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ORIGINAL RESEARCH

A novel CT-emphysema index/FEV₁ approach of phenotyping COPD to predict mortality

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Background: COPD-associated mortality was examined using a novel approach of phenotyping COPD based on computed tomography (CT)-emphysema index from quantitative CT (QCT) and post-bronchodilator (BD) forced expiratory volume in 1 second (FEV_1) in a local Malaysian cohort.

Patients and methods: Prospectively collected data of 112 eligible COPD subjects (mean age, 67 years; male, 93%; mean post-BD FEV_1, 45.7%) was available for mortality analysis. Median follow-up time was 1,000 days (range, 60–1,400). QCT and clinicodemographic data were collected at study entry. Based on CT-emphysema index and post-BD FEV_1% predicted, subjects were categorized into "emphysema-dominant," "airway-dominant," "mild mixed airway-emphysema," and "severe mixed airway-emphysema" diseases.

Results: Sixteen patients (14.2%) died of COPD-associated causes. There were 29 (25.9%) "mild mixed," 23 (20.5%) "airway-dominant," 15 (13.4%) "emphysema-dominant," and 45 (40.2%) "severe mixed" cases. "Mild mixed" disease was proportionately more in Global Initiative for Chronic Obstructive Lung Disease (GOLD) Group A, while "severe mixed" disease was proportionately more in GOLD Groups B and D. Kaplan–Meier survival estimates showed increased mortality risk with "severe mixed" disease (log rank test, $p=0.03$) but not with GOLD groups ($p=0.08$). Univariate Cox proportionate hazard analysis showed that age, body mass index, long-term oxygen therapy, FEV_1, forced volume capacity, COPD Assessment Test score, modified Medical Research Council score, St Georges' Respiratory Questionnaire score, CT-emphysema index, and "severe mixed" disease (vs "mild mixed" disease) were associated with mortality. Multivariate Cox analysis showed that age, body mass index, and COPD Assessment Test score remain independently associated with mortality.

Conclusion: "Severe mixed airway-emphysema" disease may predict COPD-associated mortality. Age, body mass index, and COPD Assessment Test score remain as key mortality risk factors in our cohort.

Keywords: computed tomography, emphysema, forced expiratory volume, COPD, mortality

Introduction

COPD is a leading cause of death globally.[1] Its heterogeneity presents a challenge to research and pursuit of effective treatment. Many factors like airflow obstruction by spirometry, exercise capacity, frequency of exacerbation, body mass index (BMI), and comorbidities have been shown to influence prognosis.[2] Since 2011, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) initiative has advocated a 2-dimensional combined approach (based on symptoms and exacerbation risk/forced expiratory volume in 1 second [FEV_1]) to classifying COPD (into Groups A–D) to guide treatment. From the 2017 guidelines, GOLD committee has removed FEV_1 from to ease ranking.[3] In recent years, quantitative computed tomography (QCT)

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is being recognized as a valuable tool of phenotyping and prognosticating COPD.[4,5] All these approaches will help to prognosticate COPD with a view to recommend therapy.

Compared to the pre-2011 GOLD classification (based solely on post-bronchodilator [BD] FEV_1), some researchers have questioned the ability of the GOLD combined approach to better predict mortality.[6,7] It is unclear if the exclusion of FEV_1 from GOLD combined assessment in 2017 further affects this. QCT measurement of emphysema, air-trapping, and airways in COPD has significantly improved over the years[8] and has been shown to correlate with physiologic parameters and clinical outcomes like exacerbations, quality of life, and mortality.[4,5,9] Among the QCT measurements, CT-emphysema index is probably the most robust parameter that is least subjected to external influences like inspiratory volume and measurement biases.[8,10]

Lee et al[11] were the first researchers who explored the use of CT-emphysema index and FEV_1 to subtype COPD into 4 phenotypes of "airway-dominant," "emphysema-dominant," "mild mixed airway-emphysema," and "severe mixed airway-emphysema" disease. They showed that "emphysema-dominant" subtype alone showed least improvement of FEV_1 and dyspnea to 3-month treatment with combined inhaled corticosteroids and long-acting β_2 agonist compared to others. Such a combination of morphologic and physiologic assessments is logical to approach a complex disease like COPD. In this study, we hypothesized that this CT-emphysema index/FEV_1 approach of phenotyping COPD may predict mortality. In a local cohort of well-characterized stable multiethnic COPD patients followed up in a chest clinic of an urban-based general hospital, we studied the COPD-associated mortality and its risk factors according to these phenotypes. We also compared this approach with that of GOLD 2017 combined assessment.

Patients and methods
Patient population
All eligible patients with stable COPD who were referred to or followed up in the chest clinic of the 1,200-bed Penang Hospital, Malaysia, were invited to participate. The inclusion criteria were age ≥40 years old, smoking history of ≥10 pack-years, a diagnosis of COPD by GOLD criteria (inclusive of post-BD FEV_1/forced volume capacity [FVC] <0.7), Asian ethnicity, and willingness to undergo study-related testing that included thorax CT. The exclusion criteria were COPD exacerbation within the past 1 month, tuberculosis-destroyed lung (defined as post-tuberculosis scarring involving more than one lung lobe), presence of significant concomitant lung

conditions like bronchiectasis or interstitial lung disease, previous lung resection surgery, uncontrolled cancer, and pregnancy. The recruitment began in September 2013. This study forms part of a larger longitudinal cohort study of Asian Network of Obstructive Lung Disease (ANOLD)[12] that looks at the heterogeneity of COPD. To date, this research network consists of eleven Asian countries. Written informed consent was obtained from all participants. Research and ethical approval was obtained from the National Research and Ethics Committee of Malaysia (NNMR-13-313-15138).

Data collection including mortality
Demographic and clinical data were collected by a single investigator (OCK) via face-to-face interview and self-administered questionnaires. The data included respiratory symptoms, spirometry, St George's Respiratory Questionnaire (SGRQ),[13] breathlessness score (using modified Medical Council Research Scale [mMRC][14]), COPD Assessment Tool (CAT),[15] respiratory diagnoses, Charlson's Comorbidity Index,[16] health care utilization, medication use, and COPD risk factors. Spirometry data were obtained before and after administration of a short-acting β-agonist, and its quality was independently reviewed by ANOLD study coordinating center in Seoul to ensure that American Thoracic Society criteria were met.[17] Participants were followed up at least once annually on spirometry and mortality. For subjects who died, the specific dates and causes of death were obtained from hospital medical records or family members with verification from official death certificate whenever possible. Death directly due to COPD or recognized COPD-associated comorbidities was considered as COPD-associated death.

QCT measurement
Objective analysis of the lung parenchyma and airways was performed on volumetric CT scans of thorax at full inspiration using a 64-MDCT scanner (Somaton Sensation 64; Siemens Medical Solutions, Forchheim, Germany) in Loh Guan Lye Specialist Centre, Penang. All CT scans were obtained based on standardized protocol from Research Institute of Radiology, Asan Medical Center in Seoul.[18,19] Briefly, scan parameters included 0.75 mm collimation, 100 eff mAs, 140 kVp, and pitch 1.0. Patients were scanned craniocaudally in supine position. Images were reconstructed using a soft kernel (B30f; Siemens Medical Solutions) from thoracic inlet to lung base. The CT-emphysema index (or Low Attenuation Area percent) was determined by automatic calculation from the CT data of the volume fraction of the lungs below −950 HU at full inspiration. Airway dimensions

including the wall area (WA), lumen area (LA), and WA (WA%), defined as WA/(WA + LA) ×100, were measured near the origin of the 4 segmental bronchi (RB1, LBI+2, RB10, LB10) using in-house software in Asan Medical Center. Quality of images and compliance to protocol in Penang center were verified by Asan Medical Center prior to commencement of scanning COPD study subjects.

Combined COPD assessment

Patients were categorized into Groups A–D according to GOLD 2017 classification (refer to GOLD 2017). The cut-off point between high and low risk of future exacerbation was based on previous reported hospitalized exacerbations of two times a year (ie, high risk of exacerbation when ≥2 times a year). The cut-off point between the "more" or "less" symptoms followed the GOLD recommendation of CAT of 10 and mMRC of 2 (whichever is higher) (ie, "more" symptoms when CAT ≥10 or mMRC ≥2).

Classification into CT-emphysema index/FEV$_1$ phenotypes

Patients were categorized into "mild mixed airway-emphysema," "airway-dominant," "emphysema-dominant," and "mixed airway-emphysema" disease based on CT-emphysema index at cut-off points of 15% (ie, ≥15% for emphysema) and post-BD FEV$_1$ of 50% predicted normal (ie, FEV$_1$ of <50% predicted normal for airway-dominant).[11] Emphysema is normally considered present when >10% of pixels fall below the cut-off values of −910 or −920 HU, depending on slice thickness and the reconstruction algorithm employed.[20] We used 15% of −950 HU as cut-off to distinguish between emphysema and nonemphysema status in our Asian patients based on measurements derived from 48 healthy Korean nonsmokers that showed a −950 HU range between 0.15% and 13.25% with a mean of 4.66% (unpublished data). As such, we are confident that −950 HU values of <15% are compatible with no or trivial emphysema.[21,22] A cut-off of FEV$_1$ 50% predicted normal is based on GOLD 2017 recommendation of severe airflow limitation when FEV$_1$ is <50% predicted (GOLD 2017 recommendation).

Statistical analysis

Standard descriptive analyses were performed on patient baseline characteristics. Kaplan–Meier survival estimates were performed to examine the probability of death with CT-emphysema index/FEV$_1$ phenotypes and GOLD 2017 classification. Log rank tests were used to test for differences between groups. Univariate and multivariate Cox proportional hazards analyses were performed to investigate the associations of clinicodemographic indices and CT-emphysema index/FEV$_1$ phenotypes with COPD-associated mortality. Proportional-hazards assumption tests were used to ensure that the variables fit the regression models. A *p*-value of <0.05 was considered as statistical significant. All analyses were performed using Stata Version 13.1 (Stata Corporation, College Station, TX, USA).

Results

Baseline patient characteristics

One hundred and twenty-three patients were recruited. Three declined QCT. Eight subjects' QCT data were not interpretable due to quality issues. Four subjects were lost to follow-up and their survival data were censored till the date of last follow-up visit (follow-up rate, 96.4%). Final analyzable data were based on 112 subjects. Their baseline characteristics are shown in Table 1. The cohort appeared to represent those with a more severe disease characterized by a mean FEV$_1$ of 46% predicted normal, frequent exacerbations, and high treatment burden including home oxygen use.

CT-emphysema index/FEV$_1$ phenotypes and GOLD classification

The number (percentage) of patients in each CT-emphysema index/FEV$_1$ phenotype was as follows: 29 (25.9%) "mild mixed airway-emphysema" disease, 23 (20.5%) "airway-dominant," 15 (13.4%) "emphysema-dominant," and 45 (40.2%) "severe mixed airway-emphysema" disease. The number (percentage) of patients in each GOLD group was as follows: 35 (31.3%) Group A, 33 (29.5%) Group B, 7 (6.2%) Group C, and 37 (33%) Group D. The relationship between the proportion of patients according to GOLD classification and CT-emphysema index/FEV$_1$ phenotypes are shown in a scatterplot (Figure 1). Proportionately more patients of Groups B and D had "severe mixed airway-emphysema" disease while more patients of Group A had "mild mixed" disease.

Mortality data

The median follow-up time as of June 30, 2017 was 1,000 days (2 years and 9 months) (range, 60–1,400 days). Eighteen out of 112 (16%) died during this time. Causes of death were as follows: COPD (n=8), pneumonia (n=4), congestive cardiac failure/coronary artery disease (n=2), lung carcinoma (n=1), stroke (n=1), motor traffic accident (n=1), and intestinal obstruction (n=1). The final 2 causes were considered as

Table I Baseline patient characteristics (n=112)

Characteristics	Value	Range
Age, year	67±7.4	49–84
Gender		
Male	105 (93.7)	–
Female	7 (6.3)	–
Ethnicity		
Malay	31 (27.6)	–
Chinese	73 (65.2)	–
Indians	8 (7.2)	–
BMI, kg/m²	22±4.6	13–38
Weight classes		
Underweight	17 (15.2)	–
Normal	47 (41.9)	–
Overweight	31 (27.6)	–
Obese	17 (15.3)	–
Smoking history		
Current smoker	20 (17.8)	–
Former smoker	92 (82.2)	–
Smoking pack-years	60.3±36.5	10–204
Spirometry		
FEV_1, liters	1.08±0.46	0.36–2.50
FEV_1, % predicted	45.7±17.2	16–97
FVC, liters	2.04±0.65	0.55–3.92
FVC, % predicted	62.6±18.2	23–97
FEV_1/FVC ratio	0.52±0.10	0.26–0.70
Hospitalized/12 months		
None	38 (33.9)	–
1–2	44 (39.2)	–
3–4	24 (21.4)	–
≥5	6 (5.3)	–
Comorbidities		
Ischemic heart disease	12 (10.8)	–
Congestive cardiac failure	3 (2.7)	–
Stroke	4 (3.6)	–
Peptic ulcer disease	24 (21.4)	–
Diabetes mellitus	20 (18.0)	–
Chronic renal disease	1 (0.9)	–
Cancer	2 (1.8)	–
Charlson comorbidity index		
1	62 (56.3)	–
2	36 (32.7)	–
≥3	12 (10.9)	–
Regular therapy		
ICS + LABA + LAMA	32 (28.8)	–
LTOT	11 (9.9)	–
GOLD classification		
A	35 (31.3)	–
B	33 (29.5)	–
C	7 (6.2)	–
D	37 (33.0)	–
QCT-defined		
LAA% (CT-emphysema index)	19.7±14.39	0.1–60.6
WA%	51.3±9.52	25.8–76.5
CT-emphysema index/FEV_1 phenotypes		
Mild mixed disease	29 (25.9)	–
Predominantly airway	23 (20.5)	–
Predominantly emphysema	15 (13.4)	–
Severe mixed disease	45 (40.2)	–

Note: Data are presented as mean ± SD or counts (percentage).
Abbreviations: BD, bronchodilator; BMI, body mass index; CT, computed tomography; FEV_1, post-BD forced expiratory volume in 1 second; FVC, post-BD forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroids; LAA%, low attenuation area percent; LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist; LTOT, long-term oxygen therapy; QCT, quantitative CT; WA%, wall area percent.

non-COPD-associated causes. As such, 16 patients died of COPD-associated death (14.2%).

Kaplan–Meier survival estimates

There was significant difference of survival estimates with CT-emphysema index/FEV_1 phenotypes (*p*=0.03, log rank test) but not with GOLD classification (*p*=0.08). These are shown in Figures 2 and 3.

Cox proportional hazards analyses on predictors of mortality

All demographic and clinical parameters were entered for univariate analyses. The parameters shown to predict mortality were age, BMI, use of long-term oxygen therapy (LTOT), FEV_1, FVC, CAT score, SGRQ, CT-emphysema index, and "severe mixed airway-emphysema" disease (compared to "mild mixed" disease) (Table 2).

All indices predictive of mortality on univariate analyses (except for LTOT) were entered into multivariate analyses to investigate the relationship between CT-emphysema index/FEV_1 and mortality. LTOT was not selected as it is primarily a treatment outcome. CT-emphysema index and FEV_1 are also not entered into the multivariate model as separate factors since they contribute to the CT-emphysema index/FEV_1 phenotypes. Multivariate analyses showed that only age, BMI, and CAT score remained predictive of COPD-associate mortality (Table 2). In fact, the lack of change of hazard ratios of these three parameters indicates their independence with COPD-associated mortality.

Discussion

We explored the potential of a novel CT-emphysema index/FEV_1 approach to predict COPD-associated mortality and showed in our cohort that "severe mixed airway-emphysema" had a higher mortality risk than "mild mixed" phenotype. The survival model seems to perform better than GOLD 2017 classification. However, only age, BMI, and CAT score were independently predictive of mortality in multivariate analyses. Our findings of age, BMI, and CAT score as independent predictors of COPD-associated mortality lend support to the existing bulk of evidence of their importance in prognosticating COPD.[2,3]

Our main study limitation is that our cohort size was not powered for mortality analysis. However, it is still plausible that we are encountering a genuine observation and that our current findings can be considered as hypothesis generating. Combining a morphology assessment with a physiologic parameter makes much clinical and research sense to help
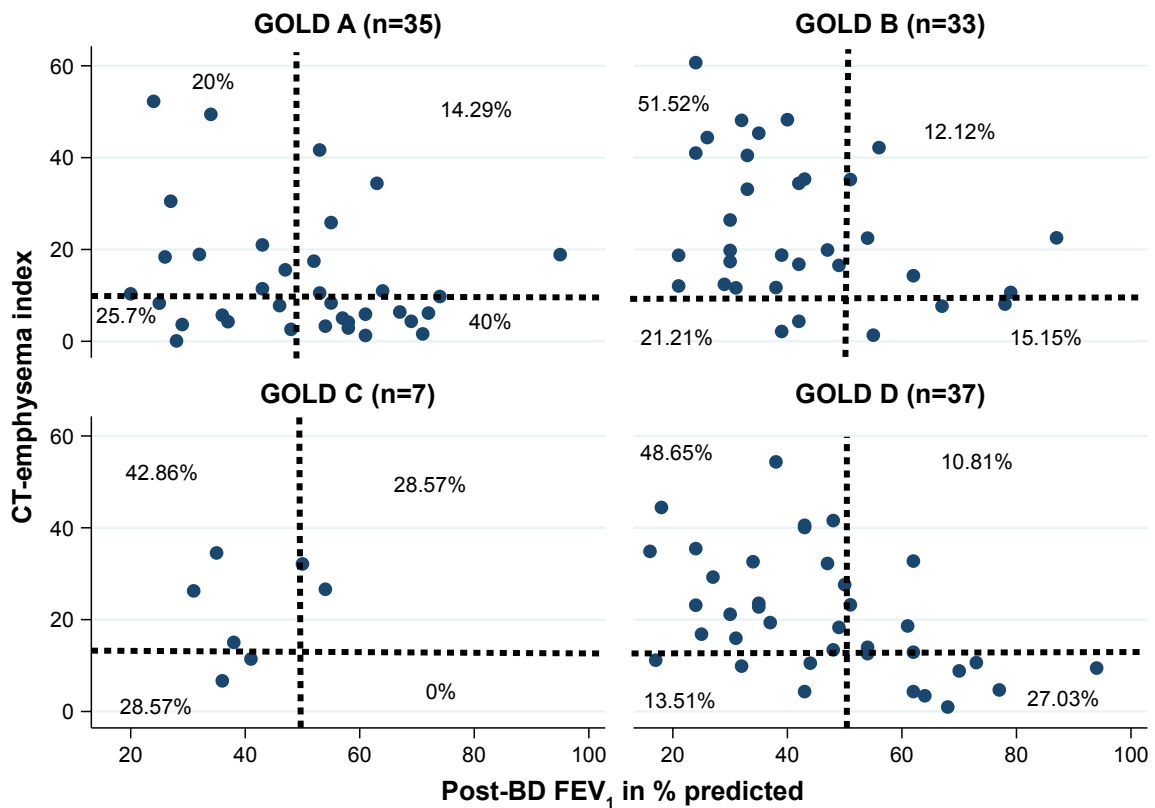
Figure 1 Scatter plot showing relationships between CT-emphysema index/FEV$_1$ COPD phenotypes and GOLD groups among patients (n=112).
Note: Right upper quadrant = emphysema-dominant; right lower quadrant = mild mixed airway-emphysema disease; left lower quadrant = airway-dominant; left upper quadrant = severe mixed airway-emphysema.
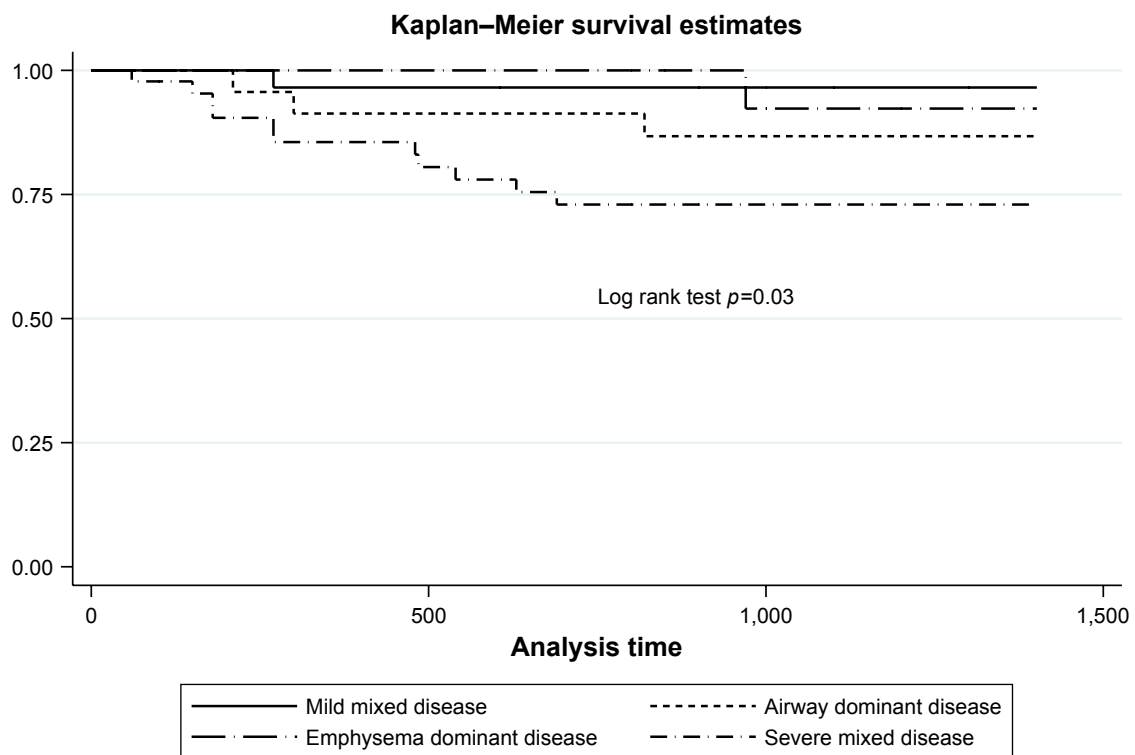**Abbreviations:** BD, bronchodilator; CT, computed tomography; FEV$_1$, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Figure 2 Kaplan–Meier survival probability estimates according to CT-emphysema index/FEV$_1$ COPD phenotypes.
Abbreviations: CT, computed tomography; FEV$_1$, forced expiratory volume in 1 second.

Kaplan–Meier survival estimates
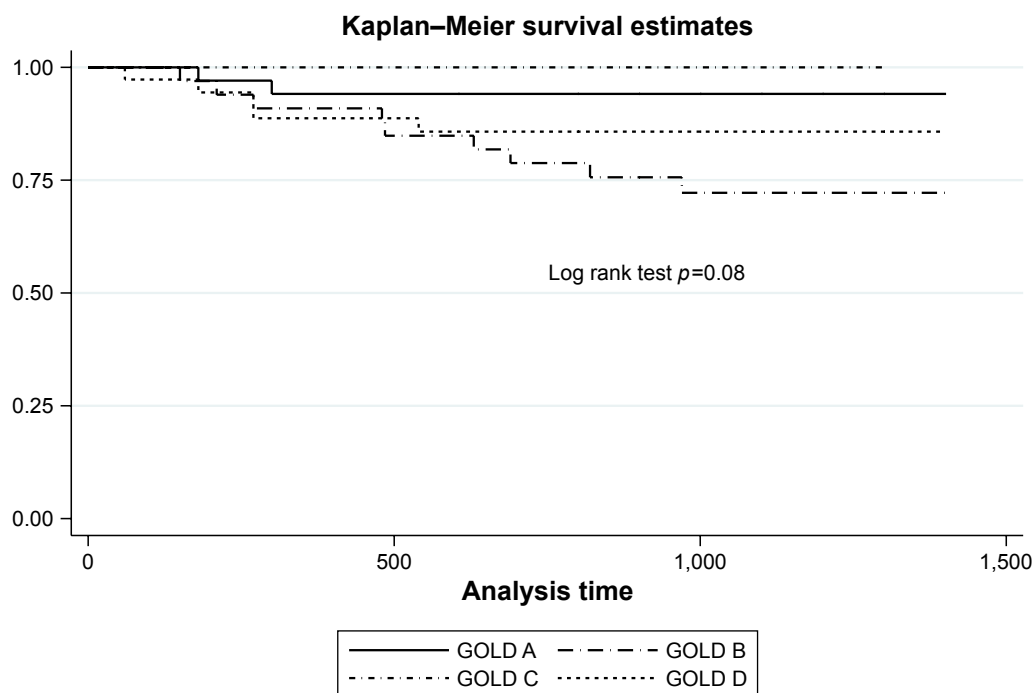
Figure 3 Kaplan–Meier survival probability estimates according to GOLD 2017 groups.
Abbreviation: GOLD, Global Initiative for Chronic Obstructive Lung Disease.

assess a complex disease like COPD. Our preliminary finding from a small local cohort may point toward the relevance of a certain "severe mixed airway-emphysema" disease that carries a worse prognosis. Together with the reports of Lee et al,[11] this novel QCT/FEV$_1$ approach to phenotyping or subtyping COPD may be worth exploring further. Larger sample size studies are obviously necessary to validate this possibility. We hope to compare our findings with other COPD cohorts of the ANOLD network based on this CT-emphysema index/FEV$_1$ approach.

Another important study limitation is that we only collected general data on comorbidities, which are not specific enough on severity (eg, those of cardiac failure or diabetes). This may bias our survival results. Also, it should be noted that the discriminative capacity of our QCT/FEV$_1$ approach (over this period of follow-up) was limited to discriminating those with "severe mixed airway-emphysema" disease from "mild mixed" disease. The other 2 groups had either a different charted course or one in which QCT/FEV$_1$ approach is not discriminative enough.

We also showed that there was generally a lack of correlation in the distribution of subjects classified under CT-emphysema index/FEV$_1$ and GOLD 2017 groups. GOLD A group has proportionately more "mild mixed"

Table 2 Predictors in Cox proportional hazard models of COPD-associated mortality

Parameters	Crude HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Age, years	1.10 (1.02–1.19)	0.013	1.11 (1.02–1.20)	0.014
BMI, kg/m²	0.83 (0.72–0.95)	0.011	0.83 (0.70–0.98)	0.036
LTOT	4.62 (1.60–13.35)	0.005	–	–
FEV$_1$ (L)	0.16 (0.03–0.72)	0.017	–	–
FVC (L)	0.37 (0.16–0.85)	0.020	1.13 (0.36–3.50)	0.822
CAT score	1.08 (1.01–1.16)	0.024	1.16 (1.00–1.34)	0.049
mMRC	1.75 (1.03–2.98)	0.036	0.92 (0.36–2.30)	0.862
SGRQ	1.03 (1.00–1.06)	0.027	0.98 (0.92–1.04)	0.610
Emphysema index	1.04 (1.01–1.07)	0.004	–	–
Severe mixed AE disease (vs normal)	8.88 (1.14–68.81)	0.037	3.36 (0.34–33.08)	0.299

Abbreviations: AE, airway-emphysema; BD, bronchodilator; BMI, mean body mass index; CAT, COPD Assessment Tool; CI, 95% confidence interval; FEV$_1$, post-BD forced expiratory volume in 1 second; FVC, post-BD forced volume capacity; LTOT, long-term oxygen therapy; mMRC, modified Medical Research Council scale; SGRQ, St Georges Respiratory Questionnaire.

disease, while GOLD B and D groups have proportionately more "severe mixed" disease. The latter may suggest a morphologic/physiologic similarity (ie, more emphysema and airflow obstruction) of GOLD B and D groups that explain their higher degree of symptoms (compared to A and C groups). This also supports a possible "severe mixed" disease as a relevant COPD phenotype. It is unclear what the prevalence of airway or emphysema-dominant or mixed disease in the general COPD population is. It is likely that its prevalence would vary according to the differing COPD populations and based on geography. In an epidemiology survey of over 1,400 Japanese COPD patients, Tatsumi et al[23] showed that 90% were of emphysema-dominant phenotype based on QCT. Some researchers have shown that emphysema-dominant disease is probably a COPD phenotype that is less responsive to both anti-inflammatory and bronchodilator therapy.[24] In our cohort, "emphysema-dominant" was the least common of the 4 phenotypes.

The mortality rate of COPD patients varies significantly depending on disease severity. In their review, Nishimura and Tsukino[25] suggested that the 5-year COPD mortality can be as high as 40%–70%, a figure that is similar to many malignancies.[25] The near 4-year absolute mortality rate attributable to COPD was around 14% in our cohort of moderate-to-severe COPD patients. Preliminary comparison with some ANOLD Asian sites suggests that the mortality rate of our cohort is considered high. This may be due to our COPD cohort having more severe disease.

At the time of writing, the GOLD 2018 guidelines have just been published. It acknowledges that the "ABCD" combined assessment performed no better than the earlier GOLD spirometric classification in predicting mortality or other health outcomes.[26] Despite this, they suggest that the "ABCD" assessment can still be used to provide therapeutic recommendations and also advised that spirometric assessment will remain vital for diagnosis and prognostication, considering other therapeutic approaches (eg, lung volume reduction surgery) as complement to the GOLD 2017 "ABCD" assessment tool (where FEV$_1$ is dropped). This perhaps explains our observation of our CT-emphysema index/FEV$_1$ model predicting mortality better than the GOLD 2017 model.

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Disclosure

The authors report no conflicts of interest in this work.

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