 2013, the Outpatient Respiratory Medicine Clinic at the National Center for Geriatrics and Gerontology (NCGG) has conducted a cohort study on subjects with COPD.[7,14,17] Participants meeting the inclusion criteria and providing consent were evaluated every six months, which included pulmonary function tests. In 2015, the Kihon Checklist was added to assess frailty. For this analysis, the baseline was defined as the first administration of the Kihon Checklist, with changes in the total score tracked over five years.

Eligible participants were clinically stable COPD patients aged 50 years or older, with a smoking history of more than 10 pack-years and a post-bronchodilator FEV_1/FVC ratio below 0.7. Patients were excluded if they had a self-reported history of asthma, abnormal chest radiographs, or active lung disease. Additional exclusion criteria included unresolved comorbidities or an acute exacerbation of COPD within three months prior to study enrollment. All patients had been receiving regular treatment at the clinic for at least six months prior to inclusion, ensuring that any observed changes could not be attributed to new medical interventions. The study adhered to the ethical standards of the Declaration of Helsinki and was approved by the NCGG Ethics Committee (No. 1138–3; updated July 2020). Written informed consent was obtained from all participants before inclusion.

Patient recruitment occurred between February 2015 and March 2018, with participants encouraged to complete 11 evaluations over five years. To ensure robust data analysis, only participants who completed at least three evaluations during the five-year period were included. The final assessment was completed in March 2023. When participants experienced an acute exacerbation within three months prior to a scheduled evaluation, assessments were delayed ensuring compliance with the exclusion criteria.

Study Assessment

During each visit, participants were instructed to refrain from using bronchodilators for at least 12 hours prior to testing. Spirometry was performed using a CHESTAC-8800 spirometer (Chest, Tokyo, Japan) following inhalation of a long-acting bronchodilator in dry powder form under physician supervision. Residual volume (RV) was measured using the closed-circuit helium dilution method, and diffusing capacity for carbon monoxide (DL_{CO}) was assessed using the single-

breath technique. All tests were conducted in accordance with the protocols of the American Thoracic Society and the European Respiratory Society.[30] Predicted values for lung function parameters were calculated based on the guidelines of the Japanese Respiratory Society.[31]

The Kihon Checklist consists of 25 questions assessing daily living activities, physical abilities, nutritional status, oral health, cognitive function, and risk of depression.[26,32,33] The total score ranges from 0 (no frailty) to 25 (severe frailty), with participants classified as robust (0–3), pre-frail (4–7), or frail (8–25) based on their score.[27] Body mass index (BMI) was calculated using measurements obtained at the same time as the pulmonary function test, rather than self-reported data.

Statistical Analysis

Patient backgrounds were compared using the Kruskal–Wallis test or Fisher's exact test. The relationship between time and changes in GOLD and frailty classifications was analyzed using a generalized linear mixed model (GLMM) with a cumulative logit link function for the ordinal response variable. Random effects accounted for subject-specific variability, while fixed effects included time (years). Annual changes in FEV_1 and Kihon Checklist total scores for the entire cohort were estimated using a linear mixed model, with each metric as the dependent variable, time as a fixed effect, and subjects as a random effect. Covariate adjustments were not applied. Means and 95% confidence intervals (CIs) at each measurement point were estimated using a linear mixed model, with timepoint as a fixed effect and subjects as a random effect. The Type III test of fixed effects assessed whether the values of each metric remained constant over time. Pairwise comparisons were performed to identify differences from baseline values, applying the Bonferroni method to adjust for multiple comparisons. Summary statistics are presented as mean ± standard deviation or estimated mean with 95% CIs. All analyses were performed using SPSS Statistics, version 28.0 (IBM Corp)., with p-values below 0.05 considered statistically significant.

Results

Subject Characteristics

There were 87 participants, 80 of whom were male, with varying degrees of airflow limitation ranging from mild to very severe. The mean age of the participants was 75.3 years, and the average FEV_1 was 1.79 L (71.7% predicted) at baseline (Table 1). Based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification, 29 patients (33.3%) were categorized as GOLD 1 ($FEV_1 \geq 80\%$ predicted), 44 (50.6%) as GOLD 2 ($50\% \leq FEV_1 < 80\%$ predicted), 11 (12.6%) as GOLD 3 ($30\% \leq FEV_1 < 50\%$ predicted), and 3 (3.4%) as GOLD 4 ($FEV_1 < 30\%$ predicted). Due to the

Table 1 Comparison of Patient Characteristics at Baseline Between Robust, Pre-Frail and Frail Groups Classified by the Kihon Checklist Total Score in 87 Subjects with COPD

		Total (N=87)			Robust (N=44)			Pre-Frail (N=25)			Frail (N=18)			Comparison between 3 Groups	
		Mean		SD	Mean		SD	Mean		SD	Mean		SD	p value	
Age	Years	75.3	±	6.2	73.6	±	6.3	77.3	±	5.8	76.6	±	5.5	0.056	†
BMI	Kg/m^2	22.5	±	3.4	23.0	±	3.3	21.8	±	3.1	22.1	±	3.9	0.408	†
Cumulative Smoking	Pack-years	59.0	±	32.0	56.7	±	32.6	58.0	±	32.7	66.2	±	30.0	0.229	†
FEV_1	Liters	1.79	±	0.56	1.93	±	0.54	1.73	±	0.63	1.51	±	0.40	0.014	†
FEV_1	%pred	71.7	±	20.6	73.2	±	19.9	72.3	±	24.4	67.3	±	17.0	0.534	†
FEV_1/FVC	%	57.0	±	10.7	58.6	±	10.0	54.5	±	11.7	56.6	±	10.8	0.336	†
RV/TLC	%	43.7	±	10.0*	41.5	±	8.7**	44.7	±	10.8	47.5	±	11.0	0.071	†
DLco	%pred	51.5	±	20.4*	58.9	±	19.2**	49.5	±	18.8	36.5	±	17.0	<0.001	†
Sex	Male / Female	80 / 7			43 / 1			22 / 3			15 / 3			0.073	§
GOLD stage	1/2/3+4	29 / 44 / 14			17 / 22 / 5			9 / 10 / 6			3 / 12 / 3			0.279	§

Note: *N=86, **N=43; GOLD, Global Initiative for Chronic Obstructive Lung Disease; †: Kruskal–Wallis test, §: Fisher's exact test.

small number of patients in the GOLD 3 and 4 categories, these were combined into a single group of 14 patients for subsequent analyses.

At baseline, frailty status was assessed using the Kihon Checklist total score, with 44 patients (50.6%) classified as robust, 25 (28.7%) as pre-frail, and 18 (20.7%) as frail (Table 1). A comparison of physiological measures among the robust, pre-frail, and frail groups revealed significant differences in FEV_1 and DLco ($p = 0.014$ and $p < 0.001$, respectively; by Kruskal–Wallis test). Advanced frailty was associated with greater airflow limitation and reduced pulmonary diffusion capacity.

At the end of the five-year follow-up, 63 participants were still alive, 12 had died, and information was unavailable for 12 participants. Among the 87 participants, 12 completed all 11 biannual assessments over the study period, 23 completed 10 assessments (the most common number), and 10 completed 9 assessments. Conversely, 8 participants completed only 3 assessments, 4 completed 4 assessments, and 6 completed 5 assessments; all were included in the analysis.

Five-year Progress of GOLD Stage and Frailty Status

The severity of GOLD airflow limitation, classified by FEV_1, and frailty status, classified by the Kihon Checklist total score, were assessed at six-monthly intervals over a five-year period, as shown in Figures 1 and 2. However, variability in the number of cases analyzed at each visit limited the ability to draw definitive conclusions from the raw data alone.

An analysis was conducted to evaluate whether GOLD classification changed over time, using a generalized linear mixed model (GLMM) with GOLD 1, GOLD 2, and GOLD 3+4 as the outcome variables. The results revealed that neither the fixed effect nor the fixed coefficient was statistically significant. The odds ratio was estimated to be 1.013, indicating a minimal increase in the probability of advancing to a higher GOLD category with each passing year. However, this finding was not statistically significant ($p = 0.900$). Therefore, it cannot be concluded that GOLD classification progresses over time.

In contrast, analysis focusing on frailty categorization (robust, pre-frail, frail) showed a different trend. The odds ratio was estimated at 1.224, suggesting that the likelihood of transitioning to a higher frailty category increased by 1.224 times per year. A significant relationship was identified between the passage of time and a deterioration in frailty classification.

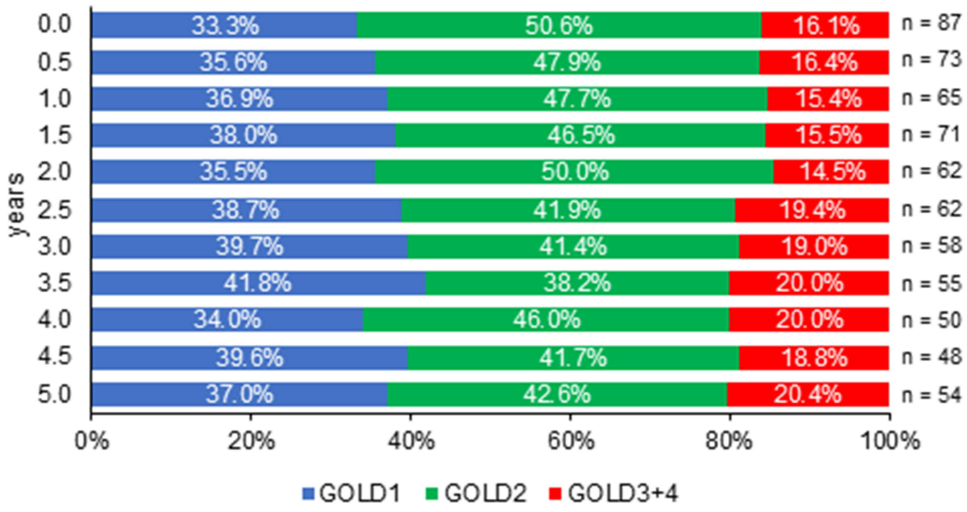

Figure 1 The distribution of the number of participants classified by the severity of Global Initiative for Chronic Obstructive Lung Disease (GOLD) airflow limitation at each six-monthly visit throughout a five-year period. The participants are categorized into GOLD 1, GOLD 2, and GOLD 3+4 groups, represented by blue, green, and red bars respectively. It is important to note that the number of individuals assessed at each time point is different.

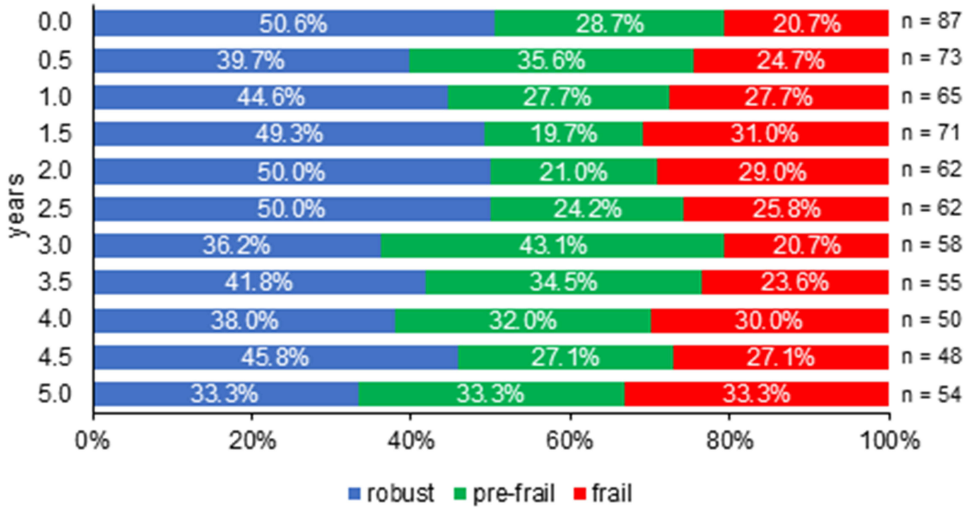

Figure 2 The fluctuating distribution of participants among the robust, pre-frail, and frail groups at six-monthly intervals for a period of five years. The robust group is represented by blue, the pre-frail group by green, and the frail group by red. It should be noted that the number of subjects assessed at each measurement point differed each time.

Five-year Progress of FEV_1 and Kihon Checklist Total Score

The group as a whole exhibited a mean annual decline in FEV_1 of 28.6 mL per year (95% CI: 18.9–38.4, $p < 0.001$) and a mean change in the Kihon Checklist total score of 0.30 per year (95% CI: 0.09–0.51, $p = 0.006$), as estimated by the linear mixed model. The fixed-effect Type III test yielded statistically significant results for both measures. The linear mixed model provided estimated means and 95% CIs for each measurement point at six-monthly intervals over a five-year period, revealing a progressive decline in FEV_1 over time. Significant differences were identified at the two-year mark and subsequently, when compared with baseline values (Figure 3; see Table S1 in the electronic supplementary material for details). The Kihon Checklist total score remained relatively stable, plateauing over an extended period, with a significant increase observed only at the five-year mark (Figure 4; see Table S1 in the electronic supplementary material for details).

Comparisons of Five-year Progress Between Baseline Classifications

The differences in FEV_1 between baseline and estimates derived from a linear mixed model at six-monthly intervals are shown for the robust, pre-frail, and frail groups (Figure 5; absolute FEV_1 values are provided in Table S2 of the

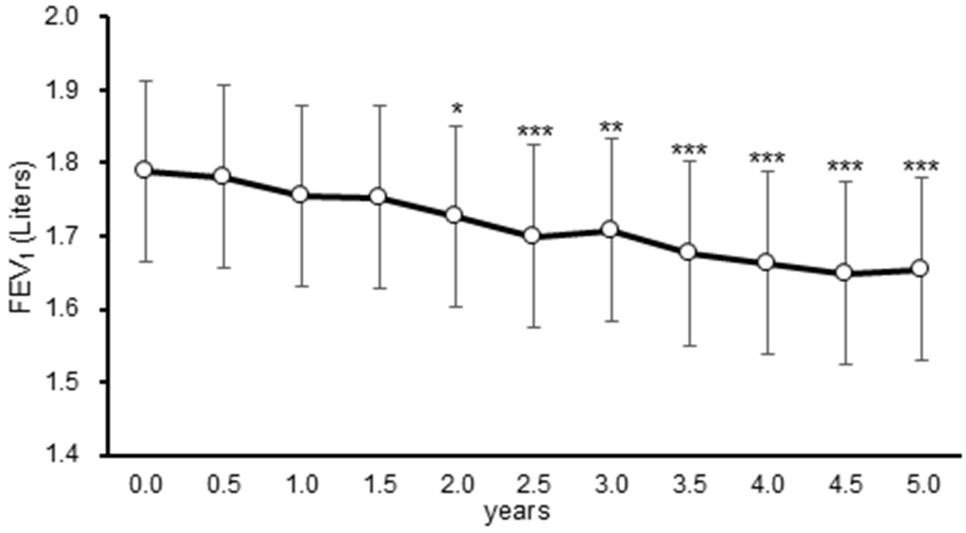

Figure 3 The estimated mean and its 95% confidence interval of forced expiratory volume in 1 second (FEV_1) (Liters) by a linear mixed model for each measurement point every 6 months during a 5-year period. ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$ in comparison with baseline.

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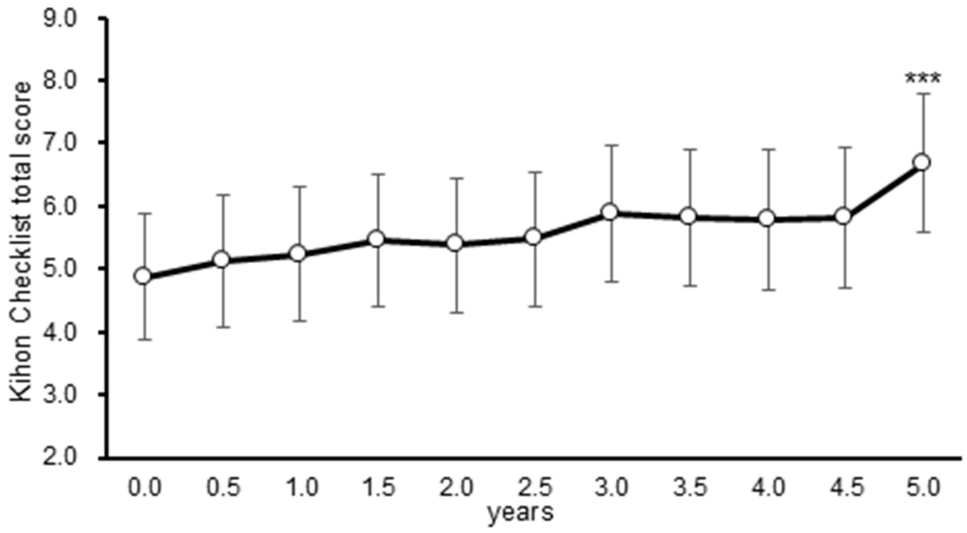

Figure 4 The estimated mean and its 95% confidence interval of the Kihon Checklist total score by a linear mixed model for each measurement point every 6 months during a 5-year period. ***$p < 0.001$ in comparison with baseline.

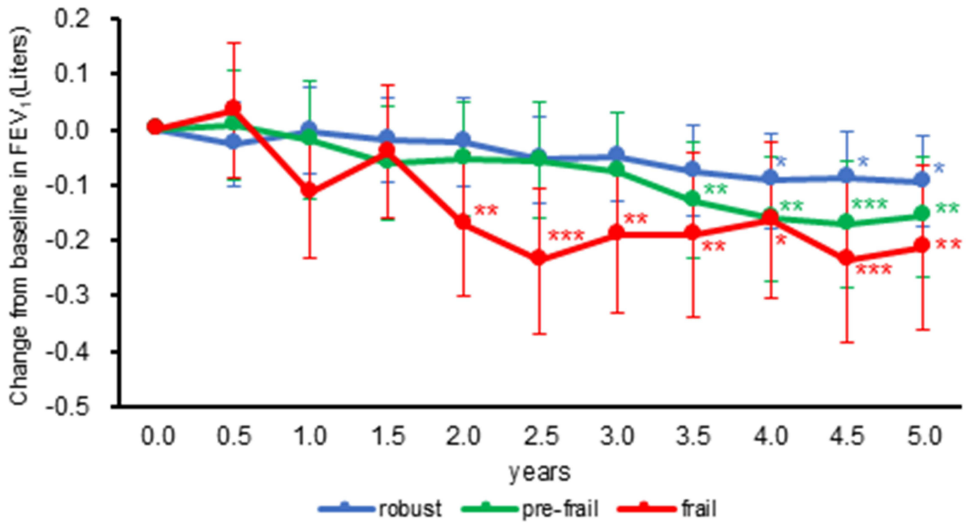

Figure 5 The difference in forced expiratory volume in 1 second (FEV_1) (Liters) between baseline and FEV_1 estimated by a linear mixed model for the robust, pre-frail, and frail groups at each 6-monthly measurement point over a 5-year period. The bars represent the 95% confidence interval. The robust group is denoted by blue, the pre-frail group by green, and the frail group by red. ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$ in comparison with baseline.

electronic supplementary material). When the interaction was assessed using a fixed-effect Type III test, a statistically significant difference was identified in the pattern of change among the three groups ($p = 0.003$). Estimated FEV_1 values were significantly lower than baseline after two years in the frail group ($p < 0.01$), after 3.5 years in the pre-frail group ($p < 0.01$), and after four years in the robust group ($p<0.05$).

Figure 6 illustrates the differences in the Kihon Checklist total score between baseline and estimates calculated by a linear mixed model at six-monthly intervals for the GOLD 1, GOLD 2, and GOLD 3+4 groups (absolute Kihon Checklist total scores are provided in Table S3 of the electronic supplementary material). The Type III test for fixed effects was not significant ($p = 0.293$), indicating no significant differences in the pattern of change among the three groups. After 3.5 years, the GOLD 3+4 group demonstrated a significant increase in Kihon Checklist total scores compared to baseline, whereas the GOLD 1 and GOLD 2 groups showed no significant changes in scores over the five-year study period.

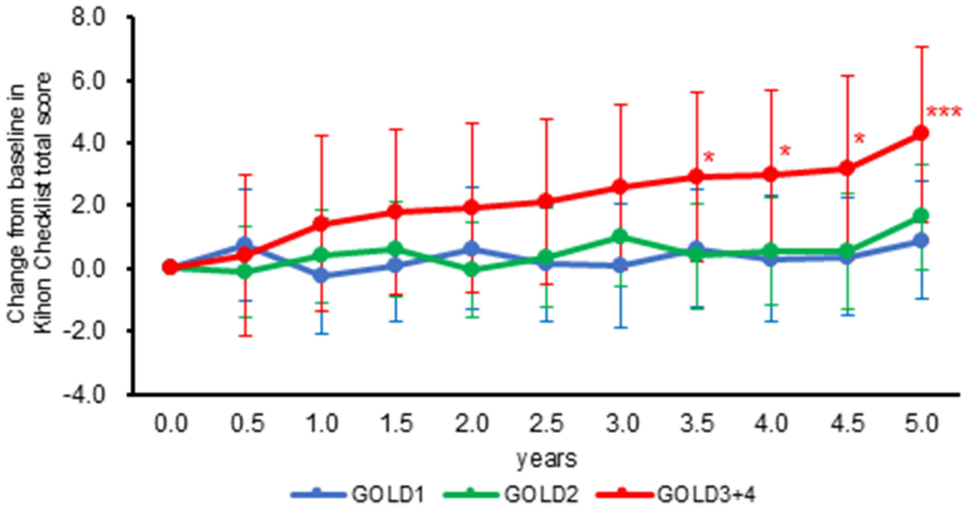

Figure 6 The difference in the Kihon Checklist total score between baseline and those estimated by a linear mixed model for the GOLD 1, GOLD 2, and GOLD 3+4 groups at the beginning for each measurement point every 6 months during a 5-year period. The bars show the 95% confidence interval. Participants with GOLD 1 classification are represented by the blue line, GOLD 2 by the green line, and GOLD 3+4 by the red line. ***$p < 0.001$, *$p < 0.05$ in comparison with baseline.

Discussion

While there have been reports on the cross-sectional association between COPD and frailty, this study represents, to the best of our knowledge, the first attempt to take a step further in understanding their relationship by comparing the progression of both COPD and frailty over time. Throughout the five-year study period, significant deterioration was observed in both FEV_1, a determinant of GOLD severity, and the Kihon Checklist total score, a measure used to define frailty. Specifically, FEV_1 declined by 28.6 mL per year, while the Kihon Checklist total score increased by 0.30 points annually across the entire cohort. Conversely, the three frailty categories, as defined by the Kihon Checklist total score—robust, pre-frail, and frail—exhibited progression over the five-year period. This indicates an annual probability of 1.224 for transitioning to a higher frailty category, such as from robust to pre-frail or from pre-frail to frail. However, the GOLD categories (GOLD 1, GOLD 2, and GOLD 3+4), defined by FEV_1, did not exhibit similar progression during the same period. The lack of apparent migration between GOLD categories over five years suggests that this timeframe may be insufficient to observe changes within these groupings. As such, FEV_1 and the Kihon Checklist total score were used as continuous measures to further explore the relationship between COPD progression and frailty.

The most significant finding from this study is that, in comparison with robust COPD patients, frail COPD patients experienced a more rapid decline in FEV_1, indicating faster COPD progression. Conversely, for individuals who had already developed COPD, the progression of the Kihon Checklist total score did not appear to be so influenced by the stage of COPD. The cross-sectional association between frailty and COPD, as demonstrated in numerous previous studies, suggests that frailty may be one of the possible contributors to COPD progression.

In this study, the authors assessed frailty by evaluating the Kihon Checklist total score, a method currently employed only in Japan. In a longitudinal study focusing on community-dwelling older adults, Ohashi et al reported that the median Kihon Checklist total score increased from 2 in 2011 to 3 in 2016.[28] Moreover, Imai et al observed a significant increase in the Kihon Checklist total score, rising from 2 in 2016 to 3 in 2022.[29] They also reported increases of 1 point in the Kihon Checklist total score over five years and six years, respectively.[28,29] Our research on COPD patients revealed that the mean Kihon Checklist total score rose from 4.9 to 6.7 over five years, and estimated an average annual increase of 0.30 points, suggesting a slightly faster pace of deterioration. Given that the participants were COPD patients, it is not surprising that their scores were comparatively higher. This discrepancy of the deterioration speed may be attributed to the higher baseline scores in our cohort.

One study on COPD patients, which monitored 119 individuals over two years, found that 17.6% showed an improvement in frailty status, 11.7% experienced a decline, and 70.5% remained stable.[34] Two studies conducted in Japanese community-dwelling older adults that examined changes in the Kihon Checklist total score also reported transitions between frailty states, suggesting

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that the rate of change is generally similar.[28,29] In the present study, the estimated probability of transitioning to a higher frailty category increasing by 1.224 times annually aligns closely with existing findings in the literature. Furthermore, when comparing studies of community-dwelling older adults and COPD patients, it is unlikely that any disparities were found in the rate of frailty progression. These facts may be findings consistent with the results observed in this study, which showed no differences in the rate of deterioration of Kihon Checklist total score by GOLD stage.

Historically, a decline in FEV_1 has been regarded as a hallmark of COPD progression, and COPD has been considered a progressive disease.[25,35] Smoking cessation has been demonstrated to lessen FEV_1 decline and slow the progression of COPD,[36–38] even though numerous clinical trials have used the rate of FEV_1 decline as a primary or secondary endpoint.[37,39,40] However, research involving large patient cohorts has shown significant variability in the annual rate of FEV_1 decline among individuals.[41] In this study, the frequency distribution of cases with respect to the annual rate of FEV_1 decline also exhibited wide variability, consistent with findings from previous reports. Conversely, minimal attention has been given to transitions between severity classification groups, such as GOLD 1 to GOLD 4, which are based on FEV_1.

All clinical indicators should fulfil three essential roles: the ability to distinguish subjects (discriminative property), the ability to detect changes (evaluative property), and the ability to predict future outcomes (predictive property). In terms of evaluative property, it is crucial to gather insights from two perspectives: evaluating improvements through medical interventions and assessing the progression of deterioration over time in progressive diseases. The discriminative and predictive properties of frailty have been widely investigated,[5–18] alongside potential improvements achieved through rehabilitation.[34,42–45] Furthermore, substantial evidence has been accumulated regarding the progression of frailty through cohort studies spanning several years.[28,29,46–48] Most of these studies are epidemiological investigations involving large cohorts of elderly individuals in the general population. This study, however, focused on COPD patients, a population known for high dropout rates and substantial missing data in research, requiring careful attention during data analysis.[49] To tackle these challenges, the analysis predominantly employed linear mixed models, enabling the filling in of missing data and facilitating strong statistical analysis.

One of the main limitations of this study is its observational, single-center design and the relatively small sample size, which prevented robust multivariate analyses from being conducted. This limitation restricted our ability to statistically adjust for baseline values of lung function and frailty, thus introducing the potential for regression to the mean, a well-known phenomenon that may affect longitudinal data interpretation. Additionally, the high dropout rate and missing data inherent in real-world clinical practice further limited statistical power. Therefore, the findings should be interpreted cautiously, and future studies with larger sample sizes and comprehensive multivariate approaches are necessary to confirm our observations. Despite these limitations, our study provides valuable insights reflecting the reality of clinical COPD management. Another major problem is that this study used the Kihon Checklist to assess frailty. This tool is only used in Japan, so international comparisons are difficult. In fact, one longitudinal epidemiological study on the progression of COPD and frailty was conducted using FI.[20] Finally, this was an observational study, and therefore, causal relationships cannot be inferred; only associations can be discussed.

Conclusion

Three main conclusions can be drawn from our findings. First, in individuals with COPD, the probability of transitioning to a higher frailty category, such as from robust to pre-frail or from pre-frail to frail, was estimated to increase by 1.224 times annually. However, the GOLD categories, including GOLD 1 to GOLD 4, did not exhibit significant progression over the five-year study period. Second, the cohort as a whole demonstrated a significant annual change in FEV_1 of −28.6 mL per year and an increase in the Kihon Checklist total score of 0.30 per year, as estimated by the linear mixed model. Third, the findings suggest that frailty progression may be one of the factors involved in the progression of COPD, which could be related to the frequent association observed between frailty and COPD.

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Author Contributions

The authors meet the criteria for authorship as recommended by the International Committee of Medical Journal Editors, take responsibility for the integrity of the work as a whole, contributed to the writing and reviewing of the manuscript, and have given final approval for the version to be published. 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.

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