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ORIGINAL RESEARCH

Predictors of Clinical Stability and Mortality in COPD: A Longitudinal Study

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Background: There is no consensus on the definition of clinical stability in chronic obstructive pulmonary disease (COPD), and it is less frequently used as a treatment target compared to severe asthma. The factors that determine clinical stability and their effects on mortality are less well-studied in patients with COPD.

Methods: To address this gap, we conducted a prospective longitudinal cohort study to identify predictors of two-year clinical stability, defined as no exacerbations and stable symptoms (<2 point change in CAT score from baseline), and the impact of comorbid cardiovascular disease (CVD) on clinical stability and mortality in COPD patients.

Results: A total of 463 patients (mean age 71 ± 9 years) were enrolled in this study. The cohort was predominantly Chinese (81.7%) and 45.6% of participants were current smokers. The majority (55.7%) had a history of CVD. Approximately 36% of the cohort achieved clinical stability at one year, and one-third achieved stability at two years. Predictors of 2-year clinical stability included higher body mass index (BMI) (p<0.001), higher post-bronchodilator FEV1/FVC ratio (p=0.0132), fewer baseline exacerbations (p=0.007), absence of bronchiectasis (p=0.045), preserved hemoglobin levels (p=0.019), and successful smoking cessation (p=0.039). Notably, while 2-year clinical stability did not predict subsequent mortality, the presence of CVD was a significant predictor of 5-years mortality (HR 1.48, 95% CI 0.99–2.22; p=0.05).

Conclusion: Our study identified several predictors of 2-year clinical stability in patients with COPD. However, clinical stability at 2 years did not predict subsequent mortality. These findings suggest that clinical stability and mortality are distinct outcomes that are driven by different sets of predictive variables. This underscores the need for a comprehensive approach to COPD management that not only addresses exacerbations and symptoms, but also considers a broader range of factors influencing survival, particularly the management of comorbidities such as cardiovascular disease.

Keywords: stability, mortality, cardiovascular disease, South East Asia, multi-ethnic, comorbidities

Introduction

Chronic obstructive pulmonary disease (COPD) remains a major global health concern, with an, estimated prevalence of 6.2% in Asia and 5.9% in Singapore.[1,2] It is the fourth leading cause of death worldwide and ranks eighth in the disability-adjusted life years lost.[3] The disease burden is more substantial in Asia, with the highest prevalence and mortality of COPD in the Asia-Pacific region.[4,5]

Mortality and exacerbations are pivotal clinical outcomes in COPD and frequently serve as important endpoints in clinical studies.[6,7] Composite endpoints have been introduced to capture a more comprehensive assessment of disease progression and treatment efficacy. One such measure is clinically important deterioration (CID), which integrates multiple indicators of worsening health status, including declines in lung function, exacerbations, and deterioration in patient-reported outcomes such as St. George's Respiratory Questionnaire (SGRQ) or COPD Assessment Test (CAT) scores.[8] Pharmacological therapy has been shown to reduce the risk of CID, triple therapy more so than dual therapy,[8,9]

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while older age and lower Forced Expiratory Volume in 1 second (FEV1) increase the risk of CID.[10] While markers of clinical deterioration are essential for evaluating disease progression, and the concept of clinical stability is less frequently utilized in COPD. Recognizing and quantifying clinical stability is crucial as it reflects effective disease management and may inform therapeutic decisions. Efforts have been made in recent years to better understand disease stability in COPD, defined variably as the absence of exacerbation, as well as the absence of significant clinical deterioration or the presence of improvement over a period of time.[11–15] This has led to calls for the pursuit of clinical stability in the management of COPD patients.[12] However, there remains a lack of consensus on a defined duration for clinical stability. With the emergence of biologics in treatment of airway diseases, including the recent approval of biologics for COPD,[16] it is essential to explore and refine the concept of disease stability, drawing parallels to advancements made in the field of severe asthma.[17]

Cardiovascular comorbidities are increasingly recognized as a significant contributor to the morbidity and mortality of COPD,[18] with the prevalence of cardiovascular disease (CVD) among COPD patients estimated to be between 20% to 60%.[19,20] A meta-analysis showed a more than two-fold increase in the risk of CVD in patients with COPD compared to patients without COPD.[19] Such an association arises from shared risk factors and increased systemic inflammation from chronic and intermittent hypoxia.[21,22] Although ethnic disparities in susceptibility to cardiovascular disease and mortality have been reported, their impact on individuals with both COPD and CVD in multi-ethnic Asian cohorts remains underexplored. The REGARDS COPD cohort from the United States found no significant difference in all-cause mortality between Black and White individuals.[23] However, there was a 40% higher risk of cardiovascular mortality among Black women compared to White women.[23] Data from the Asia-Pacific region indicate an increased mortality risk in COPD patients with concomitant atrial fibrillation.[24] Additionally, analyses of COPD patients of Chinese ethnicity in South East Asia showed that patients with cardiovascular disease are at higher risk of mortality.[25] An older study examining cardiovascular disease in a multi-ethnic Singaporean cohort reported higher ischemic heart disease related mortality in Indian individuals compared to Malay and Chinese ethnic groups.[26] However, the prevalence and impact of comorbid CVD on clinical stability and mortality in a multi-ethnic South East Asian COPD cohort remains underexplored.

Therefore, our objective was to identify the predictors of two-year clinical stability of COPD and the impact of comorbid CVD on clinical stability and five-year mortality, by conducting a prospective longitudinal observational study.

Methods

Patients with COPD aged 40 years and above attending a multidisciplinary COPD clinic consisting of pulmonologists, COPD nurses, physiotherapists, pharmacists, and smoking cessation counselors at Singapore General Hospital were prospectively recruited from 2013 to 2024. Patient with confirmed COPD who were able to provide written informed consent were included in the study. Those who did not provide consent were excluded. COPD was defined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2013 as the presence of respiratory symptoms and/or risk factor exposure and post-bronchodilator $FEV_1/FVC<0.7$.[27,28] Patient demographics, smoking history, clinical data including symptom score (CAT score), exacerbations, and hospitalization in the previous year, comorbidities, spirometry, year of COPD diagnosis, CT thorax, blood eosinophil count, hemoglobin level, and baseline treatment were obtained from patient histories and supplemented by verification from medical records at recruitment. During annual follow-up visits, smoking history, CAT score, number of exacerbations, spirometry results, and COPD treatment were obtained and recorded. The duration of COPD at study entry was determined on the basis of the year of the first recorded spirometry. Exacerbation was defined as acute worsening of symptoms requiring corticosteroids and/or antibiotics. Frequent exacerbators were defined as having two or more exacerbations in the year preceding study recruitment as well as moderate exacerbations, which refer to COPD exacerbations necessitating emergency visits or hospital admission. Cardiovascular disease was defined as the presence of coronary artery disease, heart failure, atrial fibrillation and flutter, cerebrovascular disease, hypertensive heart disease, peripheral arterial disease, pulmonary arterial hypertension, cardiomyopathy, and valvular heart disease.[29,30] All deaths in Singapore were automatically updated in our national electronic health record and the date of death was recorded. We defined COPD stability at 1- and 2-years as having met both the following criteria: (1) no exacerbations requiring oral corticosteroids, antibiotics, and/or hospitalization and (2) a stable CAT score (<2 points change from baseline) over 1 and 2 years. For the evaluation of 2-year

stability, patients who died before the 2-year assessment or who were lost to follow-up were excluded because the cause of death was not available. Patients who were included in the evaluation of 2-year stability were subsequently included in the analysis of 5-year mortality. Study data were collected and managed using REDCap electronic data capture tools hosted at Singapore General Hospital.[31,32]

This study was approved by the SingHealth Centralized Institutional Review Board under CIRB 2018/2186 (2013/184/C) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants at recruitment.

Statistical Analysis

Data were analyzed using the R software (version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria). Normality was assessed using the Shapiro–Wilk test. Continuous variables with a normal distribution were presented as mean ± standard deviation, whereas non-normally distributed variables were reported as medians with interquartile ranges. The Mann–Whitney *U*-test was used to compare non-normally distributed continuous variables between the two groups. Categorical variables were compared using the chi-square test, and the Kruskal–Wallis test followed by Dunn's test with false discovery rate correction was used for multiple group comparisons. Additionally, multivariate logistic regression for CVD were performed by including variables that were significant in the univariate analysis and clinically relevant. The Hosmer–Lemeshow test was used to evaluate goodness of fit, with a p-value > 0.05 indicating acceptable calibration. Multicollinearity was assessed using variance inflation factors (VIFs), and no variables exceeded the conventional threshold (VIF > 5). Missing data were present in fewer than 20% of all the variables except for education level and were handled by complete-case analysis whereby cases with missing values were excluded from the relevant analyses. Mortality analysis was performed using Kaplan-Meier survival curves and the Cox proportional hazard ratio. Variables with a p-value <0.05, in the univariate Cox proportional hazard analysis for mortality, were included in the multivariate model. Proportional hazards assumption was tested using Schoenfeld residuals and the global test was not statistically significant indicating that the assumption was adequately met.

Results

Baseline Characteristics of the Study Cohort

In total, 463 patients were recruited between 2013–2024 (Figure 1). The baseline characteristics of the study cohort are summarized in Table 1. The mean age of the patients was 71 (standard deviation [SD], 9), with male accounting for 96.3% of the cohort. The majority of the cohort was of Chinese ethnicity (81.7%), followed by Malay (10.8%), closely mirroring Singapore's demographic composition. Current smokers represented 45.6% of the cohort, with median pack years of 50.0 (interquartile range [IQR] 40–68). The median duration of COPD at time of study recruitment was 2 years (IQR 1–5), 113 (24%) were newly diagnosed with COPD at initial assessment. The median COPD assessment test (CAT) score was 13.0 (IQR 7–20) and the median modified medical research council (mMRC) dyspnea score was 2.00 (IQR 1–3), indicating

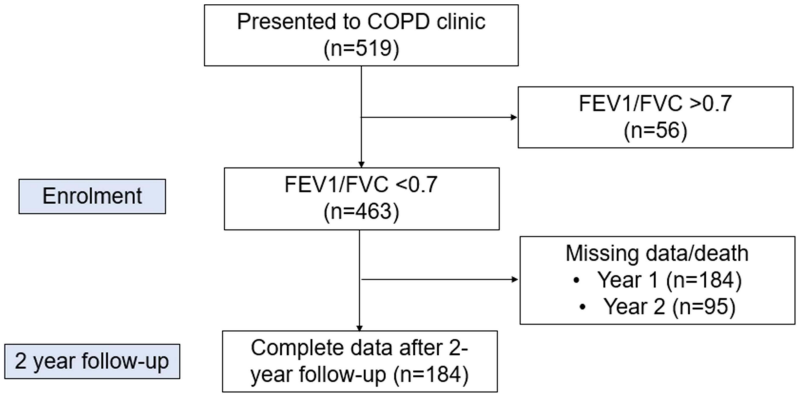

Figure 1 STROBE flowchart of study.

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Table 1 Baseline Characteristics of the Overall Cohort and with and Without Cardiovascular Disease (CVD)

	Overall	No CVD	CVD	P-value
	(N=463)	(N=205)	(N=258)	
Age (year), Mean (SD)	**71 (9)**	**69 (9)**	**73 (8)**	**<0.001**
Age at diagnosis (year), Mean (SD)	**68 (9)**	**66 (9)**	**69 (9)**	**<0.001**
Sex, n (%)				0.858
Female	17 (3.7%)	9 (4.4%)	8 (3.1%)	
Male	446 (96.3%)	196 (95.6%)	250 (96.9%)	
BMI (kg/m^2), Median [Q1, Q3]	**21.5 [18.4, 24.7]**	**20.6 [17.6, 23.6]**	**22.1 [19.4, 25.1]**	**<0.001**
Highest level of education, n (%)				0.792
Missing	219 (47.3%)	89 (43.4%)	130 (50.4%)	
No formal education	46 (9.9%)	26 (12.7%)	20 (7.8%)	
Primary	107 (23.1%)	46 (22.4%)	61 (23.6%)	
Secondary	77 (16.7%)	37 (18.1%)	40 (15.5%)	
Diploma/Uni	14 (3.0%)	7 (3.4%)	7 (2.7%)	
Duration of COPD, Median [Q1, Q3]	**2.00 [1.00, 5.00]**	**1.00 [0, 3.75]**	**2.00 [1.00, 6.00]**	**0.008**
Missing Duration of COPD	6 (1.3%)	3 (1.5%)	3 (1.2%)	
Ethnicity				0.752
Chinese	378 (81.7%)	162 (79.0%)	216 (83.7%)	
Indian	27 (5.8%)	11 (5.4%)	16 (6.2%)	
Malay	50 (10.8%)	27 (13.2%)	23 (8.9%)	
Other	8 (1.7%)	5 (2.4%)	3 (1.2%)	
Smoking Status, n (%)				0.728
Current smoker	211 (45.6%)	100 (48.8%)	111 (43.0%)	
Ex-smoker (quit <6 month)	27 (5.8%)	13 (6.3%)	14 (5.4%)	
Ex-smoker (quit ≥6 month)	225 (48.6%)	92 (44.9%)	133 (51.6%)	
Smoking pack years, Median [Q1, Q3]	**50.0 [40.0, 68.0]**	**47.0 [35.0, 60.0]**	**50.0 [40.0, 80.0]**	**0.025**
Missing Smoking pack years	85 (18.4%)	32 (15.6%)	53 (20.5%)	
Post -BD FEV_1% predicted, Median [Q1, Q3]	53.0 [40.0, 66.0]	51.0 [39.0, 64.0]	54.0 [43.0, 67.0]	0.054
Post-BD FEV_1/FVC ratio, Median [Q1, Q3]	52.9 [45.9, 60.0]	52.0 [44.0, 59.3]	53.2 [46.0, 61.0]	0.149
CAT score at baseline, Median [Q1, Q3]	13.0 [7.00, 20.0]	13.0 [6.00, 19.5]	13.0 [8.00, 19.5]	0.835
Missing CAT score	6 (1.3%)	2 (1.0%)	4 (1.6%)	
mMRC score, Median [Q1, Q3]	2.00 [1.00, 3.00]	2.00 [1.00, 3.00]	2.00 [1.00, 3.00]	0.237
Frequent exacerbator (>2 exacerbations/year) in the past year, n(%)	164 (35.4%)	70 (34.1%)	94 (36.4%)	0.877
Hyperlipidemia, n (%)	**219 (47.3%)**	**39 (19.0%)**	**180 (69.8%)**	**<0.001**
Diabetes mellitus, n (%)	**73 (15.8%)**	**17 (8.3%)**	**56 (21.7%)**	**<0.001**

(*Continued*)

Table 1 (Continued).

	Overall	No CVD	CVD	P-value
	(N=463)	(N=205)	(N=258)	
Peptic Ulcer Disease, n (%)	16 (3.5%)	7 (3.4%)	9 (3.5%)	0.999
Gastritis, n (%)	21 (4.5%)	8 (3.9%)	13 (5.0%)	0.843
Gastroesophageal reflux disease, n (%)	38 (8.2%)	15 (7.3%)	23 (8.9%)	0.824
Chronic kidney disease, n (%)	**42 (9.1%)**	**4 (2.0%)**	**38 (14.7%)**	**<0.001**
Osteoporosis, n (%)	16 (3.5%)	5 (2.4%)	11 (4.3%)	0.566
Obstructive sleep apnea, n (%)	8 (1.7%)	1 (0.5%)	7 (2.7%)	0.189
Anxiety, n (%)	3 (0.6%)	1 (0.5%)	2 (0.8%)	0.929
Depression, n (%)	**11 (2.4%)**	**1 (0.5%)**	**10 (3.9%)**	**0.038**
Previous pulmonary tuberculosis, n (%)	68 (14.7%)	32 (15.6%)	36 (14.0%)	0.882
Cancer, n (%)	49 (10.6%)	23 (11.2%)	26 (10.1%)	0.924
Bronchiectasis, n (%)				0.889
No previous CT thorax	67 (14.5%)	30 (14.7%)	37 (14.3%)	
No	302 (65.2%)	129 (62.9%)	173 (67.1%)	
Yes	94 (20.3)	46 (22.4%)	48 (18.6%)	
Chronic bronchitis, n (%)	134 (28.9%)	67 (32.7%)	67 (26.0%)	0.139
Hemoglobin (g/dL), Median [Q1, Q3]	14.1 [12.9, 15.0]	14.1 [13.0, 15.0]	14.0 [12.9, 15.0]	0.994
Missing Hemoglobin	30 (6.5%)	19 (9.3%)	11 (4.3%)	
Blood eosinophil count ($x10^9$/L), Median [Q1, Q3]	0.190 [0.070, 0.360]	0.170 [0.060, 0.343]	0.200 [0.080, 0.360]	0.158
Missing Eosinophil count	37 (8.0%)	21 (10.2%)	16 (6.2%)	
Baseline treatment, n (%)				0.868
SAMA/SABA as necessary	18 (3.9%)	12 (5.9%)	6 (2.3%)	
LABA	8 (1.7%)	5 (2.4%)	3 (1.2%)	
LABA/ICS	34 (7.3%)	14 (6.8%)	20 (7.8%)	
LABA/LAMA	175 (37.8%)	76 (37.1%)	99 (38.4%)	
LAMA	55 (11.9%)	22 (10.7%)	33 (12.8%)	
Triple	173 (37.4%)	76 (37.1%)	97 (37.5%)	

Abbreviations: CVD, cardiovascular disease; SD, standard deviation; BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; Post-BD, post-bronchodilator; FEV_1, Forced Expiratory Volume in 1 second; FVC, Forced Vital Capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; CAT, COPD assessment tool; mMRC, modified Medical Research Council dyspnea score; CT, computed tomography; SABA, Short-acting beta-agonist; SAMA, Short-acting muscarinic antagonist; LABA, Long-acting beta-agonist; LAMA, Long-acting muscarinic antagonist; ICS, Inhaled corticosteroid. Continuous variables were compared using Mann–Whitney *U*-test and chi-square test for categorical variables. Bolded variables are variables that are statistically significant.

moderate symptom burden among the study cohort. Most patients were receiving either dual bronchodilator therapy (37.8%, n=175) or triple therapy (37.4%, n=173) at baseline.

Characteristics of COPD Patients with and Without Cardiovascular Disease

A large proportion of our cohort (55.7%; n=258) had a history of CVD (Table 1). COPD patients with CVD were generally older (mean 73 vs 69 years; p<0.001) and had a longer duration of COPD (median 2 vs 1 year; p=0.008),

higher smoking pack years (median 50 vs 47 years; p=0.025), and higher body mass index (BMI) (median 22.1 vs 20.6; p<0.001). There was no significant difference in the prevalence of CVD among different ethnic groups. Patients with CVD were also more likely to have other comorbidities, including hyperlipidemia (69.8% vs 19.0%; p<0.001), diabetes mellitus (21.7% vs 8.3%; p<0.001), chronic kidney disease (CKD) (14.7% vs 2.0%; p<0.001), and depression (3.9% vs 0.5%; p=0.038). Multivariate logistic regression identified several factors significantly associated with the presence of CVD (Supplementary Table 1). Older age (OR 1.05, 95% CI 1.02–1.08; p = 0.003) and higher BMI (OR 1.07, 95% CI 1.01–1.14; p = 0.028) were associated with moderate but clinically relevant incremental risks. Greater smoking pack years showed a trend towards significance (OR 1.01 per pack-year, 95% CI 1.00–1.01; p = 0.060). Importantly, hyperlipidaemia was associated with a substantial increase in risk, more than eightfold (OR 8.44, 95% CI 4.93–14.44; p < 0.001) highlighting a major clinical impact. Similarly, CKD increased the odds of CVD by approximately fourfold (OR 4.00, 95% CI 1.08–14.76; p = 0.037), underscoring its clinical relevance. In contrast, other variables including gender, diabetes, and depression were not significantly associated with CVD and showed effect sizes of limited clinical importance in this cohort. The logistic regression model demonstrated good fit (Hosmer–Lemeshow test, p = 0.303). No significant multicollinearity was detected (all VIFs < 2).

COPD Duration and Disease Severity

A longer COPD duration at the time of recruitment was associated with several indicators of disease severity, including lower lung function (Figure 2A), higher symptom burden, and an increased frequency of exacerbations (Figure 2B). Additionally, patients with a longer COPD duration were more likely to have cardiovascular disease (Figure 2C), a higher prevalence of concomitant bronchiectasis (Figure 2D), a lower blood eosinophil count, quit smoking, and more frequent triple therapy. Longer COPD duration was also associated with increased exacerbations and higher baseline symptom (CAT) scores.

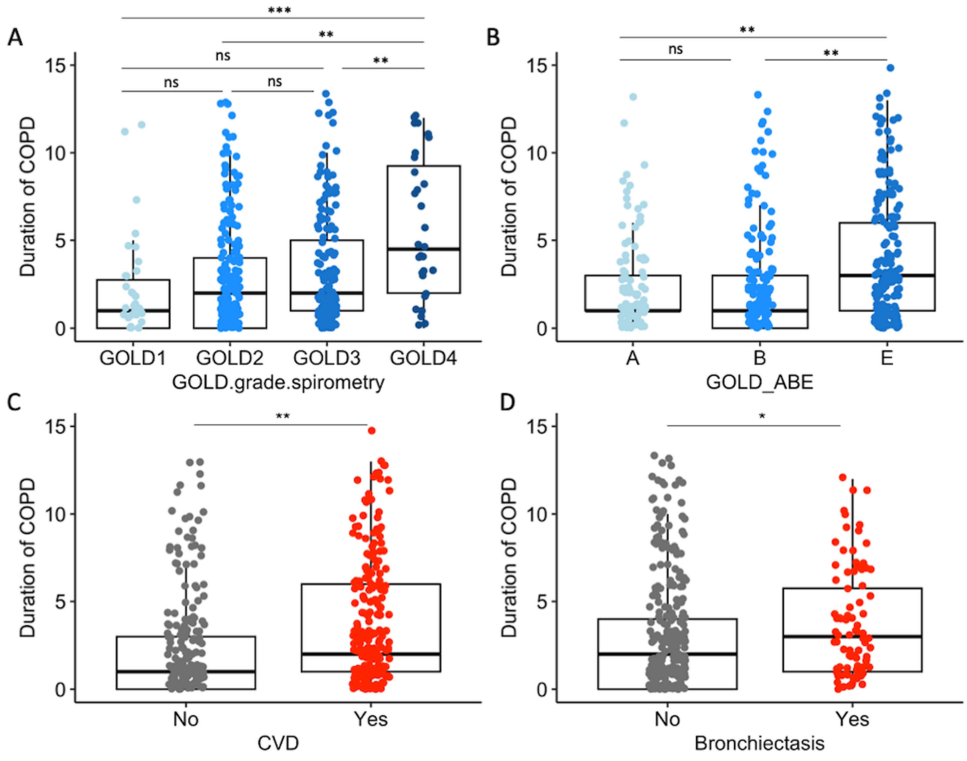

Figure 2 Scatter boxplot of illustrating the association of COPD duration with (**A**) GOLD spirometry grade, (**B**) GOLD ABE group, (**C**) presence (Yes) or absence (No) of cardiovascular disease and (**D**) presence (Yes) or absence (No) of bronchiectasis. Box plots indicate the median and interquartile range and the largest and smallest values above or below the 75th and 25th percentile, respectively. ***p<0.001,. ns: not significant **p<0.01, *p<0.05, ns: not significant.
Abbreviation: GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Predictors of Clinical Stability in COPD at Two years

We next assessed longitudinal two-year clinical stability based on symptoms (CAT score) and exacerbations. Fifty-seven patients died before the two-year assessment and were excluded; and complete two-year longitudinal data were available for 184 patients. The baseline characteristics of the patients with and without 2-year longitudinal data are summarized in Supplementary Table 2. Overall, the number of exacerbations significantly decreased from baseline to year 1 and 2. The proportion of patients with frequent exacerbations at baseline was 46.0% (n=85), compared to 31.0% (n=57) at year 1 and 36.4% (n=67) at year 2 (p=0.009, Kruskal Wallis test) (Figure 3A). In contrast, there was no significant change in the proportion of patients with CAT scores <10 over the 2-year follow-up period (baseline: 34.8% (n=64); year 1: n= 37.0% (n=68); year 2: 29.3% (n=54); p=0.282, Kruskal Wallis test) (Figure 3B). The proportion of patients who remained clinically stable was similar between years 1 (34.6%, n=64) and year 2 (32.6%, n=60) (p=0.741, Kruskal Wallis test) (Figure 3C).

Predictors of clinical stability in COPD at two years include higher BMI (p<0.001), higher post-bronchodilator FEV_1 /FVC ratio (p=0.0132), fewer exacerbations at baseline (p=0.007), absence of concomitant bronchiectasis (p=0.045), and higher hemoglobin levels (p=0.019) (Table 2). Additionally, the presence of hyperlipidemia (p=0.019) and treatment with lipid-lowering agents (p=0.035) were associated with clinical stability at 2-years. Notably, a greater proportion of patients who achieved stability had quit smoking (67% vs 33%; p=0.039) during the 2-year period. Patients with clinical stability were less likely to be on triple therapy (36.7% vs 57.3%; p=0.033).

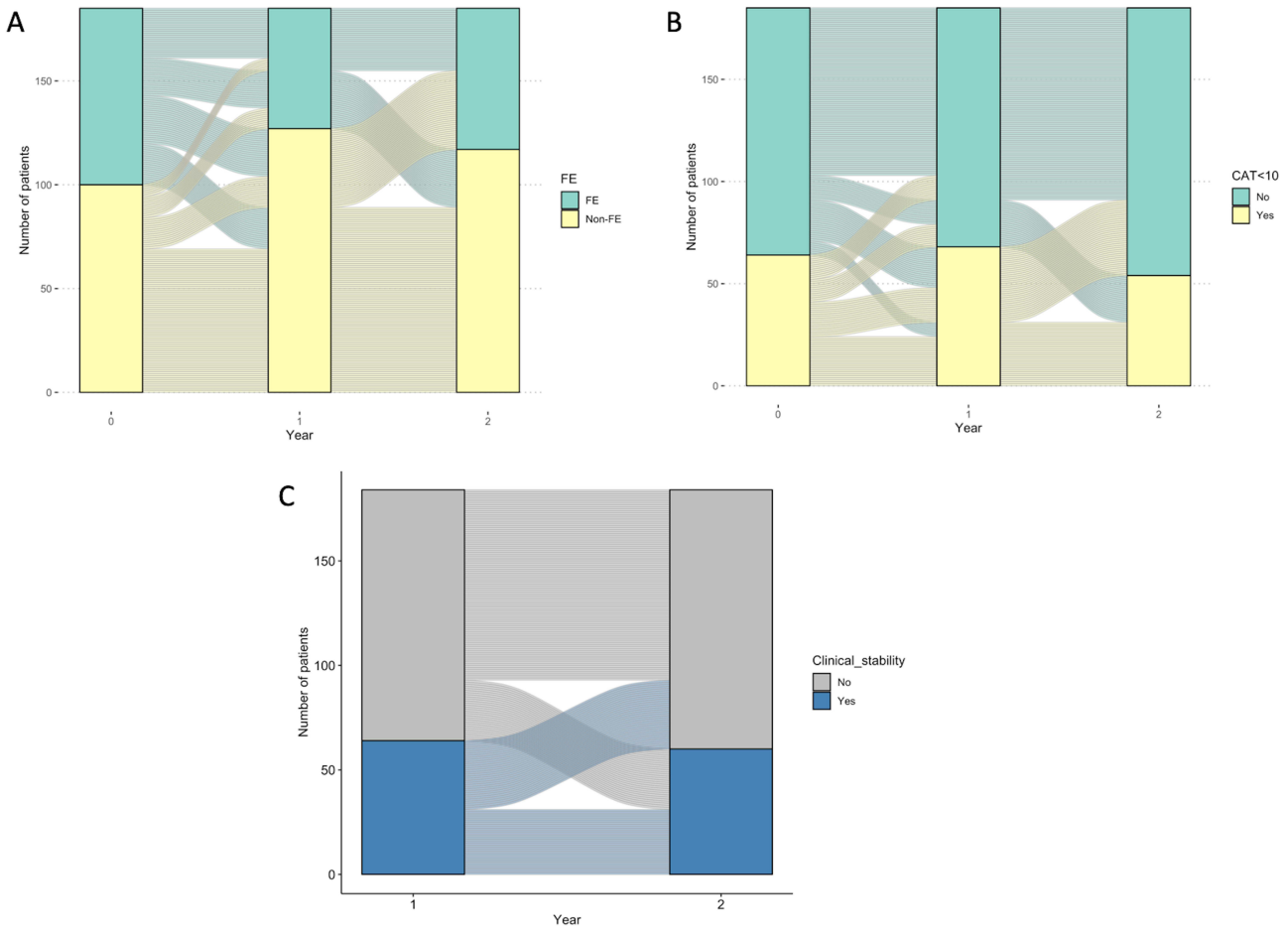

Figure 3 Sankey plots illustrating the changes in the proportion of patients with (**A**) frequent exacerbation (FE), (**B**) CAT score of less than 10, and (**C**) clinical stability from baseline to 2 years of follow-up.
Abbreviation: CAT, COPD Assessment test.

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Table 2 Characteristics of Patients with and Without Clinical Stability After 2 years

	Overall	No Stability	Stability	P-value
	(N=184)	(N=124)	(N=60)	
Age (year), Mean (SD)	70 (8)	70 (9)	68 (8)	0.416
Sex, n (%)				0.223
Female	6 (3.3%)	6 (4.8%)	0 (0%)	
Male	178 (96.7%)	118 (95.2%)	60 (100%)	
BMI (kg/m^2), Median [Q1, Q3]	**21.8 [18.7, 24.5]**	**21.1 [18.3, 23.6]**	**23.1 [21.2, 27.0]**	**<0.001**
Highest level of education, n (%)				0.328
Missing	52 (28.3%)	40 (32.3%)	12 (20.0%)	
No formal education	20 (10.9%)	16 (12.9%)	4 (6.7%)	
Primary	54 (29.3%)	30 (24.2%)	24 (40.0%)	
Secondary	50 (27.2%)	31 (25.0%)	19 (31.7%)	
Diploma/Uni	8 (4.3%)	7 (5.6%)	1 (1.6%)	
Duration of COPD, Median [Q1, Q3]	2.00 [1.00, 4.00]	2.00 [0, 5.00]	2.00 [0.75, 3.00]	0.497
Missing Duration of COPD	1 (0.5%)	1 (0.8%)	0 (0.0%)	
Ethnicity				0.434
Chinese	152 (82.6%)	104 (83.9%)	48 (80.0%)	
Indian	16 (8.7%)	7 (5.6%)	9 (15.0%)	
Malay	14 (7.6%)	11 (8.9%)	3 (5.0%)	
Other	2 (1.1%)	2 (1.6%)	0 (0%)	
Smoking Status, n (%)				0.348
Current smoker	91 (49.5%)	58 (46.8%)	33 (55.0%)	
Ex-smoker (quit <6 month)	8 (4.3%)	8 (6.4%)	0 (0%)	
Ex-smoker (quit ≥6 month)	85 (46.2%)	58 (46.8%)	27 (45.0%)	
Smoking pack years, Median [Q1, Q3]	48.0 [40.0, 60.0]	50.0 [39.5, 62.0]	45.5 [40.0, 59.5]	0.877
Missing smoking pack years	30 (16.3%)	20 (16.1%)	10 (16.7%)	
Smoking cessation from baseline, n (%)	**21 (23.1%)**	**7 (33.3%)**	**14 (66.7%)**	**0.039**
Post -BD FEV_1% predicted, Median [Q1, Q3]	52.5 [39.8, 63.3]	49.0 [38.0, 63.0]	55.5 [40.8, 65.3]	0.166
Post-BD FEV_1/FVC ratio, Median [Q1, Q3]	**51.0 [44.0, 59.0]**	**50.5 [42.8, 57.0]**	**53.0 [48.0, 62.0]**	**0.0132**
CAT score at baseline, Median [Q1, Q3]	13.0 [6.00, 19.0]	13.0 [6.00, 19.5]	13.0 [6.75, 19.0]	0.995
mMRC score, Median [Q1, Q3]	2.00 [1.00, 2.00]	2.00 [1.00, 2.00]	2.00 [1.00, 2.00]	0.975
Number of exacerbations at baseline, Median [Q1, Q3]	**1.00 [0, 2.25]**	**1.00 [0, 3.00]**	**0 [0, 2.00]**	**0.007**
Cardiovascular disease, n (%)	88 (47.8%)	53 (42.7%)	35 (58.3%)	0.068
Hyperlipidemia, n (%)	**77 (41.8%)**	**44 (35.5%)**	**33 (55.0%)**	**0.019**

(*Continued*)

Table 2 (Continued).

	Overall	No Stability	Stability	P-value
	(N=184)	(N=124)	(N=60)	
Anti-lipid medication, n (%)	**59 (32.1%)**	**33 (26.6%)**	**26 (43.3%)**	**0.035**
Diabetes mellitus (DM), n (%)	31 (16.8%)	18 (14.5%)	13 (21.7%)	0.478
DM medication, n (%)	26 (14.1%)	13 (10.5%)	13 (21.7%)	0.069
Peptic Ulcer Disease, n (%)	7 (3.8%)	2 (1.6%)	5 (8.3%)	0.068
Gastritis, n (%)	9 (4.9%)	6 (4.8%)	3 (5.0%)	0.999
Gastroesophageal reflux disease, n (%)	23 (12.5%)	15 (12.1%)	8 (13.3%)	0.972
Chronic kidney disease, n (%)	17 (9.2%)	8 (6.5%)	9 (15.0%)	0.108
Osteoporosis, n (%)	3 (1.6%)	3 (2.4%)	0 (0%)	0.478
Obstructive sleep apnea, n (%)	**6 (3.3%)**	**1 (0.8%)**	**5 (8.3%)**	**0.026**
Anxiety, n (%)	1 (0.5%)	1 (0.8%)	0 (0%)	0.784
Depression, n (%)	3 (1.6%)	2 (1.6%)	1 (1.7%)	1
Previous pulmonary tuberculosis, n (%)	28 (15.2%)	5 (8.3%)	23 (18.5%)	0.112
Cancer, n (%)	16 (8.7%)	12 (9.7%)	4 (6.7%)	0.794
Bronchiectasis, n (%)				**0.045**
No previous CT thorax	**20 (10.9%)**	**15 (12.1%)**	**5 (8.3%)**	
No	**123 (66.8%)**	**76 (61.3%)**	**47 (78.4%)**	
Yes	**41 (22.3)**	**33 (26.6%)**	**8 (13.3%)**	
Chronic bronchitis, n (%)	57 (31.0%)	43 (34.7%)	14 (23.3%)	0.296
Hemoglobin (g/dL), Median [Q1, Q3]	**14.3 [13.4, 15.1]**	**14.2 [13.3, 15.0]**	**14.7 [14.0, 15.4]**	**0.019**
Missing Hemoglobin	9 (4.9%)	3 (2.4%)	6 (10.0%)	
Blood eosinophil count ($x10^9$/L), Median [Q1, Q3]	0.180 [0.070, 0.350]	0.160 [0.070, 0.310]	0.200 [0.080, 0.403]	0.603
Missing Blood eosinophil count	9 (4.9%)	5 (4.0%)	4 (6.7%)	
Baseline treatment, n (%)				0.999
SAMA/SABA as necessary	3 (1.6%)	2 (1.6%)	1 (1.7%)	
LABA	4 (2.2%)	2 (1.6%)	2 (3.3%)	
LABA/ICS	14 (7.6%)	10 (8.1%)	4 (6.7%)	
LABA/LAMA	67 (36.4%)	44 (35.5%)	23 (38.3%)	
LAMA	18 (9.8%)	11 (8.9%)	7 (11.7%)	
Triple	78 (42.4%)	55 (44.4%)	23 (38.3%)	

(*Continued*)

Table 2 (Continued).

	Overall (N=184)	No Stability (N=124)	Stability (N=60)	P-value
Treatment at 2 years follow-up, n (%)				**0.033**
LABA/ICS	**6 (3.3%)**	**5 (4.0%)**	**1 (1.6%)**	
LABA/LAMA	**75 (40.8%)**	**42 (33.9%)**	**33 (55.0%)**	
LAMA	**10 (5.4%)**	**6 (4.8%)**	**4 (6.7%)**	
Triple	**93 (50.5%)**	**71 (57.3%)**	**22 (36.7%)**	

Abbreviations: SD, standard deviation; BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; Post-BD, post-bronchodilator; FEV_1, Forced Expiratory Volume in 1 second; FVC, Forced Vital Capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; CAT, COPD assessment tool; mMRC, modified Medical Research Council dyspnea score; CT, computed tomography; SABA, Short-acting beta-agonist; SAMA, Short-acting muscarinic antagonist; LABA, Long-acting beta-agonist; LAMA, Long-acting muscarinic antagonist; ICS, Inhaled corticosteroid. Bolded variables are variables that are statistically significant.

Impact of Clinical Stability and Cardiovascular Disease on Mortality

Having determined clinical stability, we next evaluated the 5 years-mortality in patients with and without 2-year stability. The median follow-up period was 1780 (IQR 1100–2780) days. Interestingly, clinical stability at two years was not associated with subsequent mortality. The Kaplan-Meier survival curve demonstrated no significant difference in all-cause mortality between patients who achieved clinical stability at 2 years and those who did not (p=0.73) (Figure 4A). In contrast, patients with CVD had significantly higher mortality rates than those without (p=0.017) (Figure 4B). This association persisted (hazard ratio for CVD 1.48, 95% CI 0.99–2.22; p=0.05) even after adjusting for potential confounders, including age, gender, smoking pack years, FEV1% predicted and duration of COPD (Supplementary Table 3). The model was stratified by BMI category to account for its non-proportional effect over time. The global test for the proportional hazards assumption was not significant (p=0.075), and no individual covariates showed evidence of non-proportionality, suggesting that the final model adequately satisfies the proportional hazard assumption. Other factors associated with 5-years mortality include older age, higher baseline dyspnea (mMRC) scores, and history of pulmonary tuberculosis (Supplementary Tables 4 and 5).

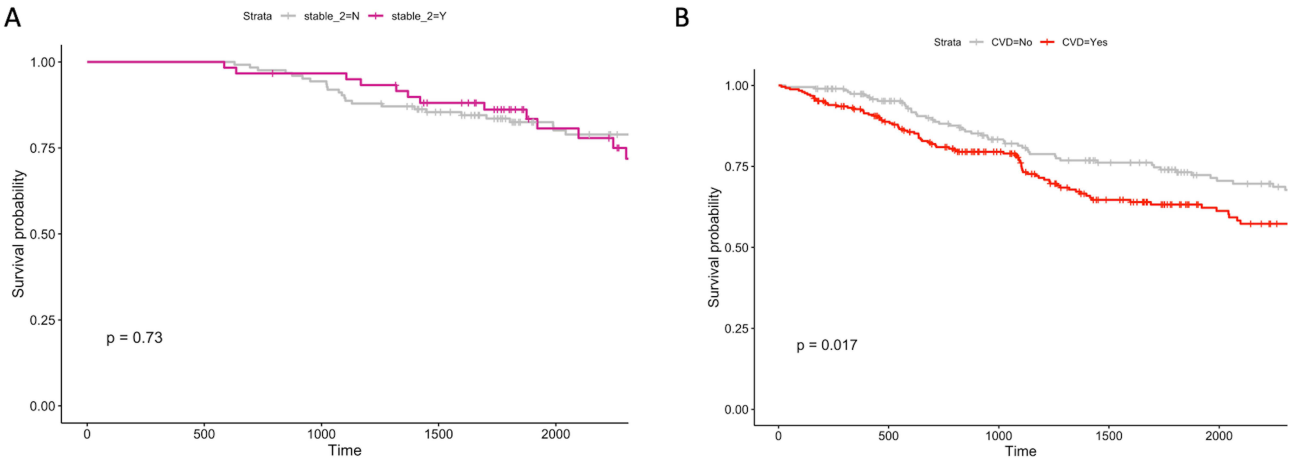

Figure 4 Kaplan-Meier curves illustrating the survival differences between (**A**) patients with (Y) and without (N) 2-year clinical stability and (**B**) cardiovascular disease (CVD). stable_2: 2-year clinical.

Discussion

In our study, clinical stability, defined by the absence of exacerbations and having stable symptom control, was achieved in 34.6% of patients at year one and 32.6% at year two following optimization of COPD management in a multidisciplinary clinic setting. The factors associated with attaining clinical stability at two years included a higher body mass index (BMI), better lung function, preserved hemoglobin levels, fewer baseline exacerbations, successful smoking cessation, hyperlipidemia treated with lipid-lowering agents, and the absence of concomitant bronchiectasis. These findings underscore the value of a multidisciplinary approach to COPD management that emphasizes personalized treatment and targeting of treatable traits to mitigate disease progression and prevent complications. Notably, achieving clinical stability at two years did not correlate with subsequent mortality, suggesting that factors beyond short-term clinical stability, such as comorbid CVD, significantly influenced long-term survival outcomes. More than half of the patients with COPD in our cohort had comorbid CVD, which was associated with older age, higher cumulative smoking exposure, increased BMI, longer COPD duration, and a higher prevalence of metabolic comorbidities. Key predictors of mortality included older age, higher dyspnea score, presence of CVD, and history of pulmonary tuberculosis. Additionally, longer COPD duration was linked to worse lung function, greater symptom burden, more frequent exacerbations, and the presence of comorbid CVD and bronchiectasis at study entry. This suggests that COPD worsens over time, leading to increased disease burden and complications, highlighting the importance of early diagnosis in preventing disease progression. Despite these associations, the duration of COPD did not affect the clinical stability at two years. These findings highlight the complex interplay between factors influencing disease progression and outcomes in patients with COPD, emphasizing the need for comprehensive and individualized management strategies.

Efforts made to phenotype COPD patients may have led to more personalized treatment, but does not account for the variability that may occur over time.[14,33] Concepts of clinical control and stability have thus emerged to account for these temporal variations, but predictors of such an endpoint have remained elusive.[34] Our study suggests that easily obtainable clinical data such BMI, lung function tests, haemoglobin levels and number of exacerbations may help to predict clinical stability of COPD and further refine treatment targets. Indeed, this highlights the benefit and importance of early recognition and multidisciplinary management of COPD encouraged by the GOLD guidelines.[27] This include a personalized treatment approach targeting treatable traits in COPD management, such as preservation of lung function with pharmacotherapy, nutritional support to optimize BMI, and smoking cessation to help achieve stability.[35,36] The introduction and optimization of pharmacological therapy is also important in reducing CID and exacerbations in COPD,[8,10] although its effect may be attenuated by older age, particularly as the mean age of our cohort is higher than that of many other studies.[10] Nonetheless, these remain fundamental in preventing exacerbations and reducing mortality.

Despite efforts to achieve clinical stability, the absence of a difference in mortality between clinically stable and unstable patients reflects the complexity of COPD. Moreover, our results indicate that while a longer duration of COPD is associated with more severe disease and increased exacerbations, it does not influence 2-year stability in our cohort. This suggests that achieving 2-year stability is possible even in severe diseases with a multidisciplinary team (MDT) approach and personalized treatment strategies. An MDT approach that incorporates guideline-directed therapy and comprehensive COPD management plays a crucial role in optimizing patient outcomes.[37] By leveraging the expertise of various healthcare professionals, the MDT ensures a holistic and individualized care plan that addresses the diverse needs of COPD patients.[37] The team typically includes physicians, nurses, and allied health professionals such as physiotherapists, dietitians, and social workers, each contributing to patient education, symptom management, and tailored interventions.[35,37] Through coordinated efforts, the MDT with treatable trait approach improves quality of life in patients with chronic airway disease.[35,38]

Although clinical stability may serve as a useful short-term treatment endpoint, it fails to capture the full extent of the factors driving mortality in COPD. Other important predictors of COPD mortality include cardiovascular disease, older age, dyspnea score, previous exacerbations, male sex, hypoxemia, use of long-term oxygen therapy, body mass index, prior pulmonary tuberculosis, and lower FEV1.[25,39–43] This is consistent with our findings; however, in multivariate analysis, neither lung function nor BMI remained significant predictors of mortality. Overall, this finding suggests that clinical stability and mortality are distinct outcomes, each driven by different sets of predictive variables, underscoring

the need for a comprehensive approach to COPD management that addresses both clinical stability (exacerbations and symptoms) and a broad range of factors that influence long-term survival.

While studies have identified ethnic differences in COPD comorbidities and CVD, our findings did not show significant differences in CVD between ethnic groups.[26,44] A cross-sectional study in the US (1999–2018) found variation in CVD risk between Hispanic white and black populations, but these differences were largely explained by social determinants of health.[45] Similarly, a prospective cohort study from the UK reported adiposity as an important risk factor for CVD irrespective of ethnicity.[46] These findings suggest that factors beyond ethnicity, such as socioeconomic status, healthcare access, and risk factor exposure, may play a more substantial role in determining CVD risk. Additionally, the small number of Malay and Indian patients with COPD in our cohort may have limited our ability to detect ethnic differences because these ethnic groups have been shown to have a higher incidence of cardiovascular comorbidities.[47]

Nonetheless, our study contributes to a growing body of evidence highlighting the importance of early identification and management of CVD in COPD, irrespective of ethnicity.[19,25,39,41] This is especially crucial in patients with a history of heavy smoking (>40 pack-years), given its deleterious effects on both the cardiovascular and respiratory systems.[21,48] Furthermore, evidence of manifestations of metabolic comorbidities, such as hyperlipidemia and diabetes mellitus, suggests chronicity of the underlying inflammatory milieu, reinforcing the need to screen these patients for CVD.[49,50] Early multidisciplinary management of CVD in COPD is essential to improve outcomes.

Although our study provides valuable insights as a longitudinal prospective analysis with 2 years of follow-up data on clinical stability and 5 years of mortality outcomes in an Asian population, it has several limitations. First, it was conducted at a single tertiary center, which limits its generalizability. However, this limitation is mitigated by Singapore's small geographical size, and our hospital is a tertiary referral center that receives referrals from various regions of Singapore.[51] Second, the cohort was predominantly male, consistent with other Asian COPD studies[52] where male patients with lower BMI are commonly observed compared to Western cohorts.[53,54] Third, the absence of detailed cause of death data precluded differentiation between respiratory and non-respiratory causes of mortality. Additionally, follow-up spirometry data were unavailable for all patients; therefore, they were not included in the definition of clinical stability. We did not perform sensitivity analyses to test the robustness of our findings against alternative definitions or assumptions. This may limit the generalizability of our results. Future studies could incorporate validated criteria and sensitivity analyses on predictor of COPD stability and mortality. Finally, longitudinal data on the development of cardiovascular disease and its association with acute exacerbations are unavailable and fall beyond the scope of this study.

Conclusion

In this prospective longitudinal study, we identified several clinical and modifiable factors including higher BMI, better lung function, preserved haemoglobin levels, fewer baseline exacerbations, successful smoking cessation, and absence of concomitant bronchiectasis as significant predictors of two-year clinical stability in patients with COPD. However, achieving clinical stability did not predict long-term survival. Instead, key predictors of five-year mortality were comorbid cardiovascular disease, prior pulmonary tuberculosis, older age, and higher dyspnea scores. These findings highlight the complex and multifactorial nature of COPD progression and outcomes, underscoring the importance of a comprehensive, individualized approach to COPD management that addresses both respiratory and systemic comorbidities to improve short- and long-term outcomes.

Data Sharing Statement

The datasets generated and analyzed during the current study are not available in public domains but can be requested from the corresponding author.

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Disclosure

P.Y.T was on advisory boards for AstraZeneca and Sanofi outside the submitted work. M. S. K has received research grants from AstraZeneca and honorarium paid to her employer (Singapore General Hospital) from GSK, AstraZeneca, Sanofi, Novartis and Boehringer Ingelheim outside the submitted work. The authors report no other conflicts of interest in this work.

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