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Predicting severe chronic obstructive pulmonary disease exacerbations using quantitative CT: a retrospective model development and external validation study

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For more on **SPIROMCIS** see https://www.spiromics.org

For more on **COPDGene** see https://www.copdgene.org

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Summary

Background—Quantitative CT is becoming increasingly common for the characterisation of lung disease; however, its added potential as a clinical tool for predicting severe exacerbations remains understudied. We aimed to develop and validate quantitative CT-based models for predicting severe chronic obstructive pulmonary disease (COPD) exacerbations.

Methods—We analysed the Subpopulations and Intermediate Outcome Measures In COPD Study (SPIROMICS) cohort, a multicentre study done at 12 clinical sites across the USA, of individuals aged 40–80 years from four strata: individuals who never smoked, individuals who smoked but had normal spirometry, individuals who smoked and had mild to moderate COPD, and individuals who smoked and had severe COPD. We used 3-year follow-up data to develop logistic regression classifiers for predicting severe exacerbations. Predictors included age, sex, race, BMI, pulmonary function, exacerbation history, smoking status, respiratory quality of life, and

CT-based measures of density gradient texture and airway structure. We externally validated our models in a subset from the Genetic Epidemiology of COPD (COPDGene) cohort. Discriminative model performance was assessed using the area under the receiver operating characteristic curve (AUC), which was also compared with other predictors, including exacerbation history and the BMI, airflow obstruction, dyspnoea, and exercise capacity (BODE) index. We evaluated model calibration using calibration plots and Brier scores.

Findings—Participants in SPIROMICS were enrolled between Nov 12, 2010, and July 31, 2015. Participants in COPDGene were enrolled between Jan 10, 2008, and April 15, 2011. We included 1956 participants from the SPIROMICS cohort who had complete 3-year follow-up data: the mean age of the cohort was 63·1 years (SD 9·2) and 1017 (52%) were men and 939 (48%) were women. Among the 1956 participants, 434 (22%) had a history of at least one severe exacerbation. For the CT-based models, the AUC was 0·854 (95% CI 0·852–0·855) for at least one severe exacerbation within 3 years and 0·931 (0·930–0·933) for consistent exacerbations (defined as ≥1 acute episode in each of the 3 years). Models were well calibrated with low Brier scores (0·121 for at least one severe exacerbation; 0·039 for consistent exacerbations). For the prediction of at least one severe event during 3-year follow-up, AUCs were significantly higher with CT biomarkers (0·854 [0·852–0·855]) than exacerbation history (0·823 [0·822–0·825]) and BODE index 0·812 [0·811–0·814]). 6965 participants were included in the external validation cohort, with a mean age of 60·5 years (SD 8·9). In this cohort, AUC for at least one severe exacerbation was 0·768 (0·767–0·769; Brier score 0·088).

Interpretation—CT-based prediction models can be used for identification of patients with COPD who are at high risk of severe exacerbations. The newly identified CT biomarkers could potentially enable investigation into underlying disease mechanisms responsible for exacerbations.

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Introduction

Acute exacerbations of chronic obstructive pulmonary disease (COPD) result in a rapid decline in lung function and poor quality of life.[1,2] An increased frequency of these events can lead to hospital admission, with an increased risk of mortality in the following year (as high as 21% in some cases).[3,4] Treatment options for patients who exacerbate consistently or require admission to hospital are scarce and expensive. In 2010, the estimated financial burden of COPD in the USA was US$32 billion,[5] 70% of which could be attributed to COPD-related hospital admissions.[6] Therefore, identification of individuals at risk of severe and persistent exacerbations is crucial for preserving quality of life, reducing overall disease burden, and identifying appropriate subpopulations for whom interventions can be assessed and applied.

A previous history of exacerbations is the most widely used predictor of future exacerbations.[7,8] However, it has been shown to be highly inconsistent with changing patient exposures and inherent recall bias, and might not be applicable to individuals without a previous exacerbation history.[7] Moreover, this predictor does not provide insights into the underlying mechanisms that could help understand an individual's risk of experiencing an episode.

Quantitative CT is becoming increasingly common for assessing various pulmonary abnormalities, including COPD,[9–11] which has led to the development of several quantitative CT biomarkers for phenotyping COPD. Quantitative CT-based measures of parenchymal texture have been used to assess local changes in pulmonary ventilation and quantify regional patterns of emphysema and related textural abnormalities.[12–14] Similarly, quantitative CT-based measures of airway wall thickening have been associated with decline in lung function.[15] Although there is increasing evidence that highlights the clinical potential of quantitative CT biomarkers, their role as predictors of severe COPD exacerbations remains largely unexplored. We hypothesised that quantitative CT-derived measures of parenchymal texture and airway wall thickness can predict severe and persistent exacerbations of COPD.

We aimed to develop and validate quantitative CT-based models for predicting COPD exacerbations and to use these models to compare the performance of CT biomarkers with the history of exacerbations and the BMI, airflow obstruction, dyspnoea, and exercise capacity (BODE) index.[7,16] To further assess generalisability of the CT-based biomarkers, we aimed to validate our models using an external validation cohort.

Methods

Study design and data sources

We used the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis statement guidelines for reporting the exacerbation prediction models in our study.[17] We analysed longitudinal data from the Subpopulations and Intermediate Outcome Measures In COPD Study (SPIROMICS),[18] an ongoing multicentre cohort study done at 12 clinical sites across the USA. SPIROMICS enrolled 2981 participants aged 40–80 years from four strata: individuals who never smoked, individuals who smoked but had normal spirometry, individuals who smoked and had mild to moderate COPD, and individuals who smoked and had severe COPD. All participants were taught how to inspire to total lung capacity and then had high-resolution chest CT scans at total lung capacity.[19] Participants also underwent annual follow-up visits and received quarterly telephone follow-up calls to monitor health status and exacerbations. We used 3-year follow-up data to develop prediction models for severe exacerbations.[18]

We externally validated our models in a cohort from the Genetic Epidemiology of COPD (COPDGene) study,[20] a multicentre observational study conducted at 21 different clinical sites across the USA. Written consent for both parent studies was provided by all participants, and study protocols were approved by the institutional review boards of each participating study centre.

Outcomes

In this study, we evaluated severe acute exacerbations of COPD over a follow-up duration of 3 years. Acute exacerbations were defined as episodes of sustained symptom worsening that might require specialised treatment, either by medication, hospital admission, or visit to an emergency department. Severe acute exacerbations were defined as respiratory flare-ups

that specifically required admission to hospital or an emergency department visit.[21] Both the SPIROMICS and COPDGene studies used similar definitions for severe exacerbations that accounted for episodes treated either by hospital admission or emergency care.[21] Since the COPDGene study followed up participants for a longer duration than SPIROMICS, we censored the data at 3 years to ensure consistency across the development and external validation cohorts. In addition to severe exacerbations, we investigated the consistent acute exacerbation phenotype, defined as at least one acute episode per year for each of the 3 years.[7] We investigated this phenotype, in addition to severe exacerbations, because consistent exacerbations are a major contributor to overall disease burden.[7]

Predictor variables

Predictors were age, sex, race, BMI, forced expiratory volume in 1 s (FEV_1), history of all acute exacerbations within the year preceding enrolment, current smoking status, respiratory quality of life (quantified by the St George's Respiratory Questionnaire [SGRQ] score[22]), CT density gradient (CTDG) textures, wall area percentage, and the square root of airway wall area of a hypothetical airway with an internal perimeter of 10 mm (Pi10). CTDG texture of the lung parenchyma was derived from CT at total lung capacity using the adaptive multiple feature method (AMFM).[13,23] AMFM was trained using three dimensional image patches, annotated using in-house software by a series of highly trained, board-certified chest radiologists and pulmonologists from multiple institutions. A Bayesian classifier, trained using these annotations, was used to automatically quantify various lung tissue textures in the CT images, including ground glass-like opacities, honeycomb-like textures, and normal lung tissue (appendix pp 2–3).

In this study, the AMFM characterisation of honeycombing was largely limited to regions surrounding bronchovascular bundles or fissures, and mostly captured higher attenuation CTDG textures that were not observed in our population. Since this pattern was not typical of subpleural honeycombing that is identified by radiologists in patients with pulmonary fibrosis, we decided to address it differently from its traditional radiological context and use the term CTDG. Since AMFM was trained on pre-annotated image patches, it offers considerable flexibility for improving texture quantification in clinical use under minimal guidance by a radiologist. To capture changes in airway morphology, quantitative airway measures such as segmental airway wall area percentage and Pi10 were included in analysis.[15] These airway measures were automatically calculated by Apollo 2.0 software.

Model development and validation

We did univariate and multivariable zero-inflated negative binomial regression analysis to assess potential associations of quantitative CT biomarkers with severe acute exacerbations. Negative binomial regression modelled the count for severe exacerbations over the 3-year follow-up period, while the zero-inflation component, which used a logistic model, was added to account for excessive zeros within the response variable. Incidence rate ratios and odds ratios were calculated using two-part, zero-inflated negative binomial regression analysis. The quantitative CT biomarkers were then used to train logistic regression classifiers for estimating an individual's risk of a severe or consistent exacerbation. To

counter the model's susceptibility to misclassification or overfitting, we used a regularised version of the logistic model.

For each experiment, we used bootstrapping (1000 repeats) to ensure robust model evaluation. Within each iteration, the data was randomly split into disjoint training (70%) and held-out testing (30%) sets. Model discrimination was evaluated using the receiver operating characteristic curve (ROC) and the corresponding area under the ROC (AUC). We used DeLong's test to compare differences in ROC curves of two different models, and DeLong's method was used to compute 95% CIs of the AUCs. A p value of less than 0·z05 was considered to indicate a statistically significant difference. Calibration plots or reliability diagrams were computed between the observed and model-predicted risk to visually assess likelihood calibration.[24] Calibration was quantitatively evaluated using Brier scores (0–1; a score of 0 indicated perfect model calibration, a score of 1 corresponded to poor model calibration). To improve model calibration on the external validation cohort, we used a held-out validation set from the development cohort to learn a post-hoc transformation that calibrated model predictions on the external cohort. We used an ensemble of two post-hoc transformations: Platt scaling, followed by its single parameter variant, temperature scaling.[25] Model performance was compared using history of all acute exacerbations within the year preceding enrolment and the BODE index as predictors. The performance of CTDG texture and Pi10 alone was also compared with exacerbation history and BODE index. Prediction models over a shorter duration of 2-year follow-up were also developed and evaluated. To further ascertain the robustness of CT biomarkers, we also compared the biomarkers with two other classification methods: Gaussian Naive Bayes and random forest. To assess model performance for clinical use, we did an ROC curve analysis for jointly maximising model sensitivity and specificity corresponding to an optimal threshold. Analysis was done using Python (version 3.7.0) and R (version 3.6.2; appendix p 3).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

We analysed data from 2981 individuals enrolled during the first phase of SPIROMICS between Nov 12, 2010, and July 31, 2015.[18] Eight individuals withdrew consent, and 754 individuals were excluded due to missing values (figure 1). At 3 years, 263 individuals were lost to follow-up; thus 1956 participants had complete 3-year follow-up data for acute COPD exacerbations (figure 1). Of the 1956 participants with complete 3-year follow-up data, 434 (22·2%) had a history of at least one severe exacerbation and 226 (11·6%) had a history of two or more severe exacerbations (table 1). The mean age of participants in the SPIROMICS cohort at follow-up was 63·1 years (SD 9·2), of whom 1017 (52%) of 1956 participants were men, 939 (48%) were women, and 707 (36%) individuals smoked at the time of enrolment (table 1). The distribution of Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages in participants who had severe exacerbations is reported in

the appendix (p 4). For external validation of the proposed biomarkers, we analysed the COPDGene cohort which comprised 10 305 participants, enrolled between Jan 10, 2008, and April 15, 2011. 980 of 10 305 participants had missing data (figure 1). The prediction models were developed using data from 1956 individuals from the SPIROMICS cohort who had data available at the 3-year follow-up (figure 2). After censoring, data from 6965 participants with complete 3-year follow-up data were available for external validation (table 1). The mean age of participants in the COPDGene cohort was 60·5 years (SD 8·9), of whom 3508 (50%) of 6965 participants were men, 3457 (50%) were women, and 3172 (46%) smoked at enrolment (table 1). In the COPDGene cohort, 1389 (20%) of 6965 participants had a history of at least one severe acute exacerbation and 552 (8%) had a history of at least two severe acute exacerbations.

In univariate zero-inflated negative binomial regression analysis, Pi10 and CTDG textures were associated with severe exacerbation episodes in the next 3 years (both $p<0·0001$; appendix p 5). CTDG texture was associated with severe exacerbations ($p=0·026$), as indicated by the inflation component of the model (table 2). Wall area percentage was not associated with severe exacerbations in any of the univariate or multivariable regression analyses and was hence excluded from the set of variables used to develop prediction models.

The CT-based models that included age, sex, race, BMI, FEV_1, exacerbation history, smoking status, SGRQ, CTDG texture, and Pi10 had an AUC of 0·854 (95% CI 0·852–0·855) for at least one severe exacerbation event in 3 years (figure 2A), an AUC of 0·869 (0·867–0·871) for at least two severe episodes in 3 years (figure 2B), and an AUC of 0·892 (0·890–0·894) for at least three severe acute episodes in 3 years (figure 2C). The AUC for predicting consistent acute exacerbations was 0·931 (95% CI 0·930–0·933; figure 2D). Performance of the model was compared with history of exacerbations, which was adjusted for age, sex, race, and FEV_1 (figure 2). Model performance was also compared with the BODE index, and adjusted for age, sex, race, and history of exacerbations (figure 2). AUCs were significantly higher for quantitative CT biomarkers than history of exacerbations and BODE index (with adjustment; DeLong's test $p<0·0001$ for both). CT-based models performed consistently better than history of exacerbations and BODE index (figure 2). Discriminative ability of CTDG texture and Pi10 has also been evaluated independently in comparison with exacerbation history and BODE index (appendix pp 6–9). A likelihood ratio test identified a significant difference between nested models with and without CTDG texture ($p=0·02$), suggesting that the inclusion of CTDG in the model improved predictive ability (appendix p 13).

Calibration plots corresponding to four CT-based models indicated that predicted rates were in agreement with observed rates of severe exacerbations (figure 3). Models were well calibrated with a Brier score of 0·121 for at least one severe episode (figure 3A), 0·077 for at least two severe episodes (figure 3B), 0·045 for at least three severe episodes (figure 3C), and 0·039 for consistent acute episodes (figure 3D). We also evaluated model calibration for CTDG texture and Pi10 alone (appendix pp 6–9). Model performance was similar when quantitative CT biomarkers were used to predict severe episodes for a shorter follow-up

duration of 2 years, performing consistently better than history of exacerbations and BODE index (appendix p 10).

When the prediction models developed on the SPIROMICS cohort were evaluated in the COPDGene cohort, the quantitative CT biomarkers performed well with an AUC of 0·768 (95% CI 0·767–0·769) for at least one severe episode (figure 4A), and an AUC of 0·810 (0·809–0·811) for at least two severe episodes during 3-year follow-up (figure 4C). The AUCs for at least one and two severe episodes during 3-year follow-up were higher than for history of exacerbations (DeLong's test p<0·0001 for both). Ensemble model calibration yielded a Brier score of 0·088 for at least one severe episode (figure 4B) and 0·044 for at least two severe episodes, which showed good agreement between the predicted and observed proportions in the validation cohort (figure 4D). A similar trend was observed when classification performance was compared across different classifiers (appendix p 12).

For predicting at least one severe exacerbation, CT biomarkers had higher sensitivity (78·44% [95% CI 78·32–78·56]) than exacerbation history (75·00% [74·88–75·13]). For the same task, CT biomarkers had higher specificity (78·39% [78·28–78·51]) than exacerbation history (75·00% [74·87–75·12]). Model performance was similar in the COPDGene cohort, whereby CT biomarkers had a higher sensitivity (71·05% [71.03–71·07]) than exacerbation history (68·56% [68·53–68·59]). A detailed analysis for both SPIROMICS and COPDGene cohorts is included in the appendix (pp 11–12). The CTDG texture pattern identified in a patient with severe exacerbations was absent in a participant with no exacerbations during 3-year follow-up (figure 5).

Discussion

We aimed to investigate the utility of quantitative CT biomarkers as potential clinical tools for predicting severe COPD exacerbations. We analysed CT biomarkers of lung tissue texture and airway structure in comparison with well known predictors, including exacerbation history and BODE index. We found Pi10 and CTDG texture were predictive of severe and consistent exacerbations. These biomarkers performed significantly better than exacerbation history and BODE index. For the prediction of at least one severe event during 3-year follow-up, AUCs were significantly higher with CT biomarkers than exacerbation history (3% difference; 0·854 for CT biomarkers *vs* 0·823 for exacerbation history; p<0·0001) and BODE index (4% difference; 0·854 for CT biomarkers *vs* 0·812 for BODE index; p<0·0001). A similar difference was observed between the AUCs of quantitative CT biomarkers and history of exacerbations in the external validation cohort. ROC curve analysis in both cohorts showed CT biomarker models had higher sensitivity and specificity than exacerbation history and the BODE index. Quantitative CT biomarkers might also overcome some inherent clinical limitations of exacerbation history and the BODE index. A previous history of exacerbations, which is currently used to identify patients at a higher risk of experiencing an acute episode,[7,8] is susceptible to recall bias and might not be applicable to individuals at risk without a previous history of exacerbations. Additionally, individuals with a similar exacerbation history have been shown to have a highly inconsistent trajectory of future episodes, since this predictor was unable to account for extrinsic patient exposures.[7] BODE index, which was also used to predict future

exacerbations, performed less reliably than exacerbation history and depended on potentially variable exercise capacity indices.[26,27] In addition to providing more reliable estimates of future exacerbations, the quantitative CT biomarkers can be automatically extracted from a single total lung capacity CT scan, which is routinely acquired in clinical settings. The CT biomarkers can be used for individuals without previous history of exacerbations. External validation of these markers further indicated the general applicability of these measures to other cohorts with different image acquisition protocols.

A CT-derived pulmonary artery to aorta diameter ratio greater than one has also been associated with severe COPD exacerbations.[28] Parametric response mapping (PRM)-based emphysema and small airways disease have been associated with frequency of exacerbations.[29] However, the pulmonary artery to aorta diameter ratio requires measurement of the vessels on a CT scan, which might require human oversight, and PRM requires CT scans at two different inflation levels, which increases cost, radiation dose, and scan time. Two previous studies investigated potential associations of these measures with exacerbations, but did not develop or validate prediction models for clinical use. The proposed quantitative CT biomarkers can be automatically computed from a single total lung capacity CT scan. We also present a comprehensive assessment of model discrimination and calibration, which strengthens our recommendation that these models can be readily deployed for clinical decision making.

Guerra and colleagues[30] evaluated 27 prediction models for COPD exacerbations, most of which had poor clinical applicability or availability of predictors, or were not externally validated. The highest performance among the 27 models was an AUC of 0·81, while the AUCs in most studies were between 0·60 and 0·75.[30] The relatively lower predictive performance of these models compared with other predictive tasks, such as predicting COPD status and the presence of tumours (AUCs of around 0·90), highlighted the underlying complexity of predicting future exacerbations. Adibi and colleagues[31] attempted to address these limitations by proposing use of the ACCEPT exacerbation prediction tool, which was externally validated in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) cohort.[31] Most of the predictors used in the study were simple measures of disease severity or accounted for current medication use, which might not be indicative of structural changes in the lungs that could indicate underlying disease mechanisms.[32] Another limitation of the study was the prediction of event risk over a shorter duration (1 year), which limited applicability to detect long-term, persistent patterns of acute exacerbations. By contrast, in the present study quantitative CT biomarkers were shown to predict future exacerbations reliably over a longer duration of 3 years and a relatively shorter duration of 2 years. Our analysis using 3-year follow-up data demonstrated that the quantitative CT biomarkers were able to identify individuals at risk of consistent exacerbations.

CTDG texture was predictive of severe and consistent exacerbation events. This texture was derived from areas of lung tissue labelled as honeycombing by trained radiologists in the previous supervised training of the AMFM texture analysis framework. A visual inspection by three trained radiologists, each with at least a decade of experience, confirmed that these textures were regions of variable CT densities around the bronchovascular

bundles and fissures, which were absent in individuals who did not have any exacerbations. We hypothesise that these density gradients could be driven by a combination of peribronchovascular emphysema and underlying inflammation that were identified as high attenuation areas on a CT. In future, we intend to investigate the under lying association between CTDG texture, inflammation, and future exacerbations.

The proposed measures yielded superior performance when compared with BODE or history of exacerbations; however, our study had some limitations and was based on some underlying assumptions. The study provides predictive estimates of various exacerbation groups, but did not address causality. A key assumption of our models was the availability of chest CT for predicting exacerbations. The accuracy of CTDG texture and airway measures could be potentially sensitive to CT acquisition protocols, which were largely restricted to a set of well defined parameters and standardised lung volume in this study.[18] We observed that the model performance was lower in the COPDGene cohort than SPIROMICS. This highlighted model susceptibility to different image acquisition protocols, since COPDGene acquired CT scans at a lower dose with different acquisition parameters.[20] Although reliable external validation on a cohort that used a completely different acquisition protocol provided broader clinical applicability of quantitative CT biomarkers, it did not entirely mitigate their variability to acquisition protocols.

We developed prediction models specifically for severe and consistent acute exacerbations because they constitute most of the overall disease burden and drive health-care costs. Our analyses demonstrated that the proposed CT biomarkers can be directly used to identify individuals at risk of hospital admission or requirement for emergency care. Quantitative CT is increasingly being used to evaluate individuals with respiratory symptoms. These scans can be used within clinical practice to identify individuals who are likely to have a severe exacerbation, even without a previous history of exacerbations. The CT biomarkers could be complemented in future by other pneumological techniques such as multi-breath washout and impulse oscillometry. In summary, CTDG texture and Pi10 are effective predictors of severe exacerbations that could be integrated into clinical decision making for early identification of patients at risk of severe exacerbations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declaration of interests

EAH has received grants from the National Institutes of Health (NIH) and American Lung Association (ALA); has received royalties from VIDA Diagnostics; is a participant on Siemens photon counting CT advisory board; and is founder and shareholder of VIDA Diagnostics. JG has received grants from NIH and is a shareholder of VIDA Diagnostics. APC has received grants from NIH and is a paid consultant for GlaxoSmithKline and AstraZeneca. JDN has received grants from NIH and VIDA Diagnostics; has received royalties from Elsevier; and has received consulting fees, honoraria for lectures, travel expenses, fees for leadership roles, is also shareholder for, shares multiple patents with, and has received computer equipment from VIDA Diagnostics. PN has received grants from the NIH and honoraria from the GE Medical–University of Washington Imaging Symposium. SF has received grants from the American Thoracic Society, Fisher, and Paykel; and has served as a consultant for Genentech. GEC has received grants from the NIH; royalties from VIDA Diagnostics; fees for consultancy work from PowerPollen; and holds stocks or stock options in PowerPollen. FA has received grants from the NIH. IZB has received grants from Theravance & Viatris; fees for consultancy work from Theravance & Viatris, GlaxoSmithKline, AstraZeneca, and GE Healthcare; payment or honoraria for lectures, presentations, speaking, bureaus, manuscript writing, or educational events from Theravance & Viatris, AstraZeneca, and Grifols; is a participant on a data safety monitoring board for Theravance & Viatris, GlaxoSmithKline, and AstraZeneca; and is a member of the American Thoracic Society pulmonary function test committee. RGB has received grants from the NIH, the National Heart, Lung, and Blood Institute (NHLBI), The COPD Foundation, ALA, and the Foundation for the NIH; has received travel expenses from The COPD Foundation for an NIH-funded study; and has served The COPD Foundation in an unpaid leadership or fiduciary role. SPB has received grants from NIH; royalties from Springer Humana; fees for consultancy work from Boehringer Ingelheim, Sanofi/Regeneron, Sunovion, and GlaxoSmithKline; and holds stock options for Vigor Medical Systems. CBC has received grants from the NIH, The COPD Foundation, and the Foundation for the NIH; royalties from the Cambridge University Press; fees for consultancy work from Nuvaira and MGC Diagnostics; and personal fees from GlaxoSmithKline, and medicolegal personal fees from various law firms. MKH has received grants from the NHLBI, Sanofi, Novartis, Nuvaira, Sunovion; royalties from UpToDate and Norton Publishing; fees for consultancy work from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Pulmonx, Teva, Verona, Merck, Sanofi, DevPro, Aerogen, and United Therapeutics; payments or honoraria from Cipla, Chiesi, Astra Zeneca, Boehringer Ingelheim, and GlaxoSmithKline; has participated on a data safety monitoring board or advisory board for Novartis and MedTronic; and is a member of The COPD Foundation Board, The COPD Foundation Scientific Advisory Committee, and ALA advisory committee. FJM has received grants from NHLBI, AstraZeneca, Chiesi, GlaxoSmithKline, and Sanofi/Regeneron; fees for consultancy work from Astra Zeneca, Boehringer Ingelheim, Chiesi, CsL Behring, Gala, GlaxoSmithKline, Novartis, Polarean, PulmonX, Sanofi/Regeneron, Sunovion, Teva, Theravance & Viatris, and Virona; payment or honoraria for lectures, presentations, speaking, bureaus, manuscript writing, or educational events from UpToDate; and is a member of the data safety monitoring board of MedTronic. MGM has received grants from the NIH and NHLBI. VEO is member of an independent data safety monitoring board for Sanofi and Regeneron. RP has received grants from NHLBI, The COPD Foundation, and Department of Veteran Affairs; and has received fees for consultancy work from Partner Therapeutics. PGW has received grants from The COPD Foundation, and Genentech; fees for consultancy work from Glenmark Pharmaceuticals, the University of Wisconsin, NGM Pharma, GlaxoSmithKline, Theravance, Sanofi, and AstraZeneca; and honoraria from the Western Society of Allergy, Asthma and Immunology. JMR has received grants from the NHLBI, and The Roy J Carver Charitable Trust; royalties from VIDA Diagnostics; personal fees from Boehringer Ingelheim; payment for expert testimony from Desmarais LLP; and is a shareholder of VIDA Diagnostics. All other authors declare no competing interests.

Data sharing

Deidentified data, from both the SPIROMICS and COPDGene studies, is publicly available on request. Further details of SPIROMICS and COPDGene studies are available online.

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Research in context

Evidence before this study

A systematic analysis of 1382 prediction models for chronic obstructive pulmonary disease (COPD) exacerbations was published in 2017. Rigorous criteria were used to identify 27 models that were considered suitable for comparison. The analysis highlighted several limitations of these models, including poor clinical applicability, difficulty in obtaining data on predictor variables, and scarcity of high-quality statistical approaches. Only two of the 27 models were validated using an external cohort, and only three used appropriate statistical methods to assess their approach. None of the studies reviewed had analysed imaging biomarkers for the prediction of exacerbations. We searched PubMed for studies published between Jan 1, 2017, and Feb 20, 2022, which were related to the development and validation of prediction models for exacerbation. We used the keywords “COPD”, “exacerbation”, “prediction”, and “validation”. Although the search terms yielded 159 results, only one study reported external validation and attempted to address the concerns highlighted by the systematic review. We were unable to find a rigorous study investigating and validating imaging markers for predicting COPD exacerbations. One study noted that a CT-based pulmonary artery diameter to aorta diameter ratio greater than 1 was associated with severe COPD exacerbations, but the study did not develop or assess a predictive model for clinical use.

Added value of this study

To our knowledge, this is the first study to investigate and validate CT biomarkers for predicting severe exacerbations of COPD. We also showed that these biomarkers can be used to identify individuals who exacerbate persistently over time. Our analysis of data from a large multicentre study cohort found airway wall thickening and a novel CT density gradient texture to be highly predictive of future severe episodes. To assess generalisability, we externally validated these biomarkers in another well characterised multicentre study cohort. Our study also shows that CT biomarkers perform significantly better than exacerbation history and the BMI, airflow obstruction, dyspnoea, exercise capacity index. In addition to their high discriminative ability, these biomarkers can be automatically extracted from chest CT scans that are routinely being acquired in clinical settings.

Implications of all the available evidence

Chest CT is routinely used to characterise various pulmonary abnormalities including COPD, lung cancer, and pulmonary fibrosis. Although this practice has led to increased generation and curation of CT data, its potential utility for estimating an individual’s risk of exacerbations remains under-investigated. Our study highlights the clinical utility and effectiveness of CT biomarkers for predicting severe and persistent exacerbations of COPD. Care providers can use the CT-based prediction models presented in this study to identify individuals at a higher risk of hospital admission or visits to the emergency department. Furthermore, these models can provide risk estimates of recurrent exacerbations that are another major source of burden associated with COPD. Unlike the

highly variable previous exacerbation history, CT-based models can identify individuals who are at risk of a severe episode without necessarily having a history of exacerbations.

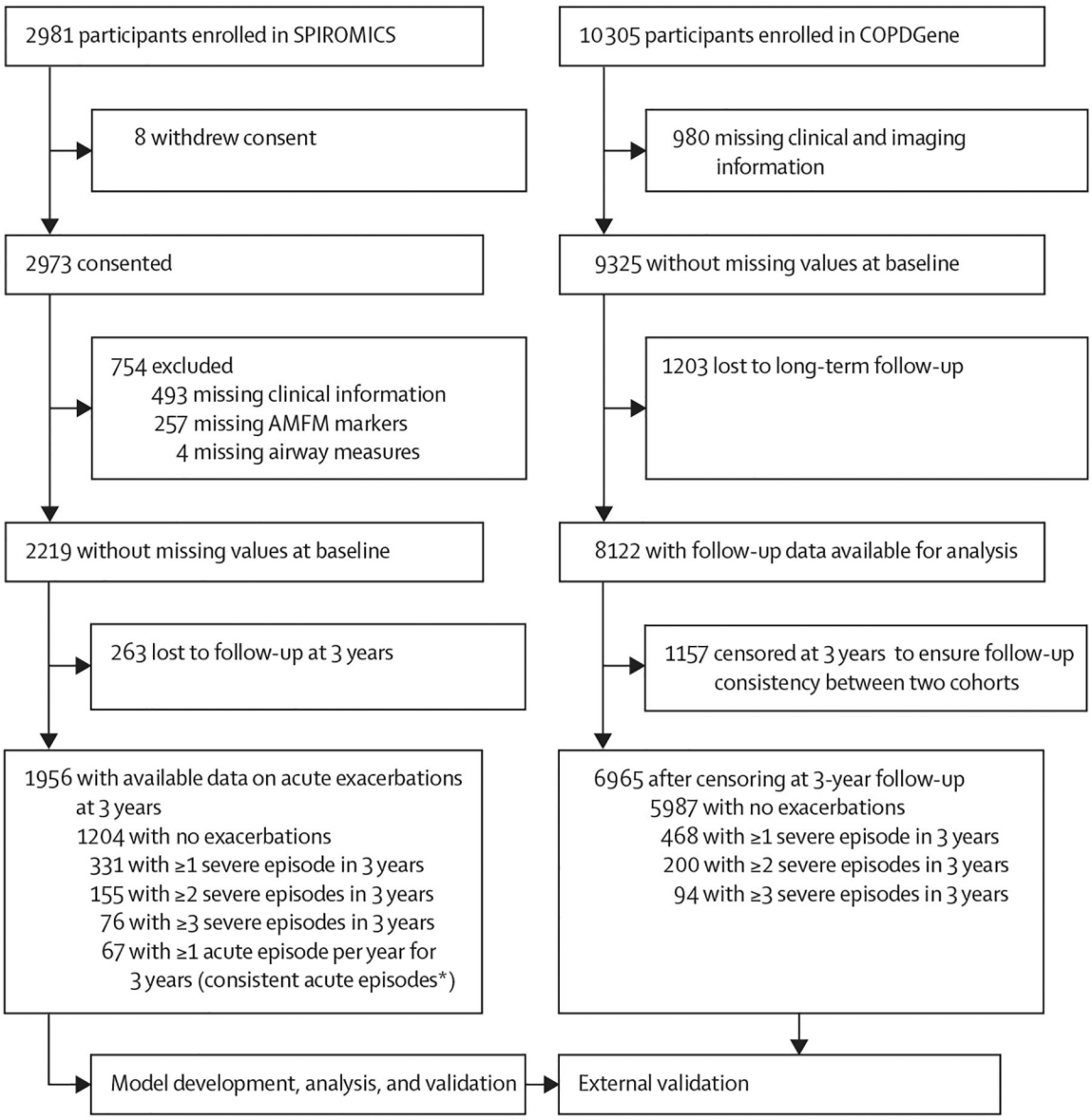

Figure 1: CONSORT diagram

AMFM=adaptive multiple feature method. *People with consistent exacerbations constituted a subgroup of individuals with high susceptibility to severe exacerbations, as defined by Han and colleagues.[7]

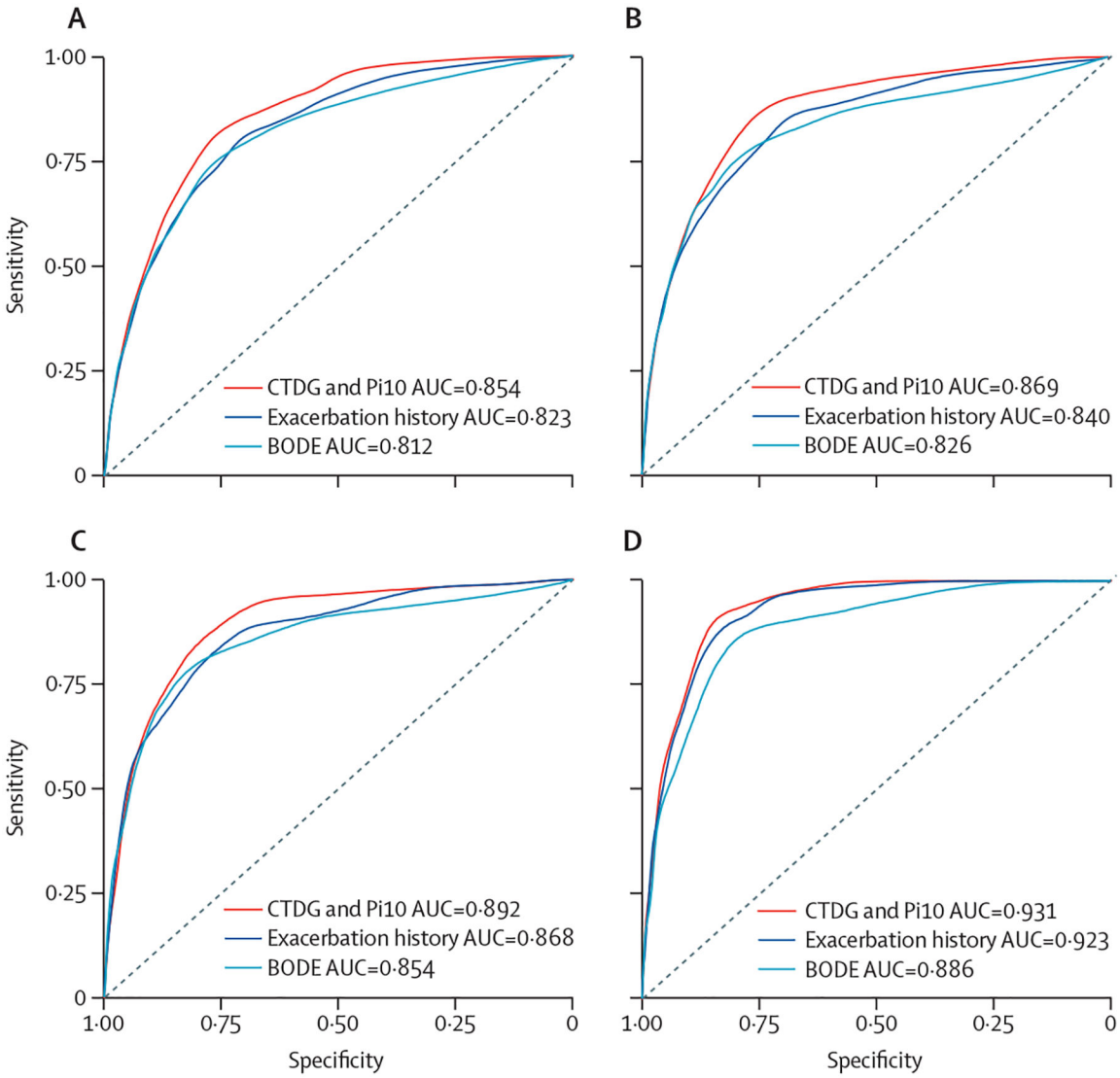

Figure 2: Discriminative performance of quantitative CT biomarkers for predicting future severe acute exacerbations in the SPIROMICS cohort

ROC for predicting ≥1 severe episode in 3 years (A), ≥2 severe episodes in 3 years (B), ≥3 severe acute episodes in 3 years (C), and consistent exacerbations (≥1 acute episode in each year for 3 consecutive years; D). DeLong's test was used to compare ROC curves of quantitative CT-based predictors (CTDG and Pi10 with adjustment) with exacerbation history (with adjustment) and BODE index (with adjustment). AUCs were higher for quantitative CT biomarkers than exacerbation history and BODE index (DeLong's test p<0·0001 for both). SPIROMICS=Subpopulations and Intermediate Outcome Measures In COPD Study. ROC=receiver operating characteristic curve. CTDG=CT density gradients. Pi10=square root of airway wall area of a hypothetical airway with an internal perimeter of 10 mm. BODE=BMI, obstruction, dyspnoea, and exercise capacity index. AUC=area under the ROC.

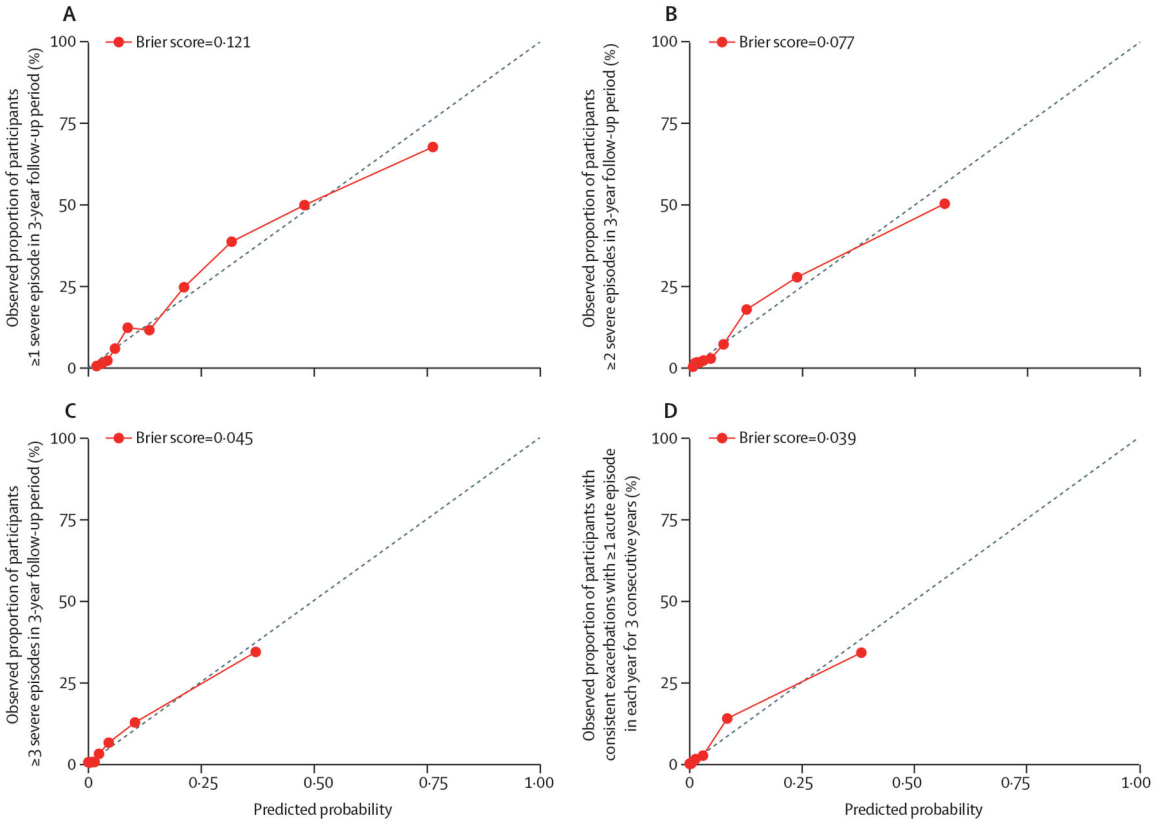

Figure 3: Calibration plots for predicting severe exacerbations in SPIROMICS during 3-year follow-up using quantitative CT biomarkers

Comparison between deciles of observed rates of exacerbations and predicted likelihoods from logistic regression classifiers trained to predict ≥1 severe episode in 3 years (A), ≥2 severe episodes in 3 years (B), ≥3 severe episodes in 3 years (C), and consistent exacerbations with ≥1 acute episode in each year for 3 consecutive years (D). Brier scores were used to quantify calibration performance, with a score of 0 indicating a perfectly calibrated model, and a score of 1 indicating a poorly calibrated model. SPIROMICS=Subpopulations and Intermediate Outcome Measures In COPD Study.

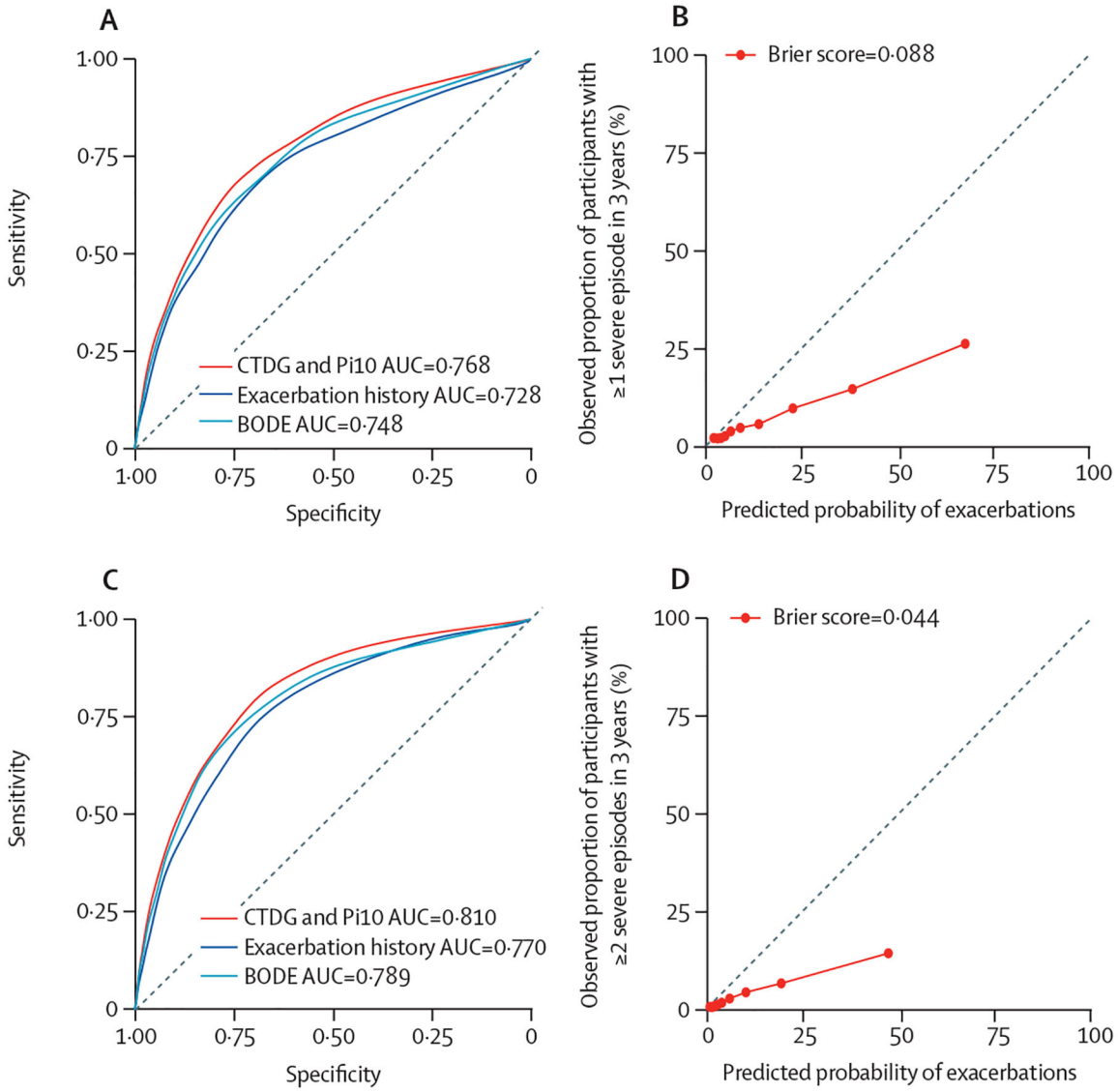

Figure 4: External validation of quantitative CT biomarkers using the COPDGene cohort

ROC and calibration plot between deciles of observed exacerbations and predicted rates for ≥1 severe episode (A, B) and ≥2 severe episodes in 3 years (C, D). The quantitative CT biomarkers included CTDG and Pi10 (with adjustment variables). Correlated ROCs were compared using DeLong's test, which indicated significantly higher AUCs for quantitative CT biomarkers than exacerbation history and BODE index ($p<0·0001$). Low Brier scores indicated near optimal model calibration. Severe exacerbations in COPDGene and SPIROMICS were defined to be similar with each episode requiring hospital admission or a visit to an emergency department. COPDGene=Genetic Epidemiology of COPD. ROC=receiver operating characteristic curve. CTDG=computed tomography density gradients. Pi10=the square root of airway wall area of a hypothetical airway with an internal perimeter of 10 mm. AUC=area under the receiver operating characteristic curve. BODE=body mass index, obstruction, dyspnoea, and exercise capacity index. SPIROMICS=Subpopulations and Intermediate Outcome Measures In COPD Study.

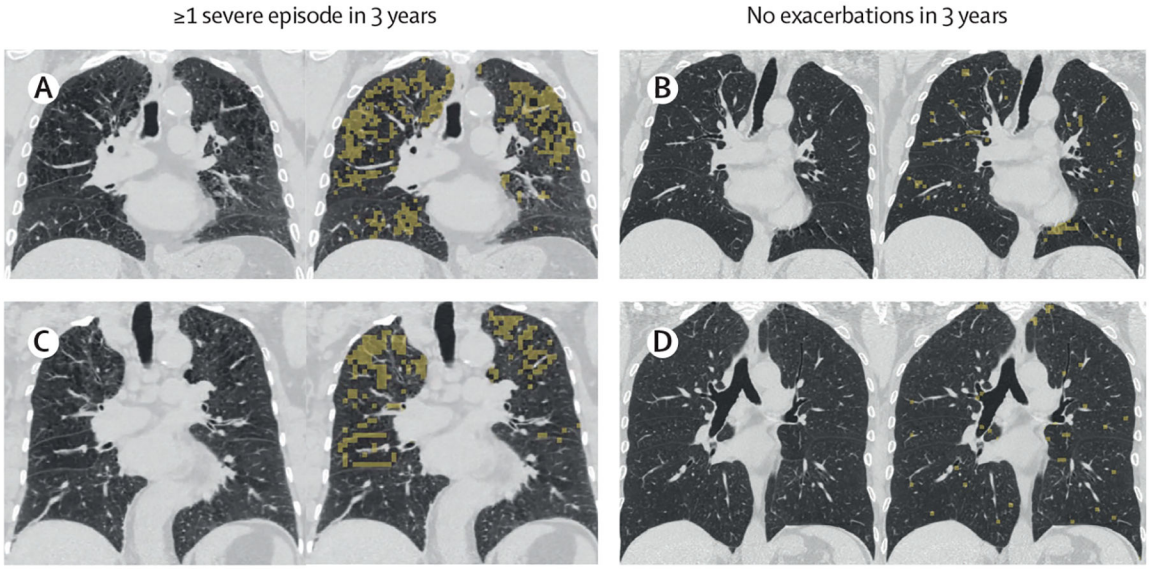

Figure 5: CTDG texture characterisation by AMFM in participants with and without severe exacerbations

Each panel shows a pair of mid-coronal CT slices with and without the highlighted CTDG texture (shown in yellow). (A, C) CTDG texture surrounding the bronchovascular bundles and fissures for two different individuals with at least one severe exacerbation in 3 years. (B, D) Density gradients texture for two individuals who did not experience any exacerbation in 3 years. CTDG texture, which can be clearly identified in individuals with ≥1 severe exacerbation, was negligible in individuals who did not exacerbate. It should be noted that the AMFM uses a three dimensional block of the image for texture assignment. Thus, the assignment of a texture feature, as observed in two dimensions in this figure, includes textures that are both above and below the displayed slices (appendix pp 2–3). CTDG=computed tomography density gradients. AMFM=adaptive multiple feature method.

Table 1:

Characteristics of study participants from the SPIROMICS and COPDGene cohorts

	SPIROMICS		COPDGene
	Baseline (n=2219)	**Follow-up (n=1956)**	**Follow-up (n=6965)**
Age, years	63·0 (9·2)	63·1 (9·2)	60·5 (8·9)
Sex			
Male	1167 (52·6%)	1017 (52·0%)	3508 (50·4%)
Female	1052 (47·4%)	939 (48·0%)	3457 (49·6%)
Ethnicity			
White	1706 (76·9%)	1518 (77·6%)	5115 (73·4%)
Black	417 (18·8%)	358 (18·3%)	1850 (26·6%)
Asian	24 (1·1%)	21 (1·1%)	0
American Indian or Alaska Native	8 (0·4%)	7 (0·4%)	0
Mixed	50 (2·3%)	40 (2·0%)	0
Not reported	14 (0·6%)	12 (0·6%)	0
BMI, kg/m^2	28·0 (5·2)	28·9 (5·2)	29·0 (6·1)
Current smokers	828 (37·3%)	707 (36·1%)	3172 (45·5%)
Smoking pack years*	45·7 (28·1)	45·5 (27·4)	43·1 (24·7)
Postbronchodilator FEV_1, % predicted	75·5 (26·2)	76·2 (25·9)	78·2 (24·3)
FEV_1/FVC ratio	80·4 (21·2)	80·9 (21·0)	67·4 (15·3)
BODE index	1·5 (2·0)	1·4 (1·9)	1·6 (2·1)
Total SGRQ score†	30·9 (20·6)	30·2 (20·5)	24·3 (21·6)
GOLD stage			
0	702 (31·6%)	617 (31·5%)	3041 (43·7%)
1	304 (13·7%)	276 (14·1%)	588 (8·4%)
2	605 (27·3%)	535 (27·4%)	1376 (19·8%)
3	332 (15·0%)	289 (14·8%)	775 (11·1%)
4	121 (5·5%)	94 (4·8%)	280 (4·0%)
Never smokers	155 (7·0%)	145 (7·4%)	100 (1·4%)
PRISm	NA	NA	805 (11·6%)
CT density gradients	4·1 (3·1)	4·0 (3·1)	2·4 (2·3)
Wall area percentage, %	40·1 (3·3)	40·1 (3·3)	61·2 (3·1)
Pi10	3·7 (0·1)	3·7 (0·2)	3·7 (0·1)
History of one or more severe exacerbations‡	238 (10·7%)	434 (22·2%)	1389 (19·9%)
History of two or more severe exacerbations‡	75 (3·4%)	226 (11·6%)	552 (7·9%)
Consistent exacerbations	NA	67 (3·4%)	NA

Data are mean (SD) or n (%). SPIROMICS=Subpopulations and Intermediate Outcome Measures In COPD Study. COPDGene=Genetic Epidemiology of COPD. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity BODE=BMI, airflow obstruction, dyspnoea, and exercise capacity index. SGRQ=St George's Respiratory Questionnaire. GOLD=Global Initiative for Chronic Obstructive Lung Disease. PRISm=preserved ratio impaired spirometry. Pi10=square root of airway wall area of a hypothetical airway with an internal perimeter of 10 mm. NA=not available.

*Pack years defined as the number of packs of cigarettes smoked in a day multiplied by the number of years an individual has smoked.

[†]Total score ranged between 0 and 100, with a higher score indicating increased symptom burden.

[‡]History of exacerbations included all severe episodes requiring hospital admission or a visit to an emergency department within the year preceding enrolment.

Table 2:

Multivariable zero-inflated negative binomial regression analysis of the association between quantitative CT biomarkers and severe exacerbations during 3-year follow-up in the SPIROMICS cohort

	Count component		Inflation component	
	Incidence rate ratio (95% CI)	**p value**	**Odds ratio (95% CI)**	**p value**
Age	0·991 (0·974–1·008)	0·281	0·942 (0·885–1·002)	0·058
Sex	1·259 (0·972–1·632)	0·081	1·277 (0·586–2·781)	0·539
Race (White *vs* other)	0·901 (0·684–1·187)	0·459	2·240 (0·768–6·530)	0·14
Baseline FEV_1 (% predicted)	0·986 (0·978–0·993)	0·0002	1·007 (0·982–1·033)	0·579
Smoking status	0·907 (0·658–1·251)	0·553	0·577 (0·210–1·591)	0·288
BMI, kg/m^2	1·011 (0·986–1·037)	0·376	0·982 (0·911–1·058)	0·628
History of exacerbations *	1·137 (1·028–1·259)	0·013	0·132 (0·027–0·640)	0·012
SGRQ †	1·006 (0·997–1·015)	0·204	0·921 (0·888–0·955)	<0·0001
CT density gradient	0·979 (0·939–1·020)	0·311	0·758 (0·595–0·967)	0·026
Wall area, %	0·019 (0·0002–1·560)	0·078	0·0003 (0–1654·17)	0·312
Pi10	3·174 (0·942–10·700)	0·062	1·827 (0·040–84·027)	0·758

1535 participants were included in the analysis (1204 with no exacerbations and 331 with at least one acute episode in 3 years) across GOLD stages (0–4), including individuals who never smoked. The zero-inflated negative binomial regression model was adjusted for age, sex, postbronchodilator FEV_1, smoking status, BMI, history of exacerbations, and symptom burden score quantified by SGRQ. SPIROMICS=Subpopulations and Intermediate Outcome Measures In COPD Study. GOLD=Global Initiative for Chronic Obstructive Lung Disease. FEV_1=forced expiratory volume in 1 s. SGRQ=St George's Respiratory Questionnaire. Pi10=square root of airway wall area of a hypothetical airway with an internal perimeter of 10 mm.

* Exacerbation history included count of all exacerbation episodes within the year preceding enrolment.

† The score ranges between 0 and 100, higher scores indicating increased symptom burden.