Chronic Obstructive Pulmonary Disease (COPD): Bridging the Knowledge Gap for Early Intervention and Prevention of Disease Progression

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Abstract

Chronic Obstructive Pulmonary Disease (COPD) is a progressive respiratory disorder, the leading cause of non-parturition hospital stay in Canada and the third leading cause of death globally, known for heterogeneity in its development, presentation, and progression. Treatment planning targets prevention and management of exacerbations since these aggressively impact lung function deterioration even in mild-moderate disease severity stage.

There are gaps in our knowledge, among those with mild-moderate COPD, to support the detection of rapid decliners and the development of targeted therapeutics. Prevalent knowledge has evolved mainly through studies in severely ill patients and is not generalizable to milder stages. The overarching goal of this thesis is to bridge some of these pressing knowledge gaps. The Canadian Cohort of Obstructive Lung Disease (CanCOLD) participants are reflective of patients at family medicine practices with mild-moderate COPD and, hence, were selected to study characteristics of those likely to experience rapid decline. Clinically important deterioration (CID), a composite measure; the recently recalibrated Acute COPD Exacerbation Prediction Tool (ACCEPT) 2.0; and the ratio of biomarkers Advanced Glycation Endproducts (AGE)/ soluble receptor for AGE (sRAGE) were assessed for the first time for use in this population.

In Manuscript 1, short-term CID (2 definitions) was examined as an indicator of deterioration in disease and dyspnea in the following short-term period. This was assessed via suitable models adjusted for age, sex, BMI, and pack-years alongside a second set of models controlled additionally for comorbidity and biomarkers. The outcomes of a) ≥100 and 200 mL declines in

forced expiratory volume in 1 second (FEV1), worsening health status [≥ 4 and 8 unit increases in St. George respiratory Questionnaire score, and ≥2 and 4 unit in COPD Assessment Test] and dyspnea (≥1 unit increase in Medical Research Council score) were analyzed using logistic regression models; b) new moderate/severe exacerbations using Cox Proportional Hazards models; and c) the incidence of such exacerbations using Poisson regression models. Results show that while composite CID definition will need to be adapted for this population, health status measure and exacerbation were informative components (third component: FEV1 decline). A study to validate the findings is underway using the United Kingdom primary care data (protocol included).

In Manuscript 2, the ACCEPT 2.0 model was compared to the exacerbation history (last 12 months) in the CanCOLD cohort. The observed discrimination for the ACCEPT 2.0 model was superior to the adapted exacerbation definitions used in the study. Area under the time-dependent Receiver Operating Characteristic Curve was compared using the DeLong Test, and calibration plots were reviewed. The findings support a future study in a larger cohort to recalibrate the model for the mild-moderate COPD population.

Biomarkers are clinically informative and included in prediction models to improve accuracy. The pathophysiology of AGE-RAGE stress and AGE/sRAGE ratio as a disease activity marker in COPD is reviewed in Manuscript 3. Manuscript 4 reports and discusses the serum concentrations and correlations of AGE, sRAGE, and AGE/sRAGE in a CanCOLD sub-cohort with clearly defined 3 groups: healthy controls excluding conditions and drugs known to influence the biomarker levels; non-COPD smokers; and those with COPD. The ratio was significantly higher in the at-risk and COPD groups (compared to the healthy group). The data suggests the potential for AGE/sRAGE as a promising new biomarker in mild-moderate COPD.

However, further evaluations are needed to explore the correlations observed here and with other available markers of COPD.

The gaps identified and studies conducted in this thesis add important knowledge that dovetails toward the goal of personalized care in mild-moderate COPD.

Abrégé

La maladie pulmonaire obstructive chronique (MPOC) est un trouble respiratoire progressif, la principale cause d'hospitalisation sans accouchement au Canada et la troisième cause de décès dans le monde, connue pour son hétérogénéité dans son développement, sa présentation et sa progression. La planification du traitement vise à prévenir et à gérer les exacerbations, car celles-ci ont un impact agressif sur la détérioration de la fonction pulmonaire, même au stade de gravité légère à modérée de la maladie.

Il existe des lacunes dans nos connaissances, parmi les personnes atteintes de MPOC légère à modérée, pour soutenir la détection des déclins rapides et le développement de thérapies ciblées. Les connaissances prévalentes ont évolué principalement grâce à des études menées auprès de patients gravement malades et ne sont pas généralisables aux stades plus légers. L'objectif global de cette thèse est de combler certaines de ces lacunes pressantes dans les connaissances. Les participants à la cohorte canadienne de maladies pulmonaires obstructives (CanCOLD) sont représentatifs des patients des cabinets de médecine familiale atteints de MPOC légère à modérée et, par conséquent, ont été sélectionnés pour étudier les caractéristiques des personnes susceptibles de connaître un déclin rapide. Détérioration cliniquement importante (CID), une mesure composite ; l'outil de prédiction des exacerbations aiguës de la MPOC (ACCEPT) 2.0 récemment recalibré et le rapport des biomarqueurs Advanced Glycation Endproducts (AGE)/soluble receptor for AGE (sRAGE) ont été évalués pour la première fois pour une utilisation dans cette population.

Dans le Manuscrit 1, le CID à court terme (2 définitions) a été examiné comme indicateur de détérioration de la maladie et de dyspnée au cours de la période à court terme suivante. Cela a été

évalué via des modèles appropriés ajustés pour l'âge, le sexe, l'IMC et les paquets-années ainsi qu'un deuxième ensemble de modèles contrôlés en plus pour la comorbidité et les biomarqueurs. Les résultats de a) des baisses ≥ 100 et 200 ml du volume expiratoire maximal en 1 seconde (VEMS), de l'aggravation de l'état de santé [augmentations ≥ 4 et 8 unités du score du questionnaire respiratoire de St. George et ≥ 2 et 4 unités du test d'évaluation de la MPOC] et de la dyspnée (augmentation ≥ 1 unité du score du Medical Research Council) ont été analysés à l'aide de modèles de régression logistique ; b) de nouvelles exacerbations modérées/graves à l'aide de modèles de risques proportionnels de Cox ; et c) l'incidence de ces exacerbations à l'aide de modèles de régression de Poisson. Les résultats montrent que même si la définition composite du CID devra être adaptée à cette population, la mesure de l'état de santé et l'exacerbation étaient des composantes informatives (troisième composante : baisse du VEMS). Une étude visant à valider les résultats est en cours à l'aide des données des soins primaires du Royaume-Uni (protocole inclus).

Dans le Manuscrit 2, le modèle ACCEPT 2.0 a été comparé à l'historique des exacerbations (12 derniers mois) dans la cohorte CanCOLD. La discrimination observée pour le modèle ACCEPT 2.0 était supérieure pour les définitions d'exacerbation adaptées utilisées dans l'étude. L'aire sous la courbe caractéristique d'exploitation du récepteur dépendante du temps a été comparée à l'aide du test de DeLong et les tracés d'étalonnage ont été examinés. Les résultats soutiennent une future étude dans une cohorte plus large pour recalibrer le modèle pour la population atteinte de MPOC légère à modérée.

Les biomarqueurs sont cliniquement informatifs et inclus dans les modèles de prédiction pour améliorer la précision. La physiopathologie du stress AGE-RAGE et le rapport AGE/sRAGE en tant que marqueur d'activité de la maladie dans la MPOC sont examinés dans le Manuscrit 3. Le

Manuscrit 4 rapporte et discute les concentrations sériques et les corrélations d'AGE, de sRAGE et d'AGE/sRAGE dans une sous-cohorte CanCOLD avec 3 groupes clairement définis : témoins sains excluant les conditions et les médicaments connus pour influencer les niveaux de biomarqueurs ; fumeurs non atteints de MPOC ; et ceux atteints de MPOC. Le rapport était significativement plus élevé dans les groupes à risque et MPOC (par rapport au groupe sain). Les données suggèrent le potentiel d'AGE/sRAGE en tant que nouveau biomarqueur prometteur dans la MPOC légère à modérée. Cependant, d'autres évaluations sont nécessaires pour explorer les corrélations observées ici et avec d'autres marqueurs disponibles de la MPOC.

Les lacunes identifiées et les études menées dans cette thèse ajoutent des connaissances importantes qui concordent avec l'objectif de soins personnalisés dans la MPOC légère à modérée.

List of Abbreviations

AGE	Advanced Glycated Endproducts
ACCEPT	Acute COPD Exacerbation Prediction Tool
AATD	Alpha-1-antitrypsin deficiency
AUC	Area under the ROC Curve
ACOS	Asthma-COPD overlap syndrome
BMI	Body Mass Index
CVD	Cardiovascular Disease
CanCOLD	Canadian Cohort Obstructive Lung Disease
CPET	Cardiopulmonary Exercise Test
COPD	Chronic Obstructive Pulmonary Disease
cRAGE	cleaved Receptor for Advanced Glycated Endproducts
CID	Clinically Important Deterioration
COMCOLD	COMorbidities in COPD
CAT	COPD Assessment Test
COVID-19	Coronavirus Disease 2019
CRP	C-Reactive Protein
DLCO	Diffusing Capacity for carbon monoxide
esRAGE	Endogenous Secretory Receptor for Advanced Glycated Endproducts
ELISA	Enzyme-Linked Immunosorbent Assay
FEV1	Forced Expiratory Volume in 1 s
FVC	Forced Vital Capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease.
HES	Hospital Episode Statistics
ICD 10	International Classification of Diseases version 10
LAA-950	Low Attenuation Areas less than a threshold of -950 Hounsfield units
MRC	Medical Research Council
MCID	Minimum Clinically Important Difference
mMRC	Modified Medical Research Council
PROM	Patient Reported Outcome Measures
PRISm	Preserved ratio impaired spirometry
PFT	Pulmonary Function Test
ROS	Reactive Oxygen Species
ROC	Receiver Operating Characteristic
RAGE	Receptor for Advanced Glycated Endproducts
6MWT	Six-Minute Walking Test
SAF	Skin Autofluorescence
sRAGE	Soluble Receptor for Advanced Glycated Endproducts
SGRQ	St. George's Respiratory Questionnaire
UK-CPRD	United Kingdom-Clinical Practice Research Datalink
US-FDA	United States Food and Drug Administration

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Acknowledgments

I am very grateful to Dr. Bourbeau for accepting me as one of his students and for being a transformational force in my life. The COVID-19 outbreak impacted my doctoral journey, disrupting my research plans and schedules while surrounded by a lot of uncertainty, obscuring alternate options. However, for me, this period has come to be associated with immense experiential learning and growth. I thank you, Dr. Bourbeau, for the opportunities to engage in unique grants and clinical trials under your leadership and supervision, where I could put my knowledge and skills to the test. No words will be enough to express my gratitude for the diverse research exposures I have had, to learn from you and to grow academically and as a professional. Your kindness and unrelenting commitment to the success of your patients, projects, and especially your students is inspirational. I am thankful for your guidance and unwavering support in developing and finalizing this thesis through every challenging twist and turn.

I take this opportunity to express my deep gratitude to my thesis advisory committee members, Dr. David Buckeridge, Dr. Benjamin Smith, and Dr. Nancy Mayo, for their guidance, constructive recommendations, and support throughout the various studies. I especially thank Dr. Kailash Prasad from the University of Saskatchewan for agreeing to advise me and guide my studies involving AGEs and sRAGE.

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unforeseeable challenges, that created a stress-free environment and helped me focus on completing my thesis.

Importantly, I express my unfathomable gratitude to my parents and husband for their unending thoughtfulness, unconditional support, prayers, and sacrifices. Finally, I take this opportunity to thank all my teachers, peers, seniors, and well-wishers for believing in me.

Contribution of Authors

This thesis includes four manuscripts and an approved protocol. These have been listed below. The author contributions section provides the details corresponding to each. Under the guidance of my supervisor, Dr. Bourbeau, I developed the overarching goal, themes, individual study research questions, study designs, and analysis. Data analyst Pei Zhi Li reviewed and advised on all included analyses.

I have drafted the manuscripts and am responsible for the analysis presented. My supervisor, Dr. Bourbeau, advised and reviewed the initial drafts. For studies using Canadian Cohort Obstructive Lung Disease (CanCOLD) data, I submitted data access requests and completed the request process.

Dr. Kailash Prasad, my external thesis committee member from the University of Saskatchewan, guided the studies under the biomarker theme while developing the study design. Serum levels obtained were examined in consultation with Dr. Prasad and the respective manufacturer's lab before being included in the analysis. Dr. Prasad also guided the pathophysiology paper development and reviewed the manuscript.

My academic advisor, Dr. Nancy Mayo, advised adding group-based trajectory analysis to the paper investigating short-term clinically important deterioration (CID) as currently defined in predicting exacerbations and other clinically important outcomes over a similar period subsequent to the assessment of CID in the CanCOLD mild-moderate Chronic Obstructive Pulmonary Disease (COPD) population.

Under the guidance of my supervisor, I developed, designed and drafted the protocol proposed to examine the reproducibility of findings from the CanCOLD study using the United Kingdom-Clinical Practice Research Datalink (UK-CPRD) data to replicate the CanCOLD cohort in this larger database and carry out additional analysis to examine effect of varying outcome period, CID

definition in not only the larger cohort resembling primary-care patient population like CanCOLD participants, given the large size also assess sub-groups, such as, by comorbidity combination and smoking status etc. My committee members, Dr. David Buckeridge and Dr. Benjamin Smith, reviewed and guided the protocol development. The study was delayed, and as data extraction (data linkages included) is underway, Dr. Buckeridge and Dr. Smith will advise on the data cleaning and analysis stages.

For the study assessing the Acute COPD Exacerbation Prediction Tool (ACCEPT) 2.0 performance in the CanCOLD cohort, I consulted with Dr. Mohsen Sadatsafavi during the development of the study design regarding the ACCEPT version advisable for my study goal. Dr. Sadatsafavi and his team at the University of British Columbia developed ACCEPT and versions of ACCEPT.

Co-authors from the Collaborative Research Group and the Canadian Respiratory Research Network have reviewed and approved Manuscript 1, which was submitted to and is currently under review for publication in the European Respiratory Journal-Open Research.

Impact of Coronavirus Disease 2019 (COVID-19) on thesis studies and author contributions:

It is important to mention that my supervisor, committee members, and academic advisor have reviewed and advised another study initially developed as part of my thesis. This phase III double-blinded randomized controlled trial on an investigational new drug was proposed as a multicentric (USA and Canada) investigator-initiated trial under my supervisor, Dr. Bourbeau, as the principal investigator, which cleared institutional ethics review board approval as well as no-objection go-ahead from the US-FDA and the Health Canada. I was a co-investigator on the trial, contributing to developing protocol and correspondence with the regulatory authorities, and was overseeing the setting up and operations of this remote trial for an anti-inflammatory medication. A study to inform

response (reduce/ prevent hospitalization) to early intervention during an acute event such as COVID-19 on the elderly population with COPD and underlying comorbidities was planned as part of my thesis.

Serious delays due to schedules of the research ethics board of the leading Canadian University hospital site impacted timelines. These waiting periods meant the study needed to align with the subsequent COVID-19 wave (even once the approval was obtained), thus creeping into study drug expiry and aggravating funding constraints. Though the study was initiated, it was limited to fewer sites (2 in Canada and 2 in the USA). The participants recruited in the study completed the trial follow-ups. However, due to the significant delays, the thesis- study became incompatible with my thesis timelines.

This was not the only study that experienced a significant impact. The study under theme 1, titled "Short-term clinically important deterioration (CID) as an indicator of medium and long-term Chronic Obstructive Pulmonary Disease (COPD) progression: An external validation of Canadian population-based longitudinal Cohort findings in the UK primary care population," was the second study to be directly impacted. The travel bans and prolonged uncertainties needed a complete overhaul of the logistics of undertaking the study, including finding new funds to support an application for a single study license from CPRD, obtaining 'new client' approval from the data custodians in the UK for data access from the Research Institute of McGill University Health Centre location. However, even after these were obtained, delays due to ascertainment of legalities rising from the disparities in definitions of roles of parties to the contract, among others, led to significant wait periods before the commencement of the data access process for the approved protocol. Thus, this study's completion became incompatible with my thesis timeline.

Manuscript 1

Title: Clinically Important Deterioration (CID) in a mild-moderate COPD population

Authors: Sharmistha Biswas, Dany Doiron, Pei Zhi Li, Shawn D. Aaron, Kenneth R. Chapman, Paul Hernandez, François Maltais, Darcy D. Marciniuk, Denis O'Donnel, Don D. Sin, Brandie Walker, Gilbert Nadeau, Chris Compton, Wan C. Tan, and Jean Bourbeau; for the CanCOLD Collaborative Research Group and the Canadian Respiratory Research Network

Status: Submitted to the *European Respiratory Journal-Open Research*- revision underway

Approved protocol:

Title: Short-term clinically important deterioration (CID) as an indicator of medium and long-term Chronic Obstructive Pulmonary Disease (COPD) progression: An external validation of Canadian population-based longitudinal Cohort findings in the UK primary care population.

Authors: Sharmistha Biswas, David Buckeridge, Benjamin Smith, Dany Doiron, Pei Zhi Li, Jean Bourbeau

Manuscript 2:

Title: ACCEPT 2.0 in CanCOLD study cohort of participants with mild-moderate COPD

Authors: Sharmistha Biswas, Pei Zhi Li, Shawn D. Aaron, Kenneth R. Chapman, Paul Hernandez, François Maltais, Darcy D. Marciniuk, Denis O'Donnel, Don D. Sin, Brandie Walker, Wan C. Tan, Mohsen Sadatsafavi and Jean Bourbeau; for the CanCOLD Collaborative Research Group and the Canadian Respiratory Research Network

Status: Currently being prepared for submission to the *International Journal of Chronic Obstructive Pulmonary Disease.*

Manuscript 3:

Title: 'AGE-RAGE stress,' a *potential disease activity marker*: Pathophysiology, clinical and therapeutic significance in Chronic Obstructive Pulmonary Disease (COPD).

Authors: Sharmistha Biswas, Jean Bourbeau, and Kailash Prasad

Status: Currently being prepared for submission to the *PLoS-One Journal.*

Manuscript 4:

Title: Understanding a Novel Potential Marker of Disease Activity in COPD: Findings from our evaluation of AGE/sRAGE ratio in a CanCOLD sub-cohort

Authors: Sharmistha Biswas, Pei Zhi Li, Shawn D. Aaron, Kenneth R. Chapman, Paul Hernandez, François Maltais, Darcy D. Marciniuk, Denis O'Donnel, Don D. Sin, Brandie Walker, Gilbert Nadeau, Chris Compton, Wan C. Tan, Jean Bourbeau; for the CanCOLD Collaborative Research Group and the Canadian Respiratory Research Network; and Kailash Prasad

Status: Currently being prepared for submission to the journal *Respiratory Medicine*

Note: Manuscripts in preparation for submission are at various stages of review and feedback with co-authors.

Thesis Structure and Contribution to New Knowledge

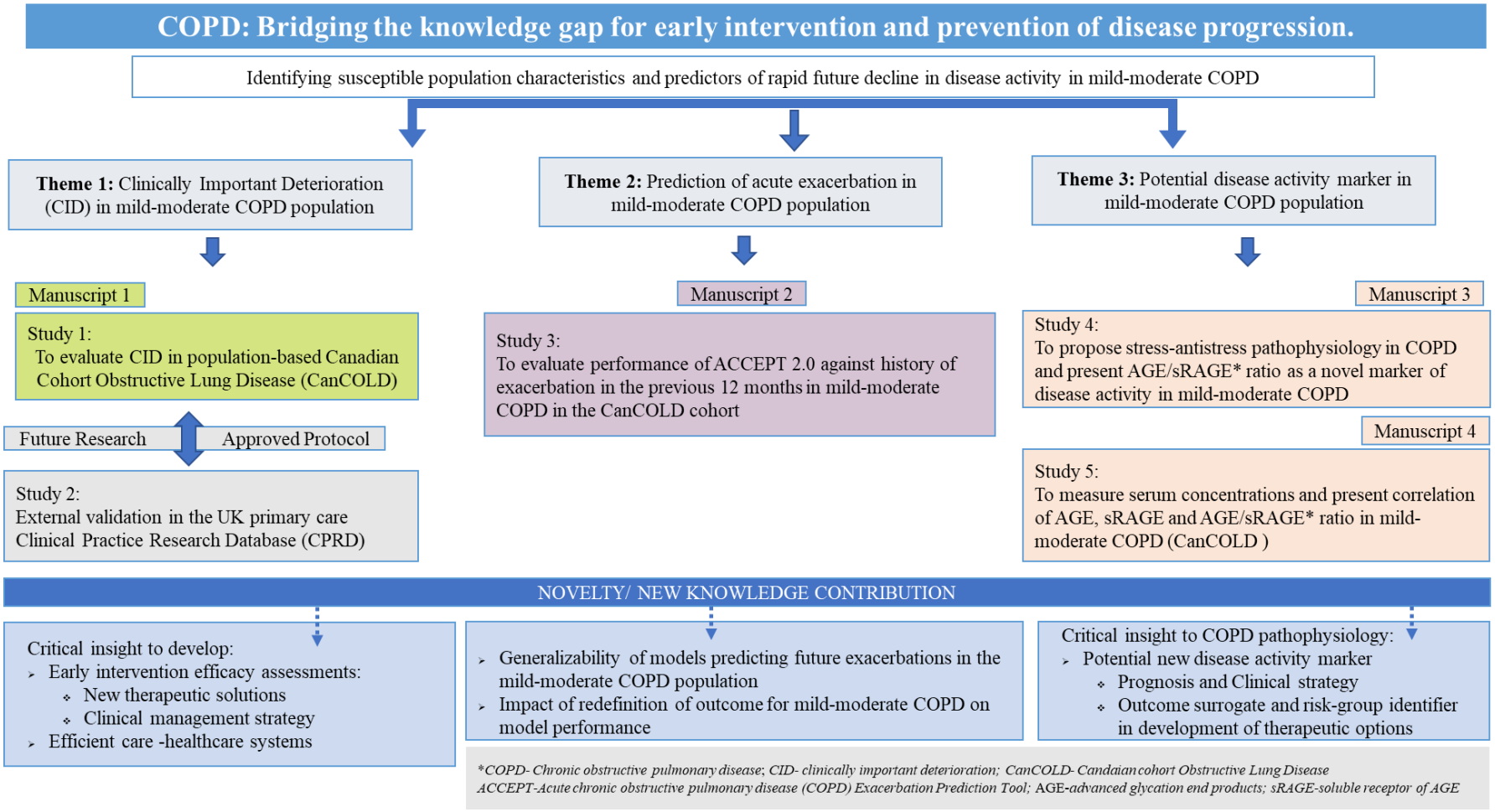


Figure 1: Schematic representation of research themes, studies undertaken under each, resultant manuscripts, and new knowledge contribution of this thesis.

Thesis structure

This thesis was developed to contribute new knowledge towards supporting efforts in personalized care in chronic obstructive pulmonary disease (COPD) aligned with a philosophy of early detection and intervention to prevent rapid decline. These efforts are multipronged and inclusive of, among others, a need for:

- identification of patients with COPD early on who are susceptible to experience rapid decline both in real-world and trial settings;
- identification and better characterize the validity of tools to indicate a clinically meaningful change in outcome that is clinically implementable for future treatment decision-making, which in trial settings can help assess the efficacy of investigational treatment;
- identification and exploration of new and informative biomarkers suitable in a patient population manifesting heterogeneity due to diversity of pathogenesis and influence of co-morbidities.

This thesis was designed to investigate a clinical tool, a risk prediction model, and a biomarker among those with mild-moderate COPD to support identifying and treating those likely to experience rapid decline in a primary care setting.

It is structured around three themes, encompassing five studies discussed in four manuscripts and one approved protocol, as seen in the diagrammatic representation above.

There are eight chapters in this thesis. In Chapter 1, I introduce the challenges and knowledge gaps in the context of mild-moderate COPD. In Chapter 2, I describe the rationale and overarching goal of the thesis with detailed research objectives. In Chapter 3, I present

contextual background information on the evolving understanding of COPD, highlighting recent additions and modifications of definitions, management strategies, clinical tools, and essential concepts such as disease progression and disease progression markers to summarise specific knowledge gaps. Chapter 4 discusses the data and analytical methods used to address the research questions.

In Chapter 5, I present the clinical tool, Clinically Important Deterioration (CID), and evaluate it in the mild-moderate COPD population of the Canadian Cohort of Obstructive Lung Disease (CanCOLD) study. Further, I present the study protocol approved to externally validate these findings in the United Kingdom (UK) primary care population. This is ongoing research emerging from this thesis. Chapter 6 is dedicated to presenting my assessment of the Acute COPD Exacerbation Prediction Tool (ACCEPT) 2.0, proposed to predict future exacerbation using the CanCOLD cohort data and summarising understanding of the generalizability of such models to mild-moderate COPD population. In Chapter 7, I propose the potential role of stress-antistress imbalance as captured through the ratio of Advanced Glycation End-products (AGE) over its soluble receptor (sRAGE) in the pathophysiology of COPD and discuss the ratio as a potential marker of disease activity in COPD. Following up the proposal of a novel marker, I measure the serum concentrations in a defined sub-cohort of the CanCOLD cohort and present correlations of the proposed novel marker, the AGE/sRAGE ratio, along with those of the biomarkers individually in the context of current literature. Finally, in Chapter 8, I summarize my findings from this thesis, discuss strengths and limitations, and implications for further research. I have obtained written permission from the copyright owner(s) for any tables or figures reproduced from published material. Obtained copyright clearances have been included in appendices.

Contribution to new knowledge

I am the sole author of this thesis. The manuscripts represent my original work. The studies on CID (a composite measure of deterioration used as a surrogate outcome as well as a predictor of future decline) and ACCEPT 2.0 (future exacerbation risk prediction model) in this thesis are the first ones to assess them, respectively, in population-based mild-moderate COPD population (reflective of primary care patient population). Findings suggest that the composite CID, as defined, is not applicable to the mild-moderate COPD population, though two of its components may be informative. A larger study is underway to reassess CID in a primary care population and examine new definitions of CID in this population.

In the study on ACCEPT 2.0, findings show that while the model discrimination accuracy is similar to those observed in the moderate-severe COPD cohorts, the model calibration has to be tuned to this population's profile. The findings from the ratio of serum AGE/sRAGE study conducted in a defined sub-cohort of CanCOLD is the first study, to our knowledge, to examine the serum levels of both biomarkers AGE and sRAGE in a population-based mild-moderate COPD cohort. Due to the carefully selected healthy control group, this study shows that AGE/sRAGE can be a new biomarker for mild-moderate COPD.

The studies in this thesis add to the existing knowledge of COPD populations by including observations from mild-moderate COPD in the continuum of information available from more severe COPD populations.

This thesis submission has been approved by my supervisor.

1. Introduction

Globally, non-communicable diseases (NCDs) contribute to 41 million deaths annually (74% of deaths) and over 61% of total disability-adjusted life years (DALYs) [1, 2]. The World Health Organization (WHO) Noncommunicable diseases fact sheet September 2022 reports chronic respiratory diseases [such as Chronic Obstructive Pulmonary Disease (COPD)] as the third (out of four) leading cause of annual mortality (4.1 million) globally, after cardiovascular diseases (17.9 million) and cancer (9.3 million) and is followed by diabetes (2.0 million; includes kidney disease deaths caused by diabetes) as the fourth contributor. In Canada, COPD is currently a leading cause of hospitalization [3] and is associated with a significant healthcare cost burden [4].

Cloaked under the seemingly benign term of ‘Chronic Obstructive Pulmonary Disease,’ or simply put ‘long-term lung problem,’ COPD is a rather complex progressive respiratory disorder with a diverse underlying pathophysiology (“endotypes”) encompassing emphysema, chronic bronchitis, and small airway disease. Patients with COPD experience increasing breathlessness and cough due to airflow obstruction arising from either damaged or destroyed small airways and alveoli, while they are increasingly susceptible to infections and periodic ‘crisis’ episodes of severe worsening or ‘lung attacks’ often requiring treatment or hospitalization. These ‘lung attack’ events, referred to as exacerbations, have a significant deleterious effect on prognosis associated with an accelerated annual loss of lung function, worsening health status, and increased mortality [5].

While the diagnosis of COPD relies on lung function assessment via spirometry, the extent of post-bronchodilator airflow obstruction present contributes to the determination not only of the diagnosis but also of disease severity and management plan where the current treatment strategy is guided by symptom burden and the risk of COPD exacerbations. This is mainly because most of the recent randomized clinical trials have enrolled patients based on the severity of their airflow obstruction and the burden of worsening symptoms and previous exacerbations [6,7]. A diverse underlying pathophysiology is responsible for the significant heterogeneity in the observed presentation and progression of the disease, which has led to the establishment of "phenotypes" and "treatable traits" of COPD to guide patient care of this currently 'not completely reversible' condition [8]. Therapy aims to use this treatable trait approach towards a more personalized treatment plan [9].

Given the heterogeneity, a working definition for exacerbation in COPD is a sustained worsening of the patient's condition from the stable state, beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD. The 2023 GOLD report refines the definition to "an event characterized by dyspnea and/or cough and sputum that worsen over ≤14 days, which may be accompanied by tachypnea and/or tachycardia and is often associated with increased local and systemic inflammation caused by airway infection, pollution, or other insult to the airways" [9].

The evolving understanding of disease pathogenesis is another area through which emerging knowledge has impacted clinical practice. Though tobacco smoking, traditionally and still, continues to be recognized as the major risk factor [10-12], it is also documented that only an estimated 10%–20% of chronic heavy smokers go on to develop symptomatic COPD [13,14]. Smoking cessation has been integral to COPD care management since the '90s, alongside a

persistent investigation of the natural history of COPD given that about 25% - 45% of COPD patients have never smoked [15], a significant proportion (80%) of the non-smoker patient population are women [14] and even among smokers, women have demonstrated compelling differences in disease trajectories compared to the men [16,17]. Studies in lower- and middle-income countries have helped the understanding of other significant risks, such as significant exposure to noxious particles or gases, e.g., ambient pollution [18,19] and biomass exposure [20-23]. Scientific investigations have also revealed that host factors, including genetic variations associated with lung function and COPD susceptibility [15,24,25], contribute to heterogeneity alongside abnormal lung development [26,27].

Significant comorbidities may also influence the progression, impacting morbidity and mortality toll of this condition [28]. The 2022 World Lung Day report from the Forum of International Respiratory Societies (FIRS) estimates COPD to be affecting over 200 million individuals (reported figures range from 212–392 million [29-31]) and accounting for about 3.2 million deaths each year, making COPD by itself the third leading cause of death globally [32-35]. Further, COPD patients have shown a higher incidence of early vascular disease compared to smokers without COPD and non-smokers [36]. About 1 % of COPD patients develop lung cancer annually [37], with evidence suggesting that COPD patients are more likely to develop lung cancer compared to current or former smokers with normal pulmonary function [38]. It is anticipated that COPD will be the potential leading cause of mortality globally over the next decade [39].

Currently, COPD patients come to be identified and managed at advanced stages and ages when these patients have often developed other chronic health conditions, thus requiring resource-intensive management on all fronts. The Conference Board of Canada estimates the combined

direct and indirect annual costs of COPD to increase 140% from $4 billion in 2010 to around $9.5 billion by 2030 [40]. While the estimated figures are significant, these are likely conservative given the prevalent undiscovered COPD patient population who continue to deal with their increasing lung crisis in silence. Several observations have been documented indicative of this, such as an estimated undiagnosed population of 70% of mild and moderate symptomatic COPD patients [41]; lack of consistent use of spirometry even among the at-risk populations given its use reported only in 30%-50% of diagnosed cases [42]; attribution of illness and mortality to other comorbidities like pneumonia in older adults [43], etc. At the 2022 European Respiratory Society Congress [44], it was announced that the real-world prevalence of COPD is likely 22–126% higher than today's most cited estimates (i.e., over 480 million), and by 2050, the prevalence is expected to reach 592- 645.6 million according to Boers et al.

This discussion makes a strong case in favor of urgent guidelines for active screening programs for COPD to enable the detection of patients before they suffer severe airflow obstruction and symptoms. The interest of clinicians and the population to suspect and detect COPD needs to be supported by new knowledge allowing the identification of COPD patients who, while experiencing mild airflow obstruction and/ or symptoms, are susceptible to disease progression to guide decision algorithms and interventions with the potential to alter clinical outcomes. Currently, studies of interventions to prevent disease progression are primarily concentrated in clinical cohorts of moderate to very severe disease [45,46], with poor representation of sub-groups with mild airflow obstruction and symptoms found in the general population attached to primary care setups [41]. However, the growing body of evidence from current efforts has led to the redefinition of our understanding of COPD and the continuum of heterogeneity, thus highlighting the gaps in early engagement strategies for an integrated management approach

exploring beyond the older population and smoking as a risk factor [47]. The criticality of a 'heart attack' is not lost on anyone, given the awareness among clinicians and the general population, supported by well-studied care management algorithms, therapeutics, and holistic health discussions surrounding it. At the same time, the same cannot be said about a 'lung attack' [48].

In view of the advancements in understanding the natural history, therapeutics, and non-pharmacological interventions, it is essential to investigate the mild-moderate COPD population to identify characteristics of those susceptible to rapid decline from their baseline with the intention to later study disease modulation interventions, allowing change the current practice with timely interventions to arrest the deterioration. Knowledge of such characteristics will help bridge some of the pressing yet existing gaps (in other words, 'imminent opportunities') which will have multipronged implications in supporting the efforts to surmount the evident COPD challenge. Primarily, this will lead to well defined study cohort and endpoint definitions to support the development of therapeutics and treatment guidelines oriented for these susceptible groups. Secondly, this will help develop clinical prediction tools [49,50] applicable to the mild-moderate COPD population to support clinicians in monitoring and planning care management effectively, given the evidence supporting the benefits of preventing acute exacerbation on disease progression, especially in this population [51]. This thesis aims to address both these 'imminent opportunities' to address the challenges of COPD. Undertakings such as this encourage further research to develop the refinements necessary for an early preventative personalized care approach for a heterogeneous condition such as COPD.

2. Thesis Goal and Research Objectives

The **overarching goal** of this work is to contribute knowledge toward the identification of characteristics of mild-moderate COPD patients susceptible to disease progression. This is approached as follows in the present thesis:

A. To assess in a cohort of mild-moderate COPD patients drawn from the general population and/or family medicine practice, the generalizability of the currently proposed tools in identifying those at risk of disease progression:
    i. Clinically important deteriorations (CIDs)
    ii. Acute chronic obstructive pulmonary disease (COPD) Exacerbation Prediction Tool (ACCEPT) 2.0

F. To identify a potentially suitable primary care cohort and design a study proposal to validate CID findings from the population-based cohort.

F. To assess the role of emerging risk factors in refining the application of these tools in this population.

F. To propose a novel potential disease activity biomarker in COPD, an indicator of the overall stress-antistress balance, and evaluate it in this mild-moderate COPD cohort.

Based on this, the thesis is divided into the following 3 themes, and listed below are their respective study objectives:

Research Theme 1: Clinically Important Deterioration (CID) in mild-moderate COPD population

Study 1 Objective

Original study using the population-based cohort CanCOLD

Primary objective:

To assess the currently defined short-term CID as an indicator of disease and dyspnea worsening in the following similar short-term period in a population-based mild-moderate COPD from cohort.

Secondary objective:

- To assess the impact of including comorbidity (any cardiovascular disease) and biomarkers (absolute eosinophil count, C-reactive protein (CRP), and fibrinogen) in the models with CID adjusted for age, sex, BMI, and smoking pack-years.

Exploratory objective:

- To assess for existing sub-groups by examining the differences in trajectories of lung function deterioration over 3 years for potential clues for identification of rapid decliners.

Study 2

Original proposal/study protocol-accepted funding and approved by CPRD for data access

Primary objective:

To determine whether the short-term CID, as currently defined in the literature, is a predictor of medium and long-term outcomes (FEV1, MRC score, CAT score, and exacerbations) in mild-

moderate COPD patients by replicating population-based CanCOLD cohort in the external validation general practice CPRD cohort.

Secondary objective:

To assess the current definition of CID in mild-moderate COPD subjects from a population-based sample in CanCOLD compared to a convenient sample in a family medicine practice (CPRD-derived clinical cohort).

Research Theme 2: Prediction of acute exacerbation in mild-moderate COPD population

Study 3 Objective:

Original study using the population-based CanCOLD study cohort

Primary objective:

To assess ACCEPT 2.0 model performance in the population-based longitudinal cohort of CanCOLD compared to a history of exacerbation alone in the preceding 12 months.

Research Theme 3: Search for a potential marker of disease activity in COPD- a novel biomarker index

Study 4 Objective

Comprehensive literature review

To propose the stress-antistress index, the ratio of Advanced glycation end products (AGE) over its soluble receptor (sRAGE), as a novel potential marker of disease activity among COPD patients with multiple comorbidities.

Study 5 Objective:

Original study using a defined sub-cohort of the population-based CanCOLD study cohort

Primary objective:

To describe the biomarkers, AGE,sRAGE, and their ratio AGE/sRAGE, and their respective correlations as observed in a defined sub-cohort of the CanCOLD largely comprised of participants with mild-moderate COPD reflective of the primary-care patient population.

3. Background

This chapter presents an overview of the concepts and definitions important to the thesis research, which will lay the groundwork for the evolving understanding of COPD, the growing understanding of the need for personalized treatment approach in the heterogenous disease population with a growing sense of a need to shift to early intervention, making rapid deterioration susceptible patient group in the mild-moderate COPD population of interest. However, studies are predominantly available in the moderate-severe clinical COPD population. The concepts and definitions elaborated in the sections below dovetail into a systematic discussion leading to the identification of the gaps, such as biomarkers of disease activity and clinical tools for exacerbation risk assessment, that need to be addressed to support primary care/family medicine physicians assess disease progression and tailor suitable management plan.

The following sections start with COPD and the current understanding of its pathophysiology; courses through recent definitions surrounding concepts of *early* relative to age, to disease process and disease activity; finally discuss the evolution of treatment strategy; and clinical tools and markers needed for a personalized care approach leading to the summarisation of the knowledge gaps identified that this thesis addresses.

3.1 Recent updates

3.1.1 Recent refinement of definitions

A. Chronic Obstructive Pulmonary Disease (COPD)

Chronic Obstructive Pulmonary Disease (COPD) is a progressive respiratory disorder where patients experience cough and increasing breathlessness due to airflow obstruction arising from either damaged or destroyed small airways and alveoli. 'COPD' is an umbrella term for a complex condition and diverse underlying pathophysiology encompassing emphysema, chronic bronchitis, and small airway disease with airflow obstruction, adding to the natural age-related pulmonary decline [13, 52]. Patients suffering from COPD not only experience increasing breathlessness, but they are also increasingly susceptible to infections and periodic exacerbations, which interfere with their ability to perform activities of daily living and contribute to a subsequent reduction in health-related quality of life.

The term "COPD" came to be used for a chronic lung condition from obstruction of airflow and marked by cough and mucus production around the mid-1900s. This condition had already been discussed in one form or another dating back to 1679 in the references of "voluminous lungs" by physician Théophile Bonet [53] and nearly a century later in the mentions of "turgid" lungs from anatomist Giovanni Morgagni [54]. Around the early 1800s, observations of emphysema and bronchitis as components of this debilitating condition had already started being recorded with references to air pollution and genetic factors as important causal factors. However, these causes were soon replaced by smoking as it became a socially popular recreational practice. Ever since smoking was identified as the pivotal risk factor for COPD, smoking cessation has been the most

important and powerful armament in the arsenal of modern COPD treatment and mitigation strategies [10]. However, over the years, with data from studies across the globe, the importance of air pollution and genetic (and developmental) mechanisms for COPD are now well established and are in focus to uncover the heterogeneity observed among COPD patients as the search for curative and restorative solutions, imminent though seemingly obscure presently, continues.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) Science Committee, composed of leading scientific minds in the field globally, reviews published research literature in the areas of COPD management and prevention to compile and update recommendations in their annual Global Strategy for the Diagnosis, Management, and Prevention of COPD report. The committee incorporated major revisions towards their 2023 report [9] in view of the evolving understanding of COPD and strategies to manage this complex condition where treatment is currently limited by a lack of curative options [55,56].

The definition of COPD has evolved over the years [57,58], and the latest interpretation in the 2023 GOLD report defines COPD as "a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, expectoration, exacerbations) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction" [9].

The GOLD committee, in its 2023 report, recognizes the need and has expanded the taxonomy (classification) of COPD to highlight the importance of etiologic contributors, other than cigarette smoking, which determines the pathogenetic processes leading to the heterogeneity in the clinical presentations of COPD, or the types (*'etioypes'*) of COPD.

B. Proposed Taxonomy (Etiotypes) for COPD

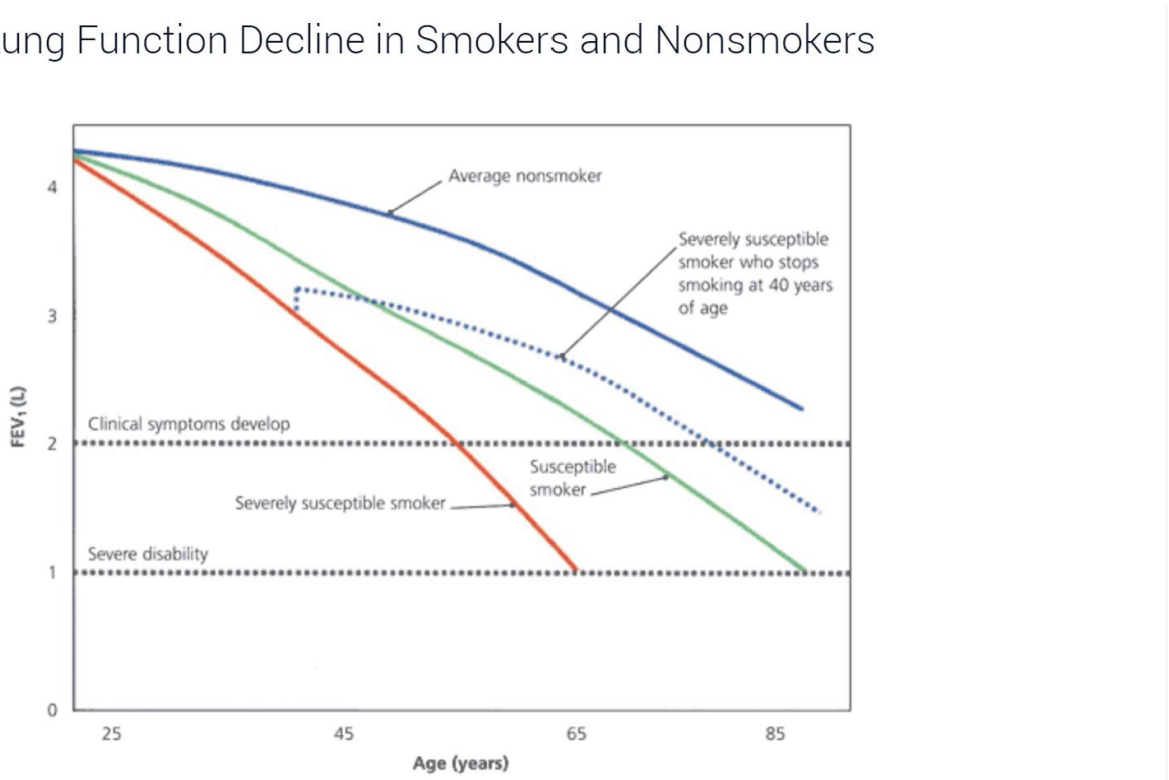
The 2023 GOLD report lays out a detailed account of other risk factors that have emerged through scientific rigor in the proposed expanded taxonomy of COPD, inclusive of non-smoking etiology-related types (etiotypes) of COPD to guide future explorations of management strategies and research in therapy-based on etiotypes. Table 1 shows the types included in the GOLD report as well as other types that have been reported.

Table 1: Proposed Taxonomy (etiotypes) of COPD

Classification	Description	Reference
Genetically determined COPD (COPD-G)	Alpha-1-antitrypsin deficiency (AATD) Other genetic variants with smaller effects acting in combination	GOLD 2023 report
COPD Due to Abnormal Lung Development (COPD-D)	Early life events, including premature births and low birth weight, among others	GOLD 2023 report
Environmental COPD		
Cigarette smoking COPD (COPD-C)	Exposure to tobacco smoke, including in utero/ via passive smoking, Vaping/ e-cigarette use, and/ or Cannabis	GOLD 2023 report
Biomass and pollution exposure COPD (COPD-P)	Exposure to household pollution, ambient air pollution, wildfire smoke, occupational hazards	GOLD 2023 report
COPD Due to Infections (COPD-I)	Childhood infections, tuberculosis-associated COPD, HIV-associated COPD	GOLD 2023 report
COPD and Asthma (COPD-A)	Particularly childhood asthma	GOLD 2023 report
COPD of Unknown Cause (COPD-U)		GOLD 2023 report
COPD of Mixed Causes (COPD-M)	*Presence of several causal factors*	*Celli B.et al. Definition and Nomenclature of Chronic Obstructive Pulmonary Disease: Time for Its Revision. Am J Respir Crit Care Med. 2022 Dec 1;206(11):1317-1325.*

C. Understanding 'early intervention' in COPD

Traditionally, COPD has been regarded as an illness of the elderly since it is often diagnosed at severe stages among elderly patients presenting to the hospital with a 'lung attack' or from their comorbidities. Building on Fletcher and Peto's work [10] on the trajectories of lung function loss in COPD (Figure1) [10] and recognizing that smoking-related changes may be attributed to a subpopulation of susceptible smokers, Dewar et al. discuss various trajectories corresponding to the impact of cigarette smoke on lung function at various stages. Martinez et al. refer to work from Rennard et al. and discuss unentangling the impacts of individual contributors, such as genetic predisposition, passive exposure at fetal and developmental stages, adult exposure alongside environmental contributors, and interplay of comorbidities, would be difficult at this stage, they propose studying those under the age of 50 years for a perspective of 'early' intervention strategies to arrest progression before irreversible damage occurs [59, 60].



The natural history of lung function decline. Smokers who are susceptible to lung injury experience an increase in the rate of age-related loss in FEV1 compared with nonsmokers (red, green, and blue lines). After lung function declines to threshold levels, clinical symptoms develop (black dotted lines). When a smoker stops smoking, the rate of FEV1 loss again approximates to that of a nonsmoker (blue dotted line). (FEV1 = forced expiratory volume in one second.)

Figure 1: Lung function decline trajectories

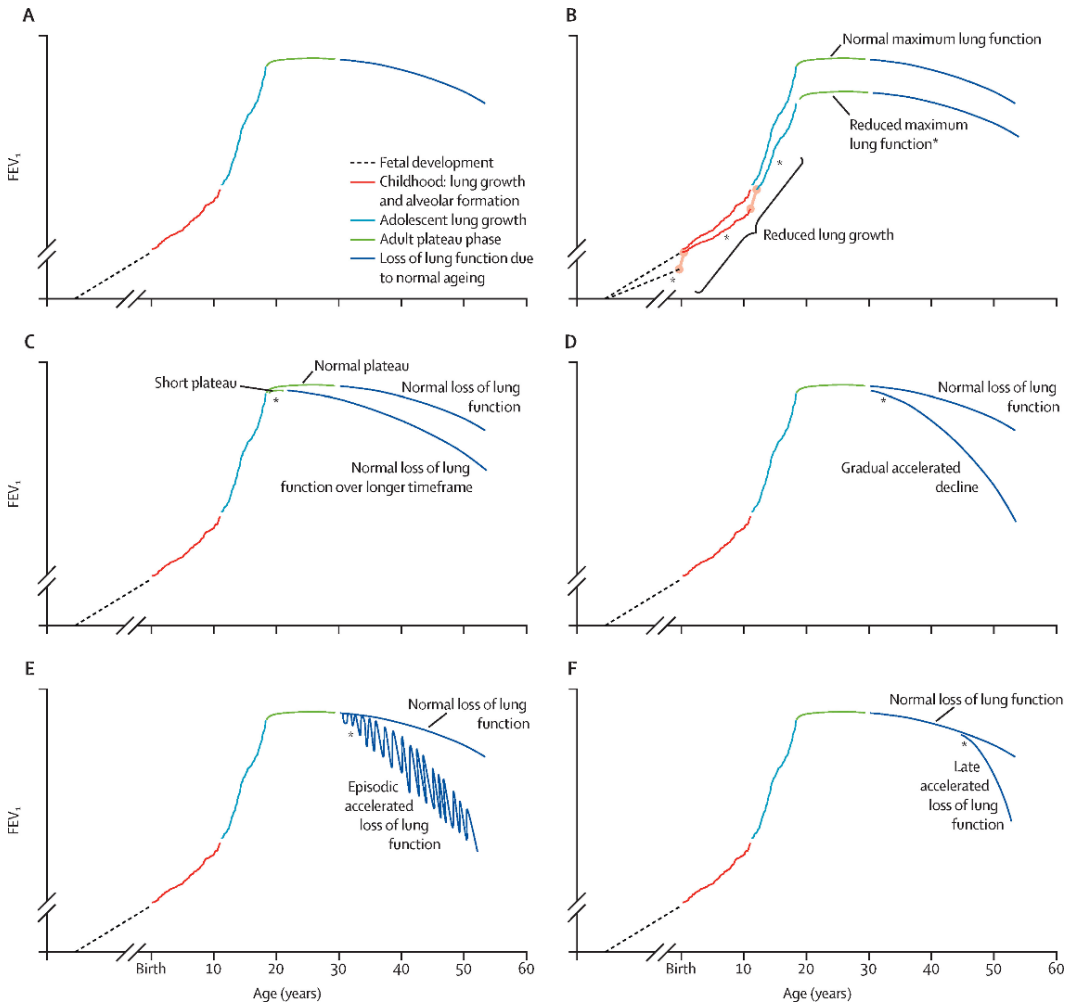


Figure 2. Trajectory of lung function loss and development of chronic obstructive pulmonary disease

(A) Normal lung function trajectory. (B) Reduced lung growth during fetal development, childhood, or adolescence (which might be independent), any of which can reduce attained lung function. (C) Shortened plateau. (D) Accelerated lung function loss during adulthood. (E) Episodic loss of lung function without full recovery. (F) Late accelerated loss of lung function. FEV_1=forced expiratory volume in 1 s. *Presence of early disease for each disease natural history.

In order to design studies to investigate interventions to arrest disease progression before irreversibility sets in or reverse changes, it is important to define 'early disease.' While based on

the degree of airflow obstruction, levels of severity have been defined as mild, moderate, severe, and very severe COPD; however, there has been a growing need to arrive at a consensus around the definition of 'early disease.' An evolved understanding of COPD has developed beyond seeing COPD as an incompletely reversible respiratory obstruction in the elderly attained through an accelerated adult decline of lung function brought about by cigarette smoking. It is now known that there are other subgroups of COPD patients who failed to reach normal lung function in early adulthood and then succumbed to age-related decline [61] and that smoking cessation, when initiated early enough, can result not only in symptom relief but could also bring about a slowing of the rate of decline to the extent of even returning lung functions to age-expected levels [62]. Thus, in their 2023 report, GOLD proposed definitions for 'early' and 'young' as well as 'pre-COPD' and 'PRISm' to clearly distinguish between the terms and facilitate further research.

Table 2: Defining "early" vs. "young" COPD

Mild-COPD	Early-COPD	Young-COPD
Based on spirometry indicates the severity of airflow obstruction	Early, based on biological chronology and not to be confused with clinical symptom manifestation chronology.	Based on the age of the patient, 20-50 years (against traditional COPD described mostly in the elderly aged 60 years or older).

Table 3: Defining "Pre-COPD" vs. "PRISm"

Mild-COPD *COPD-mild severity*	Pre-COPD *Pre-disease stage*	PRISm *Preserved Ratio Impaired Spirometry*
Based on post-bronchodilator forced spirometry indicates the presence of airflow obstruction (FEV1/FVC ratio< 0.7) to meet the diagnostic threshold for COPD.	Based on the presence of respiratory symptoms in the absence of airflow obstruction on forced spirometry with/without structural and/or functional abnormalities in individuals of any age.	Based on post-bronchodilator spirometry, there is impairment indicated by FEV1<80% but no indication of obstruction on forced spirometry.
May/may not progress to greater severity of COPD	May/ may not progress to develop COPD	May/ may not progress to develop COPD

FEV1: forced expiratory volume in 1 second; FVC: Forced Vital Capacity

i. 'Early' COPD

The 2023 GOLD and subsequent GOLD report highlights that COPD can start very early in life and continue to progress sub-clinically via various underlying pathways, to eventually lead to the manifestation of clinical symptoms with spirometrically observable airway obstruction in some while not producing clinical symptoms and/or airway obstruction in other, thus making understanding these processes "near the beginning" of the disease process critical to early intervention strategies [9].

ii. 'Mild' COPD

'Mild' refers to post-bronchodilator spirometrically observable airway obstruction of mild severity, or GOLD 1 as described in Table-4 [FEV1/FEV ratio < 0.7 with an FEV1 level ≥80% of the predicted level for sex, height, and age].

Table 4: GOLD 2025 report-based COPD severity grades

GOLD Grades for COPD	Severity of airflow obstruction	Post- bronchodilator spirometry-based criteria
GOLD 1	Mild	FEV1 ≥80% predicted
GOLD 2	Moderate	loss ≤FEV1 <80% predicted
GOLD 3	Severe	30% ≤FEV1 <50% predicted
GOLD 4	Very Severe	FEV1 < 30% predicted

Ref: Global Initiative for Chronic Obstructive Lung Disease. Global strategy for prevention, diagnosis, and management of chronic obstructive pulmonary disease 2025 report. chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://goldcopd.org/wp-content/uploads/2024/11/GOLD-2025-Report-v1.0-15Nov2024_WMV.pdf. Accessed November 24, 2024.

iii. PRISm

Post bronchodilator spirometry in individuals, often current and former smokers, may reveal an FEV1 that is <80% of that predicted for their sex, height, and age; however, they do not satisfy

the COPD diagnosis criteria of airflow obstruction (FEV1/FEV ratio < 0.7) [62, 63]. Hence, they are classified as those with Preserved Ratio Impaired Spirometry, or PRISm. This is an important group, with a reported prevalence of 7%- 20% [64]. Though not considered as having COPD, they are recommended to be considered as 'patients' since they may present symptoms and/or functional and/or structural abnormalities remaining susceptible to transition to normal or obstructed spirometry with time [62, 63]. This group presents an immense opportunity to study pathogenesis and investigate therapeutic interventions [62, 63].

3.1.2 Recent refinement of management strategy guidelines

A. Screening and Case-finding: 'Young' COPD and 'Pre-COPD'

The initiation point along the pathogenetic pathway is critical for a disease-modifying intervention to render optimal outcomes, e.g., smoking cessation, and its impact on the annual rate of FEV1 decline [65,66]. For preventative approaches, the pre-disease stage is a potential target point.

In an attempt, a category of those "at-risk" was defined as a pre-disease stage classified as COPD-0 in the GOLD 2001 report and later abandoned since most patients that belonged to this group were found not to progress to a diagnosis of COPD [67]. COPD-0 was aimed at those considered at high risk of progressing to a diagnosis of COPD and was defined to include those exposed to risk factors, such as cigarette smoke, experiencing respiratory symptoms like cough and sputum or exertional dyspnea [68].

The existence of a pre-disease stage in COPD is not only highly probable; cohorts such as the CanCOLD, COPDGene, and the SubPopulations and InteRmediate Outcome Measures In COPD Study (SPIROMICS) have demonstrated the existence of a group of individuals who were prescribed bronchodilators or inhaled corticosteroids likely in view of their symptom burden though they could not be diagnosed as COPD [69].

In view of the growing body of knowledge, GOLD, in the 2023 report, re-introduced a pre-disease stage, which is not heavily dependent on symptoms alone, “Pre-COPD” defined as “individuals of any age who have respiratory symptoms and/or other detectable structural and/or functional abnormalities, in the absence of airflow obstruction on forced spirometry”. GOLD recognizes that such individuals may/may not progress to develop COPD [69] and echoes the publications highlighting a need for further research and RCTs in this group [70]. Figure 3 depicts the proposed conceptualization of pre-COPD by authors Han et al.

A recent study estimated a prevalence of 22.3% and observed that those with pre-COPD patients were comprised largely of younger females with similar symptoms and comorbidity burdens as those with COPD while with lower proportions of smokers/ ex-smokers. However, they demonstrated spirometric parameters, history of asthma, use of respiratory medication, and blood eosinophil counts similar to those without COPD [71]

“Young COPD” is another term introduced in the GOLD 2023 report. As the name suggests, this group is based on chronological age, for those with COPD aged between 20 and 50 years. These individuals represent those with the onset of COPD early in life, often reported to have existing

family history of respiratory diseases and/or hospitalization/events needing medical attention as early as before the age of 5 years [72]

This group, with an estimated prevalence of 6%, has been reported to be comprised of largely current/former smoking males with higher symptoms and comorbidity burden compared to those without COPD, including pre-COPD. They may report a history of asthma and have higher eosinophil count. These individuals demonstrated similar airflow limitation, symptoms, and exacerbation burden as those with COPD despite better exercise capacity [71].

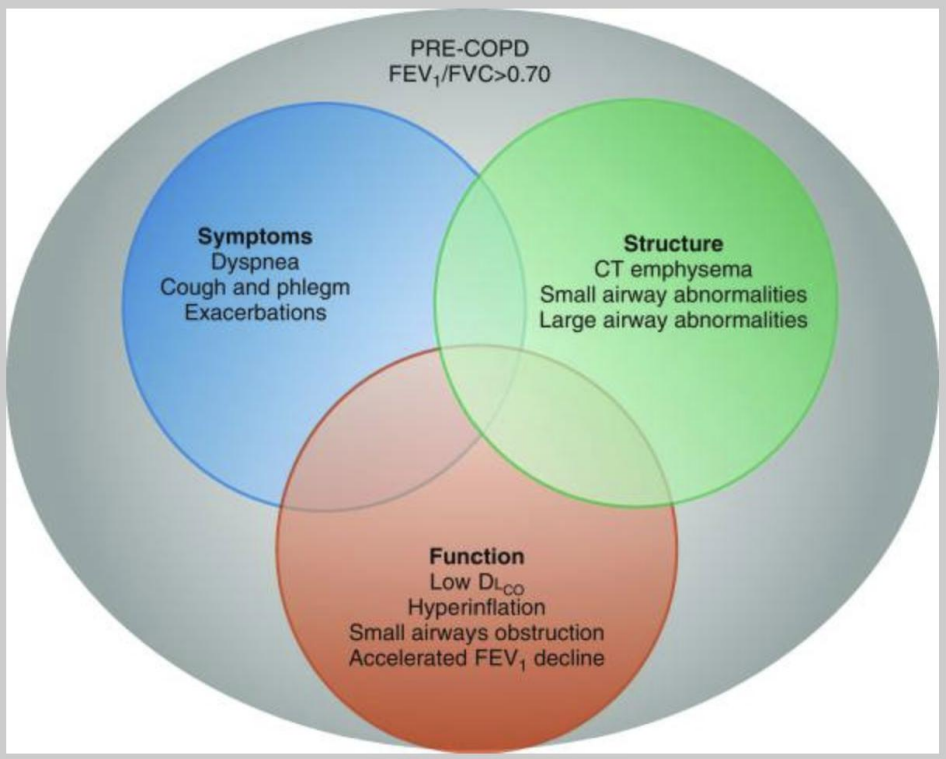


Figure 3: Conceptualized understanding of the relationships among symptoms, structure, and function with respect to pre-COPD.

COPD = chronic obstructive pulmonary disease; CT = computed tomography.

The heterogeneity in onset and progress challenge of COPD aside, even when patients may be symptomatic, they may associate these with simply aging and fitness level or smoking, thus failing to report these [73] while these symptoms cause them to suffer in silence as they cope with their impacts on activities of daily living reducing quality of life experience [74]. Thus making these individuals susceptible to social isolation and deconditioning with adverse impacts on their mood and mental health [75,76]. Studies have reported that even among those suffering mild airway obstruction and experiencing symptoms, due to the non-specific nature of these symptoms, even during exacerbation events, they may go undiagnosed as COPD [77] and rather be diagnosed with respiratory tract infection and treated accordingly. Lung function decline is well documented in mild COPD [5, 78] and is most pronounced during this early disease severity period in a COPD patient's disease journey [79]. These may well appear to stress the need for population screening; however, a targeted case finding is recommended currently, in view of current definitions and unique challenges of COPD (e.g., poor perception of one's symptom burden; negative screening findings sending a misleading message to smokers; treatment side-effects from a blanket approach especially that though there are therapeutics in COPD, these are not for aimed at early and/or milder severity stages, etc.) [80].

B. ABE-Assessment Tool and Implication on Initial Intervention (pharmacological)

Treatment initiation and management of COPD patients was largely guided by a cumulative consideration of spirometry-guided assessment of airflow limitation; patient-reported symptom burden assessed using the modified Medical Research (mMRC) questionnaire [81] or the COPD

Assessment Test (CAT) questionnaire [82]; and the frequency of previous exacerbations. Given the heterogeneity of COPD patients, spirometry is currently recommended to diagnose patients, thus making recommendations to support clinicians personalizing individual scenarios as against a blanket approach [9]. Cognizant of the importance of exacerbation in the trajectory of COPD patients, GOLD 2023 recommendation has proposed categories A, B, and E [Figure 4] by combining erstwhile categories C and D proposed in their 2017 report [Figure 5]. Category E is now proposed to include all COPD patients who have experienced 2 or more moderate exacerbations or a severe exacerbation requiring hospitalization, irrespective of their symptom burden. Previously, category C included individuals reporting symptoms scored as 0-1 using mMRC or less than 10 using CAT and considered less symptom high risk; and category D included individuals reporting symptoms scored as 2 and higher using mMRC or 10 and higher using CAT, considered more symptoms high risk while category A included those with mMRC score 0-1 and CAT <10 (considered less symptom low risk) and category B included those with mMRC score of 10 or higher and CAT score of 10 or higher (considered more symptoms low risk). The 2017 classification takes a combined approach using exacerbation history and symptoms while spirometry was recommended for use in diagnosing and consideration in prognostication and care management planning. The 2017 classification was a revised version of their 2011 classification [Figure 5], which was a triad approach including measurement of airflow limitation (based on FEV1 % predicted) towards the determination of the patient-group. The GOLD report has revised its recommendations for pharmacological intervention initiation to correspond to the latest ABE assessment tool [Figure 6].

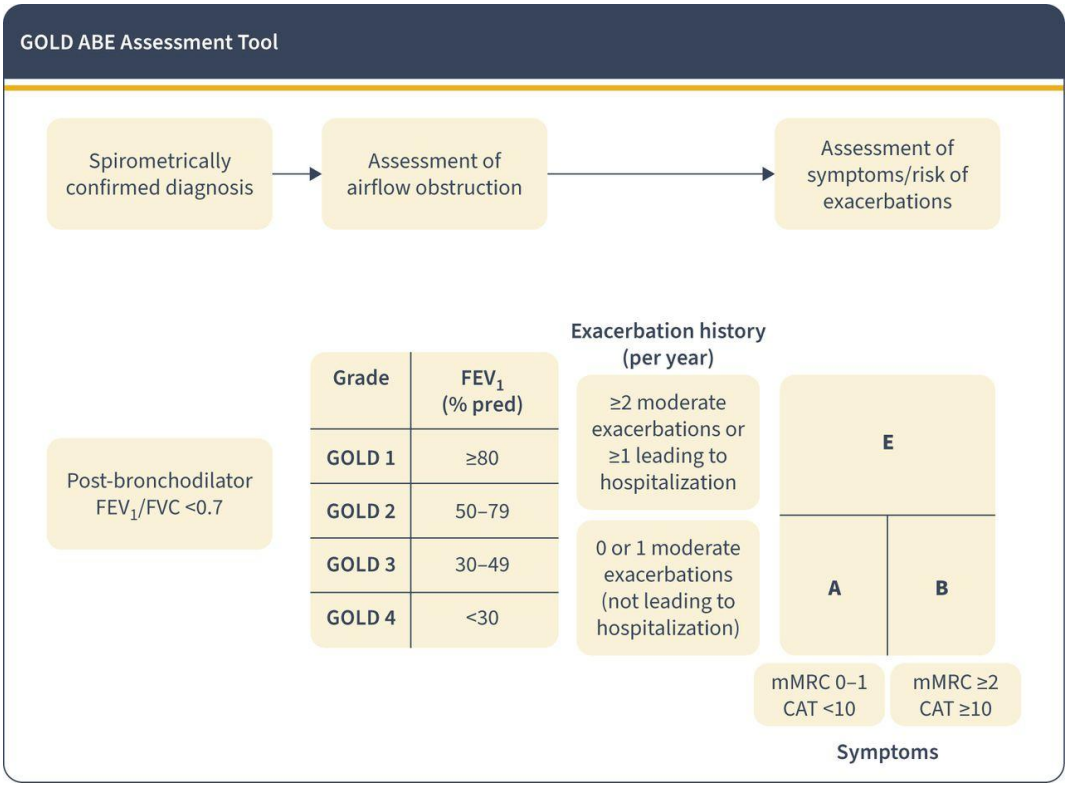


Figure 4: GOLD ABE assessment tool.

Exacerbation history refers to exacerbations suffered the previous year.

mMRC: modified Medical Research Council Dyspnea Questionnaire; CAT: COPD Assessment Test; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity.

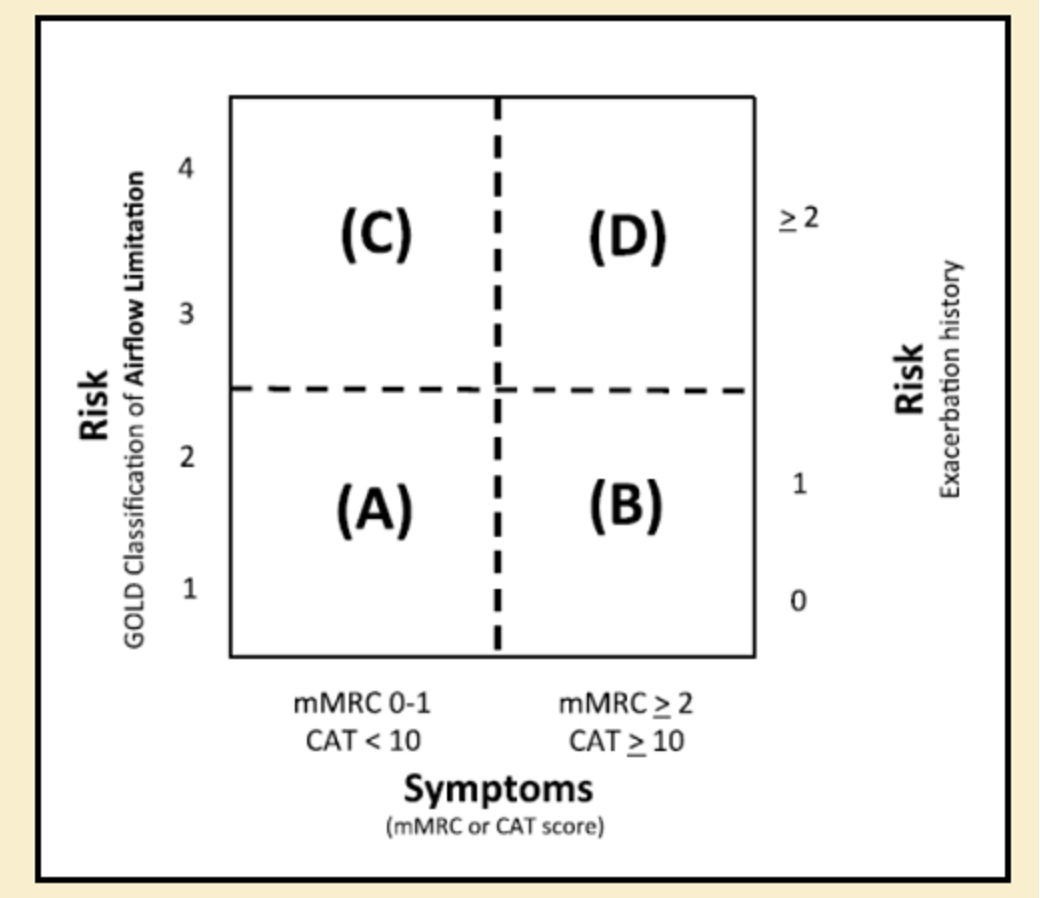


Figure 5: Combined COPD assessment.

Choose the highest risk according to GOLD spirometric grade or exacerbation history when assessing risk.

 Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, Barnes PJ, Fabbri LM, Martinez FJ, Nishimura M, Stockley RA, Sin DD, Rodriguez-Roisin R. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2013 Feb 15;187(4):347-65. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society.

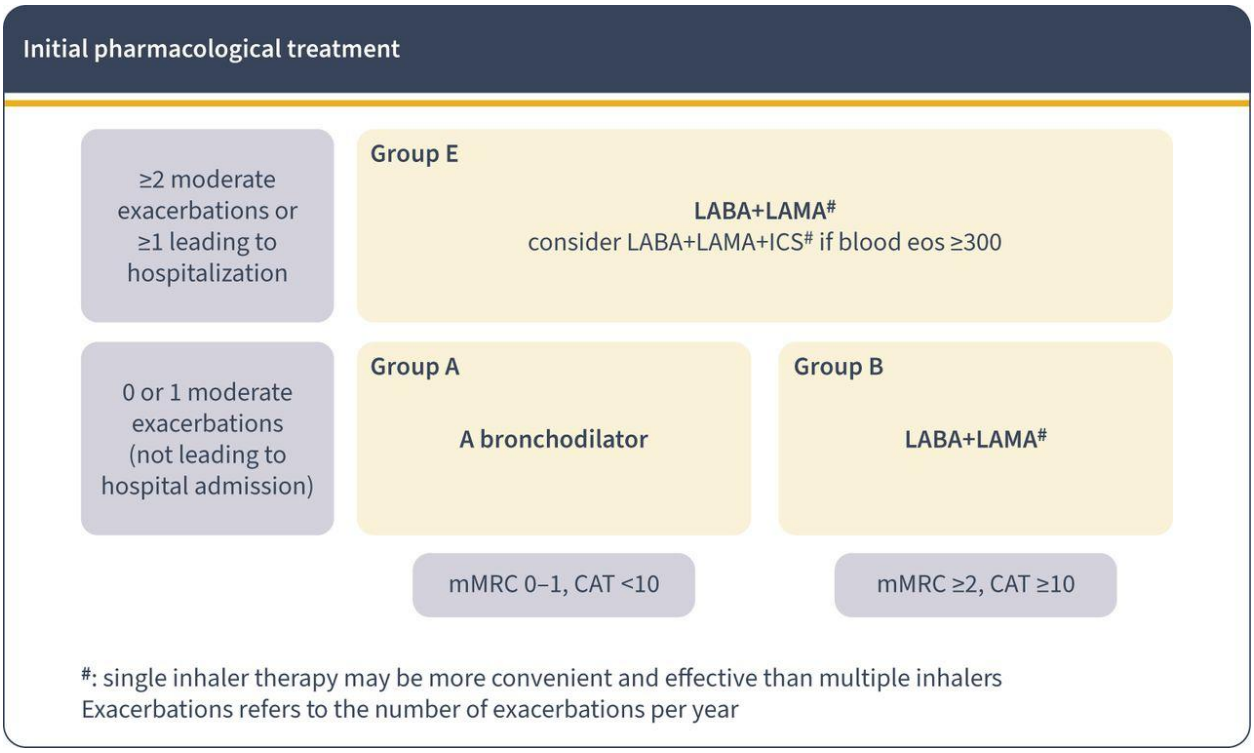


Figure 6: Initial pharmacological treatment.

mMRC: modified Medical Research Council Dyspnea Questionnaire; CAT: COPD Assessment Test; LAMA: long-acting anti-muscarinic antagonist; LABA: long-acting β2 receptor agonist; ICS: inhaled corticosteroid; eos: eosinophils.

3.1.3 Important concepts

A. Disease 'Severity' vs Disease 'Activity' in COPD

It is integral to distinguish and understand the differences between disease *'activity'* and *'severity'* in COPD since individuals on similar pathological pathways manifest across a spectrum clinically while those manifesting similar symptoms at a point in time may be progressing along diverse pathological pathways thus presenting different susceptibilities to future deterioration [83,84].

Disease 'activity' is a cross-sectional assessment of the state of the ongoing underlying pathological process. Whereas disease 'severity' indicates the resultant organ damage as a fall-out of the ongoing pathological process. Thus, with the knowledge trajectories of FEV1 and FVC in healthy individuals, FVC being age-dependent, has a similar effect on the ratio of FEV1/FVC (airflow obstruction), such that at ages corresponding to a smaller value, a significant fall in the value of the ratio is expected [85]. Also, the rate of changes in FEV1 with age is non-linear, and even in the presence of a constant disease activity, may manifest the relation [86,87]. While understanding the pathological processes and indicators of organ damage are of research and clinical interest to develop better care strategies, the burden of the disease is its 'impact' on the individual's quality of life experience. Thus, patients do not present to a clinic till the burden of their condition is perceived to be negatively impacting their daily lives. Also, care management objectives aim to minimize and prevent impacts and improve a patient's quality of life. Knowledge of disease activity and severity supports the scientific community in delivering on this objective. As a result, FEV1 levels (upon spirometry) serve as a marker of pulmonary impairment, informing the 'severity' of disease, and tools such as the SGRQ and CAT assess

health-related quality of life and are informative of ‘impact.’ While several biomarkers have been proposed as disease ‘activity’ markers, this remains an active research area. Currently, changes in FEV1 are used to appreciate disease activity. However, it is a surrogate indicative of the presence of pathological occurrences impacting a patient’s airflow obstruction and patient outcome.

There are several characteristics that have been proposed to define an ideal candidate [88]. Not only does the marker need to be important to the pathophysiological process of the disease, but it should also relate to disease ‘severity,’ being stable while having the ability to reflect disease activity progression through varying levels corresponding to related events and be predictive of disease progression. It should ideally be sensitive to therapeutic factors to support investigating new interventions and management strategies. A theoretical model has been proposed in the literature [89] to illustrate the relationship between disease severity and activity with age, as seen in Figure 7.

This discussion begs the inclusion of comorbidities when considering ideal candidates for biomarkers of disease ‘activity’ in the heterogenous condition COPD. The various pathological processes leading to COPD and/or contributing to impacting ‘activity’ levels and related ‘severity’ are continually exposed to and, in turn, influencing concurrent comorbidity-associated pathological processes. This logically plausible concept is supported by findings from emerging literature pointing to a need to study ‘multiple biomarkers’ or ‘biomarker-panels’ for a better chance at grasping the ongoing process as compared to depending on a single biomarker [90,91] “to identify these different disease activity mechanisms (endotypes), even within well-defined and well-monitored clinical phenotypes” [92].

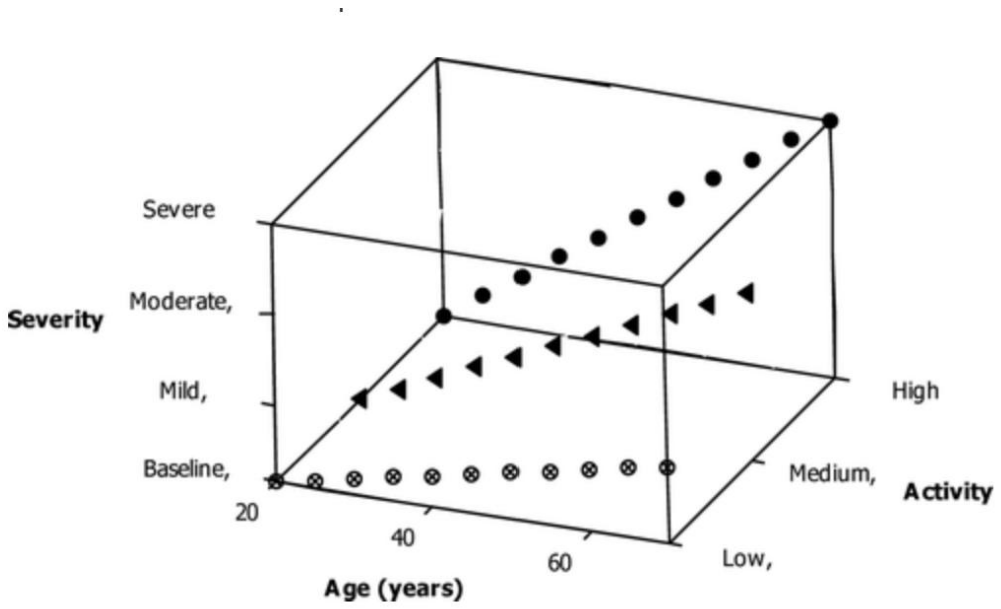


Figure 7: A Theoretical model of disease activity and severity with time.

If disease activity is stable with a similar age of onset, there will be a proportional relationship between disease severity and activity and age, reflecting the preceding activity. The presence of more severe disease at a younger age, therefore, implies either a younger age of disease onset or, more likely (based on the current understanding of the pathogenesis of COPD), this indicates a more active disease process.

B. 'Phenotype' vs. 'Endotype' in COPD

The English dictionary defines the word **phenotype** as an organism's observable properties produced by the interaction of the genotype and the environment [93]. Differences in phenotypes, while commonly attributed to the genotypic make-up of the individuals, it is equally established that the influence of the individual's environmental elements, e.g., smoking, eating

habits, exercising habits, etc., play crucial roles. Thus, in the context of COPD, phenotypes describe groups of patients manifesting similarly, including clinical, functional, imaging, and/or biological characteristics, and these can be associated with clinically meaningful outcomes.

Given the heterogeneity observed in COPD, numerous phenotypes are possible, which may have therapeutic implications. Precision medicine aims to tailor treatment to match a patient's characteristics rather than employing a "one-size-fits-all" approach [94, 83, 95]. In the year 1995, the American Thoracic Society (ATS) started by recognizing a spectrum of overlaps between asthma, chronic bronchitis, and emphysema [96] and then, around 2010, "a single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes (symptoms, exacerbations, response to therapy, the rate of disease progression, or death)" was proposed as a definition of COPD phenotypes [97]. However, it was in 2011 that GOLD led the way, in view of emerging knowledge, by recognizing and revising their pharmacological intervention recommendations to be based on symptoms and exacerbation once they meet the airflow limitation criteria for diagnosis of COPD [98]. Several phenotypes have been proposed and identified through analysis, extensive clinical observations, or an understanding of the disease, its impact on patients' day-to-day living experience, and their interaction with healthcare resources. A few examples are the upper lobe-predominant emphysema phenotype, the physical frailty phenotype, the emotional frailty phenotype, the co-morbid COPD phenotype, etc., alongside some of the phenotypes described in this section.

i. Frequent exacerbator phenotype

While as COPD progresses, exacerbations could increase in frequency and severity [99], the occurrence of 2 or more exacerbations per year is defined as 'frequent exacerbations' [9]. This impacts patient outcomes wherein this group of patients experiences worse health status and morbidity compared to those who are not frequent exacerbators [100]. An association of perception of breathlessness with event occurrence has been reported in this group [101], and though this group may be largely considered to be stable, there is a significant proportion who have a change in frequency as their FEV1 deteriorates [102]. Other associated factors reported are a ratio >1 of their pulmonary artery over aortic cross-sectional dimension [9], bronchitis [9], and a greater percentage of emphysema or thickening of airway walls on chest Computerised Tomography [9].

Currently, the GOLD report recommends initiation of maintenance therapy with long-acting bronchodilators at the earliest in this group and among those with elevated blood eosinophil levels, inhaled corticosteroids to be considered additionally with the dual bronchodilator regime, and if patients continue to experience exacerbations the treatment is stepped up [9]. History of exacerbations, anxiety, and unvaccinated status against influenza have been found to be important determinants, while cluster analysis has reported further phenotypic groups among the 'frequent exacerbators' [103].

ii. Asthma-COPD overlap phenotype

While asthma and COPD are separate conditions with characteristic presentations and pathophysiology, it has been observed that in groups of COPD patients, about 12%-55% of the

two conditions overlap [104]. These patients demonstrate an incompletely reversible airway obstruction with variable airflow. As a result, they do not meet the definition of either COPD or asthma, thus being excluded from clinical trials in both these conditions, though they experience a high symptom burden and exacerbations [105-108].

This group in itself presents a spectrum, and thus, there is a need to develop a consensus definition that would recognise such an overlap condition. To guide diagnosis, in 2012, by consensus was developed that recommended identification based on the presence of two major or one major and two minor criteria. Major criteria included: a positive bronchodilator test (increase in FEV1≥15% predicted and ≥400ml), eosinophilia in sputum, and personal history of asthma, while the minor criteria included: high total Immunoglobulin-E, personal history of atopy and positive bronchodilator test (increase in FEV1≥12% predicted and ≥200ml) on two or more occasions [109]. In the 2014 report from the joint project of the Global Initiative for Asthma (GINA) and GOLD, Asthma-COPD overlap syndrome (ACOS) was described as: “characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. ASOC is therefore identified by the features that it shares with both asthma and COPD” [110]. However, since the condition is not a single disease, the use of “syndrome” is not supported, and the term Asthma-COPD overlap (ACO) has been preferred [].

A specific definition is still lacking, with a need to study further evidence [111]. There have been variations in the outlook for diagnosis and treatment regarding ACO in reports from countries and associations such as Spain [112,113], Check Republic [114], Canadian Thoracic Society [115], and the ATS [116] and such inconsistencies, likely led to the GOLD 2020 report update of its recommendation to clarify: “we no longer refer to asthma-COPD overlap (ACO). Instead, we

emphasize that asthma and COPD are different disorders, although they may coexist in an individual patient. If a concurrent diagnosis of asthma is suspected, pharmacotherapy should primarily follow asthma guidelines, but pharmacological and non-pharmacological approaches may also be needed for their COPD." [111].

iii. Rapid decliner phenotype

COPD is an umbrella term for a complex condition and diverse underlying pathophysiology encompassing emphysema, chronic bronchitis, and small airway disease with airflow obstruction. There is heterogeneity in the patient presentations and their responses to treatment [117]. While underlying pathophysiological mechanisms are at the heart of this, clinically, identifying the risk profile of patients susceptible to experiencing a rapid decline in lung function will help in timely intervention. While the knowledge of underlying pathophysiological mechanisms is still to emerge, researchers have employed cluster analysis to identify common characteristics of those susceptible to rapid decline using large datasets of COPD patients [118]. "Fast decliners" were reported to be largely "younger patients with lung function loss with an increased number of COPD exacerbations". The most common risk factors reported for lung function decline were sex, COPD severity, and exacerbations [118].

"Endotype," on the other hand, refers to what lies beneath the observable characteristics or phenotypes and, thus, includes the cellular and molecular pathway(s) contributing to the disease pathogenesis [119]. This implies that causal molecular pathways must be established before considering molecular markers corresponding to endotypes [120]. Establishing endotypes has

significant implications for clinicians since phenotypes and biomarkers are accessible in a clinical setting. Phenotypes play an important role in hypothesis generation and prediction modeling for developing targeted pathway/molecular-level disease modification treatments. Figure 8 illustrates a proposed relationship between endotypes and phenotypes in COPD [121].

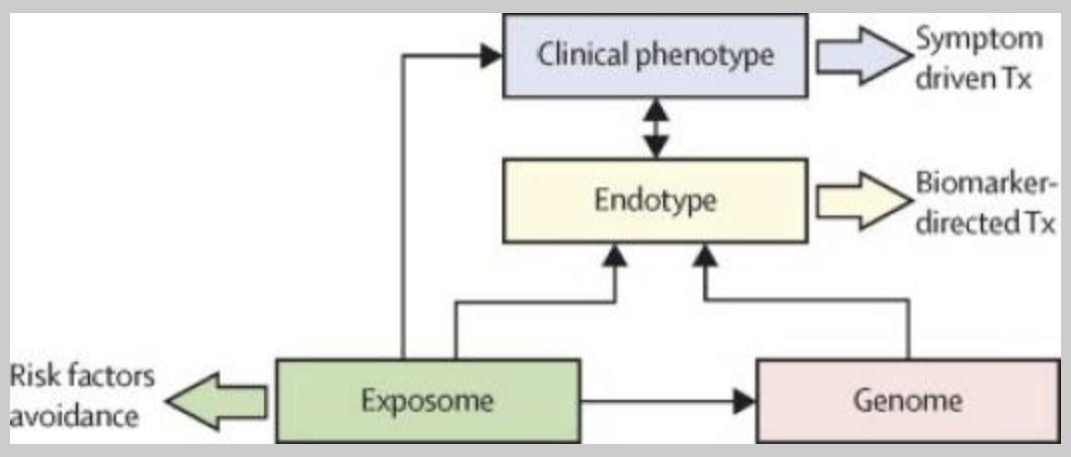


Figure 8: Diagram depicting the inter-relationships between the 'Exposome,' the 'Genome,' the 'Endotype,' and the final clinical expression of the disease

(small arrows) between the 'exposome' (a term that describes the "totality of human environmental exposures, from conception onwards"), the genetic background of the individual (Genome), the Endotype (biological networks that enable and restrict reactions), and the final clinical expression of the disease (Clinical Phenotype). Large arrows indicate different therapeutic strategies.

Alpha-1 antitrypsin deficiency (AATD) is a well-established example of an endotype where clinical characteristics, biomarkers, genetics, pathophysiology, clear epidemiology, and treatment responses have been well described [122].

Besides AATD, which is uniquely a Mendelian disorder, there are a number of endotypes that are understandably more complex development arising from the influence of external environmental factors on the internal genetic makeup of individuals. Several such endotypes are under investigation with a focus on therapeutic implications applicable to COPD [121]. These potential endotypes include COPD with persistent systemic inflammation, COPD with bacterial colonization, Eosinophilic/Th2-high COPD, Biological sub-types of COPD exacerbations, Comorbidities, and Lung cancer. Figure 9 has been proposed to illustrate the current understanding of these endotypes in COPD.

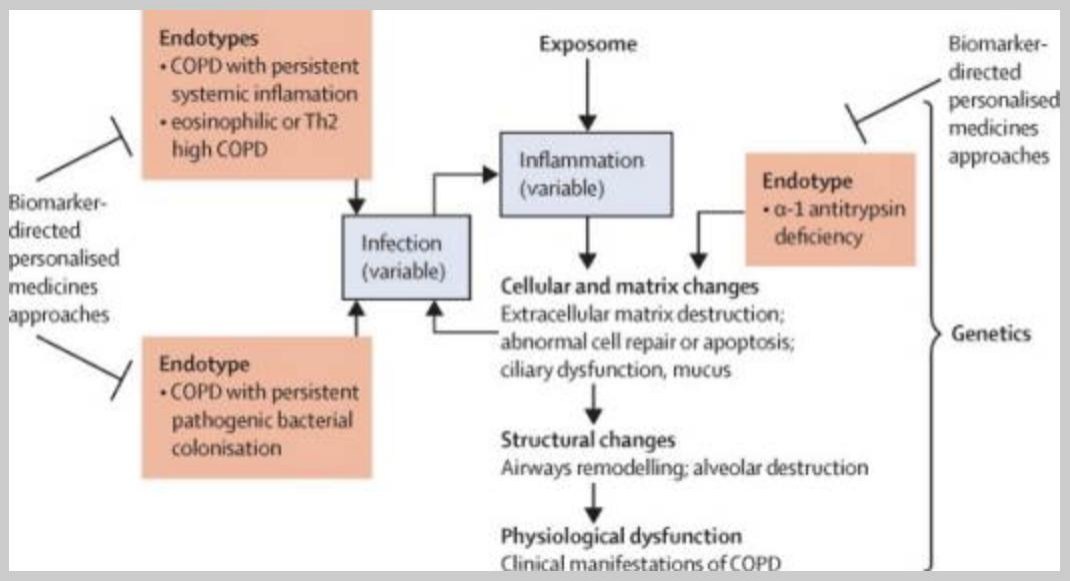


Figure 9: Our current understanding of potential endotypes of COPD.

Depicted are the relationships between inflammation, cellular changes, structural changes, and physiological dysfunction in COPD and the role that chronic infection can play in perpetuating inflammation. Superimposed are potential endotypes of COPD (in red textboxes) that relate to subtypes of inflammation, the presence of colonization with pathogenic bacteria, and the absence of a mechanism protective against extracellular matrix destruction (alpha-1 antitrypsin deficiency).

Table 5: Proposed potential COPD endotypes with treatment implications under investigation

Endotype proposed	Proposed characteristics	Associated Biomarker(s) proposed	Treatment implication	Reference
COPD with persistent systemic inflammation	Persistently elevated inflammatory biomarker levels in the blood; high all-cause mortality and exacerbation rate.	White blood cell count, C-reactive protein, interleukin (IL)-6, and fibrinogen	Unclear	[123]
COPD with bacterial colonization	Bacterial colonization led to increased inflammation and risk of exacerbation	Marker of bacterial infection (e.g., procalcitonin) colonization (e.g., volatile organic compound) and surrogates for outcome (e.g., Tumour necrosis factor-receptor-75)	antibiotic, azithromycin	[124-126]
Eosinophilic/Th2-high COPD	Elevated T-helper type 2 (Th2) cytokines (IL-5, IL-4 and IL-13)	Eosinophilia (sputum and blood)	Potential responders to corticosteroids and Th2 cell-produced cytokine blockers (e.g., anti-IL-5 receptor alpha monoclonal antibody-bevacizumab)	[105, 127]
Biological sub-types of COPD exacerbations	Biomarker profile corresponding subtypes for biological pathways	Sputum IL-1β (for bacterial), serum CXCL10 (viral), and blood eosinophils (eosinophilic and pauci-inflammatory)	Corticosteroids and antibiotics selection based on biomarker profile	[125, 128]
Comorbidities	Shared molecular pathway with certain comorbidities	Comorbidities-cluster specific marker	Potential specific marker-based treatment	[129, 130]
Lung cancer	Potential molecular mechanisms linking COPD (and emphysema) and lung cancer	Under investigation-Chronic inflammatory response markers and global molecular and adjacent airway field cancerization marker	Potential chemopreventive and immune-therapeutic strategies	[131, 132]

C. Disease progression marker landscape: Search for a marker of disease activity

As recently as GOLD 2023 report, while describing abnormal inflammation of the lungs to be characteristic of COPD mainly resulting from inhalation of noxious particles or toxic gases, especially cigarette smoke, also recognizes a plethora of extrapulmonary manifestations that have been described in COPD patients [9]. Various potential molecular mechanisms have been proposed, including inflammation, oxidative stress, airway remodeling, and lung aging [133]. These complex mechanisms are currently of research interest to bridge the knowledge gaps in developing therapeutics and designing treatment plans. The knowledge of such mechanisms will inform potential therapeutic molecules. It will also lead to the identification of biomarker(s) in the associated patient sub-populations, which can, in turn, help define patient sub-groups and serve as surrogate endpoints and enable better clinical trial design with adequate statistical power towards discovering preventative and curative personalizable solutions in COPD.

Multiple comorbidities are commonly reported in COPD patients, with over 80% of patients with COPD estimated to have at least one comorbid chronic condition [134]. The term chronic systemic inflammatory syndrome has been proposed in COPD to underscore the frequent additional complexity of chronic comorbidities in COPD patients [134]. Incorporating a comorbidities-inclusive approach to COPD is currently recommended in view of increasing evidence of strong associations of specific comorbidities like cardiovascular disease, diabetes, and hypertension, as well as multiple comorbidities with clinical outcomes in COPD such as dyspnoea, exacerbation and quality of life [135]. COPD-specific comorbidity indices, COPD-specific comorbidity test (COTE index) [136], and COMCOLD index [137] have also been

proposed, which have been developed to be predictive of mortality and health status, respectively.

The potential of COPD and certain comorbidities sharing molecular pathways has been proposed [129] in the context of COPD endotypes, and from a phenotype point of view, there is emerging knowledge of the association of comorbidities and distinct phenotypes in COPD, including among those with mild-moderate disease [138] indicating a potential complex association between comorbidities and systemic inflammation in COPD. There are two streams of thoughts: one that sees it as an "overspill" of the primary lung disease [139], whereas the other outlook is that of COPD being the respiratory manifestation of the systemic inflammation affecting multiple organs [134, 140]. Studies exploring biomarkers in COPD have put forth varying findings, leading to proposals for considering combinations of biomarkers among various COPD sub-groups in predicting disease progression [90]. Thus, this is an important area for new knowledge in COPD.

D. Towards personalized treatment: Clinical tools and risk assessment models

Given the knowledge of heterogeneity observed in COPD, it is a constant challenge for clinicians, especially those in family medicine and primary care practices, to assess prognosis and tailor care plans to prevent exacerbations and improve the quality of life experience in their current patients while also being able to detect COPD [141].

Several composite indices have been developed for clinical application in COPD. However, most of these have been assessed to be 'not ideal' for prognostication [142]. Table 6 shows the indices developed for clinical application and gaps.

Table 6: Summary of indices developed with clinical application aim.

[From: ref 142]

Index; Scale (and year published)	Predictors used	Outcome(s)	Age group (developed among)	Reported strengths/Flaws	Reference
ADO; 10-point scale (2009)	**A**ge, **D**yspnoea (MRC or GCRQ), and **O**bstruction (FEV1%)	Death	elderly	Validated; Good accuracy, but for elderly patients	[143]
BODE; 10-point scale, 4 categories (2009)	**B**MI, **O**bstruction (FEV1%), **D**yspnoea (MRC score) and **E**xercise tolerance (6MWD)	Death, Respiratory death	elderly	Validated; Good discrimination but for severe COPD only (CVD excluded)	[144]
CPI: COPD Prognostic Index; 100-point scale, 3 categories (2008)	Quality of life (SGRQ/CRQ), Obstruction (FEV_1%), Age, Gender, BMI, History of ED/exacerbation, History of CVD	Death, Hospitalization, Exacerbation	elderly	Validated, Adequate statistics, Large sample, Selective reporting Pooled analysis	[145]
DOSE; 8-point scale (2009)	**D**yspnoea (MRC score) **O**bstruction (FEV1%), **S**moking and **E**xacerbations	Correlation BODE Exacerbation Hospitalization for exacerbation	elderly	Difficult, complex, and selective reporting, Violated own protocol.	[146]
HADO; 12-point scale, 3 categories (2006)	**H**ealth (new questionnaire), **A**ctivity (new questionnaire), **D**yspnoea (Fletcher) and **O**bstruction (FEV1%)	Death	elderly	Clear descriptions, Compared to FEV_1%, Modest discrimination, Predictors debatable	[147]
Niewoehner (1); 422-point scale (2007)	Age, Obstruction (FEV1%), Hospitalization, COPD duration, Productive cough, Antibiotics, Systemic corticosteroids and Theophylline	Exacerbation	elderly	Large sample, No validation cohort, Severe COPD/males only, No outcome confirmation	[148]
Niewoehner (2); 249-point scale (2007)	Age, Obstruction (FEV1%), Hospitalization, Unscheduled visits, Cardiovascular disease and Oral corticosteroids	Hospitalization for exacerbation	elderly	Good discrimination, Large sample, No validation cohort,	

Index; Scale (and year published)	Predictors used	Outcome(s)	Age group (developed among)	Reported strengths/Flaws	Reference
				Severe COPD/males only, No outcome confirmation, Predictor is outcome	
PILE; 10-point scale, 4 categories (2010)	Obstruction (FEV_1%), Interleukin-6 and Knee extensor strength	Death	elderly	Long follow-up, Good statistic, No validation cohort	[149]
SAFE; 9-point scale, 4 categories (2007)	**S**GRQ score (questionnaire), **A**ir-**f**low limitation (FEV_1%) and **E**xercise tolerance (6MWD)	Exacerbation (correlation)	elderly	Small sample, Poor statistics	[150]
Schembri (TARDIS); 16-point scale (2009)	Age, BMI, Dyspnoea (MRC score), Obstruction (FEV_1%), Hospitalization and Influenza vaccination	Composite of Hospitalization for COPD or respiratory death	Unclear	Large sample, No validation cohort, Composite outcome, Limited statistics	[151]

More recently, a number of multivariable outcome prediction models have been developed for clinical use to support hospitalization and treatment strategy decision-making. A systematic review reported 408 prognostic models developed across settings including out-patient, in-patient, and emergency department [152]. The authors observe a lack of external validation in the case of many of these models and recommend impact studies to assess and optimize for clinical applicability. Some of these were updated versions of previously proposed indices, including ADO, which suffered from poor calibration and was recalibrated and externally validated to the updated ADO model, and an extended ADO version with two additional variables. The B-AE-D [**B**MI, severe **A**cute **E**xacerbations of COPD frequency and Dyspnoea (mMRC)], B-AE-D-C (with additional variable **C**opeptin), and a model developed by Bertens et al. have also been assessed to have low-risk of bias with results available from externally

validation studies. The BODE index, an extensively validated model, has been recommended by GOLD to identify suitable candidates for lung transplants [28], predict mortality, and plan post-discharge follow-up of patients.

Table 7: Prediction model and indices emerging from external validation or newly developed to predict patient outcomes with low risk of bias in COPD patients.

Index	Used in	Outcome	Reference
BODE (updated with recalibration)	Ambulatory COPD patients	Mortality	[144]
ADO (externally validated and recalibrated)	Ambulatory COPD patients (originally developed to predict 3-year mortality in moderate-severe COPD patients in secondary case-setting)	Mortality	[143]
B-AE-D and **B-AE-D-C**	For stable patients [COPD stage II -IV] to be used in an outpatient setting	risk of two years for all-cause mortality	[153]
Model by Bertens et al.	For stable COPD patients	risk of future exacerbations at two years	[154]

i. Treatable traits and Personalised treatment

The concept of "treatable traits" was proposed in 2013 [95] to determine "therapy" based on observed "traits" or phenotypes of the presenting COPD patient. In this approach, the therapy is linked to the underlying endotype associated with the observed phenotype, thus moving towards a more tailored treatment plan than a broad-brush approach, which is intuitive for the heterogeneous condition of COPD. A risk-benefit analysis needs to be considered when tailoring treatment in this approach. Figure 10 depicts the clinician's considerations in such scenarios [121].

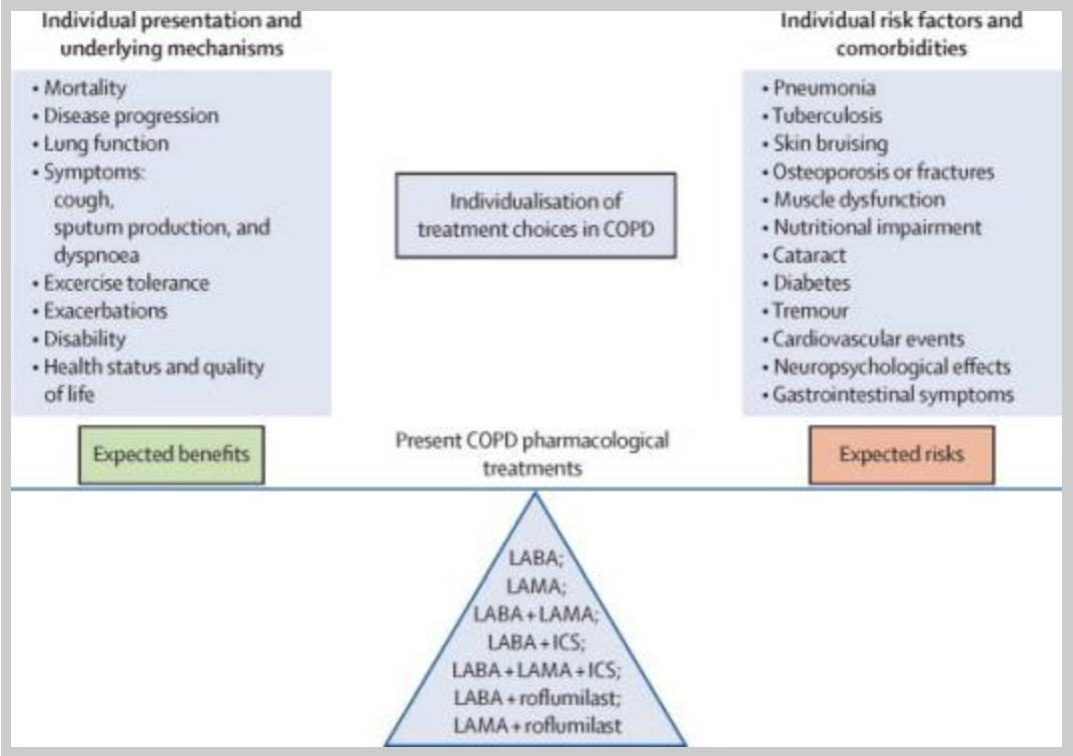


Figure 10: Considering the benefit-risk balance and its individual determinants when personalizing COPD treatment choices.

When deciding which pharmacological treatment option the clinician will prescribe to a given patient, they have to consider (i) expected benefits (left), which are determined by individual presentation and underlying mechanisms, and (ii) possible risks (right), which depend on individual risk factors and comorbidities.

The personalized therapy concept encourages the development of targeted therapeutics in the absence of which there is a limited ability to provide such treatment plans. There are some encouraging signs in the emerging monoclonal antibodies that target specific inflammatory pathways [155]. In step with the evolving understanding and as a step towards personalized care, the ANTES program (a collaborative research initiative based in Spain to improve prevention, treatment, and prognosis by anticipating the diagnosis and treatment of COPD to reduce its

public-health impact) has recently proposed a treatment decision-making algorithm (Figure 11) which takes several “treatable traits” into consideration [177,178].

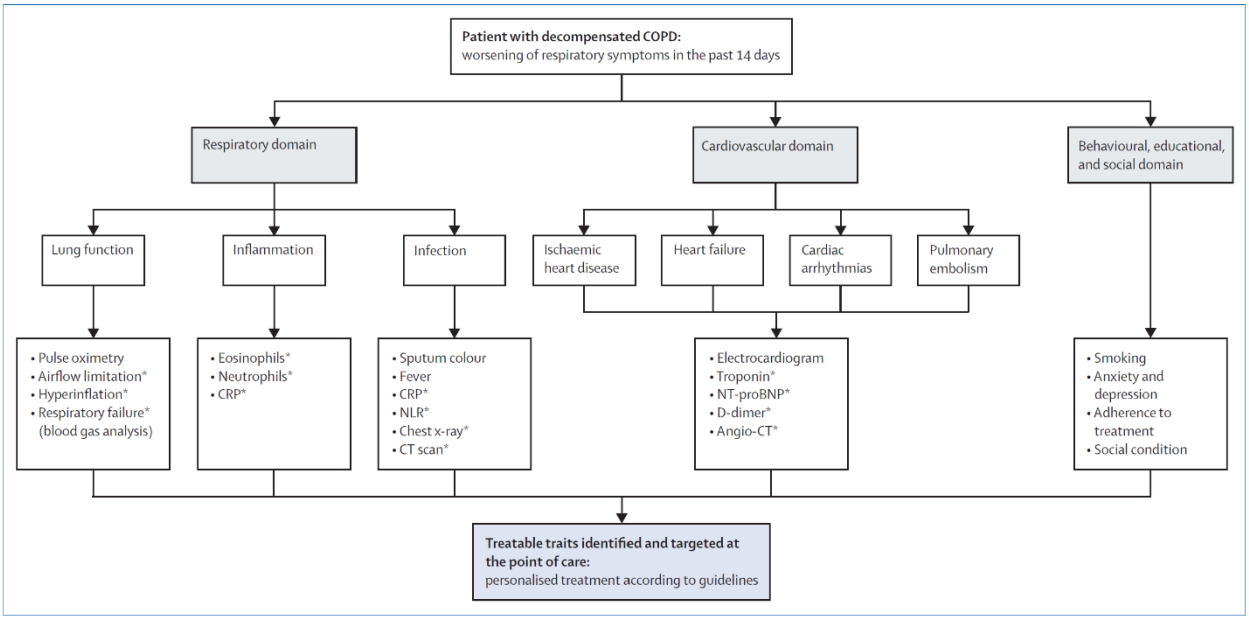


Figure 11: ANTES proposal for the treatment of patients with decompensated COPD

Biomarkers from three domains—respiratory, cardiovascular, behavioral, educational, or social—should be explored in different healthcare settings to identify treatable traits.

COPD=chronic obstructive pulmonary disease. CRP=C-reactive protein. NT-proBNP=N-terminal prohormone of brain natriuretic peptide. NLR=neutrophil to lymphocyte ratio. *Biomarkers to be tested, according to availability.

ii. "Composite outcome" vs prediction tools

Given the focus of this thesis on contributing knowledge from the mild to moderate COPD population to support efforts to develop therapeutic options and prognostication tools that are aligned with early detection and personalized care management to arrest the rapid decline, "composite outcomes" is an important concept.

Given the heterogeneity of COPD, while risk assessment is an essential aspect of care management, the heterogeneity contributes to yet another challenging aspect of quantifying and measuring treatment goals in the context of disease activity towards prevention of disease progression. This led to the development of a composite outcome, Clinically Important Deterioration (CID), comprising three critical components in COPD, namely (i) disease severity, (ii) disease activity, and (iii) disease impact. Suitable measurements corresponding to these components and their respective minimum clinically important difference (MCID) thresholds have been proposed [156]. The measure of CID is a composite outcome developed to differentiate those showing disease stability from those who may be considered to be 'worsening' to help identify the response to treatment administered/under evaluation. The proposed composite outcome needed to satisfy the following: a) address different aspects of disease progression; b) the components had to be largely independent of each other; c) be a stronger indicator of future risk as a composite compared to the individual components; and d) support the goal of identification of potential disease subgroups in the population being evaluated in the context of the pharmacological therapy administration over durations ≤ 6months in the different disease subgroups.

Assessed over the observation period, the presence of one of the three component outcomes making up the composite CID outcome determines the presence of clinically important deterioration, i.e., CID. Disease severity relates to functional impairment, and FEV1 decline (threshold: 100mL change from baseline) is the measurement component. Exacerbations inform disease activity [threshold: occurrence of an event requiring treatment with oral corticosteroids and/or antibiotics; or the occurrence of an event requiring hospitalization or an emergency room visit] while the patient's quality of life experience or health status is included as disease impact [threshold: ≥ 4units of increase in SGRQ score].

While CID may have been developed to assess and compare therapeutic efficacies, this simple clinical tool has been appreciated as a clinical tool that could assist holistic prognostic tools for clinicians, enabling them to spot 'high-risk' individuals who may benefit from early therapeutic intervention [157]. However, this potentially versatile composite outcome measure and prognostic tool has been developed and used among clinical populations of moderate-very severe COPD patients and largely in clinical trial contexts [157]. Thus, while this is a promising clinical tool that uses deterioration of any criteria of FEV1, health status, or exacerbations to help assess patients potentially susceptible to future deterioration based on the presence or absence of short-term CID, the current threshold will need to be evaluated for application in mild-moderate COPD patients primarily seen in the primary care setting. This thesis discusses and examines CID in a population with mild-moderate COPD in Chapter 5.

Having differentiated the composite CID, clinical tools that have been developed as prediction models for mortality or future exacerbation, some of these have been discussed in prior sections,

the newly proposed Acute COPD Exacerbation Prediction Tool (ACCEPT) model [158] is promising to the clinical community [159], and the team proposing the tool has validated and recalibrated the original model to ACCEPT 2.0 [50]. However, its applicability in the mild-moderate COPD population has not been assessed. In Chapter 6, this thesis discusses the ACCEPT 2.0 model and investigates its generalizability among those with mild-moderate COPD.

E. Disease progression marker landscape: Search for a marker of disease activity

This chapter, which provides background on important concepts towards personalized care management of patients with COPD, needs to include a discussion of comorbidities.

Multiple chronic illnesses, namely, lung cancer, asthma, hypertension, diabetes, cardiovascular disease, chronic renal failure, obstructive sleep apnea syndrome, metabolic syndrome, dysfunctional skeletal myopathies, osteoporosis, mental disorders, and other cancers, have not only been reported in literature among prevalent comorbidities in COPD patients [160] (Figure 12), their impact on health outcomes, mortality and cost of management have been reported as well [161]. The importance of comorbidities in COPD is reflected in the summary report 2023 from GOLD, recognizing the “invariable coexistence” of “other diseases that may significantly impact the patient’s clinical condition and prognosis” [9].

Usually, patients with COPD may have one or more co-existing chronic illnesses [137, 162-172], and this may have varying impacts on the disease progression as some may share common risk factors such as smoking and age while some may be due to the underlying pathophysiology

compounding the severity of the diseases present [173], thus making it important to understand the patient as a whole in the context of personalized treatment. Along with clinical tools, the role of biomarkers becomes important, especially those that are informative variables in understanding and planning care management and may be potential predictors of prognosis. Inflammatory biomarkers have been investigated in COPD, especially to explore their role in improving proposed prediction model accuracies when included [174].

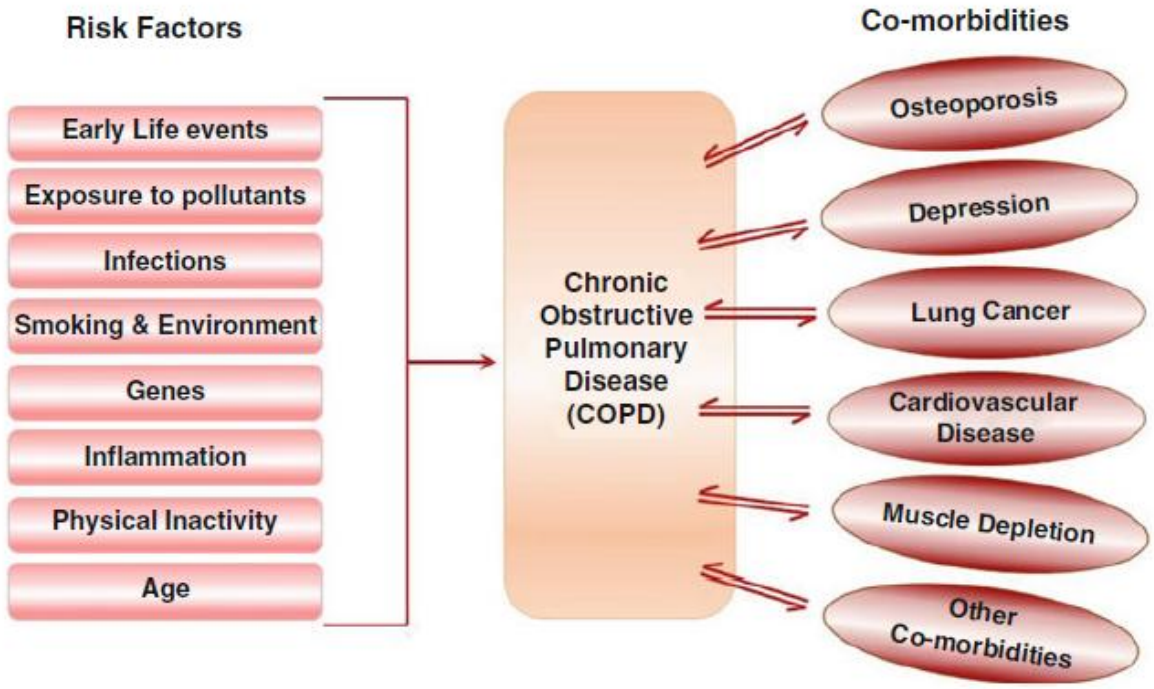


Figure 12. Association of risk factors and comorbidities with COPD.

The various risk factors are vital for predisposition to COPD. COPD, on the other hand, increases the chance of developing multiple other chronic diseases. The presence of other comorbidities alongside COPD further deteriorates the quality of life and affects the morbidity and mortality of COPD.

i. Biomarker panel in COPD

A "panel of biomarkers," which included WBC counts, IL-6, fibrinogen, CCL-18/PARC (CC chemokine ligand 18 /pulmonary and activation-regulated chemokine), CRP, IL-8, and surfactant protein-D (SP-D), was reported as being informative in increasing accuracy of a model composed of established clinical factors towards risk stratification for all-cause mortality in the patients with moderate to very severe COPD [174]. The findings were reported based on the study population comprising patients with COPD and complete biomarker data from the ECLIPSE cohort. While these biomarkers may individually contribute as informative variables to varying extents, the study reported a significant observation that the "use of integrative analyses describes better the complexity of COPD," drawing parallels with similar observations reported in cardiovascular diseases [175].

This concept was further explored, given the heterogeneity of COPD, variable disease progression potentials, and the emergence of "combined clinical variables" as more informative predictors of outcomes when compared to individual clinical variables. A study analyzed several biomarkers individually and in combinations, namely Fibrinogen, C-Reactive Protein (CRP), surfactant protein D (SP-D), soluble Receptor for AGE (Advanced Glycation Endproducts) [sRAGE], and Club Cell Secretory Protein (CC16) in 2 COPD cohorts of COPDGene and ECLIPSE to assess their predictive roles for disease severity, progression, as well as for mortality in models adjusted for clinical covariates [90]. This "multiple biomarkers" analysis using the set of biomarkers proposed by the authors revealed that a combination of biomarkers was a stronger predictor compared to individual biomarkers in the context of relevant cross-sectional and longitudinal COPD outcomes. The authors demonstrated a combination of biomarkers that were

predictive in both cohorts, strengthening the idea of "multiple biomarkers"/ "panel of biomarkers" being more information than individual biomarkers in COPD.

ii. Novel marker of disease activity in COPD

This thesis proposes a novel marker of disease activity for patients with COPD, an index or measure of "imbalance" described as 'AGE-RAGE stress' (calculated as AGE/sRAGE). This proposed index, AGE/sRAGE, is a ratio of 2 biomarkers, AGE, and sRAGE, which have been studied independently in COPD, and existing evidence is indicative of the involvement of these biomarkers in the pathophysiology of multiple chronic diseases that have also been found to co-exist in patients with COPD.

The pathophysiology involves the interaction of AGE (Advanced Glycation Endproducts) and its cell receptors (RAGE), which triggers biomolecules similar to known mediators of COPD like reactive oxygen species, protease-antiprotease, inflammation, and cell adhesion molecules and growth factors. The levels of the soluble receptor of AGE (sRAGE) influence this interaction by binding with AGE as a decoy, thus preventing the cascade triggered by the interaction of AGE and RAGE. Correlation of the levels of these individual biomarkers has been reported in many chronic diseases in relation to their respective pathophysiology. Based on the evidence, "AGE-RAGE stress" emerged as a measure of "imbalance" and expressed as the ratio of ARGE/sRAGE has been reported as a stronger informative variable when compared to the individual levels, making it suitable even in the presence of multiple comorbidities (Table 8) [176].

Table 8: Findings of AGE, sRAGE, and AGE/sRAGE ratio reported in chronic diseases.

Disease states	AGE	sRAGE	AGE/sRAGE
Diseases with low serum sRAGE			
NSTEMI	78.0% ↑	32.1% ↓	218.5% ↑
Thoracic aortic aneurysm	584.6% ↑	30.0% ↓	900.0% ↑
Hyperthyroidism	42.2% ↑	19.4% ↓	126.1% ↑
Hypercholesterolemia	89.4% ↑	36.3% ↓	249.0% ↑
Disease with high serum sRAGE			
ESRD *(also in diabetes)*	577.0% ↑	145.0% ↑	313.0% ↑

Percent changes in the serum AGE, sRAGE and AGE/sRAGE ratio in diseases
NSTEMI- non-ST-elevation myocardial infarction
ESRD- end-stage renal disease
↑ *increase* ↓ *decrease*

Reprinted from Prasad, K. Is there any evidence that AGE/sRAGE is a universal biomarker/risk marker for diseases? Mol Cell Biochem 451, 139–144 (2019). https://doi.org/10.1007/s11010-018-3400-2. Copyright © 2018, Springer Science Business Media, LLC, part of Springer Nature

This thesis proposes the potential role of AGE, RAGE, and sRAGE in the pathophysiology of COPD in detail in Chapter 7. It investigates the suitability of the AGE/sRAGE ratio as a novel potential marker of disease activity among patients with COPD, known to have multiple comorbidities.

3.1.4 Summary: Gaps in Literature

In the 2023 report, GOLD refined the definition of exacerbation to “In a patient with COPD, an exacerbation is an event characterized by dyspnea and/or cough and sputum that worsen over ≤14 days, which may be accompanied by tachypnea and/or tachycardia and is often associated with increased local and systemic inflammation caused by airway infection, pollution, or other insult to the airways” [9] thus introducing a “time” aspect to indicate ‘acuteness” of the exacerbation event. Given the knowledge that such events are present in those with mild-moderate COPD and that such events produce debilitating effects on patient’s quality of life and prognosis, it is clear that there is an imminent opportunity to expand our understanding of the applicability of existing clinical tools and models such as CID and ACCEPT in mild-moderate COPD patients [47].

There is a growing understanding of the complexities surrounding molecular mechanisms leading to the development of the disease, phenotypes, patterns of disease worsening trajectories, and treatment responses in COPD. Recommendations and guidelines have been updated continually to reflect this emerging knowledge. These include the introduction of the pre-COPD stage following the dismissal of the previously proposed symptom-based “at-risk” (COPD-0) stage. Also, the emerging realization of the presence of multiple comorbidities as a phenotype where there is a potential biologically plausible underlying mechanism in these cases could potentially be linked to observations that biomarker panels provide a more comprehensive understanding compared to identifying a single biomarker. In this context, it would be interesting to investigate an index such as the one proposed in this thesis of AGE/sRAGE that could potentially reflect the internal inflammation environment of an individual and understand

thresholds in COPD patients where multiple comorbidities and their treatments are commonplace for an informative marker of ‘disease activity’ as a comprehensive resultant of ongoing complex pathways.

The following sections of this thesis investigate these much-needed tools, models, and markers in the mild-moderate COPD population drawn from the general Canadian population to contribute to the growing body of knowledge to bridge the existing gaps towards early detection and targeted intervention of those most susceptible to deterioration.

4. Overview of Data and Methods

All analysis presented in this thesis was completed using Statistical Analysis Software (SAS) 9.4 software (version 9.4; SAS Institute Inc, Cary, NC, USA) while the ACCEPT 2.0 R- package [179] was used to obtain model predictions described in manuscript 2. Manuscript-specific discussion on data and methods used are described in the following sub-sections.

4.1 Data source:

This thesis aims to focus on mild-moderate COPD, representative of the patient population of primary care or family medicine practice, to assess tools and measures that will support the development of early detection of those likely to decline relatively faster and to support the development of treatment options to arrest such declines through early intervention. This is important considering that most of our prevalent information has largely emerged through cohorts of clinical populations at advanced disease stages in a chronic and progressive condition unique due to its diverse pathophysiology, which is further influenced by comorbidities. The currently recommended strategy is to work towards detecting and intervening early and striking a meaningful balance of improved quality of life experience while being supportive of healthcare cost and resource utilization. Given this goal, the CanCOLD study participants provide a unique opportunity to investigate existing tools and models to inform strategies to adapt them for this target population as well as develop new information, such as novel biomarkers that will potentially add vital information needed to assess disease activity that can be critical to future studies on prediction and prognosis.

The Clinical Practice Research Datalink (UK-CPRD) was identified as a potential source for developing a large cohort of the same target population that would permit further investigation of the findings from CanCOLD.

The characteristics of both these cohorts are described next.

4.1.1 Primary-The Canadian Cohort of Obstructive Lung Disease (CanCOLD)

A well-characterized, population-based, longitudinal cohort to develop an understanding of the natural course of COPD with our primary care clinical setting in mind was not available, and this need inspired the design and establishment of the Canadian Cohort Obstructive Lung Disease (CanCOLD) [41]. However, in the events leading to CanCOLD, firstly, a Canada-wide cross-sectional study was set up, named the Canadian Obstructive Lung Disease (COLD), to study the prevalence of COPD based on the protocol of an international study [Burden of Obstructive Lung Disease (BOLD)]. For the COLD study, 6,551 men and women who were 40 years and older, non-institutionalized men and from areas with a total population of > 250,000 people were recruited through random digit dialing using Statistics Canada census data from across 9 Canadian cities: Vancouver, Montreal, Calgary, Quebec, Halifax, Toronto, Kingston, Saskatoon, and Ottawa. An average participation rate of 74% (range 63–87%) has been reported across all sites [180].

Building on the cross-sectional study of COLD, CanCOLD was established. COLD participants with a) mild COPD (GOLD 1; post-bronchodilator FEV1/FVC<0.70 and FEV1≥80% predicted) and (b) with moderate-severe COPD (GOLD ≥2; post-bronchodilator FEV1/FVC<0.70 and

FEV1<80% predicted) were invited to participate in CanCOLD. Sex and age-matched (±2 years) non-COPD participants were then invited contributing to the (c) healthy "at-risk" subjects (i.e., ever-smoker with post-bronchodilator FEV1/FVC≥0.70), and healthy "normal" subjects (i.e., never smokers with post-BD FEV1/FVC≥0.70). These participants make up the 1561 participants of CanCOLD. Data collection protocols have been published [NCT00920348] and are briefly captured in Table 9. Over the years since the establishment of the CanCOLD cohort, along with directly collected data, biobank samples of the participants have supported various ancillary studies, contributing immensely to our understanding of this target population representative for women (42%) [181], the majority with mild COPD (55%) [182], previously undiagnosed (70%) [183] among those with COPD.

Table 9: Broad description of data collected at each follow-up phase of CanCOLD

Phase	**Measurements**
Visit 1 (2009-2015) [n=1561] *Baseline*	Informed consent, Questionnaires (socio-demographics, comorbidities, lifestyle and risk factors, health status, quality-of-life, respiratory health, psychological health, signs and symptoms, occupation and health, sleep quality, medication intake), blood samples, spirometry tests, PFT, CPET, CT scan
Visit 2 (2011-2015) [n=1019] *Median follow-up 18 months*	Same questionnaires as Visit 1, blood samples, spirometry, and 6MWT
Visit 3 (2013-2019) [n=1198] *Median follow-up 3 years*	Same questionnaires as Visit 1, blood samples, spirometry, CPET, CT scan
Visit 4 (2022-2024) Ongoing: Median follow-up 10 years	Same questionnaires as Visit 1, blood samples, spirometry, PFT, CPET, CT scan
Every 3 months	COPD exacerbation questionnaire (telephone/online)
PFT=Pulmonary function tests PFT, CPET=cardiopulmonary exercise test, CT scan=multidetector computerized tomography scan, 6MWT=6-minute walking test, COPD=Chronic Obstructive Pulmonary Disease	

The mean age of the cohort was reported to be 66.7 years, with 56% males and 55% of those with COPD were GOLD 1. Among those with COPD, only about 16% were current smokers (50% were former smokers), where 35% of them were never smokers, and a majority of them had three or more comorbidities [182].

4.1.2 Secondary- The United Kingdom primary care cohort using the Clinical Practice Research Datalink (UK-CPRD)

The United Kingdom (UK) primary care cohort using the Clinical Practice Research Datalink (CPRD) covers about 19.83% of the UK population. It contains anonymized data from general practices that have agreed to share patient data [184]. In the UK National Health Service (NHS), a general practitioner (GP) refers patients to diagnostic tests and secondary care, and over 98% of the population has been reported to be registered with a GP practice in England [185]. The CRPD is the combined database of two similarly structured complementary databases: CPRD GOLD and CPRD AURUM. Practices contribute to the CPRD through either of these based on the patient management software system provider used: Vision® software system (CRPD GOLD database) or the EMIS® software system (CPRD AURUM database) [186]. A majority of these practices have consented to participate in the CPRD linkage scheme and provide patient-level information.

CPRD Aurum database reports over 19 million patients in England, of whom 7 million were included as alive and currently contributing and representative of approximately 13% of the population of England [187]. Considering a period between 1995 and September 2018, the study

reported a median follow-up of 4.2 years (IQR: 1.5–11.4) for all patients and 9.1 years (IQR: 3.3–20.1) for the patients. Additional practices from Northern Ireland have been added since the review, and with the combined coverage, CPRD currently includes 35 million patient lives, including 11 million reported currently registered patients [188].

CPRD reports Aurum linkage data includes patients from 890 practices in England, representing coverage of approximately 99% of CPRD Aurum practices, and 28,618,186 patients as currently eligible for linkage as available in the August 2019 build [188]. Data from patients from all practices in CPRD Aurum can be linked to a range of health-related data sources, including secondary care, disease registries, and death registration records. NHS England Digital, a trusted third party, uses an NHS number, exact date of birth, sex, and patient residence postcode [189] to link CPRD Aurum to other patient-level health data, making available only de-identified data through the CPRD.

The Hospital Episode Statistics (HES) datasets are of primary interest to the proposed study. It contains details of all admissions to or attendances at English NHS healthcare providers, including all patients treated in NHS hospitals and treatment centers (including the independent sector) funded by the NHS. HES includes details such as dates, specialty, clinical diagnosis, and procedures across Admitted Patient Care (APC) data; Outpatient (OP) records of outpatient care in England; Accident and Emergency (A&E) care records in England; Diagnostic Imaging Dataset (DID) taken from NHS radiological information systems; and Patient Reported Outcome Measures (PROM). Diagnostic data is recorded using the International Classification of Diseases version 10 (ICD10) coding frame, and procedure information is coded using the UK Office of Population, Census and Surveys classification (OPCS) 4.6 [188].

The CPRD database has been used to study COPD [190] with reported availability of good-quality spirometry, investigation, hospitalization, prescription, and mortality records. Given that this is a GP database, we expect to have the opportunity to access a sizable proportion of COPD patients with mild or moderate disease through this database. Additionally, the General Medical Services (GMS) contract Quality and Outcomes Framework (QOF) of the National Health Services (NHS) included COPD indicators in April 2004 to incentivize high-quality care and the use of a standardized reporting system. The guidelines include spirometry assessments among symptomatic patients as a positive evaluator for the quality of physician services. Medical Research Council-MRC dyspnea grade has been routinely collected in the annual review of patients with COPD since April 2009 [191-194]. This makes CRPD a potential source of good quality longitudinal data on COPD patients with repeat spirometry and MRC Dyspnea Scale evaluations along with exacerbation information, making this a suitable data source to identify a study cohort of those with mild-moderate COPD to assess findings from CanCOLD cohort.

4.2 Methods

4.2.1 Research Theme 1 Methods: Clinically Important Deterioration (CID) in mild-moderate COPD population

The primary objective in this study (manuscript 1) was to assess CID, as currently defined, in predicting disease and dyspnea worsening at 18 months among patients with mild-moderate COPD. I carried out the assessment in the CanCOLD cohort. Continuing to work with the CanCOLD cohort, the secondary objective was to reassess by including biomarkers in the models. Finally, to investigate the potential existence of sub-groups with different decline trajectories of lung function over 3 years to identify rapid decliners, I examined, as an exploratory objective, if sub-groups emerged by using Group-Based Trajectory Modeling (GBTM).

Chi-square and Fisher's exact test were used for categorical variables, Student's t-test and Mann–Whitney U test for continuous variables based on normal and non-normal distribution, respectively. Descriptive analysis was reported along with differences between groups were analyzed. Logistic regression models were used to assess the association between short-term CID and the outcomes of declines in FEV1, changes in health status, and dyspnoea over a further short term, and Odds Ratios are reported with a 95% Confidence Interval (CI). For the outcome of time to a new moderate/severe exacerbation from visit 2, the Cox Proportional Hazards model was used to report Hazard Ratios (95% CI). The incident rate of moderate/severe exacerbations between visit 2 and visit 3 was assessed using Poisson regression models, and Rate Ratios (95% CI) were reported. All models were adjusted for baseline age, sex, BMI, and smoking pack-years.

CID is a composite outcome. The analysis was repeated for each component. Out of the three biomarkers, blood eosinophil (EOS), CRP, and fibrinogen, those found to be significantly associated with CID in this cohort were included in the models. Two model versions were considered. While model 1 adjusted for baseline age, sex, BMI, and smoking packing years, model 2 additionally adjusted for any CVD and absolute EOS count. The discussed analysis was repeated for a second definition of CID, and I report findings from both definitions. Lastly, GBTM was carried out to assess for potential sub-groups demonstrating relative rapid decline, where data from 3 visits was included to inform the trajectory. I report the sub-groups and their trajectories that emerged and describe their characteristics.

In this theme, the approved protocol for the study proposed using the UK-CPRD data to validate the findings from CanCOLD is also included [approved protocol in Appendix-]. A cohort, a validation cohort, will be identifying and applying inclusion criteria aligned with those of CanCOLD. While the CPRD comprises electronic records from primary care or general practice (GP) visits, since the GPs are critical to healthcare delivery in the UK, providing referrals for specialized/ hospital care along with primary care for the patients registered with these practices, the CPRD has records for all clinical events and referrals inclusive of demographic information, prescription, and hospital admission data. The UK-CPRD uses Read codes cross-referenced to the International Classification of Diseases, Tenth Edition (ICD-10) using which occurrence of exacerbation (hospitalization, emergency room visit following exacerbation) and severity (through the treatment offered) can be ascertained for the validation cohort, using the Hospital Episode Statistics (HES) Data linkages of Admitted Patient Care (HES-APC), records of outpatient care (HES-OP) and records of Accident and Emergency care (HES-A&E).

The analysis discussed in Manuscript 1 will be performed in this cohort to examine and report if the findings from CanCOLD are replicated in this large primary-care clinical cohort of those with mild-moderate COPD from the UK. This study is currently underway, so only the approved protocol is included to confirm further research supported by the study discussed in Manuscript 1.

4.2.2 Research Theme 2 Methods: Prediction of acute exacerbation in mild-moderate COPD population

The goal of this study (discussed in Manuscrip2) is to assess the predictive capability of the ACCEPT 2.0 model in the CanCOLD cohort comprising participants with mild-moderate COPD, compared to using preceding 1-year exacerbation history to predict potential future exacerbation outcome. The study cohort comprised those with complete data for 1-year follow-up for outcome. Given the thrust on understanding how this existing model translates to the context of mild-moderate COPD, I considered different definitions of the outcome of exacerbation and reported the findings. Using the R-package, model predictions were obtained which were further analyzed using SAS.

I assess for both discrimination and calibration capabilities. “Discrimination” refers to the accuracy of classification for actual outcomes, whereas “calibration” refers to the ability to correctly rank by risk. A time-dependent receiver operating characteristic curve (ROC) at 1-year follow-up was plotted to assess the model's discrimination capacity. I report the area under the ROC or AUC (c-statistic) with a 95% confidence interval (CI). Using the DeLong test (non-parametric approach), I also compare and report the observed ROCs for ACCEPT 2.0 (for defined outcome definition) vs using the past year’s exacerbation history alone.

4.2.3 Research Theme 3 Methods: Search for a potential marker of disease activity- a novel biomarker index in COPD

There are 2 studies under this theme. For the first, Manuscript 3, I describe the biomarkers, AGE, and sRAGE, and summarise findings reported to highlight the potential novel marker of disease activity in the complex condition of COPD, which is the ratio of AGE/sRAGE. This is supported by a discussion of the plausible role of the AGE-RAGE axis in the pathophysiology of COPD and the rationale supporting the ratio over either of the individual biomarkers as the potential informative marker.

In the subsequent study, discussed as Manuscript 4, I identify a sub-cohort of CanCOLD participants who meet the selection criteria, with data from the 3 completed visits and whose serum samples are available in the Montreal Biobank. Serum AGE was assessed using Cell Biolabs' OxiSelect™ ELISA kits according to the protocol recommended. Serum sRAGE was assessed using Quantikine® ELISA from R&D systems according to the protocol recommended.

Both kits are recommended for use in research. Results were examined in consultation with domain-knowledge experts and the respective manufacturer lab prior to being included in the analysis.

The goal was to summarise findings of serum levels of AGE, sRAGE among those with the disease condition of study (COPD), free of disease condition of study but those exposed to a major risk factor for the disease (cigarette smoking) compared to healthy controls where exposures reported to be associated with the biomarkers were ruled out. The levels are compared using the Kruskal-Wallis test. I also report the observed correlations for the individual

biomarkers and the proposed ratio against variables of interest, namely age, pack-years of cigarettes smoked, FEV1, FEV1 % predicted, FVC, diffusing capacity for carbon monoxide (DLCO), Emphysema Score, and low attenuation areas less than a threshold of -950 Hounsfield units (LAA-950) from CT scan using Pearson- method.

5. Research Theme 1: Clinically Important Deterioration (CID) in mild-moderate COPD population

5.1 Preface Study 1: [Short Title "Clinically Important Deterioration (CID) in a mild-moderate COPD population."]

Title: *Understanding Clinically Important Deterioration (CID) in mild-moderate COPD population: Inferences from the Canadian Cohort of Obstructive Lung Disease (CanCOLD) study.*

In this chapter, I present the clinical tool, Clinically Important Deterioration (CID), and evaluate it in the mild-moderate COPD population of the Canadian Cohort of Obstructive Lung Disease (CanCOLD) study.

The tool, CID, is a composite measure comprising 3 components, namely: exacerbation occurrence, change in health-related quality of life score, and measure of FEV1 decline over a defined period of time, such as 18 months. Components must meet the defined thresholds to be considered present. The presence of at least one of the components is used to assess the presence of clinically important deterioration.

The primary objective was to assess if short-term CID, as currently defined in studies among clinical COPD cohorts, can be used to predict outcomes of disease and dyspnoea worsening that

would occur over the subsequent follow-up period of similar short-term duration in a population-based mild-moderate COPD cohort.

Additionally, my secondary objectives assessed if including comorbidity (any cardiovascular disease) and biomarkers (absolute eosinophil count, C-reactive protein (CRP) and fibrinogen) in the models with CID would improve prediction abilities. All models were adjusted for age, sex, BMI and pack-years of cigarette smoked.

Background, data, and methods have already been discussed in detail in previous dedicated chapters.

Results are discussed in the manuscript. The references relevant to the manuscript are included in this chapter.

5.1.1 Manuscript 1

TITLE: Clinically Important Deterioration (CID) in a mild-moderate COPD population

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KEYWORDS: Clinically Important Deterioration (CID), Chronic Obstructive Pulmonary Disease (COPD), mild-moderate COPD, disease progression

Summary of the "take home" message of the paper, social media.

Population-based studies are needed to better understand predictors of decline in disease severity in mild-moderate COPD to develop suitable clinical tools for a “reach-out early” strategy to better support those susceptible to decline rapidly.

ABSTRACT

Introduction: Clinically Important Deterioration (CID), a composite of exacerbation, declines in lung function, and health status, has been studied as an indicator of disease worsening in moderate-severe Chronic Obstructive Pulmonary Disease (COPD) clinical populations. We assessed if CID is predictive of worsening over 18 months in a population-based mild-moderate COPD cohort.

Methods: Canadian Cohort Obstructive Lung Disease (CanCOLD) participants with COPD were assessed for outcomes over 18 months for CID and over the next 18 months. Their association was then examined: a) defined into threshold-based binary variables, the declines in FEV1, health status, and dyspnoea, using logistic regression models; b) time to moderate/severe exacerbation and rates of moderate/severe exacerbations using Cox Proportional Hazards and Poisson regression respectively.

Results: Out of 429 individuals assessed, 255 (60%) demonstrated CID. The presence of CID at 18 months showed an association (not statistically significant) with future moderate/severe exacerbation, worsening health status (CAT score), and dyspnoea. As a component, FEV1 was found to be less informative, compared to exacerbation for health status outcome [OR (95% CI): for ≥8 unit increase in SGRQ, 4.31 (1.29-14.41)] alongside future exacerbation, and SGRQ-health status component, for future health status decline [OR (95% CI): for ≥4 unit increase in SGRQ, 0.33 (0.17-0.66); for ≥2 unit increase CAT score, 0.53 (0.30-0.94)].

Discussion: Our finding of informative CID components seems to support recommendations emphasizing exacerbation history and health status over severity of airway obstruction in clinical assessments to predict outcomes. Suitable adaptations of the current CID definition may be needed for the mild-moderate COPD population.

INTRODUCTION:

Heterogeneity of presentation and progression is a well-established concept in the understanding of chronic obstructive pulmonary disease (COPD). Emerging new knowledge indicates potential multiple underlying pathophysiological mechanisms and risk factors [1-6], trajectories, and treatment responses across patients with COPD. Thus, to differentiate those likely to worsen vs.

stabilize [7] in the short-term, e.g., over 6 months or less, there is an acute need to be able to assess future risk of decline through a holistic measure reflective of the different independent COPD key aspects. Identifying those individuals who are susceptible to experiencing rapid clinical deterioration continues to be a challenge to clinicians aiming to provide personalized care plans aimed at preventing exacerbations and, in turn, disease progression [8].

The *impact* of COPD as perceived by a patient is intrinsically linked to their *disease severity*, e.g., the extent of airway obstruction [post-bronchodilator Forced Expiratory Volume in 1 second (post-BD FEV1)] or reduced exercise capacity and also impacted by the level of *disease activity* such as exacerbations. Based on this understanding, in 2016 [9] Clinically Important Deterioration (CID) was proposed to study a composite measure of early: i) deterioration of lung function (≥100 mL change in post-BD FEV1 [10]), ii) deterioration in health status using self-reported scores on Health Related Quality of Life (HRQoL) questionnaires [≥ 4 units St George's Respiratory Questionnaire (SGRQ)] [11] and iii) moderate-severe exacerbations [≥ 1 moderate (requiring treatment with oral corticosteroids and/or antibiotics) or severe (requiring hospitalization or an emergency room visit)] that predict poorer medium-term outcomes [8,12]. The component thresholds correspond to minimal clinically important difference (MCID) indicative of poor medium-term disease prognosis in a clinical trial context. While the health status measure of SGRQ is respiratory disease-specific and highly comprehensive [13], a shorter 8-item instrument, the COPD Assessment Test (CAT) [14], has also been used in clinical and research settings. CAT has been found to closely track with SGRQ [15], and the correlation between their changes is well studied where at the patient level, 2 units of change in CAT score has been found to correspond with the MCID of 4 points change in SGRQ [15].

Since its proposal, CID has been used in post-hoc analysis studies [16-21] and prospectively [22-25] to assess the therapeutic efficacy of treatment alternatives. Thus, CID defined and used among patients with moderate-severe COPD in selective clinical settings remains to be tested in patients with mild-moderate COPD from the general population who are likely to be managed at primary care or family medicine settings in order to prevent early disease progression in susceptible individuals.

In this study, the primary objective was to assess the currently defined CID in patients with mild-moderate COPD from a population-based cohort in predicting disease and dyspnea worsening at 18 months. The secondary objective was to assess the impact of including biomarkers in the models. The exploratory objective was to assess existing sub-groups by examining the differences in trajectories of lung function deterioration over 3 years for potential clues for identification of rapid decliners.

METHODS

Study population

The Canadian Cohort of Chronic Obstructive Lung Disease (CanCOLD) study recruited its participants from the Canadian Chronic Obstructive Lung Disease (COLD) study, a prevalence study with a random sample of 6551 noninstitutionalized participants from 9 cities aged 40 years or older at recruitment (2005-2009) registered at ClinicalTrials (NCT00920348) [26]. CanCOLD has 1556 participants from the two COLD groups: individuals with COPD [as defined by Global Initiative for Chronic Obstructive Lung Disease (GOLD)] [8] and age and sex-matched non-COPD controls, split between ever- and never-smokers [26]. The study protocol was approved

by each site's institutional research ethics board. Informed consent was obtained from all participants. CanCOLD has a median follow-up of 37 months (range: 24 to 84 months) across 3 completed in-site visits: first (2009-2015), second (2011-2015), and third (2013-2019), along with participant-reported exacerbation data collected through quarterly telephonic questionnaires.

The main analysis population included CanCOLD participants with mild-moderate COPD (GOLD 1 and 2) at both visits 1 and 2, and with data for assessment of CID, i.e., post-BD spirometry; SGRQ or CAT; and of exacerbation occurrence within 12 months prior to visit 2. Exacerbation was defined as acute worsening of COPD; moderate, and severe.

Short-term CID variable

In this study, we used the current definition of short-term (between visits 1 and 2) CID [18], CID-D1, a composite of (i) decreases of ≥100 mL in post-BD FEV_1; and/or (ii) increase of ≥4 units in SGRQ score; and/or (iii) incidence of a moderate/severe exacerbation. The analysis from a second CID definition using the increase of ≥2 units in CAT score instead of SGRQ [15], CID-D2, has been included in Supplementary material.

Outcome variables:

Changes between visits 2 and 3 were used to assess outcomes. Health status decline outcome was defined as an increase of≥4 units and ≥8 units using the SGRQ score or ≥2 units and ≥4 units using the CAT score. The decline in FEV1 outcome was assessed for a decrease of ≥100 mL and ≥200 mL. Moderate/severe exacerbation events between visits 2 and 3 were included in the analysis. An increase in dyspnoea was defined as a ≥1 unit increase in the Medical Research Council (MRC) score.

Baseline variables included age, sex, BMI (calculated from measured height and weight using standard protocol), self-reported cigarette smoking status (as current, former, or never smokers), and self-reported pack-years smoked (calculated by multiplying the mean number of cigarettes smoked per day dividing by 20, and the number of years smoked. Models 1 and 2 were both adjusted for these covariates. Additionally, model 2 included covariates for the secondary objective: the presence of any cardiovascular disease (CVD) and absolute blood eosinophil counts. Other biomarkers considered were C-reactive protein (CRP) and fibrinogen.

Statistical analysis

A descriptive analysis was reported. Differences between groups were analyzed using Chi-square and Fisher's exact test for categorical variables, Student's t-test, and Mann–Whitney U test for continuous variables with normal and non-normal distribution, respectively. The association of short-term CID and the medium-term outcomes of declines in FEV1, changes in health status, and dyspnoea were examined using logistic regression models, and Odds Ratios were reported with 95% Confidence Interval (CI). Cox Proportional Hazards models were used for the outcome of time to a new moderate/severe exacerbation from visit 2, and Hazard Ratios (95% CI) were reported. Finally, incident rates of moderate/severe exacerbations between visit 2 and visit 3 were also assessed using Poisson regression models, and Rate Ratios (95% CI) were reported. All models were adjusted for baseline age, sex, BMI, and smoking pack-years.

Assessments were repeated with individual components of CID. Three biomarkers, namely, blood eosinophil (EOS), CRP, and fibrinogen, were examined in univariate analysis and as an extension of the sensitivity analysis. Biomarkers not significantly associated with CID in the cohort were not included in the analysis since these are not confounders. Two models were employed: model 1 adjusted for baseline age, sex, BMI, and smoking packing years, and model 2 additionally adjusted

for any CVD and absolute EOS count. For the proposed exploratory objective, based on repeated measurements of FEV1 at visits 1, 2, and 3, Group-Based Trajectory Modeling (GBTM) was carried out to assess potential sub-groups to describe their characteristics. Statistical analyses were performed using SAS (version 9.4; SAS Institute Inc, Cary, NC, USA).

RESULTS

Participant characteristics

CID was assessable in a total of 429 COPD participants either using SGRQ score (CID-D1) or CAT score (CID-D2). Figure 1 shows the population flow diagram. Participant demographics and baseline characteristics are presented in Table 1. The analysis population had a mean age (±SD) of 67.1 (±9.9) years, was overweight [BMI of 27.7 (± 5.3)], was 65% former-smokers, and 59.7% males. The CanCOLD COPD group at visit 1 (n=739), the analysis population (n= 429), and those excluded (n=310) were similar except for differences in FEV1 % predicted. The excluded group had the highest mean FEV1 % predicted.

Figure 2 presents a detailed description of the composite CID make-up of the 420 participants of the analysis population, where 60% (n=252) demonstrated short-term CID and were similar to those without CID demographically, on airflow limitation, dyspnoea score, biomarkers, and respiratory medication use (Supplement-Table1). Statistical significance, defined by $p< 0.05$, was used to interpret the results.

Composite CID at 18 months

Table 2 presents the association of the short-term composite CID with the study-defined worsening outcomes from model 1 and corresponding model 2 over the following 18 months.

In the analysis population, compared to those without CID, those with CID were observed to be significantly less likely for FEV1 decline outcomes. Though statistically not significant, the following were observed: a) A decreased odds for the decline in health status outcomes defined with changes in SGRQ total scores while showing increased odds for the decline in health status when using changes in CAT total scores. Increased odds (not statistically significant) were seen for increasing dyspnoea. b) The direction of the associations was maintained in the corresponding model 2. c) For exacerbation outcomes, compared to those without CID, those with CID showed: i) an elevated rate of moderate/severe exacerbations over 12 months and during the follow-up period and ii) elevated risk of a moderate/severe exacerbation within 12 months (Table 2).

Components of CID

Table 3 presents the association of each of the CID components with the outcomes in the population. One or more moderate/severe exacerbations in the year preceding visit 2 were present in 11.5% of those with CID (Figure 2) and were significantly associated with increased risk and rate of future exacerbations over the following year. This association was also seen in corresponding model 2. However, for health status outcomes, it was significantly associated with increased odds of decline, defined as ≥8 unit increase in SGRQ total score among those with CID in model 2. Though not statistically significant, the following were observed: a) CID component of exacerbation showed -increased odds of decline in health status outcomes measured using CAT score as well as for increased dyspnoea; b) Reduced odds for decline in FEV1 and for the outcome of ≥4 unit increase in SGRQ total score (Table 3A).

The health status component of CID, ≥4 unit increase in SGRQ total score, was present in 43.3% of those with CID (Figure 2). This component was significantly associated with decreased odds of health status decline outcome of ≥4 unit increase in SGRQ total score and of ≥2 unit increase in

CAT total score. Though not statistically significant, the health status decline component of CID showed increased odds for increasing dyspnoea and future exacerbation while showing decreased odds for FEV1 decline and the remaining health status decline outcomes (Table 3B).

The FEV1 decline was observed in 74.2% of those with CID (Figure 2) and was significantly associated with decreased odds of study-defined medium-term FEV1 declines. Though not statistically significant, decreased odds for health status decline outcomes of ≥8-unit and ≥4-unit increases in SGRQ score (model2) and for increased dyspnoea were observed. The FEV1 decline component was not indicative of future rate or risk of exacerbation (Table 3C).

Exploratory findings from Group-Based Trajectory Modeling

Based on FEV1 trajectories among the 366 participants (complete case analysis), as seen in Figure 3, two groups were identified. The baseline characteristics of the two groups are detailed in Table 4. The trajectories of Group 1 vs Group 2 demonstrated a steady linear decline while the slopes remained parallel (Figure 3). The group with the higher baseline FEV1, Group 2, was significantly younger, predominantly male, had a lower absolute eosinophil count, milder COPD severity with a higher percentage of predicted FEV1, and better health status by SGRQ score and Short-Form 36 physical component. This group comprised lower proportions of participants reporting experiences of at least one moderate/severe exacerbation in the preceding year and those on respiratory medications (namely, SABD, ICS combined with LABA/LAMA) in the previous year. (Table 4). This group also had lower proportions of current smokers and reported lower pack-years of cigarette smoked. Plots of health status and exacerbation trajectories for the 2 groups are included in Supplementary Figure 2.

DISCUSSION

This study is the first to assess CID, a widely used measure of clinical worsening in mild-moderate COPD. This is also the first study in a population-based cohort against the selective clinical cohorts and contributes important generalizability insight especially needed to support clinicians and therapeutics research. The analysis population in this study has an 18-month period for early CID assessment with at least one moderate/severe exacerbation over 12 months at CID assessment and 18 months of prospective follow-up thereafter.

Consistent with current evidence, short-term CID and its exacerbation component were predictive of future exacerbation [24, 25]. The inclusion of SGRQ to define CID over the shorter CAT questionnaire was observed to be more suitable in the study population as CID-D1 was positively associated with increased odds of declines in health status (CAT score), and dyspnoea, elevated rate of moderate/severe exacerbations over 12 months, and of elevated risk of an event within 12 months though these were not found to be statistically significant. Our findings align with reports that suggest that patient-reported health status measurements may not be interchangeable [27]. In the existing literature, compared to the 3-component CAT-based CID, a two-component 'simplified CID' has been assessed excluding the health status component. The simplification did not impact the CID's prediction capacity adversely, while an improvement was reported [25].

Short-term CID was not indicative of a future decline in FEV1, a marker of COPD progression [28], and rather showed an inverse association. Studies have found a single assessment spirometry to be unreliable for diagnosis in patients with mild-moderate COPD due to significant variability in results [29,30,31]. Further examination using successive consistent spirometry in external cohorts is needed. A similar inverse association was also observed for CID components. From the analysis of the EMAX study, the inclusion of FEV1 decline didn't contribute to composite CID's

capacity to differentiate in treatment effects [22]. Significant FEV1 declines in early disease severity have been reported [32], and there is evidence of exacerbations leading to increased airflow obstruction in mild-moderate COPD [33]. However, the findings in the current study are rather consistent with studies documenting heterogeneity of FEV1 trajectories [34] and supportive of re-assessment of the definition of FEV1 decline thresholds where it has been discussed that attrition, especially in the less efficient COPD treatment arm in trials, could lead to inaccurate estimations of expected mean annual rate of FEV1 decline which has informed current MCID thresholds [35]. In a recent review, the authors contemplate the need to explore alternate definitions and thresholds for CID [36].

Emerging knowledge indicates the prevalence of individuals with reduced FEV1. They include young adults with incomplete lung maturation diagnosed with COPD as they grow older [37] and others potentially on a path of rapid decline under mechanisms influenced by internal (e.g., genetic makeup [6], dysanapsis [38, 39], comorbidities, etc. [40]) and/or external factors (e.g., smoking [2], ambient pollution, etc. [4]). This would be consistent with reported subgroups of individuals with COPD demonstrating a relatively stable progression with age [41], while others may show rapid lung function decline at the early disease stage [41]. In our analysis using GTBM, on the one hand the findings are consistent with subgroups at different baseline FEV1 levels. However, over 37 months of the study observation period, these two groups were found to decline similarly.

In this population of those diagnosed with mild-moderate COPD, short-term worsening captured as the presence of CID was likely to be associated with less lung function worsening over the subsequent similar short-term period. In this population, exacerbation and health status components of CID, as assessed over 18 months, emerged to be informative over decline in lung function though greater decline in lung function is possible in the earlier stages compared to

advanced stages. The GOLD committee has persistently revised recommendations [44, 8] to draw the attention of clinicians to symptom burden and exacerbation frequency over a singular focus on spirometry in their patient care management decisions [45, 46, 47].

Strength and limitations:

Among its strengths, this is the first analysis of CID in a cohort reflective of mild-moderate COPD from the general population, compared to selective samples of clinical trials; detailed data collection in this cohort designed to study this population supported sensitivity analysis; and being an ongoing study allows close review and continued examination using successive visit data.

There are certain limitations as well. A longer follow-up may have helped in identifying differences in declines and, consequently, identification of rapid decliners as well as meaningful endpoints for assessing treatment effects in this population. However, this can be addressed in future studies upon completion of future visits. CID definition and thresholds can also be re-assessed at such examination. Secondly, administrative truncation at CanCOLD visit 2 led to a smaller sample size; though a comparison of those excluded does not indicate bias, this weakness can be overcome in analysis upon the availability of future visit data. Thirdly, these findings must be validated in primary care/family medicine-based cohorts for a detailed understanding of mild/moderate COPD trajectories. Also, data from additional visits will help validate the COPD status of this mild-moderate disease cohort and address a weakness in the current study. CanCOLD captured quarterly exacerbation information (symptomatic and event-based) in the cohort. While a history of exacerbation is a strong predictor of future exacerbations, such detailed records may not be available to clinicians. Thus, the examination of the findings in the primary care data is needed to assess CID and the components with the available exacerbation data.

Our findings highlight the challenges of primary care teams. Detecting COPD at the mild-moderate severity stages will be encouraged by the development of novel therapeutics needed to arrest progression and potentially reverse the condition. In view of the looming mortality and morbidity challenge of COPD [42, 43], further examinations are needed amongst patients with mild-moderate COPD. A validation study protocol in the primary care database of the UK- Clinical Practice Research Datalink (CPRD) has been approved recently (Protocol ID#21_000688) to continue to understand trajectories in this population and define holistic indicators of future deterioration.

CONCLUSION:

In the mild-moderate COPD population examined, short-term composite CID, as currently defined, is not informative of lung function decline over 18 months follow-up. However, SGRQ score and exacerbation were important CID components indicative of future deterioration. Our findings support the evolving GOLD recommendations that consistently encourage reliance on exacerbation and health status in assessing future disease worsening and treatment decisions. Further investigations are needed to validate these findings and understand adaptations of the current CID definition as applicable to primary-care practice populations of mild-moderate COPD.

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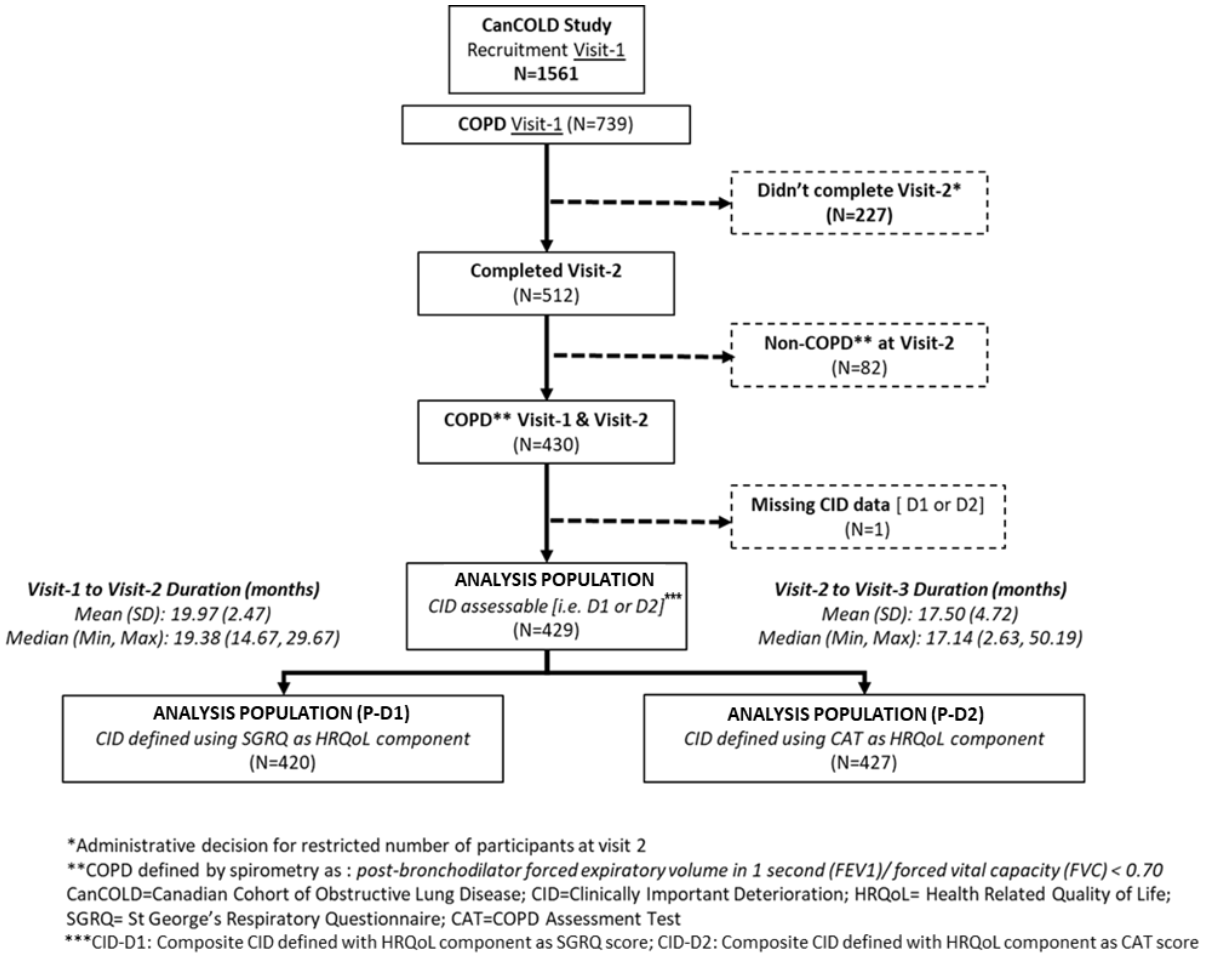


*Administrative decision for restricted number of participants at visit 2
**COPD defined by spirometry as : *post-bronchodilator forced expiratory volume in 1 second (FEV1)/ forced vital capacity (FVC) < 0.70*
CanCOLD=Canadian Cohort of Obstructive Lung Disease; CID=Clinically Important Deterioration; HRQoL= Health Related Quality of Life; SGRQ= St George's Respiratory Questionnaire; CAT=COPD Assessment Test
***CID-D1: Composite CID defined with HRQoL component as SGRQ score; CID-D2: Composite CID defined with HRQoL component as CAT score

Figure 1. Study population participant flow diagram.

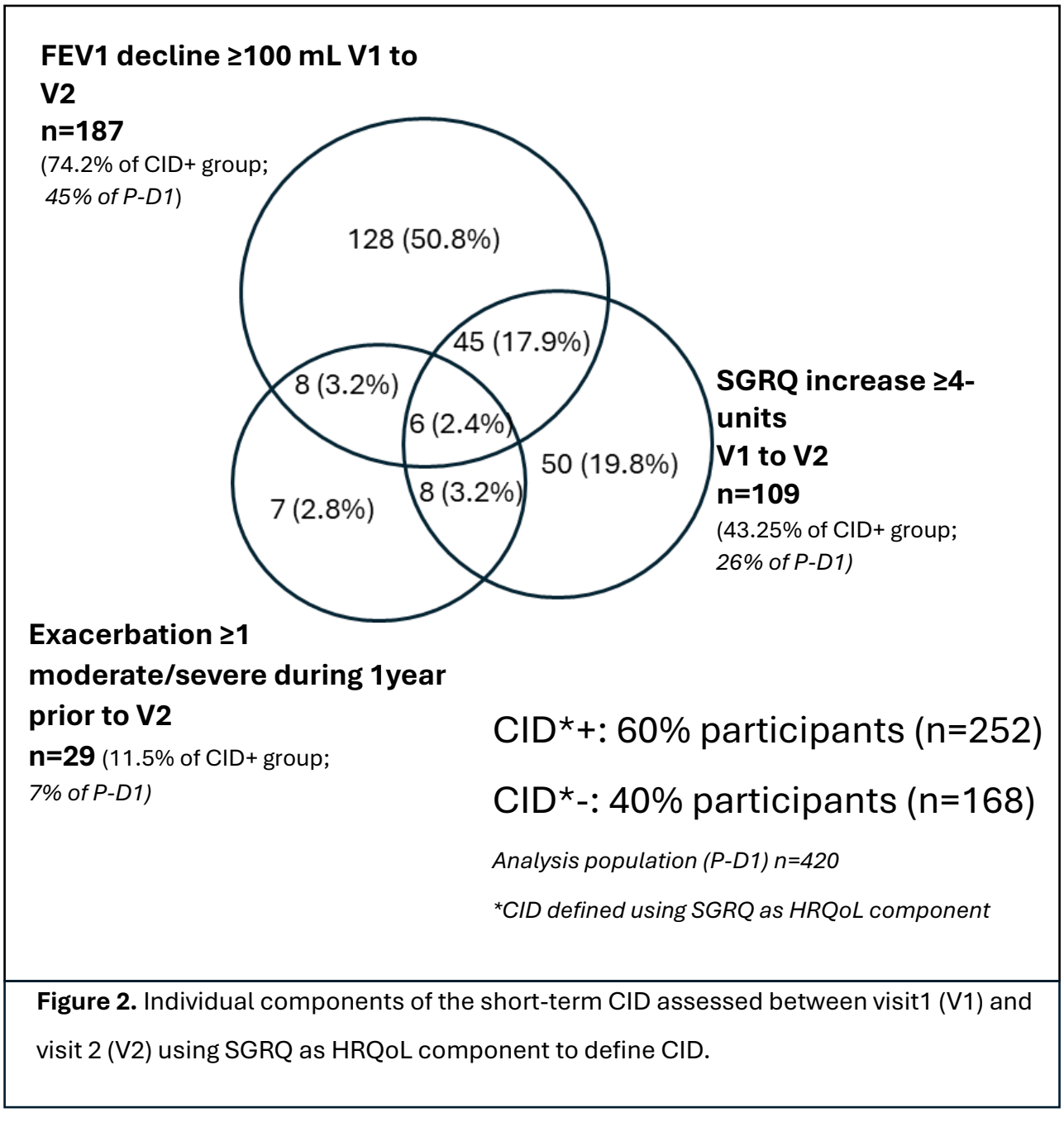
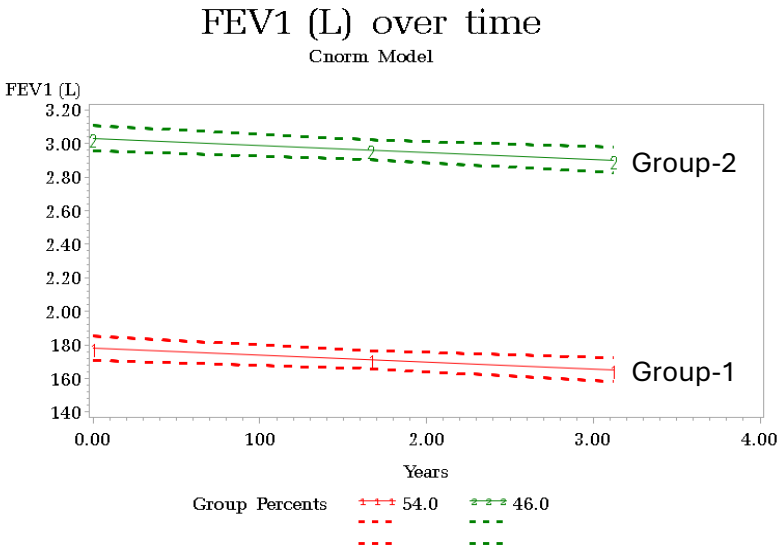


Figure 2. Individual components of the short-term CID assessed between visit1 (V1) and visit 2 (V2) using SGRQ as HRQoL component to define CID.



COPD			
FEV1 (no missing data for the three points (n=366)	Group1 (linear)	Group2 (linear)	P-value for parameter comparison between group1 and 2
N (%)	199 (54.0)	167 (46.0)	
Intercept: Parameters (SE)	1.78 (0.04)	3.03 (0.04)	<0.001*
Linear: Parameters (SE)	-0.04 (0.01)	-0.04 (0.02)	0.971

Figure 3: Group 1 and Group 2 as identified by Group Based Trajectory Modeling using FEV1 trajectory over visit 1 (V1), visit 2 (V2) and visit 3 (V3).

Table 1. Baseline characteristics of CanCOLD mild-moderate COPD population analysed and excluded

	COPD subjects (n=739)			
	Total	**Analysis Population**	**Population excluded**	**P value**
	N=739	**N=429**	**N=310**	
Age, in year	67.5 ± 10.1	67.1 ± 9.9	67.9 ± 10.3	0.227
Sex, male gender, n (%)	442 (59.8)	256 (59.7)	186 (60.0)	0.94
BMI	27.5 ± 5.3	27.4 ± 5.5	27.5 ± 5.0	0.553
Smoking status, n (%)				
Never	199 (26.9)	121 (28.2)	78 (25.2)	0.357
Former	400 (54.1)	221 (51.5)	179 (57.7)	0.094
current	140 (18.9)	87 (20.3)	53 (17.1)	0.276
Pack-years of cigarettes	23.2 ± 25.2	22.4 ± 24.1	24.4 ± 26.8	0.443
MRC Dyspnea scale Score ≥ 3/5, n (%)	61 (8.8)	32 (7.8)	29 (10.2)	0.269
$FEV_{1,}$ L	2.3 ± 0.8	2.3 ± 0.8	2.3 ± 0.8	0.792
FEV_1, % predicted	82.2 ± 19.4	80.7 ± 18.8	84.3 ± 20.1	0.008*
SGEQ-Total	16.4 ± 16.0	16.5 ± 15.4	16.3 ± 16.8	0.396
CAT score	7.9 ± 6.7	7.8 ± 6.5	8.1 ± 7.1	0.88
SF36 Physical component scale	50.3 ± 9.0	50.4 ± 8.8	50.1 ± 9.3	0.727
SF36 Mental component scale	50.0 ± 9.5	50.1 ± 9.2	49.8 ± 9.9	0.853
Respiratory medications reported in the past 12 months, n (%)				
SABD	48 (6.5)	30 (7.0)	18 (5.8)	0.549
LABA or LAMA	16 (2.2)	7 (1.6)	9 (2.9)	0.241
ICS alone	61 (8.3)	36 (8.4)	25 (8.1)	1
ICS combined with LABA/LAMA	140 (18.9)	87 (20.3)	53 (17.1)	0.276
Any above medications	265 (35.9)	160 (37.3)	105 (33.9)	0.338
Thawed blood EOS				
Absolute count, count/ microliter	0.23 ± 0.17	0.23 ± 0.17	0.25 ± 0.18	0.203
<150 Eos/micoliter	237 (37.1)	140 (37.9)	97 (36.1)	0.627
150 to <300 Eos count/ microliter	234 (36.7)	134 (36.3)	100 (37.2)	0.824
≥300 Eos count/ microliter	167 (26.2)	95 (25.7)	72 (26.8)	0.772
Percentage %	5.2 ± 3.8	5.2 ± 3.9	5.3 ± 3.7	0.679
CRP	2.50 ± 3.29	2.42 ± 3.41	2.62 ± 3.11	0.758
Fibrinogen	3.04 ± 0.69	3.00 ± 0.63	3.10 ± 0.76	0.387

Table 2. Association of short-term composite CID-D1 with outcomes over 18 months of follow-up

	COPD population					
	CID-D1 (composite of decrease of ≥100 mL in post-BD FEV1; increase of ≥4 units in SGRQ score; and incidence of a moderate/severe exacerbation)					
	Composite CID +	Composite CID-	Composite CID+ vs. CID- (model1)		Composite CID+ vs. CID- (model2)	
	n (%)	n (%)	OR /HR/RR (95% CI)	P value	OR /HR/RR (95% CI)	P value
Outcome (change from V2 to V3)						
≥100 mL decrease in FEV1[a], n (%)	74 (34.3)	87 (60.8)	0.30 (0.19-0.47)	<0.001*	0.32 (0.19-0.52)	<0.001*
≥200 mL decrease in FEV1[a], n (%	40 (18.5)	46 (32.2)	0.41 (0.24-0.69)	<0.001*	0.40 (0.23-0.70)	0.001*
≥4-unit increase in SGRQ[a], n (%)	47 (21.6)	41 (28.1)	0.69 (0.42-1.14)	0.145	0.63 (0.37-1.07)	0.086
≥8-unit increase in SGRQ[a], n (%)	24 (11.0)	20 (13.7)	0.77 (0.40-1.48)	0.433	0.74 (0.37-1.45)	0.377
≥2-unit increase in CAT[a], n (%)	69 (31.8)	39 (26.5)	1.20 (0.75-1.94)	0.448	1.16 (0.70-1.93)	0.567
≥4-unit increase in CAT[a], n (%)	38 (17.5)	24 (16.3)	1.03 (0.58-1.83)	0.925	1.04 (0.57-1.91)	0.901
≥1-unit increase in MRC[a], n (%)	35 (17.6)	18 (13.2)	1.22 (0.63-2.37)	0.548	1.45 (0.71-2.97)	0.313
Event-based exacerbation rate between V2 to V3[b], no./patient-year	0.3	0.21	1.29 (0.89 - 1.87)	0.178	1.36 (0.92 - 2.03)	0.124
Event-based exacerbation rate in 1-year follow-up from V2[b], no./patient-year	0.34	0.26	1.15 (0.75 - 1.75)	0.529	1.21 (0.77 - 1.89)	0.416
Event-based exacerbation in 1-year follow-up from V2[c], n (%)	42 (21.2)	22 (16.8)	1.20 (0.88 - 1.62)	0.248	1.28 (0.92 - 1.78)	0.14

a. OR were calculated using logistic regression model.

b. moderate/severe exacerbation incident rate between V2 to V3 or follow-up 1-year after V2, and RR (95% CI) were calculated using Poisson regression model.

c. a new moderate/severe exacerbation from V2 and HR (95% CI) was calculated using Cox model.

Model 1 series were adjusted for baseline age, sex, BMI, and smoking pack-years.

Model 2 series were adjusted for baseline age, sex, BMI, smoking pack-years, any CVD, and Absolute EOS count.

Composite CID +: Those demonstrating CID (positive for at least one of the three components of the composite).

Table 3 A. Association of exacerbation component of short-term CID-D1 (composite of decrease of ≥100 mL in post-BD FEV1; an increase of ≥4 units in SGRQ score; and incidence of a moderate/severe exacerbation) with outcomes over 18 months of follow-up

	COPD population					
	Exacerbation Component					
	CID Component + n (%)	CID Component - n (%)	CID Component + vs. CID Component- (model1) OR /HR/RR (95% CI)	P value	CID Component + vs. CID Component- (model2) OR /HR/RR (95% CI)	P value
Outcome (change from V2 to V3)						
≥100 mL decrease in FEV1[a], n (%)	7 (29.2)	158 (46.2)	0.61 (0.24-1.57)	0.307	0.56 (0.20-1.56)	0.264
≥200 mL decrease in FEV1[a], n (%	4 (16.7)	83 (24.3)	0.78 (0.24-2.46)	0.666	0.62 (0.17-2.28)	0.469
≥4-unit increase in SGRQ[a], n (%)	5 (21.7)	83 (24.2)	0.79 (0.27-2.27)	0.661	1.17 (0.39-3.54)	0.782
≥8-unit increase in SGRQ[a], n (%)	5 (21.7)	39 (11.4)	2.61 (0.85-8.02)	0.095	4.31 (1.29-14.41)	0.018*
≥2-unit increase in CAT[a], n (%)	8 (34.8)	102 (29.3)	1.17 (0.46-2.98)	0.741	1.40 (0.51-3.88)	0.516
≥4-unit increase in CAT[a], n (%)	5 (21.7)	58 (16.7)	1.18 (0.40-3.49)	0.768	1.66 (0.53-5.18)	0.382
≥1-unit increase in MRC[a], n (%)	4 (18.2)	49 (15.4)	1.09 (0.31-3.77)	0.897	1.56 (0.42-5.74)	0.504
Event-based exacerbation rate in 1-year follow-up from V2[b], no./patient-year	1.15	0.24	4.26 (2.65 - 6.85)	<0.001*	4.39 (2.63 - 7.33)	<0.001*
Event-based exacerbation rate between V2 to V3[b], no./patient-year	0.98	0.19	4.73 (3.10 - 7.22)	<0.001*	5.75 (3.60 - 9.18)	<0.001*
Event-based exacerbation in 1-year follow-up from V2[c], n (%)	14 (53.8)	50 (16.5)	2.54 (1.62 - 4.00)	<0.001*	2.56 (1.55 - 4.23)	<0.001*

CID component +: Among the CID positive group, those demonstrating the CID component reported in the table (Exacerbation component).

CID-D1: composite of decrease of ≥100 mL in post-BD FEV1; increase of ≥4 units in SGRQ score; and incidence of a moderate/severe exacerbation

a. OR were calculated using logistic regression model.

b. moderate/severe exacerbation incident rate V2-V3 or follow-up 1-year after V2, and RR (95% CI) were calculated using Poisson regression model.

c. a new moderate/severe exacerbation from V2 and HR (95% CI) was calculated using Cox model.

Model 1 series were adjusted for baseline age, sex, BMI, and smoking pack-years.

Model 2 series were adjusted for baseline age, sex, BMI, smoking pack-years, any CVD, and Absolute EOS count.

Table 3 B. Association of health status component of short-term CID-D1 with outcomes over 18 months of follow-up

	COPD population					
	Health status Component (SGRQ)					
	CID Component +	CID Component -	CID Component + vs. CID Component- (model1)		CID Component + vs. CID Component- (model2)	
	n (%)	n (%)	OR /HR/RR (95% CI)	P value	OR /HR/RR (95% CI)	P value
Outcome (change from V2 to V3)						
≥100 mL decrease in FEV1[a], n (%)	34 (36.2)	127 (47.9)	0.63 (0.38-1.03)	0.068	0.68 (0.40-1.15)	0.153
≥200 mL decrease in FEV1[a], n (%	19 (20.2)	67 (25.3)	0.77 (0.43-1.39)	0.384	0.80 (0.43-1.52)	0.499
≥4-unit increase in SGRQ[a], n (%)	11 (11.8)	77 (28.4)	0.33 (0.17-0.66)	0.002*	0.30 (0.14-0.64)	0.002*
≥8-unit increase in SGRQ[a], n (%)	7 (7.5)	37 (13.7)	0.53 (0.23-1.23)	0.14	0.50 (0.20-1.26)	0.141
≥2-unit increase in CAT[a], n (%)	19 (20.4)	89 (32.8)	0.53 (0.30-0.94)	0.031*	0.58 (0.31-1.07)	0.079
≥4-unit increase in CAT[a], n (%)	12 (12.9)	50 (18.5)	0.66 (0.33-1.32)	0.241	0.73 (0.35-1.50)	0.385
≥1-unit increase in MRC[a], n (%)	14 (16.3)	39 (15.7)	1.24 (0.61-2.52)	0.551	1.58 (0.74-3.36)	0.24
Event-based exacerbation rate in 1-year follow-up from V2[b], no./patient-year	0.42	0.27	1.42 (0.94 - 2.14)	0.095	1.49 (0.96 - 2.31)	0.076
Event-based exacerbation rate between V2 to V3[b], no./patient-year	0.34	0.24	1.38 (0.96 - 1.98)	0.082	1.39 (0.95 - 2.05)	0.094
Event-based exacerbation in 1-year follow-up from V2[c], n (%)	23 (27.1)	41 (16.8)	1.34 (0.98 - 1.82)	0.067	1.33 (0.96 - 1.86)	0.089

CID component +: Among the CID positive group, those demonstrating the CID component reported in the table (health status decline component).

CID-D1: composite of decrease of ≥100 mL in post-BD FEV1; increase of ≥4 units in SGRQ score; and incidence of a moderate/severe exacerbation

a. OR were calculated using logistic regression model.

b. moderate/severe exacerbation incident rate V2-V3 or follow-up 1-year after V2, and RR (95% CI) calculated using Poisson regression model.

c. a new moderate/severe exacerbation from V2 and HR (95% CI) was calculated using Cox model.

Model 1 series were adjusted for baseline age, sex, BMI, and smoking pack-years.

Model 2 series were adjusted for baseline age, sex, BMI, smoking pack-years, any CVD, and Absolute EOS count.

Table 3 C. Association of FEV1 decline component of short-term CID-D1 with outcomes over 18 months of follow-up

	COPD population					
	FEV1 Decline Component					
	CID Component +	CID Component -	CID Component + vs. CID Component- (model1)		CID Component + vs. CID Component- (model2)	
	n (%)	n (%)	OR /HR/RR (95% CI)	P value	OR /HR/RR (95% CI)	P value
Outcome (change from V2 to V3)						
≥100 mL decrease in FEV1[a], n (%)	44 (28.0)	121 (57.9)	0.24 (0.15-0.38)	<0.001*	0.22 (0.13-0.37)	<0.001*
≥200 mL decrease in FEV1[a], n (%	22 (14.0)	65 (31.1)	0.28 (0.16-0.51)	<0.001*	0.26 (0.13-0.49)	<0.001*
≥4-unit increase in SGRQ[a], n (%)	38 (24.1)	50 (24.0)	1.00 (0.61-1.63)	0.987	0.92 (0.54-1.57)	0.76
≥8-unit increase in SGRQ[a], n (%)	16 (10.1)	28 (13.5)	0.69 (0.36-1.35)	0.284	0.69 (0.33-1.40)	0.301
≥2-unit increase in CAT[a], n (%)	53 (33.5)	57 (26.8)	1.28 (0.81-2.03)	0.295	1.27 (0.77-2.09)	0.358
≥4-unit increase in CAT[a], n (%)	29 (18.4)	34 (16.0)	1.11 (0.64-1.94)	0.71	1.03 (0.56-1.89)	0.916
≥1-unit increase in MRC[a], n (%)	25 (17.2)	28 (14.3)	0.96 (0.51-1.82)	0.897	0.99 (0.49-1.99)	0.983
Event-based exacerbation rate in 1-year follow-up from V2[b], no./patient-year	0.29	0.33	0.82 (0.55 - 1.22)	0.332	0.87 (0.57 - 1.33)	0.51
Event-based exacerbation rate between V2 to V3[b], no./patient-year	0.23	0.25	0.80 (0.56 - 1.15)	0.23	0.88 (0.60 - 1.31)	0.542
Event-based exacerbation in 1-year follow-up from V2[c], n (%)	29 (19.9)	35 (19.1)	1.02 (0.76 - 1.36)	0.906	1.14 (0.83 - 1.56)	0.419

CID component +: Among the CID positive group, those demonstrating the CID component reported in the table (FEV1 decline component).

CID-D1: composite of decrease of ≥100 mL in post-BD FEV1; increase of ≥4 units in SGRQ score; and incidence of a moderate/severe exacerbation

a. OR were calculated using logistic regression model.

b. moderate/severe exacerbation incident rate V2-V3 or follow-up 1-year after V2, and RR (95% CI) were calculated using Poisson regression model.

c. a new moderate/severe exacerbation from V2 and HR (95% CI) was calculated using Cox model.

Model 1 series were adjusted for baseline age, sex, BMI, and smoking pack-years.

Model 2 series were adjusted for baseline age, sex, BMI, smoking pack-years, any CVD, and Absolute EOS count.

Table 4. Baseline characteristics of groups identified based on FEV1 trajectories

	COPD subjects (n=366)			
	Total	**Group1**	**Group2**	**P value**
	N=366	**N=199**	**N=167**	
Age, in year	66.5 ± 9.5	68.3 ± 9.0	64.5 ± 9.7	<0.001*
Sex, male gender, n (%)	218 (59.6)	70 (35.2)	148 (88.6)	<0.001*
BMI	27.2 ± 5.4	27.3 ± 6.3	27.1 ± 4.0	0.78
Smoking status, n (%)				
Never	110 (30.1)	52 (26.1)	58 (34.7)	0.074
Former	180 (49.2)	97 (48.7)	83 (49.7)	0.855
current	76 (20.8)	50 (25.1)	26 (15.6)	0.025*
Pack years of cigarettes	21.5 ± 23.5	25.5 ± 24.3	16.7 ± 21.6	<0.001*
MRC Dyspnea scale Score ≥ 3/5, n (%)	19 (5.4)	17 (9.1)	2 (1.2)	<0.001*
$FEV_{1,}$ L	2.4 ± 0.8	1.8 ± 0.4	3.0 ± 0.5	<0.001*
FEV_1, % predicted	81.4 ± 18.1	72.2 ± 16.0	92.3 ± 13.9	<0.001*
SGEQ-Total	15.7 ± 14.7	20.5 ± 15.8	10.0 ± 10.9	<0.001*
CAT score	0.7 ± 0.5	0.6 ± 0.5	0.8 ± 0.4	<0.001*
SF36 Physical component scale	50.9 ± 8.2	49.2 ± 8.6	52.9 ± 7.3	<0.001*
SF36 Mental component scale	50.0 ± 9.2	50.8 ± 7.7	49.0 ± 10.6	0.224
Respiratory medications reported in the past 12 months, n (%)				
SABD	30 (8.2)	23 (11.6)	7 (4.2)	0.011*
LABA or LAMA	6 (1.6)	5 (2.5)	1 (0.6)	0.226
ICS alone	32 (8.7)	20 (10.1)	12 (7.2)	0.334
ICS combined with LABA/LAMA	71 (19.4)	56 (28.1)	15 (9.0)	<0.001*
Any above medications	139 (38.0)	104 (52.3)	35 (21.0)	<0.001*
Thawed blood EOS				
Absolute count, count/ microliter	0.23 ± 0.16	0.24 ± 0.16	0.21 ± 0.16	0.024*
Percentage, %	5.15 ± 3.68	5.33 ± 3.96	4.95 ± 3.34	0.397
FEV1 CID +	157 (42.9)	89 (44.7)	68 (40.7)	0.441
CAT CID +	107 (29.4)	59 (29.8)	48 (28.9)	0.908
SGRQ CID +	94 (26.2)	55 (27.9)	39 (24.1)	0.469
Exacerbation CID +	24 (6.6)	21 (10.6)	3 (1.8)	<0.001*
Any CID + (FEV1, SGRQ, and Exacerbation)	217 (60.3)	125 (63.5)	92 (56.4)	0.195
Any CID + (FEV1, CAT, and Exacerbation)	224 (61.2)	125 (62.8)	99 (59.3)	0.49

5.2 Preface Study 2: Further Research Approved Protocol [Short Title "External Validation of CanCOLD findings for CID in the UK-CPRD"]

Title: *Short-term clinically important deterioration (CID) as an indicator of medium and long-term Chronic Obstructive Pulmonary Disease (COPD) progression: An external validation of Canadian population-based longitudinal Cohort findings in the UK primary care population.*

In recent COPD literature, as described in the chapter on background, a composite outcome index comprising of lung function decline, exacerbation, and changes in experienced health status, namely Clinically Important Deterioration (CID), has been proposed to identify individuals who are at higher risk of having important changes in disease-course (Manuscript 1: [9,36]). It has been used as a surrogate outcome measure (Manuscript 1: [18]) as well as a short-term predictor of change over a longer duration (Manuscript 1: [17,23]). Findings from study 1 (detailed in manuscript 1) suggest that in a population-based cohort of individuals with mild-moderate COPD, short-term CID is not able to predict short-term declines in disease and dyspnoea. However, its components of exacerbation and health status measures were found to be informative. Since a) the study was unable to confirm findings from past studies, which were largely from clinical cohorts of individuals with more advanced disease; b) also not able to examine different follow-up periods, a decision to assess the reproducibility of the findings from the CanCOLD cohort in a large cohort that would also be supportive of a longer follow-up period was made.

Since the target population is mild-moderate COPD, resembling the primary care/ family practice patient population, the UK-CPRD emerged as the most suitable source of data to identify a cohort to re-evaluate our findings from the CanCOLD cohort. UK-CPRD has been described in the earlier chapter on data and methods.

Also, on the aspect of feasibility for the availability of variables such as repeated spirometry measurements, health status and dyspnoea score, hospitalisation, and treatment data, as well as the potential for including biomarkers, the UK-CPRD was found suitable.

Based on preliminary assessments prior to the development of Manuscript 1, I, as the corresponding investigator, under the guidance of my supervisor and thesis advisory committee members, proposed the study to re-assess CanCOLD findings and conduct further studies to find suitable definitions for CID in this population.

The detailed protocol submitted to the CPRD was approved, and the approved protocol is included in the thesis as Appendix 1 [Supplementary Material: Manuscript 1]. The proposal includes considerations to allow for the examination of whether the period used for CID assessment and/or the duration of the following outcome-assessment period impact the prediction performance.

Unforeseeable challenges have been overcome, and the data access stage has been initiated.

6. Research Theme 2: Prediction of acute exacerbation in mild-moderate COPD population

6.1 Preface: [Short Title "ACCEPT 2.0 in CanCOLD study cohort of participants with mild-moderate COPD."]

Title: *Assessing model performance of the Acute chronic obstructive pulmonary disease (COPD) Exacerbation Prediction Tool (ACCEPT) 2.0 in mild-moderate chronic obstructive pulmonary disease (COPD) population from the Canadian Cohort of Obstructive Lung Disease (CanCOLD).*

A composite measure functioning as a surrogate outcome, like CID, discussed in the last chapter, can be an important clinical tool that helps clinicians assess the impact of their treatment decisions. Being a composite measure, it supports holistic assessment. Thus, making it a potential variable in risk-prediction models together with other informative variables given the heterogeneity of COPD for models calibrated to the uniqueness of the sub-groups observed. However, there are risk prediction models developed for the purpose of identifying the risk of crisis events known to alter disease progression, such as acute exacerbations in the case of patients with COPD. These models can also be useful in identifying those at elevated risk based on predicted risk, and thus, these are important assets in bridging the knowledge gap in the characterization of those susceptible to rapid decline to target early intervention. Notably, most prediction models in COPD have been developed and refined in clinical cohorts of moderate-

severe COPD. Important (clinically) models in COPD have been discussed in detail in the chapter on background.

The current chapter is dedicated to presenting my assessment of a parsimonious model for clinical use, available online and recently recalibrated to augment generalizability to help assess the risk and severity of future exacerbation among patients with COPD. This is the Acute COPD Exacerbation Prediction Tool (ACCEPT) 2.0.

In Manuscript 2, I have highlighted differences between populations informing model recalibration to understand observations from a mild-moderate COPD population-based cohort. The individuals with mild-moderate COPD have greater potential to deteriorate, which also makes them the group to benefit maximally from suitable mitigation options. I discuss important differences and results of model performance in the study population by also redefining the outcome event. The references relevant to the manuscript are included in this chapter.

6.1.1 Manuscript 2

TITLE: ACCEPT 2.0 in CanCOLD study cohort of participants with mild-moderate COPD.

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ABSTRACT

Introduction: There is an acute need to identify at-risk populations in mild-moderate Chronic Obstructive Pulmonary Disease (COPD) to personalize care for those likely to decline rapidly and to be able to develop targeted therapeutic options. We assessed and compared the model Acute COPD Exacerbation Prediction Tool (ACCEPT) 2.0 to the history of exacerbation alone among those with mild-moderate COPD.

Methods: We used the data from the Canadian Cohort Obstructive Lung Disease (CanCOLD) study and compared the area under the receiver operating characteristic curve [AUC (c-statistic)] for ACCEPT 2.0 model vs history of exacerbation alone in this population alongside calibration plots. Two additional outcomes were defined for the model: a) any exacerbation (symptom-based) and b) any moderate/severe exacerbation.

Results: 473 CanCOLD participants with mild-moderate COPD with complete data available at the study visit- 3 were included for analysis. The characteristics of this population were similar to the reported ACCEPT model cohorts for sex, age and BMI.

Compared to the history of exacerbation in the last 12 months, the ACCEPT 2.0 model emerged superior in discrimination accuracy [$AUC_{ACCEPT2.0\text{-ANY EXACERBATION}}$ (95% Confidence Interval - CI) =0.71 (0.65, 0.76) vs $AUC_{EXACERBATION}$ (95% CI) = 0.64 (0.59, 0.69), *p-value*=0.002*); $AUC_{ACCEPT2.0\text{-ANY MODERATE/SEVERE EXACERBATION}}$ =0.75 (0.67, 0.83) vs $AUC_{EXACERBATION}$ = 0.65 (0.57, 0.72), *p-value*=0.001*].

Examination of the calibration plots reveals that the ACCEPT 2.0 model underestimated the rate of any exacerbation if < 0.4.

Discussion: Our findings suggest that the recently recalibrated ACCEPT 2.0 model is an important step towards the tool needed to support clinicians and those developing targeted treatments in the mild-moderate disease population. However, the current study also indicates the potential need for additional variables to the model, such as comorbidity, biomarkers, etc., which may improve model performance in this population by adding important information on the target population to support the difference in the treatment profile and the lower frequency of experienced exacerbation and.

Keywords (6): mild-moderate Chronic Obstructive Pulmonary Disease (COPD), Exacerbation, Acute COPD Exacerbation Prediction Tool (ACCEPT) 2.0, Canadian Cohort Obstructive Lung Disease (CanCOLD), external validation, personalized risk prediction

Plain Language Summary (optional) 250 words

Chronic Obstructive Pulmonary Disease (COPD) significantly burdens the quality-of-life experience and healthcare costs. While the focus has been on those with severe illness, there is

an emerging recognition to focus on early identification and treatment targeting inclusive of mild-moderate disease.

Given the variations observed in disease manifestation and progression, a clinical tool, such as the Acute COPD Exacerbation Prediction Tool (ACCEPT), could support primary-care physicians in predicting the individualized risk of deterioration and personalizing patient care. Such tools could support the development of targeted interventions through the identification of at-risk populations.

Studies in COPD have largely investigated moderate-severe hospitalized patients, which are largely used in developing prediction models. This study assessed the ACCEPT 2.0 tool in the Canadian Cohort Obstructive Lung Disease (CanCOLD) study participants who are non-hospitalised individuals with mild-moderate COPD.

The tool was found to predict the future exacerbation with promising accuracy and comparatively superior to relying only on the history of exacerbation. However, patients with a lower annual rate of exacerbations were underestimated. This is a challenge since the mild-moderate disease population differs in exacerbation experience compared to severe disease populations.

Though the ACCEPT 2.0 model has been developed in the moderate-severe disease population, it has been adjusted to be applicable to a wider COPD population. Our findings suggest the need for further “tunning” to adapt the model to the mild-moderate disease population. Whether the addition of information such as comorbidity and biomarkers available to clinicians may further support such efforts remains to be investigated.

[250]

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a progressively deteriorating condition marked by increasing difficulty in breathing and decreasing quality of life experienced from irreversible damage of lung tissue [1,2]. Cloaked under the seemingly benign 'long-term lung problem' (simply put), COPD is a rather complex progressive respiratory disorder, understood as a syndrome, with diverse underlying pathophysiology and influence of comorbidities contributing to the heterogeneity in presentation and progression. While smoking is an important risk factor [3], more recent reports of non-smokers among 30% of those with COPD [4], occurrences among the younger population [5], and contributors such as air pollution [6,7], biomass [8], genetic [9] and lung developmental factors [10] mark the increasing understanding of this complex condition.

While being associated with underdiagnosis and late diagnosis after a significant loss] of the affected individual's lung capacity [11], COPD is a leading cause of hospital stays in Canada (second to only hospitalizations for childbirth) for 2022-23 [12] and the third leading cause of mortality, globally. Estimates of the global macroeconomic burden of COPD for 2020-2050 identify the high-income countries to face the highest burden in absolute terms, with the USA among the countries facing the highest burdens expressed per capita and share of GPD while low- and middle-income countries would face the highest health burden [13].

In COPD, disease progression is interspersed with acute episodes of exacerbations or 'lung attacks', which accelerate lung function decline, and such episodes have been reported even among those at a milder disease severity stage [14,15]. Studies have reported clustering of such events among those with severe exacerbations [16,17] and re-admissions in such individuals to

be associated with mortality [18]. As a result, COPD management revolves around the prevention and management of these precursory events, while the current focus is on arresting rapid decline by identifying susceptibility and targeting treatment early [19]. Thus, being able to predict exacerbation is a critical tool to enable clinicians, primarily primary-care/family physicians, to administer individualized treatment.

The Acute COPD Exacerbation Prediction Tool (ACCEPT) 2.0 [20] could be instrumental to this strategy and may hold the key to mitigating the burden of COPD on patients and the healthcare system. The originally proposed model for ACCEPT [21] has been re-calibrated for wider application, it remains to be validated in mild-moderate non-hospitalised COPD cohort. We propose to assess the model performance of ACCEPT 2.0 in the population-based longitudinal cohort of the Canadian Cohort Obstructive Lung Disease (CanCOLD; NCT00920348) [22].

METHODS

Study population

The CanCOLD study has 1556 participants made up of individuals with COPD [as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD)] [19] and age and sex-matched non-COPD controls, including smokers and non-smokers [22]. CanCOLD has a median follow-up of 9.9 years (IQR =7.9-10.9 years). across 4 in-site visits: first (2009-2015), second (2011-2015), third (2013-2019), and fourth (2022- 2024 ongoing), along with participant-reported exacerbation data collected through quarterly telephonic questionnaires [23].

Measurements

The main analysis population included CanCOLD participants with mild-moderate COPD (GOLD 1 and 2, thus excluding those with post-bronchodilator FEV1/FVC≥0.7 or GOLD3 and GOLD4) with available exacerbation data 12 months pre-visit-3 and 12 months post-visit 3. While a history of exacerbation [event-based definitions of the Global Initiative for Chronic Obstructive Lung Disease (GOLD)] over the past 12 months is a predictor in the model, the model predictions involve exacerbations experienced in the 12-month follow-up period post-visit 3. The other predictors in the model include age, sex, BMI, FEV1 % predicted, SGRQ score, smoking status (current smoker), treatment with oxygen therapy, long-acting muscarinic antagonist (LAMA), long-acting β2-agonist (LABA), inhaled corticosteroid (ICS) and statins.

Primary and secondary outcomes

For the current analysis, given the mild-moderate COPD population, the primary outcome of "any exacerbation" (symptom-based exacerbations) was defined as the presence of at least 1 major symptom (increased dyspnea, increased sputum volume, or increased sputum purulence) for at least 48 hours. while secondary outcome was considered as "any moderate/ severe exacerbation", defined as the presence of ≥ 1 exacerbation that required treatment with antibiotics and/or oral corticosteroids for moderate exacerbation or requiring visits to the emergency room or hospitalization for severe exacerbations. We also assessed for "moderate/severe outcomes" as used for the ACCEPT 2.0 model, i.e., defined as ≥ 2 moderate/ ≥ 1 severe exacerbations.

Statistical analysis

Time-dependent receiver operating characteristic curve (ROC) at 1-year follow-up were plotted for primary and secondary outcomes for the ACCEPT 2.0 model and only a 12-month history of exacerbation (prior to visit-3). The area under the ROC or AUC (c-statistic) was reported with a 95% confidence interval (CI). The AUCs were compared using the DeLong test.

The model predictions were obtained using the ACCEPT 2.0 R- package [24], while SAS 9.4 software was used for the analysis discussed in the study.

RESULTS

Out of the 1198 CanCOLD participants completing visit-3, 473 with mild-moderate COPD and with data available for exacerbation in the past 12 months, as well as 12 months of follow-up from visit-3 were included in the study [Figure 1].

The characteristics of this population were similar to the reported ACCEPT model cohorts [20] in being predominantly male, mean age >60 years, and similar average BMI. However, they were comprised of lower numbers of smokers, reporting better quality of life, with higher FEV1 % predicted, where fewer individuals were on oxygen therapy, statins, LAMA, LABA, and ICS [Table 1]. The study population had very low rates of "any exacerbation", moderate or severe, or severe exacerbation experiences in the preceding 12 months.

The AUC (c-statistic) for "any future exacerbation" was 0.709, as seen in Figure 2 [0.754 for "any moderate/severe exacerbation" and 0.731 for "≥ 2 moderate/ ≥ 1 severe exacerbations"]. On examining the model calibration plots, the ACCEPT 2.0 model was found to underestimate outcomes when the annual rate of any exacerbation < 0.4 [Figure 3].

Compared to the history of exacerbation in the last 12 months, the ACCEPT 2.0 model emerged superior in discriminating between those who experienced exacerbation vs those who did not during the 12-months follow-up as seen in Table 2 [$AUC_{ACCEPT2.0\text{-}ANY\ EXACERBATION}$ (95% Confidence Interval -CI) =0.71 (0.65-0.76) vs $AUC_{EXACERBATION}$ (95% CI) = 0.64 (0.59, 0.69); *p-value*=0.002*)] and as well in the case of any moderate/severe exacerbations [$AUC_{ACCEPT2.0\text{-}ANY\ MODERATE/SEVERE\ EXACERBATION}$ (95% CI) =0.75 (0.67-0.83) vs $AUC_{EXACERBATION}$ (95% CI) = 0.65 (0.57, 0.72); *p-value*= 0.001*)]. For ≥ 2 moderate/ ≥ 1 severe exacerbation, the $AUC_{ACCEPT2.0}$ (95% CI) =0.73 (0.59-0.88) vs $AUC_{EXACERBATION}$ (95% CI) = 0.62 (0.50, 0.74); *p-value*= 0.085).

DISCUSSION

The current study confirms the superiority of using the ACCEPT 2.0 model to predict exacerbations compared to predicting exacerbations based only on the history of exacerbation in the previous year. However, the model was limited to predicting exacerbations with accuracy when subjects with COPD had a very low annual rate, such as any exacerbation < 0.4.

The team developing ACCEPT has undertaken external validation assessments towards the generalizability of the model, recalibrated the model, and updated it to ACCEPT 2.0, which is a further parsimonious model, making it easy to administer in a clinical setup. ACCEPT 2.0 needed to be validated in an external population having similar characteristics to the population used to develop the model. CanCOLD was selected as a non-hospitalized cohort of individuals with mild-moderate COPD representative of the real-life primary-care/family medicine practice patient population.

In a previously reported validation study using the Towards a Revolution in COPD Health (TORCH) cohort, ACCEPT 2.0 emerged superior to predictors of future risk like history of

exacerbation as described in current literature, while showing good calibration irrespective of the exacerbation history of the underlying population [20]. However, patients in TORCH were more severe with inclusion prebronchodilator FEV1 of less than 60% predicted and a higher history of previous exacerbations.

We modified the definitions of primary and secondary outcomes when assessing the model in the context of the analysis population of those with mild-moderate COPD. The model was superior to the history of exacerbation in predicting future risk in the study population. This is consistent with previous reports from clinical cohorts [20]. The model discrimination is in similar c-static ranges as has been reported. The ACCEPT model [21] was originally developed using data from 3 one-year clinical trials of MACRO [25], STATCOPE [26], and OPTIMAL [27], where participants were individuals with moderate to severe COPD with a positive history of exacerbation. The model was externally validated using the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) cohort [28] that included patients with moderate to very severe disease and high risk of exacerbations. The authors recalibrated the ACCEPT model using the ECLIPSE cohort to adjust for the reported overestimation of risk among individuals without recent exacerbations and externally validated version 2.0 in the TORCH cohort where three-year data was available [20]. In the mild-moderate COPD study population from the CanCOLD study, we observed the model underestimated risk in those with very low event rate scenarios. Here, it is to be noted that the modified definition included ‘any exacerbations’ as any mild/moderate/severe exacerbation events, and we could not evaluate the outcome of severe exacerbation in view of the characteristics of the underlying population.

The study has strengths and limitations. To our knowledge, this is the first assessment of ACCEPT 2.0 in a North American population-based cohort of mild-moderate COPD. CanCOLD

is a well-defined cohort with a median follow-up period of 9.9 years (IQR 7.9-10.9 years) [20] with 4 on-site visits allowing for recurrent post-bronchodilator spirometry data to reconfirm "COPD" status in this mild-moderate disease population. Longitudinal follow-up for exacerbation data was collected through quarterly phone interviews. This study population had complete data at visit 3 for 12 months of history of exacerbation as well as 12 months of follow-up data for exacerbation. While it was outside the scope of the current study, this cohort can contribute to investigations of model adaptation for this population using a longer observation period for a history of exacerbation and additional predictors such as comorbidities and biomarkers.

We acknowledge many limitations to this study. The current model specifications have not been assessed to be applied with the modified exacerbation predictor and outcomes. However, this study observed reasonably high discrimination accuracy as reported from the external validation study, even with the use of the modified definitions in the context of the analysis population [20]. While 473 participants at visit 3 met inclusion criteria for the analysis study population, future visit data may allow for longer observation periods and the opportunity to include additional predictors as needed. Assessment of the current ACCEPT 2.0 model in larger cohorts of mild-moderate COPD, such as the UK Clinical Practice Research Datalink (CPRD) [29], may allow the opportunity to assess at-risk sub-populations with a varying definition of the exacerbation-based predictor and outcomes for a rigorous assessment towards adapting the individualized risk-prediction model for a population with mild-moderate COPD.

Given the complexity of heterogeneity in progress and prognosis among those with COPD, with the growing understanding of the impact of comorbidity burden on COPD progression [30] and pathophysiology-led emergence of biomarkers such as blood Eosinophil Counts [31-35], C-

reactive protein [36], in supporting prognosis and treatment decision, these could be potential informative predictors that could be considered in future model iterations especially in the mild-moderate population with COPD to supplement history of exacerbation predictor. Also, the observation duration and exacerbation severities to be included may be other assessments to be considered in this population. The findings of this study are supportive of future undertakings using large primary-care databases such as the UK-CPRD where long follow-ups and variables will be available to facilitate such assessments [37].

CONCLUSION

ACCEPT 2.0 is a promising clinical tool, and in view of the health and economic burden of the disease, this model could be pivotal to the strategy of personalized early intervention to arrest the rapid decline. Considering the recent finding that early detection of undiagnosed COPD and directed treatment results in a significant reduction in subsequent healthcare utilization for respiratory illness [38]. Assessments in larger cohorts of mild-moderate COPD are needed to adapt a version, including potential additional predictors, which would be beneficial to extend its use in the primary care patient population

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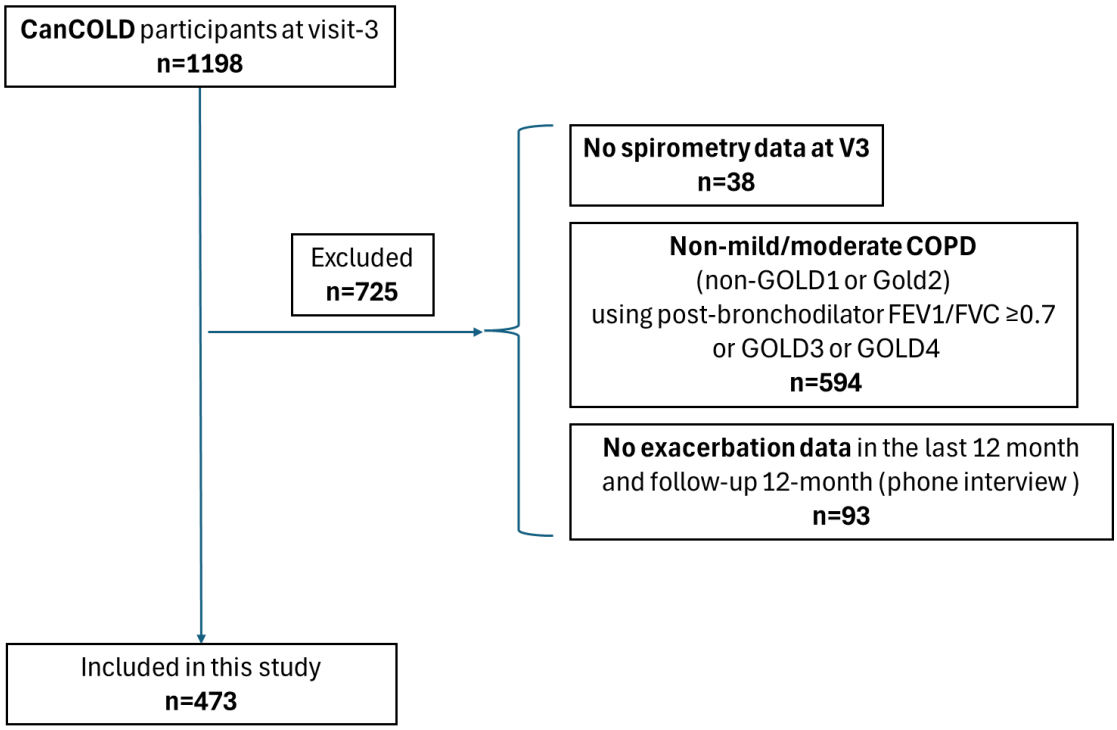


Figure 1: Flow diagram for identification of analysis population

Table1. Baseline characteristics of study population

	Total (n=473)
Sex, male gender, n (%)	289 (61.1)
Age, in year, mean (SD)	70.5 (9.3)
BMI, mean (SD)	27.4 (5.5)
Current smokers, n (%)	67 (14.2)
CAT score, mean (SD)	7.1 (6.3)
SGRQ total score, mean (SD)	14.1 (14.4)
FEV_1, % predicted, mean (SD)	84.8 (17.9)
GOLD stage1, n (%)	276 (58.4)
GOLD stage2+, n (%)	197 (41.6)
Oxygen therapy, n (%)	2 (0.4)
Statin, n (%)	97 (20.5)
LAMA, n (%)	27 (5.7)
LABA, n (%)	83 (17.5)
ICS, n (%)	111 (23.5)
Any exacerbation rate in the last 12-months, no./per-year	0.34 (0.69)
Moderate/Severe exacerbation rate in the last 12-months, no./per-year	0.13 (0.44)
Severe exacerbation rate in the last 12-months, no./per-year	0.03 (0.18)

SD= Standard Deviation; BMI= Body Mass Index; CAT= COPD Assessment Test; SGRQ= St. George's Respiratory Questionnaire; FEV1= Forced Expiratory Volume in 1 second; GOLD= Global Initiative for Chronic Obstructive Lung Disease; LAMA= Long-Acting Muscarinic Antagonist; LABA=Long-Acting Beta- Agonist; ICS= Inhaled corticosteroids

Table 2: Comparison of Time-Dependent AUC at 12 months for ACCEPT 2.0 vs only history exacerbation.

Outcome	ACCEPT2.0	Exacerbation history alone	P-value
	AUC (95% CI)	AUC (95% CI)	
Any exacerbation	0.71 (0.65, 0.76)	0.64 (0.59, 0.69)	0.002*
Any moderate/severe exacerbation	0.75 (0.67, 0.83)	0.65 (0.57, 0.72)	0.001*
Moderate/severe exacerbation (moderate ≥2 or severe ≥1)	0.73 (0.59, 0.88)	0.62 (0.50, 0.74)	0.085

ACCEPT 2.0 = Acute COPD Exacerbation Prediction Tool- recalibrated version 2.0; AUC=Area under the curve; CI= Confidence Interval.

Figure 2: Time dependent receiver operating characteristic curve (ROC) at 1-yearfollow-up

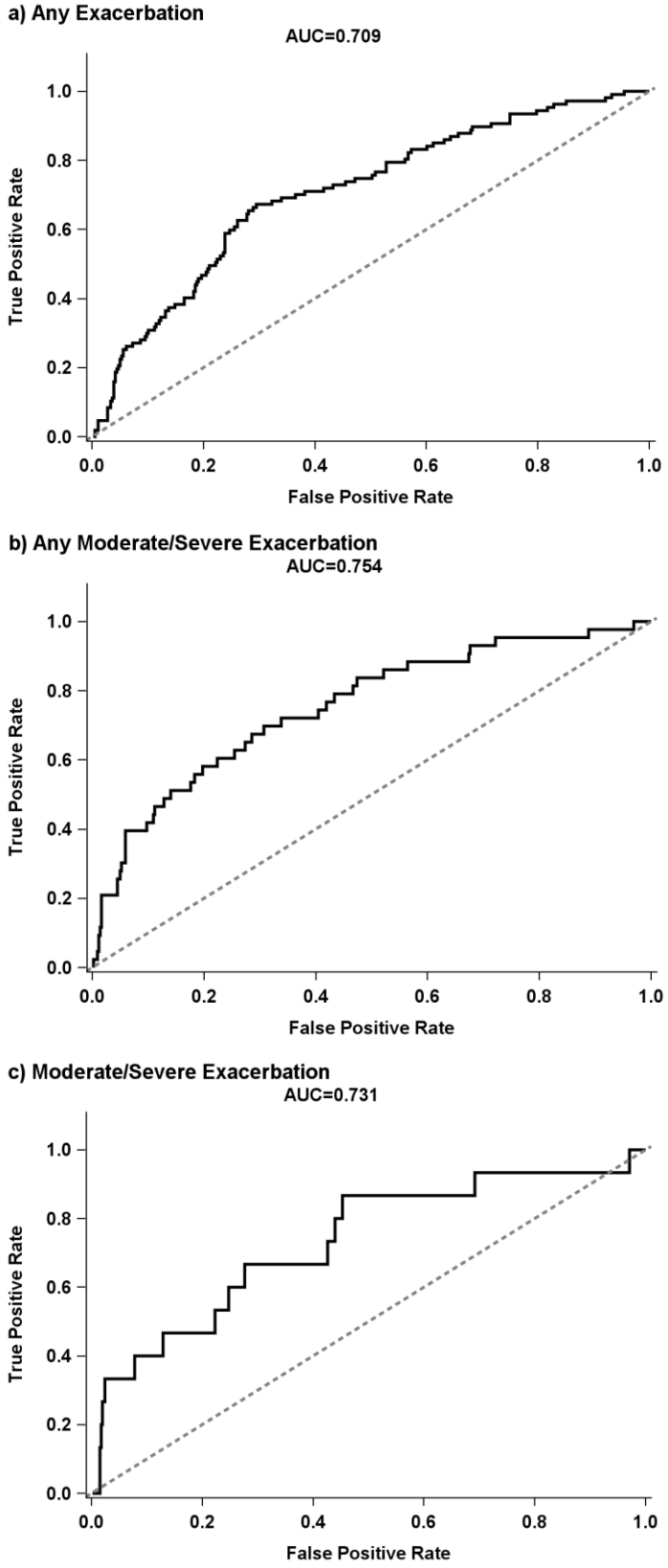
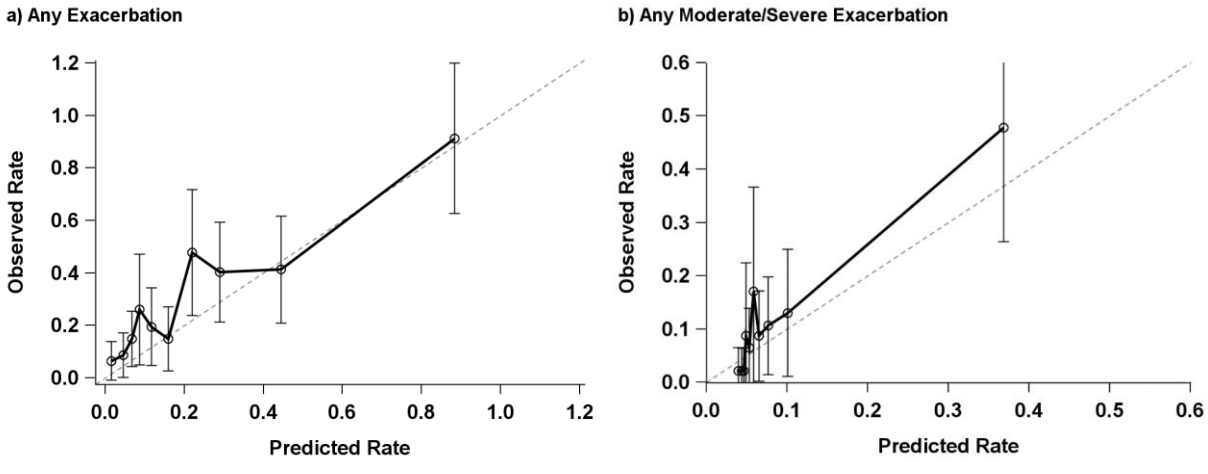


Figure 3: Calibration plots to assess the agreement between observed outcomes and predictions.



The curves are systematically above the diagonal line, indicating that the proportion of events is higher than those predicted for the respective intervals. Here the model underestimated events for lower exacerbation rates for any exacerbation and consistent underestimation in case of moderate/severe exacerbations.

7. Research Theme 3: Search for a potential marker of disease activity in COPD- a novel biomarker index

7.1 Preface: [Short Title "AGE/sRAGE ratio, a plausible disease activity marker in COPD."]

Title: *'AGE-RAGE stress,' a potential disease activity marker: Pathophysiology, clinical and therapeutic significance in Chronic Obstructive Pulmonary Disease (COPD).*

From the studies in this thesis, I have highlighted the uniqueness of individuals with mild-moderate COPD by examining a composite outcome and a risk prediction model. The concept of heterogeneity in COPD is well established and findings from the studies in this thesis indicate a unique information gap in this population. Potential variable or variable-combination that can capture a summary of the ongoing pathological pathways that are continually interacting and modifying the expression and progression of COPD, continues to be wanting. In this context, alongside potential biomarkers, multiple biomarker panels have also been examined as discussed in the chapter on background in this thesis. However, in this chapter, I examine a potential marker of disease activity: a ratio of two biomarkers, advanced glycation end products (AGE), and its soluble receptor sRAGE. In manuscript 3, I discuss the pathophysiology and rationale behind this choice. I review in detail prevalent knowledge supportive of the ratio as the potential variable that is able to calibrate a model or thresholds that may be indicators of ongoing decline potential.

The ratio of stressors and antistressors is not only intuitive but has been implicated in studies of various conditions, which are also comorbidities found amongst those with COPD. I have described biomarkers and comorbidities in the chapter on background; however, in Manuscript 3, I review the proposed ratio against the individual biomarkers and the underlying pathophysiological rationale in detail. Finally, I discuss potential remedies and some proposed therapeutics targeting components of the pathway involving AGE-RAGE interaction to highlight the potentials of the ratio, compared to the study of the individual biomarkers alone, in indicating risk-susceptibility. References are included within the manuscript below

7.1.1 Manuscript 3

Title: 'AGE-RAGE stress', a *potential disease activity marker*: Pathophysiology, clinical and therapeutic significance in Chronic Obstructive Pulmonary Disease (COPD).

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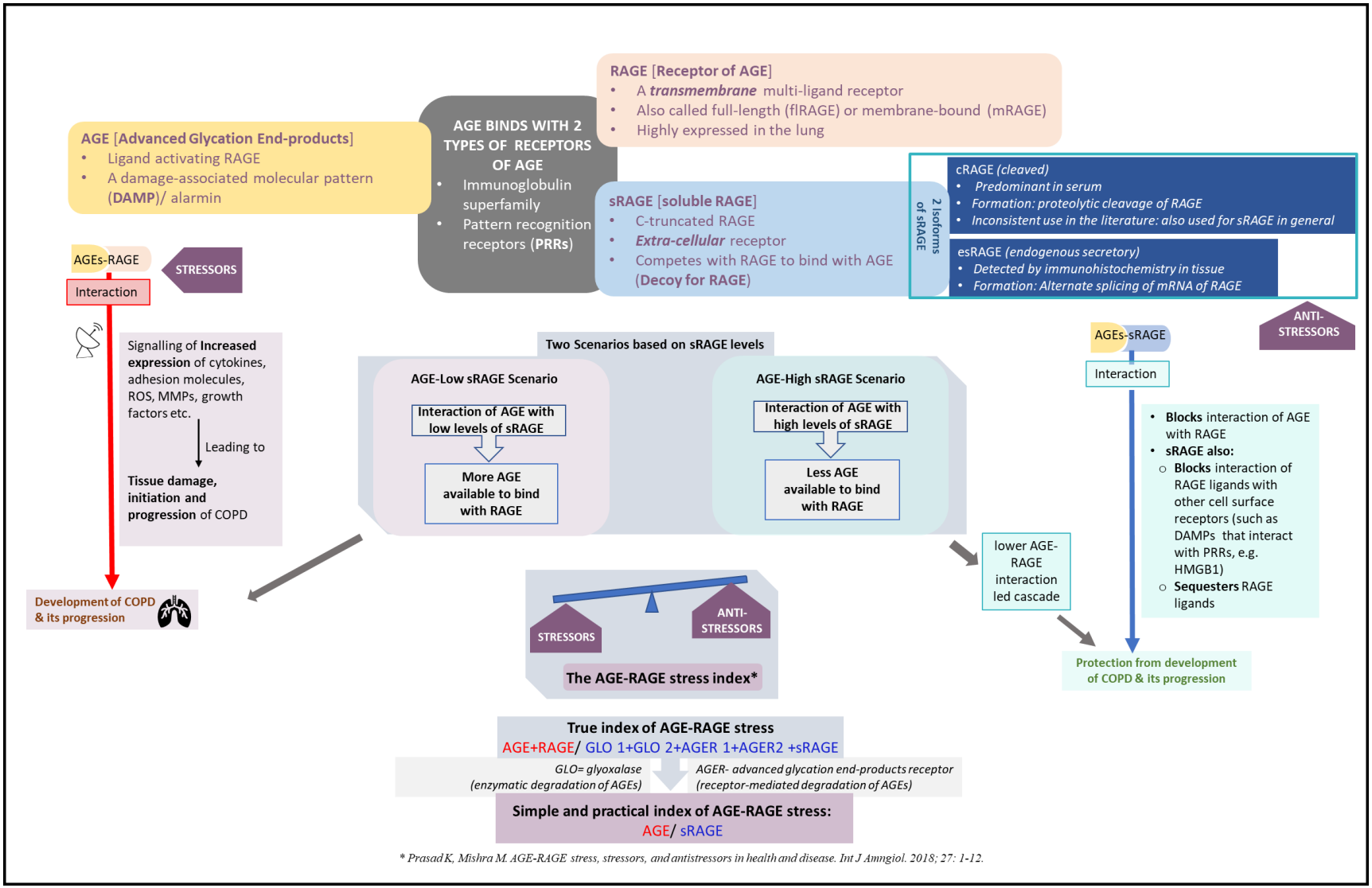
ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a progressive lung function deterioration condition characterized by bronchial lining inflammation, excessive mucus production, and alveolar damage. It is often associated with comorbid conditions and a combination of host characteristics and external exposures that leads to diverse potential pathological pathways responsible for the heterogeneous presentation and trajectories observed.

This paper describes a potential pathophysiology of COPD in association with levels of AGE (advanced glycation end products), its cell receptors (RAGE), soluble receptor (sRAGE), and 'AGE-RAGE stress.' The AGE-RAGE interaction produces biomolecules similar to known mediators of COPD, like ROS, protease-antiprotease imbalances, inflammation, cell adhesion molecules, and growth factors. sRAGE acts as a decoy for AGE, preventing the interaction between AGE and RAGE. We propose that the AGE-RAGE axis (AGE, RAGE, and sRAGE) potentially reflects disease activity where increased AGE and RAGE levels, in the presence of reduced sRAGE levels, increase the biomolecules associated with the initiation and progression of COPD.

AGE and its receptors have been studied as individual biomarkers in COPD. While reviewing these findings, this paper discusses 'AGE-RAGE stress' (AGE/sRAGE ratio) as a novel summary measure or index indicative of progression susceptibilities which could potentially have a role in developing clinical decision tools in early or milder disease stages. With this goal, we discuss potential pathophysiology to support the AGE/sRAGE ratio as a novel biomarker in COPD. The summary of this abstract is shown in Figure 1.

Graphic Abstract



* Prasad K, Mishra M. AGE-RAGE stress, stressors, and antistressors in health and disease. Int J Amngiol. 2018; 27: 1-12.

Figure 1. Graphic Abstract

Advanced glycation end products (AGE)-Receptors of advanced glycation end products (RAGE) interaction-induced mechanism tilts the balance towards disease progression. Whereas soluble RAGE (sRAGE), in the presence of high sRAGE levels, acts as a decoy for AGE, preventing this interaction and preventing disease development and progression. sRAGE may also sequester RAGE ligands and block the interaction of RAGE ligands with other cell surface receptors, like Toll-like receptions, preventing pro-inflammatory signaling. This study proposes that the AGE-RAGE axis (AGE, RAGE, and sRAGE) potentially reflects disease activity summary where increased AGE and RAGE levels, in the presence of reduced sRAGE levels, indicate an increase in biomolecules associated with initiation and progression of chronic obstructive pulmonary disease (COPD).

KEYWORDS

Advanced glycation end products (AGE), cell receptor for AGE (RAGE), soluble receptor for AGE (sRAGE), chronic obstructive pulmonary disease (COPD), risk factor, reactive oxygen species, proteases, antiproteases, NF-kB, cytokines, chemokines, mucin genes, treatment modalities, antioxidants

INTRODUCTION

Chronic obstructive pulmonary (COPD) is a chronic complex disease marked by not completely reversible airflow obstruction resulting from an interplay of multiple pathological processes in an individual, making prognosis and management challenging. COPD includes emphysema and chronic bronchitis. Chronic bronchitis is characterized by inflammation of the lining of the bronchial three and excessive mucus production [1]. Emphysema is characterized by damage to the alveoli. Tiny air sacs break down to form a large pocket reducing the overall surface area and the amount of oxygen exchange [2]. COPD is the third leading cause of death (3.23 million deaths) already by 2021 [3**].** In Canada, it is currently a leading cause of hospitalization [4] and is associated with a significant healthcare cost burden [5].
While most of the clinical research is prevalent among the advanced disease population, given the impact of COPD on quality of life and healthcare resources, a focus on early detection is warranted, and a disease activity biomarker can have a significant clinical impact on disease progression and management.

Cigarette smoking, along with inhalation of other noxious gases and particles, have been identified as potent contributors to the development and deterioration of COPD [6-9]. The lung injury is caused by inflammation, reactive oxygen species (ROS), and proteases (matrix metalloproteinases and elastase) [6]. Advanced glycation end products (AGE) and its cell receptors RAGE (receptor for AGE) and soluble receptors (sRAGE) have been implicated as risk factors in the development of numerous disease states, including atherosclerosis [10], coronary artery disease [11], hyperthyroidism [12], end-stage renal disease [13], non-ST-elevation myocardial infarction [14] and post-percutaneous coronary interventional restenosis

[15]. Interaction of AGE with RAGE increases the production of ROS [16], which activates Nuclear Factor-kappa B (NF-kB) [20], and increases the production of cytokines [18,19] and proteases [20]. These products are involved in the pathophysiology of COPD. Very little attention has been directed to the role of AGE and its receptors (AGE-RAGE axis) on the pathophysiology of COPD. Understanding the role of the AGE-RAGE axis in the pathophysiology of COPD would help form strategies for the prevention, slowing of progression, and regression of COPD. This knowledge can help support risk prediction and patient care management planning.

This review article focuses on presenting the concept and knowledge of the AGE-RAGE axis and AGE-RAGE stress. We discuss serum/plasma/ tissue levels of AGE, RAGE, and sRAGE in patients with COPD to understand whether the continuing focus on levels of AGE, sRAGE, and RAGE as individual biomarkers is helpful or if it is important to consider the complete AGE-RAGE axis and include a focus on the status of 'balance' of this axis as the biomarker (AGR/sRAGE ratio) which has implications in COPD.

AGE, RAGE production, function, AGE-RAGE-axis and 'stress':

AGE-RAGE axis

Nonenzymatic interaction of reducing sugars (Glucose, fructose, maltose, lactose) with proteins, lipids, and nucleic acids results in the formation of a heterogeneous group of irreversible adducts called advanced glycation end products (AGE) [21, 22]. There are mainly three receptors for AGEs: Full-length multiligand cell receptor (RAGE), C-truncated RAGE, which has two isoforms, cleaved RAGE (cRAGE), and endogenous secretory RAGE (esRAGE). cRAGE is

proteolytically cleaved from full-length RAGE [23], while esRAGE is formed from alternative splicing of mRNA of full-length RAGE [24]. Total sRAGE comprises both cRAGE and esRAGE (Figure 1). sRAGE and esRAGE are measured by ELISA kit, while cRAGE is calculated as the difference between sRAGE and esRAGE. Serum levels of esRAGE are 20% to 30% of the serum levels of sRAGE [25, 26]. c-RAGE and esRAGE lack cytosolic and transmembrane domains and circulate in the blood. The AGE-RAGE axis comprises AGE, RAGE, and sRAGE. Interaction of AGE with RAGE produces ROS [16], which activates NF-kB [12]. NF-kB activates numerous proinflammatory genes of cytokines [tumor necrosis factor-α(TNF-α), interleukin (IL)-1, IL-2, IL-6, Il-8, IL-9] [18 ,19]. and increases the production of matrix metalloproteinase (MMPs) [20]. Low levels of sRAGE and high levels of AGEs/sRAGE and AGEs/esRAGE increase the levels of cytokines that, in turn, increase the levels of MMPs in patients with aortic aneurysm [27]. AGE has been reported to enhance the activity of MMP-2 and ROS generation [28]. AGE-RAGE interaction enhances the expression of cell adhesion molecules such as intercellular adhesion molecule-1(ICAM-1), vascular cell adhesion molecule-1 (VCAM_1), and eSelectin [29]. ROS also upregulates cell adhesion molecules [30, 31]. The extracellular domain in sRAGE is preserved, and hence, the ligand binding capacity is similar to the RAGE receptor. sRAGE binding with AGE ligands does not activate intracellular signaling. sRAGE and esRAGE compete with RAGE for binding with AGE ligands [32] and thus have protective effects against adverse effects of binding of AGE with RAGE. sRAGE, thus, acts as a decoy for RAGE by binding with AGE [33].

It is to note that ROS increases the expression of MMP-1 [34], and MMP-2 [35]. ROS activates MMP-2 and MMP-9 in patients with acute coronary artery syndrome [36]. Proinflammatory

cytokines modulate the secretion of MMPs [37] and enhance MMP expression in monocyte cells [38].

AGE-RAGE stress

Prasad and Mishra [39] have coined “stressors”, “antistressors,” and “AGE-RAGE stress”. The adverse effects of the interaction of AGE and RAGE have been defined as “stressors,” while the agents that reduce the adverse effects of AGE-RAGE interaction have been defined as “antistressors.” Antistressors include endogenous (enzymatic degraders of AGE, AGE receptor-mediated degraders of AGE, sRAGE), and exogenous (reduction in AGE consumption, and exogenous administration of sRAGE) anti stressors. The terminology “AGE-RAGE stress” has been defined as a shift in the balance between stressors and antistressors in favor of stressors. Prasad and Mishra [39] have established equations to assess AGE-RAGE stress. The ratio of AGE/sRAGE has been proposed as a simple and feasible measure of AGE-RAGE stress in clinical practice. A high ratio of AGE-RAGE stress would indicate the initiation, presence, progression, and severity of the disease. Observations from studies of chronic conditions have been presented in Table 1.

Levels of AGE, RAGE, and understanding imbalances

- ***Plasma and tissue levels of AGEs reported in COPD***

Levels of AGE have been assessed in plasma, skin, and lung tissue. AGEs comprise Nε-carboxymethyl-lysine (CML), Nε-carboxyethyl-lysine (CEL), and pentosidine. Levels of these components have been reported in COPD with an increasing realization that the characteristics of

the control group are fundamental in understanding the results and any potential confounding factor. Similar plasma levels of CML were reported in both COPD patients and control non-COPD subjects [40]. However, considering the history of smoking, plasma levels of CML have been reported to be lower in patients with COPD compared to non-smokers (never-smokers and ex-smokers), while the levels were similar for never-smokers and ex-smokers [41]. These investigators also showed that plasma levels of CEL were higher in COPD patients compared to non-smokers (never-smokers and ex-smokers), while the levels were similar for never-smokers and ex-smokers [41]. Hoonhorst et al. [42] considered age and reported that CML levels in plasma were significantly higher in COPD patients than healthy subjects, while the plasma CML levels were higher in the younger healthy subjects. These authors [42] showed that the plasma CEL levels were higher in young healthy controls compared to COPD patients, and among healthy subjects, the younger group had higher CEL levels than the older group. These authors also studied pentosidine levels in plasma and reported similar levels in all three groups (COPD patients and young and old healthy subjects) [42]. Thus, it is important to note that when assessing AGE, underlying characteristics of the study population and controls and the AGE component investigated are integral for the nuanced interpretation needed when observing elevated, reduced or similar levels.

- ***Skin autofluorescence (SAF) levels of AGEs reported in COPD***

Skin autofluorescence (SAF) is a non-invasive measurement of AGE levels in the skin [43,44]. SAF levels are greater in patients with COPD compared to control subjects irrespective of age and gender and inversely related to predicted FEV1 [42]. Gopal et al. [41] have reported that

SAF values were significantly higher in patients with COPD as compared to non-smokers (never-smokers and ex-smokers), while the SAF values were similar for never-smokers and ex-smokers.

Using immunostaining for AGE, Wu et al. [45] observed that the intensity of positive staining for AGE in the cell membrane of alveolar walls was stronger in COPD patients as compared to non-COPD controls. These investigators also observed that the intensity of AGE staining in bronchioles-non-cartilaginous conducting airways was stronger in COPD than in patients without COPD.

Expression of RAGE in lung tissue of COPD patients

Wu et al. [45] observed that the intensity of immunostaining of RAGE on the cell membrane of alveolar walls was stronger in patients with COPD than in non-COPD control subjects, while the intensity of stain in small airways of COPD patients similar to non-COPD controls. It has been reported that RAGE was overexpressed in the airway epithelium and smooth muscle cells of patients with COPD. Considering comorbidity diabetes, the intensity of staining of both AGE and RAGE was greater in non-diabetic COPD than in non-COPD controls [45].

Serum and plasma levels of sRAGE reported in COPD

sRAGE has been measured both in serum and plasma of patients with COPD.

- ***Reported sRAGE levels among COPD vs. control, smokers, and non-smokers***

Cheng et al. [46] have measured the serum levels of sRAGE in patients with COPD, smokers, and non-smokers. The serum levels of sRAGE were lower in COPD compared to smokers and

non-smokers, but the levels were not significantly different between smokers and non-smokers. Cockayne et al. [47] measured the serum levels of sRAGE in patients with COPD, smokers without COPD, and non-smoker control. They reported that sRAGE levels were 1.6 folds lower in COPD compared to non-smoking controls.

Plasma levels of sRAGE have been reported to be lower in patients with COPD than in healthy control subjects [40]. Consistent findings have been reported when studied for smoking status and age. Considering a history of smoking, Pratte et al. [48] have reported that plasma levels of sRAGE were lower in COPD patients as compared to never-smokers, and smokers (current and former smokers) without COPD. Considering age, significantly lower sRAGE levels have been reported in patients with COPD than in young and old healthy subjects [42]. Similar findings were reported by Gopal et al. [49 to 50] for patients with COPD and non-smoker (never and ex-smoker controls. They further reported lower levels in ex-smokers compared to never-smokers. However, Iwamoto et al. reported lower sRAGE levels in smokers (with and without COPD) as compared to non-smokers [50 to 51].

- ***Reported plasma/serum sRAGE level variations with COPD severity***

sRAGE levels decreased with increasing levels of severity of COPD. Coxson et al. [52] have reported that decreases in the serum levels of sRAGE were associated with baseline lung density and its decline with time in patients with COPD. Also, they reported that lower plasma levels of sRAGE were correlated with higher SAF values in COPD. They also showed that the plasma levels of sRAGE were lower during acute exacerbation than during convalescence. When comparing patients with well-managed COPD to healthy controls, Smith et al. [49 to 51] have

reported consistent findings of lower levels of plasma sRAGE in the former. The plasma sRAGE levels have been reported to be associated with longitudinal declines in FEV_1 /FVC by Iwamoto et al. [50 to 51].

- ***Reported plasma sRAGE levels in COPD, emphysema, and asthma overlap***

Plasma levels of sRAGE were lower in patients with COPD compared to subjects with no emphysema [53, 54] and have been found to be correlated with the severity of emphysema [54]. Iwamoto et al. [55] observed that the plasma levels of sRAGE were significantly lower in COPD patients and patients with COPD-asthma overlap compared to asthmatic and control subjects.

- ***Reported plasma levels of esRAGE in COPD***

Gopal et al. [61] reported significantly lower plasma esRAGE in patients with COPD compared to non-smokers (never smokers and ex-smokers). This is consistent with sRAGE findings reported. Similarly, plasma esRAGE levels were similar for never-smokers and ex-smokers. They also found no correlation between plasma esRAGE levels and FEV_1 and FEV_1/FVC in COPD patients.

Knowledge gap: 'AGE-RAGE stress' in COPD

These data suggest that the levels of AGE in tissue (SAF and immunostaining) are consistently higher in COPD patients compared to control subjects, while plasma levels of individual

components of AGE (CML, CEL, and pentosidine) were likely more dependent on underlying characteristics of study and control groups. SAF has been shown to correlate strongly with plasma-circulating AGE [57, 58]. However, inconsistent reports have emerged indicating the likely implications of comorbidities and population characteristics, which may make plasma AGE a complex biomarker in the context of a patient with COPD. An overexpression of RAGE and an increase in the levels of AGE in the lung tissue [45] suggest that the interaction of AGE and RAGE in the lung tissue could damage the alveoli, leading to the development of COPD. However, assessing tissue levels may not be feasible across the clinical setting spectrum.

The AGE-RAGE axis comprises four important players: AGE, RAGE, sRAGE, and esRAGE. In humans, it is not practical to measure cell receptor RAGE. Prasad [59] suggested that the ratio of AGE/sRAGE should be a universal marker for diseases. Subsequently, Prasad and Mishra [39] coined the terminology "AGE-RAGE stress," which takes the "stressors" (AGE, RAGE) and the "antistressor" (sRAGE) into consideration. For practical purposes, they have used AGE/sRAGE as "AGE-RAGE stress" and demonstrated that the higher the "stress", the more the disease risk. Thus, proposing "AGE-RAGE stress" as a universal risk factor for diseases. Those investigating have not measured plasma /serum of both AGE and sRAGE in the same patients to determine "AGE-RAGE stress" in patients with COPD except Gopal et al. [40] and Hoonhorst et al. [42]. Gopal et al. [41] reported that plasma AGE levels were similar in COPD patients and control subjects, but the plasma sRAGE levels were lower in COPD patients than control subjects, suggesting that "AGE-RAGE stress" was higher in COPD than control subjects. Hoonhorst et al. [42] reported that plasma levels of AGE were significantly higher while sRAGE levels were lower in patients with COPD compared to control subjects which would contribute to an observation of higher "AGE-RAGE stress".

Knowledge of relative levels of individual components of "AGE-RAGE stress" is growing in COPD. However, "AGE-RAGE stress" (i.e., the imbalance) has not been assessed in COPD patients till now. A focus on understanding the imbalance is especially important in the context of COPD, where patients largely manifest multiple comorbidities that impact individual components, making head-to-head comparisons nuanced and potentially not feasible, whereas being able to assess the imbalance has the potential of being informative of an individual's internal environment and thus susceptibility to decline.

COPD: inflammatory condition and its mediators

Important mediators of COPD include oxidative stress, imbalance between proteases (MMP-8, MMP-9, MMP-12, and elastase) and antiproteases, and inflammation [60]. Oxidative stress is defined as a balance between ROS and antioxidants in favor of ROS. Proteases/trypsin include MMPs (MMP-8, MMP-9, MMP-12) and elastase, while antiproteases include α_1-antitrypsin and tissue inhibitor of MMP (TIMP-4) [61]. Macrophages and neutrophils produce excessive amounts of proteases, including elastase and MMPs, that destroy elastin and other components of the alveolar wall [62]. Oxidative stress is the primary cause of COPD through numerous mechanisms. It inactivates α_1-antitrypsin [63], increases pro-inflammatory cytokines gene transcription [64], activates NF-kB [65], activates TGFβ_1 [66], and stimulates MMP expression [67]. Hydrogen peroxide (H_2O_2) directly constricts bronchial muscles [68]. NF-kB activation induces the production of cytokines, chemokines, and cell adhesion molecules [64]. TGFβ_1 leads to fibrosis of the lung in COPD [69]. Expression of cell adhesion molecules such as E-selectin is increased in COPD and is critical for neutrophil recruitment in the lung [70]. Activated neutrophil secretes

MMP-8 and MMP-9 causing alveolar damage [71]. Neutrophils and macrophages generate ROS and cytokines [72]. Chemokines MCP-1 is elevated in COPD [73]. MCP-1 attracts Monocytes that are differentiated into macrophages [74]. Alveolar macrophages secrete elastolytic enzymes, including MMPs [74]. Proinflammatory cytokines are elevated in COPD [75].

AGE-RAGE axis-induced generation of COPD mediators

Figure 2 depicts the AGE-RAGE interaction-induced generation of mediators for the development of COPD and the reduction in the generation of mediators with AGE-sRAGE interaction. AGE-RAGE interaction produces ROS [16], which activates NF-kB [17]. NF-kB activates pro-inflammatory cytokines genes (IL-1, IL-2, IL-6, IL-8, TNF-α) [18, 19]. Cytokines stimulate polymorphonuclear leucocytes (PMNLs) to generate ROS [796-78]. NF-kB also generates ROS through NADPH-oxidase in PMNLs [79]. The expression of intercellular adhesion molecules-1 (ICAM-1) [80], vascular cell adhesion molecule-1 (VCAM-1) [81], and E-selectin [82] is elevated by ROS. Expression of cell adhesion molecules is upregulated by pro-inflammatory cytokines [83]. AGE-RAGE interaction upregulates the expression of insulin-like growth factor-1 (IGF-1 and platelet-derived growth factor (PDGF) [84, 85]. AGE increases the expression of transforming growth factor- β (TGF-β) that is involved in extracellular matrix formation [86, 87]. ROS activates TGF-β that mediates numerous TGF-β fibrogenic effects [88]. AGE increases the expression of monocyte chemoattractant protein-1 (MCP-1) through the generation of ROS by interacting with RAGE [89]. MCP-1 upregulation is through ROS. ROS mildly oxidizes low-density lipoprotein -C (LDL-C) to minimally modified LDL (MM-LDL), which is further oxidized to maximally modified LDL called oxidized LDL (OX-LDL). MM-LDL produces MCP-1 in endothelial and smooth muscle cells [90]. OX-LDL increases the

production of MCP-1 in serum [91]. MCP-1 assists in the migration of monocytes in subendothelial space [92]. MM-LDL stimulates the endothelial cells to produce monocyte colony-stimulating factor (M-CSF) [93], transforming monocytes into tissue macrophages. AGE increases the expression and secretion of granulocyte macrophage-colony stimulating factor (GM-CF) by macrophages [94]. OX-LDL increases the expression of cell adhesion molecules [95]. Interaction of sRAGE with AGE has protective effects against the adverse effects of AGE-RAGE interaction.

Potential mechanism of AGE-RAGE axis-induced COPD

The proposed mechanism AGE-RAGE axis-induced COPD is depicted in Fig.2. Interaction of AGE with RAGE produces ROS [16], which activates NF-kB [17] that in turn activates proinflammatory cytokines gene [18, 19]. ROS increases the expression of MMPs [96, 97] and inactivates protease inhibitors [98]. ROS upregulates the expression of MCP-1 through MM-LDL and OX-LDL [90, 91]. ROS increases the expression of TGF-β and produces pulmonary fibrosis and apoptosis [99]. Barnes et al. [100] have reported that ROS activates NF-kB, and its expression and activation are increased in COPD, particularly in airway epithelial cells and macrophages. ROS activates TGF-β signaling pathways, which induce oxidative stress and small airway fibrosis [101]. The expression of VCAM-1 is increased by ROS [102]. OX-LDL significantly induces ICAM-1, VCAM-1, and E-selectin at mRNA and protein levels [106]. ROS regulates the expression of mucin genes in COPD [104]. NF-kB is elevated in COPD [105]. TNF-α induces expression and activation of MMPs [106]. NF-kB increases the expression of proinflammatory cytokine genes [18, 19, 64], increasing cell adhesion molecule expression [107]. NF-kB induces MCP-1 and cell adhesion molecules [64]. Cell adhesion molecules,

especially E-selectin, attract neutrophils and macrophages [70]. MCP-1 attracts monocytes, which are differentiated into macrophages [74]. Tissue macrophages (alveolar macrophages) secrete elastolytic enzymes elastase and MMPs) which damages lung parenchyma [108]. Activated neutrophils and macrophages secrete MMPs [71]. Circulating neutrophils release elastase in COPD [109]. Vascular cell adhesion molecules activate MMPs in endothelial cells [110]. Hydrogen peroxide inactivates α_1-antitrypsin, the primary inhibitor of neutrophil elastase [111]. All of the above biomolecules generated by the interaction of AGE with RAGE are known to be involved in the development of COPD.

sRAGE is a part of the AGE-RAGE axis. As mentioned in the "AGE-RAGE axis" section, sRAGE competes with RAGE for binding with AGE. The binding of sRAGE with AGE does not activate intracellular signaling; hence, it has no effects but protects against adverse effects of AGE-RAGE interaction. When sRAGE binds with AGE, less amount of AGE is left to bind with RAGE and hence less adverse effects. High levels of sRAGE in blood and body fluid will protect from the adverse effects of AGE-RAGE interaction. TGF-β has been implicated in the development of COPD [112, 113]. In summary, AGE-RAGE interaction generates numerous biomolecules, including ROS, pro-inflammatory cytokines, cell adhesion molecules, and growth factors, which in turn would increase the levels of proteases (MMPs and elastase), inactivate protease inhibitors (α_1-antitrypsin, and TIMP-4) and fibrosis leading to the development of COPD.

Understanding AGE-RAGE axis in COPD: Potential targeted therapy for AGE-RAGE axis-induced COPD

Along with being able to explore the role of the AGE/RAGE ratio in analysis, development of therapeutics and prediction models in COPD, especially early or milder disease populations, the knowledge of this ratio could be used towards modifying AGE-RAGE axis-induced COPD

Considering elevated levels of plasma/tissue levels of AGE and RAGE and reduced levels of sRAGE in serum/plasma are involved in the development of COPD, the treatment targets for COPD should include reduction in levels of AGE and RAGE and elevation of sRAGE in the system. Therapeutic interventions for AGE-RAGE-induced diseases have been described in detail by Prasad and Tewari [109-111]. A brief description of existing knowledge of behavioral modification, mechanisms, and therapeutic agents that can be applied to COPD towards goals of lowering AGEs, RAGE, and elevating sRAGE is outlined in Figure 4 below.

Observations from the use of antioxidants in COPD

Considering the role of ROS in the pathogenesis of COPD and the production of ROS with AGE-RAGE interaction, the use of antioxidants would be helpful in the treatment of COPD. Antioxidants, Vitamin E [114], and secoisolariciresinol diglucoside (SDG) [115] reduced hypercholesterolemic atherosclerosis, and this effect was associated with a reduction in the levels of ROS. Other antioxidants (probucol, garlic) have been successful in the prevention of

hypercholesterolemic atherosclerosis. Studies on the treatment of COPD with antioxidants have been published in the literature. Orozco-Levi et al. [116] have extensively reviewed the effects of antioxidants in the treatment of COPD. Some of the most frequently used antioxidants are N-acetylcysteine, vitamin C, vitamin D, vitamin E, zinc, and erdosteine. Antioxidant therapy may affect important outcomes of COPD, including overcoming steroid resistance, mucus hypersecretion, inflammation, and extracellular matrix. Rahman et al. [117] have reported that N-acetylcysteine had some effects in the reduction of exacerbation in COPD. Reduction in the exacerbation of COPD with N-acetylcysteine has also been reported by other investigators [118, 119]. The benefits of vitamin E are variable. Vitamin E supplement had no additional benefit in COPD. They reported that FEV_1 was similar in COPD patients who received vitamin E or who did not receive vitamin E. However, Hanson et al. [120] have reported that vitamin E increased the FEV1 in patients with COPD. Vitamin E deficiency in patients with COPD is associated with a greater fall in FEV_1 [116]. In a large, randomized trial, the use of vitamin E daily has shown to reduced the risk of chronic lung disease [121]. Vitamin C provides protection against COPD independent of smoking history [122]. Dey, et al. [123] have shown that vitamin C reduces the exacerbation rate in COPD.

Vitamin D is considered a natural antioxidant [124]. It is controversial. In a meta-analysis, vitamin D has been shown to improve lung function (FEV_1 and FEV_1/FVC), acute exacerbation, sputum volume, and COPD assessment test (CAT) score [125]. Vitamin D supplementation has been reported to reduce the rate of moderate to severe COPD exacerbation in patients with COPD [126]. Vitamin A, vitamin C, vitamin D, and vitamin E have been shown to improve symptoms, exacerbation, pulmonary-function, and reduce the decline in FEV_1 [127].

Failure of antioxidant strategies in some cases may be due to inappropriate doses, lack of combination of antioxidants, use of antioxidants in very advanced conditions, and frequency of drug administration. The use of vitamin E alone may not be effective because during scavenging ROS, vitamin E is converted into tocopheryl radical, which is harmful [128]. Vitamin C regenerates vitamin E from tocopheryl [129]. Vitamin E should be used in combination with vitamin C in appropriate doses for the treatment of COPD. Vitamins C, D, and E are not only antioxidants [126-130], but they also reduce the formation of AGE. Vitamin D has the ability to upregulate the expression of sRAGE [135] besides being an antioxidant. These treatment modalities may serve as adjunct therapy for COPD.

Perspectives

Pathophysiology of COPD has been studied, although no attention has been given to the potential role of the AGE-RAGE axis in the development of COPD. AGE-RAGE axis has been studied in many other chronic diseases such as atherosclerosis [10], coronary artery disease [11], hyperthyroidism [12], end-stage renal disease [13], non-ST-elevation myocardial infarction [14] and post-percutaneous coronary interventional restenosis [15]. While there are reports consistent with the role of AGEs in chronic diseases, there are those that report challenging findings [136-138], e.g., in age-related macular degeneration [139] and AGE in predicting outcomes in type 2 diabetes and nephropathy [140]. This remains unexplained presently. However, it is to be noted that AGEs are a group of structurally diverse molecules with potentially varying affinity to AGE receptors, thus also varying their physiological impact, making it difficult to compare studies in different molecules; thus, the method of measurement would impact the results obtained subject to antibodies used and antigen epitopes of the ELISA assays. Not all AGEs produce autofluorescence impacting studies reporting SAF results, and currently available data are largely

from cross-sectional studies being used to understand a chronic process where sample sizes and composition (ethnicity, gender, age) vary across studies. Thus, a consensus-based approach on assay to be used and reporting AGEs being studied would help bring clarity to our growing understanding.

Plasma [40, 42, 49, 50, 51, 54, 55, 141] and serum [46, 47, 52] levels of sRAGE were consistently lower in patients with COPD compared to control subjects. Low serum/plasma levels of sRAGE have been suggested to be a biomarker of COPD [43,53,54,163,164]. However, it has been reported that sRAGE levels in serum/plasma are elevated in type 1 diabetes [143], type 2 diabetes [144], patients with impaired renal function and end-stage renal disease [145], and end-stage renal disease [146]. This suggests that sRAGE may not be a universal biomarker for diseases because serum levels of sRAGE are elevated in some diseases and reduced in other diseases [59]. This is particularly important in studies with COPD patients as they mostly present with multiple comorbidities and on multiple medications, which have an impact on the components of the AGE-RAGE axis. Thus, the proposed ratio of AGE/sRAGE presents the potential to assess the imbalance and understand impact thresholds for care management and for setting outcome targets along with therapeutic targets to tilt the balance favorably for COPD patients.

CONCLUSION

Oxidative stress, imbalance between proteases and anti-proteases and inflammation are known mediators of COPD. We, in this paper, have shown that AGE-RAGE interaction also generates mediators similar to that reported for COPD. Interaction of AGE with RAGE generates ROS, which activates NF-kB and proteases, inactivates protease inhibitors, increases expression of proinflammatory cytokine genes, cell adhesion molecules, MCP-1, M-CSF, and mucin genes,

and bronchial constriction through hydrogen peroxide (H_2O_2). NF-kB activates proinflammatory cytokines gene and cell adhesion molecules. Proinflammatory cytokines increase the expression of proteases, cell adhesion molecules, and chemokines. Cell adhesion molecules attract neutrophils and macrophages, which increases the expression of proinflammatory cytokines and secretes MMPs and elastase. The above data suggest that AGE-RAGE interaction generates all mediators required for the initiation and progression of COPD. sRAGE acts as a decoy and protects from adverse effects. AGE-RAGE interaction induced generation of mediators of COPD. The data suggest that the AGE-RAGE axis is a risk factor for COPD and needs to be explored in further studies to support better assessment of patient disease activity, development of treatment strategies, and therapeutics in the prevention, regression, and slowing of progression of COPD.

In conclusion, tissue levels of AGE and RAGE are elevated, while plasma levels of sRAGE are reduced in patients with COPD. When comparing, plasma levels of AGE may be higher, lower, or unaltered in COPD patients depending on the characteristics of the control subjects. Oxidative stress, imbalance between proteases and antiproteases, and inflammation have been reported to be important mediators of COPD. AGE-RAGE interaction could induce COPD through increases in numerous biomolecules, including ROS, NF-kB, and pro-inflammatory cytokines, activation of proteases, inactivation of protease inhibitors, increased expression of cell adhesion molecules, and mucin genes. The AGE-RAGE axis may serve as a risk factor/prognostic biomarker for COPD. The role of “AGE-RAGE stress” as a potential disease activity biomarker in COPD, especially in early disease, needs to be explored. There is evidence suggestive of beneficial outcomes of incorporating an understanding of the AGE-RAGE axis in the management of chronic diseases, including studies on the use of antioxidants in COPD. However, it is important

to understand the AGE/sRAGE ratio in COPD and assess its role as a measure or index indicative of disease activity and its potential use in the development of risk assessment tools in early or milder disease stages.

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Table 1: Findings of AGE, sRAGE and AGE/sRAGE ratio reported in chronic diseases.

Disease states	AGE	sRAGE	AGE/sRAGE
Diseases with low serum sRAGE			
NSTEMI	78.0% ↑	32.1% ↓	218.5% ↑
Thoracic aortic aneurysm	584.6% ↑	30.0% ↓	900.0% ↑
Hyperthyroidism	42.2% ↑	19.4% ↓	126.1% ↑
Hypercholesterolemia	89.4% ↑	36.3% ↓	249.0% ↑
Disease with high serum sRAGE			
ESRD *(also in diabetes)*	577.0% ↑	145.0% ↑	313.0% ↑

Percent changes in the serum AGE, sRAGE and AGE/sRAGE ratio in diseases
NSTEMI- non-ST-elevation myocardial infarction
ESRD- end-stage renal disease
↑ *increase* ↓ *decrease*

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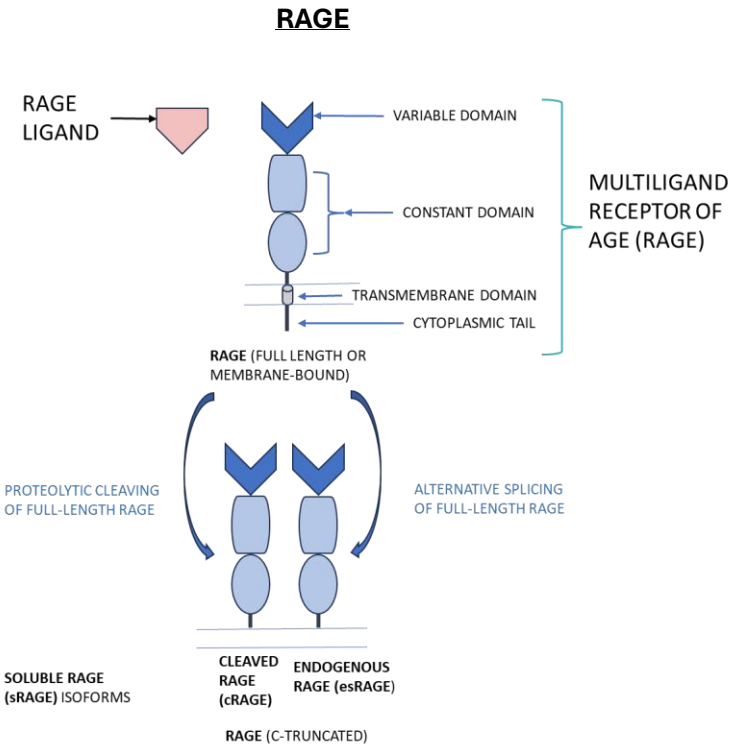

Figure 1. Receptors of advanced glycation end products (RAGE) and its soluble isoforms.

Advanced glycation end products (AGE) are primary RAGE ligand. Competitive binding interactions may exist among the various RAGE proteins for RAGE ligands.

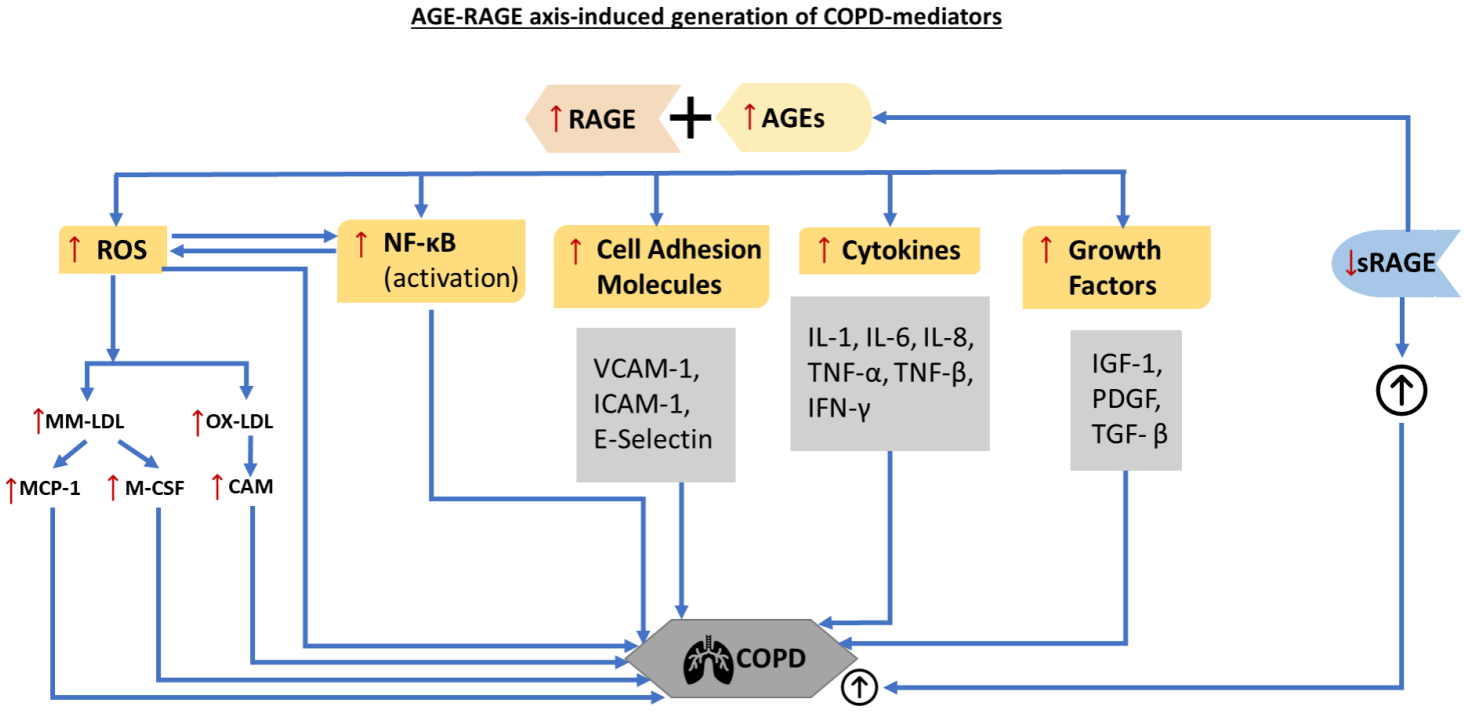

Figure.2. Effects of interaction of AGE (advanced glycation end products) with RAGE (receptor for AGE) and sRAGE (soluble receptor for AGE) on generation of biomolecules involved in development of chronic obstructive pulmonary disease (COPD).

Interaction of AGE with RAGE increases the generation of ROS (reactive oxygen species), activation of NF-kB, cell adhesion molecules, cytokines and growth factors .ROS mildly oxidizes low-density lipoprotein (LDL) to for minimally modified LDL (MM-LDL) which is further oxidized to produce oxidized LDL (OX-LDL).MM-LDL increases the production of MCP-1 (monocyte chemoattractant protein-1) and M-CSF (monocyte colony stimulating factor). OX-LDL increases the expression of CAM (celladhesion molecules).

VCAM-1= vascular cell adhesion molecule-1; ICAM-1= intercellular adhesion molecule-1; IL= interleukin; TNF-α= tumor necrosis factor-α; TNF-β= tumor necrosis factor- β; IFN-ϒ = interferon-gamma; IGF-1= insulin like growth factor-1; PDGF= platelet-derived growth factor; TGF-β= transforming growth factor-β. ↑= increase; ↓= decrease; ⇄ = rightward and leftward arrow.

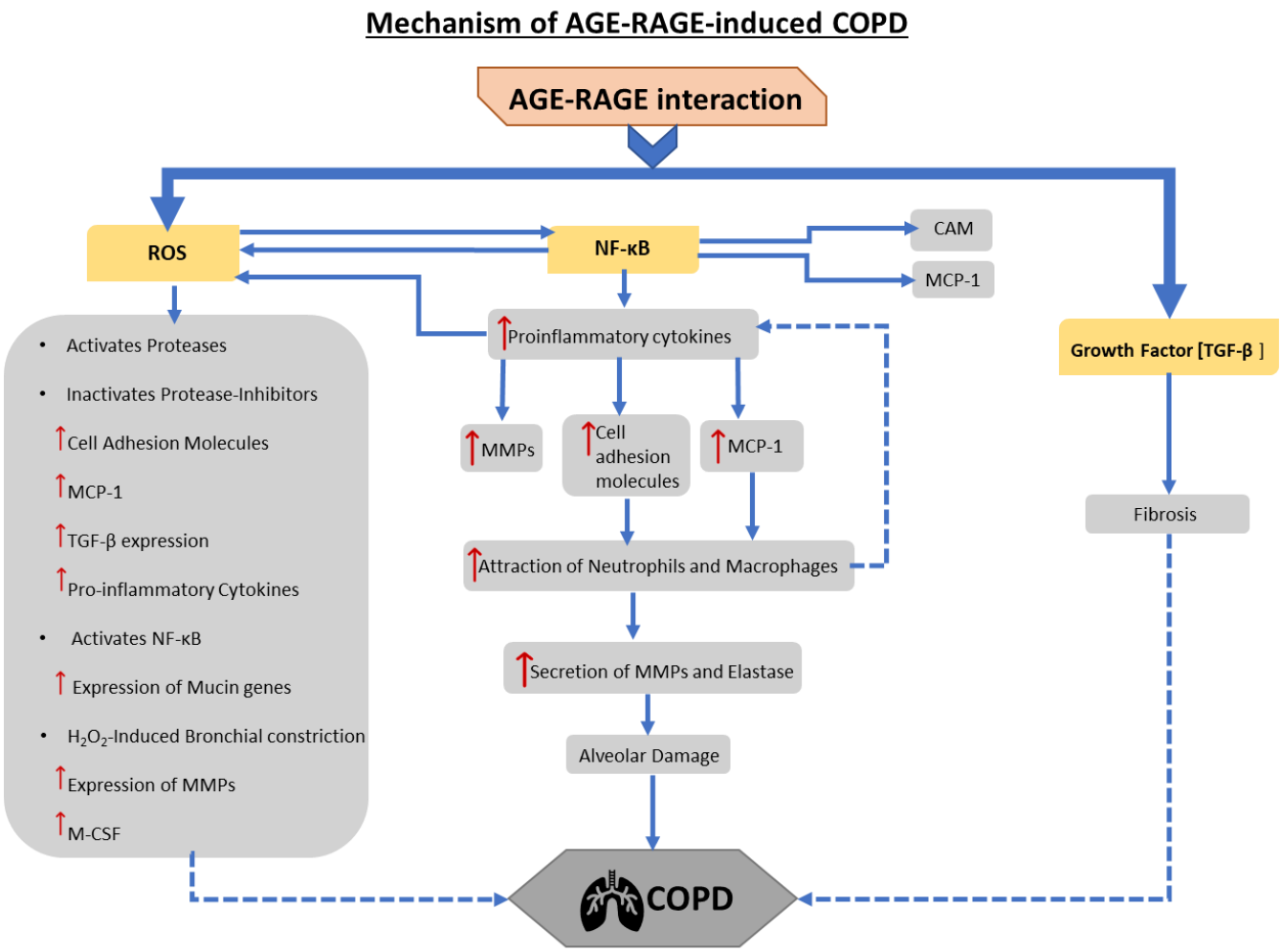

Figure 3. The role of interaction of AGE (advanced glycation end products) with RAGE (receptor for AGE) in the development of chronic obstructive pulmonary disease (COPD). AGE-RAGE interaction produces numerous biomolecules which would induce development of COPD.

ROS= reactive oxygen species; NF-kB= nuclear factor-kappa B; TGF-β= transforming growth factor-β; MCP-1= monocyte chemoattractant protein-1; H_2O_2= hydrogen peroxide; MMPs= matrix metalloproteinases ; M-CSF= monocyte colony stimulating factor; CAM= cell adhesion molecules; ↑= increase; ↓= decrease; ⇄ = rightward and leftward arrow

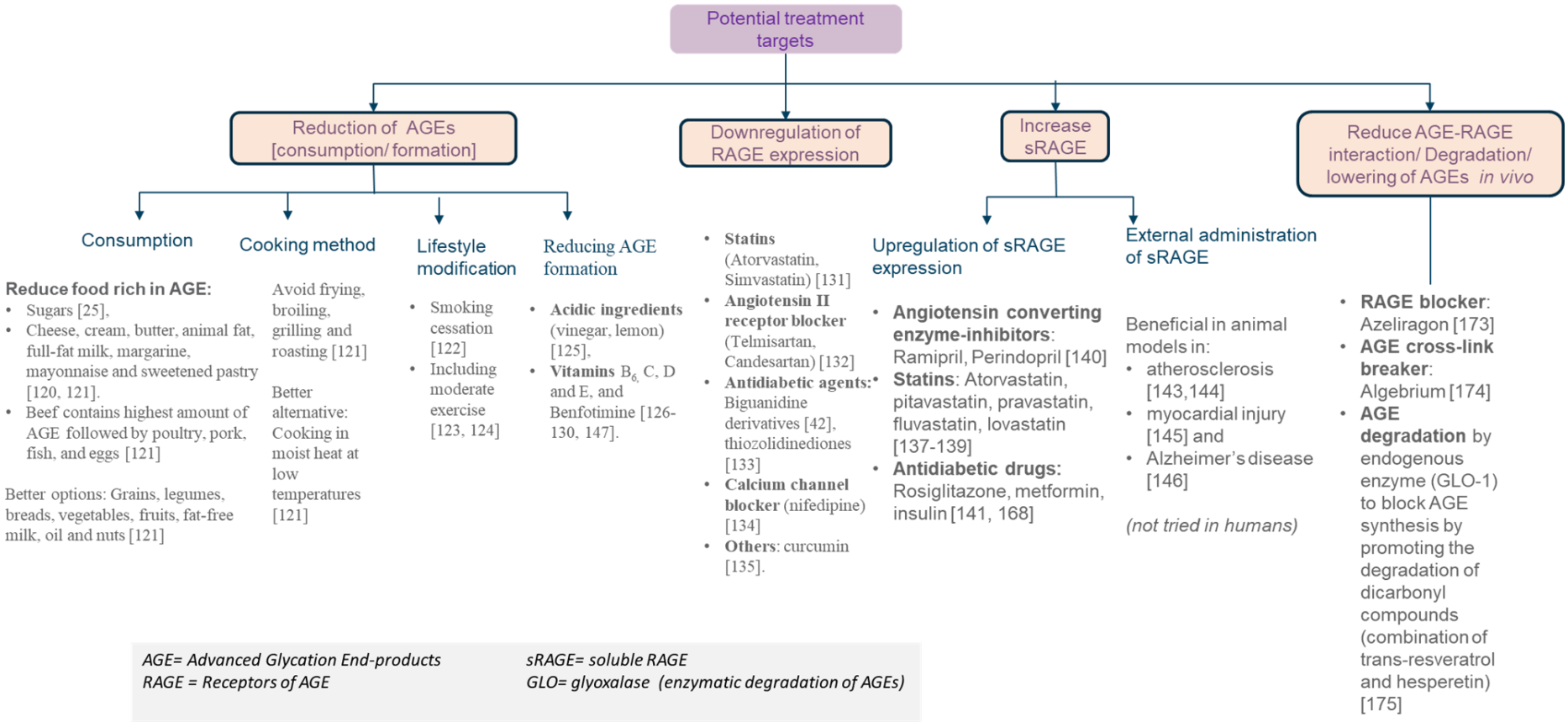

Figure 4: Potential treatment targets applicable in patients with COPD leveraging the knowledge of "AGE-RAGE stress"

7.2 Preface: [Short Title “The ratio of AGE/sRAGE in CanCOLD”]

***Title**: Understanding a Novel Potential Marker of Disease Activity in COPD: Findings from our evaluation of AGE/sRAGE ratio in a CanCOLD sub-cohort.*

In manuscript 4, I add evidence from a mild-moderate COPD cohort perspective, but importantly, I present results from analyzing serum levels of both the biomarkers that constitute the ratio, namely AGE, and sRAGE. Importantly, the results discussed in Manuscript 4 help inform some observations in existing literature in the light of observations from this study due to the careful selection of healthy controls. The healthy controls in this study are never smokers, without known comorbidities (diabetes, hypertension, asthma and CVD) and medications (statins and ACE-inhibitors) reported to influence the observations. The study includes a third group consisting of non-COPD smokers. As discussed in the chapters on introduction and background, though other risk factors have come to light, and COPD is observed among non-smokers as well, however, smokers continue to be at high risk for COPD. This study documents important relations, observed in a real-world population-based cohort, between the ratio AGE/sRAGE and other important variables of smoking pack-years, lung function measures, and measurement of lung damage in COPD. References are included within the manuscript below.

7.2.1 Manuscript 4

TITLE: Understanding a novel potential marker of disease activity in COPD: Findings from our evaluation of AGE/sRAGE ratio in a CanCOLD sub-cohort

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ABSTRACT

Introduction: In Chronic Obstructive Pulmonary Disease (COPD) literature, various biomarkers have been investigated to inform prognosis and prediction of future decline, including Advanced glycation end products (AGE) and its soluble receptor (sRAGE) with sRAGE proposed for multi-biomarker panels. However, the heterogeneity observed in COPD and the influence of comorbidities pose a unique challenge in the interpretation of observations from clinical cohorts of moderate-severe COPD. We have already established the plausible role of the ratio of

AGE/sRAGE as a potential marker of disease activity in COPD, especially for its ability to inform on the stress-antistress imbalance in populations being treated for multiple comorbidities, which impacts their presentation and progression of COPD. Here we measure and report levels and correlations to develop further knowledge in a cohort of those with predominantly mild-moderate COPD.

Methods: Baseline (visit 1) biobank (Montreal location) serum samples from a study defined Canadian Cohort Obstructive Lung Disease (CanCOLD) sub-cohort was assessed for levels of AGE and sRAGE. The serum levels of AGE and sRAGE reported are compared using the Kruskal-Wallis test and Pearson correlations with variables in 3 groups: COPD, at-risk (non-COPD cigarette smokers), and healthy subjects.

Results: Out of 1561 CanCOLD participants at baseline visit, 136 met the inclusion criteria with a mean [±Standard Deviation (SD)] age of 63.7 (±9.4) years, more males (57.4%) than females, and mean BMI of 24.4 (±4.7) kg/m2. Media (Q1, Q3) serum AGE levels and the ratio showed significant difference (p-value <0.001) being elevated among those with COPD [11.4 (8.4-17.3) mcg/ml and 13252.9 (7439.5, 18202.6) respectively] and reduced among smokers (at risk) [1.7 (1.4, 2.0) mcg/ml and 1893.8 (993.3, 2432.0) respectively] compared to those in the healthy group [6.2 (5.4, 9.8) mcg/ml and 6874.3 (4089.9, 10679.2) respectively].

Discussion: Our study findings are consistent with the relationships reported and help clarify due to the study population definitions. This study provides the first reference for the AGE/sRAGE ratio and their individual levels in clearly defined groups to support further research through an index of ongoing ‘imbalance’ in a complex disease like COPD.

Conclusion: The study suggests a potential role of AGE/sRAGE as a promising new biomarker for COPD. Further examination of the findings in larger studies is needed.

Keywords (5): mild-moderate Chronic Obstructive Pulmonary Disease (COPD), Advanced glycation end products (AGE), soluble receptor for AGE (sRAGE), AGE-RAGE stress, Canadian Cohort Obstructive Lung Disease (CanCOLD)

INTRODUCTION

Advanced Glycation Endproducts (AGEs) are a heterogeneous group of irreversible proinflammatory adducts formed as a result of nonenzymatic interaction of reducing sugars (e.g., glucose, fructose, maltose, lactose) with proteins, lipids, and nucleic acids [1]. AGE produced in the system accumulates with aging [2,3]. However, there are rapid increases in inflammatory situations like hyperglycemia and in response to reactive oxygen species [4]. Receptor for AGE (RAGE) is a cell surface macromolecule expressed abundantly in the lung alveolar epithelia under normal physiological conditions, though found in low levels in most of the tissues in a human adult [5]. This is a single membrane-spanning receptor with an extracellular and a cytosolic domain [6]. The binding of AGE with its full-length receptor promotes inflammatory pathways via the production of reactive oxygen species (ROS), or “stress”. Prasad and Mishra called these “stressors”. When full-length RAGE get C-truncated into iso forms of proteolytically cleaved RAGE (cRAGE) or endogenous secretory RAGE (esRAGE) from alternative splicing of mRNA of full -length RAGE, these form the non-membrane bound soluble RAGE (sRAGE) [7]. Contrary to AGE-RAGE interaction, AGE-sRAGE interaction does not produce ROS nor promotes inflammation. sRAGE acts as a decoy competing for binding AGEs and thus preventative potential “stress.” The authors termed sRAGE as “antistressors”. The imbalance of stressors and antistressors determines residual stress and its impact manifests through disease

activity [8]. In other words, a high AGE-RAGE stress (ratio of AGE/sRAGE) would indicate disease initiation, presence, progression, and severity [9]. This has been demonstrated in several conditions, including atherosclerosis [10], coronary artery disease [11], hyperthyroidism [12], end-stage renal disease [13], non-ST-elevation myocardial infarction [14], and post-percutaneous coronary interventional restenosis [15]. The AGE-RAGE axis is proposed among the various pathological paths potentially involved in Chronic Obstructive Pulmonary Disease (COPD) [16-19]. COPD is a chronic respiratory disease marked by progressive airflow obstruction interspersed with acute crisis episodes, called exacerbations, which are known to accelerate the deterioration, increasingly interfering with the individual's ability to perform daily activities and quality of life experience. COPD includes emphysema and chronic bronchitis. Chronic bronchitis is characterized by inflammation of the lining of the bronchial three and excessive mucus production [20]. Emphysema is characterized by damage to the alveoli, leading to the destruction of the structures of the tiny air sacs, resulting in abnormal enlargement and reduced surface area for gas exchange [21].

COPD is the third most common cause of mortality globally [22,23], with a significant health experience burden on those living with this condition and is also associated with a significant burden on healthcare resources [24]. Large undiagnosed populations and diagnosis with aggressive treatment at advanced stages of the disease have come to be associated with COPD, leading to the impression of this being an untreatable to irreversible condition. However, emerging knowledge of risk factors other than smoking [25], incentivization of spirometry through the quality of healthcare measures [26], and wider insight into the heterogeneity of COPD has been continually recognized and reflected in the care management strategy

recommendations of Global Initiative for Obstructive Lung Disease (GOLD) [27] and developments towards a personalized care strategy [28].

In this context and coupled with the heterogeneity of the condition, alongside impacts of multi-morbidity and potential polypharmacy (especially among those above 60 years of age) continually influencing disease progression in an individual living with COPD, a marker informative of the imbalance of important underlying pathophysiological processes can not only help prognostication and care management, but it can also support therapeutic development as outcome surrogate as well as risk-group identifier. Building on the proposed role of AGE-RAGE stress in COPD, the current study's objective is to describe the ratio of the biomarkers, as well as individually, along with their respective correlations as observed in an identified sub-cohort of the Canadian Cohort Obstructive Lung Disease (CanCOLD) largely comprised of participants with mild-moderate COPD reflective of primary-care patient population [29]. The cohort provides an opportunity to also study smokers without COPD and healthy (non-smokers) individuals.

METHODS:

Study population: The present study population has been derived from the CanCOLD study, a longitudinal population-based COPD cohort in Canada. CanCOLD has 1561 participants made up of individuals with COPD [as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD)] [30] and age and sex-matched non-COPD controls, including smokers and non-smokers [29]. The sites of the study span across 9 Canadian cities: Vancouver, Montreal, Calgary, Quebec, Halifax, Toronto, Kingston, Saskatoon, and Ottawa. The study protocol was

approved by each site's institutional research ethics board. Informed consent was obtained from all participants. Information on demographics, body mass index (BMI), detailed smoking history with information on pack-years of cigarette (or pipe or cigar) smoked, comorbidities, and use of statins and ACE-inhibitors are available for baseline visits for the CanCOLD participants. Blood samples were collected at each visit and biobank at two locations, Montreal and Vancouver. Post-bronchodilator (PBD) spirometry was performed at all visits. Results of the gas diffusion study, diffusing capacity for carbon monoxide (DLCO), were available for baseline visits. Low attenuation areas less than a threshold of -950 Hounsfield units (LAA-950) and emphysema scores obtained from CT scans performed at baseline visits were also available for this cohort.

Study design:

The study population is comprised of 3 groups. The"healthy" group was defined as participants from the "normal" group of the CanCOLD cohort who did not have diabetes, hypertension, CVD, or asthma and were not using ACE inhibitors or Statins. The "at-risk" group was defined to include smokers (current and ex-smokers) without COPD (also classified as "at risk" in the CanCOLD cohort). The "COPD" group included those with "COPD". To be included in the study, participants from the COPD and at-risk groups with FEV1 declines between visits 1 and 3 in the highest and lowest quartiles were considered. Those meeting these definitions, having data from 3 completed visits and baseline serum samples at the Montreal biobank of the CanCOLD study in quantities supportive of estimating the biomarker levels made up the study population (Figure 1).

Measurements

Baseline visit data for demographics, BMI, status of current smoking, pack-years of cigarette (or pipe or cigar) smoked, comorbidities, use of statins and ACE-inhibitors, FEV1, FEV1 % predicted, FVC, DLCO, LAA-950, and emphysema score, and visit 3 FEV1 available for the CanCOLD cohort was used to select the study population and summarise its characteristics. Serum samples of the identified study population were accessed from the Montreal biobank of the CanCOLD cohort and analyzed at the Meakins-Christie Laboratories, the Centre for Respiratory Research at McGill University, and the Research Institute of the McGill University Health Centre. Serum AGE was measured by commercially available OxiSelect™ enzyme-linked immunoassay (ELISA) kits from Cell Biolabs, Inc., San Diego, CA, USA. Serum sRAGE levels were assessed using commercially available Quantikine® ELISA kits from R&D systems, Minneapolis, MN, USA. Both kits are recommended for use in research.

Statistical analysis

For the primary objective, serum AGE, sRAGE, and AGE/sRAGE levels are described for healthy, at-risk, and COPD groups. The Kruskal-Wallis test was used to compare the observed data. For the secondary objective, the Pearson correlation for serum AGE, sRAGE, and AGE/sRAGE is reported against the following variables: age, pack-years of cigarettes smoked, FEV1, FEV1 % predicted, FVC, DLCO, emphysema score, and LAA-950 from CT scan. All analysis was performed using SAS 9.4 software.

RESULTS:

Study population

Figure 1 shows the flow diagram leading to the selection of the study population from the CanCOLD cohort. Out of 1561 CanCOLD participants at the baseline visit, 136 met the inclusion with a mean [±Standard Deviation (SD)] age of 63.7 (±9.4) years, a majority (57.4%) males, and a mean BMI of 24.4 (±4.7) kg/m2. Among those with COPD, 23.9 % were never-smokers and 31.9 ± 31.4 was the mean (± SD) pack-years of cigarette smoked (Table 1). The groups were similar in age, BMI, and proportion of those with MRC dyspnea score 3 and above. However, the COPD group comprised of large proportion of males (73.9%). Both at-risk and COPD groups comprised participants with multiple comorbidities, where larger proportions were observed in the latter. Those with COPD (n=46) included: GOLD1 54.3% (n=25), GOLD2 41.3% (n=19), and GOLD3=2 (4.3%).

Levels of biomarkers (AGE, sRAGE, and AGE/sRAGE), in the study population

Table 2 and Figure 2 show the levels of the biomarkers in the study population. Serum AGE was determined in 123 individuals, serum sRAGE in 134 individuals, and the ratio of AGE and sRAGE was measured in 121 individuals of the study population. Median serum AGE levels and the ratio AGE/sRAGE significantly (p-value <0.001) elevated among those with COPD and reduced among smokers (at risk) compared to those in the healthy group. Median serum sRAGE levels in the study population are different (not statistically significant) amongst the 3 groups. sRAGE levels being highest among the at-risk group, followed by that among the healthy group, and lowest in the COPD groups.

AGE/sRAGE were significantly higher in those at risk and those with COPD compared to the healthy subjects. The data suggest that AGE/sRAGE is a promising biomarker for COPD.

Relationship of AGE, sRAGE, AGE/sRAGE, and patient characteristics

Overall, serum AGE levels showed a statistically significant but weak correlation for FEV1 % predicted (negative) and LAA-950 (positive) in the study population. A similar correlation with LAA-950 was observed in the COPD group as well. Table 3 and Figure 3 show correlations observed for serum AGE levels.

Overall, serum sRAGE levels showed a statistically significant but weak correlation (negative) for packyears of cigarette smoked, FVC, and emphysema score. Similar correlations were observed in the COPD group for packyears smoked and FVC. However, in the at-risk group, a weak correlation (negative) was observed for FEV1 and FVC. Table 3 and Figure 4 show correlations observed for serum sRAGE levels.

Overall, the ratio of AGE/sRAGE showed a statistically significant weak correlation (positive) for packyears of cigarette smoked, emphysema score, and LAA-950. In the at-risk group, this was observed for FEV1 and FVC in addition to packyears of cigarette smoked and emphysema score. Table 3 and Figure 5 show correlations observed for the ratio of serum AGE/sRAGE levels.

DISCUSSION:

This study is drawn from a well-defined longitudinal cohort reflective of the real-world primary care patient population. Healthy controls were identified in the well-characterized cohort using

available information on known confounders important to this investigation of AGE-RAGE stress. To summarise our findings, AGE/sRAGE was significantly elevated among those with COPD, positively correlated with packyears of cigarette-smoked emphysema in the study population and with packyears smoked, FEV1, FVC and LAA-950 in the at-risk group. Levels of the biomarkers individually and correlations observed were largely consistent with discussions surrounding AGE-RAGE axis in COPD. In the case of sRAGE, the definition of the healthy cohort and availability of detailed characteristics of the at-risk group helped add clarification to our observations among smokers.

Serum AGE levels were elevated among patients with COPD and negatively correlated (statistically significant) for FEV1% predicted in the overall study population. At the same time, the direction for the COPD group was similar but reversed among the healthy and smokers without COPD though these correlations were not statistically significant. A positive correlation (statistically significant) with LAA-950 was noted for the overall study population and the COPD group. The elevation of AGEs has been reported in COPD and observed to be influenced by smoking in existing literature [31,32]. Inverse associations of tissue AGE levels have been reported with FEV1, FVC, FEV1 % predicted and DLCO [33,34]. A positive correlation (statistically significant) with LAA-950 was noted with serum AGE for the overall study population and the COPD group.

There has been much interest in the biomarkers, including sRAGE in COPD [35], and using multiple biomarkers have been proposed as stronger predictors and indicators of prognosis over individual biomarkers with the potential of being a potential surrogate in clinical trial scenarios [36]. Existing knowledge on this biomarker indicates a potential mechanistic role in

inflammation-associated conditions, however, making it one that is difficult to interpret and requires a nuanced approach [37].

sRAGE levels and smoking have produced variable results [38], and there is a constant effort to understand the nuances. Lower levels of circulating (plasma) sRAGE have been reported among those with COPD [39] compared to smokers without COPD as well as non-smokers [40]. Also, sRAGE levels (plasma) have been reported to be decreased in patients with COPD compared to never-smokers and ex-smokers [41]. Our findings are consistent as serum sRAGE levels in our study population were decreased in the COPD group compared to the healthy group who are never smokers. However, in our study, serum sRAGE levels, reported among 134 individuals, were relatively higher in the at-risk group (mostly former smokers) compared to the healthy group (never smokers) though this was not a statistically significant difference. The at-risk group with serum sRAGE levels reported comprised of cigarette or pipe or cigar smokers otherwise healthy, without COPD, and largely non-diabetic (Proportion $_{\text{DM-total}}$=5/134; Proportion $_{\text{DM-at risk}}$= 2/19; Proportion $_{\text{DM-COPD}}$= 4/45). A previous study has reported elevated serum sRAGE levels in "otherwise healthy, nondiabetic cigarette smokers" [42]. The authors suggested the role of increased proinflammatory biomarkers in the presence of elevated levels of sRAGE. Other studies have reported positive correlations between sRAGE and inflammatory markers in other chronic conditions such as type 2 diabetes and arthritis [43,44]. Others have debated if such a proinflammatory property influenced mechanism plays a significant role in the condition of cardiovascular disease [38]. A majority of the individuals in the at-risk group where sRAGE levels were reported in our study did not have CVD (Proportion $_{\text{CVD-total}}$=15/134; Proportion $_{\text{CVD-at risk}}$= 3/19; Proportion $_{\text{CVD-COPD}}$= 12/45)

It is important to mention that studies have evaluated “acute effects” of smoking on serum sRAGE levels where sRAGE levels are found to be reduced [45]. Pouwels et al. reported from their investigation of the impact of smoking on sRAGE and concluded that smoking may have an acute and temporary effect on serum sRAGE levels [46]. In their investigations, serum sRAGE decline started to be observed within 1 hour, reaching the lowest levels around 8 hours, following which the levels started to recover. However, the recovery was not complete at observations after 48 hours. They also reported that no difference was observed in serum sRAGE levels among active smokers and never-smokers [46]. Among other known factors that may influence the biomarker levels, the potential role of duration since smoked to sample collection as a factor influencing the observed lower sRAGE levels will need to be considered in future studies. In the context of COPD, with the emerging understanding of the impact of pollutants and biomass burning, among other risk factors contributing to the development of COPD [25,47] among never-smokers, our study findings encourage further evaluation in larger cohorts that will support sub-group analysis. Also, while Gopal et al. infer the effect of smoking on sRAGE by comparing levels among ex-smokers and never-smokers among those with COPD such a difference was not observed based on smoking status [41]. In our study, packyears of cigarette smoked were negatively correlated with serum sRAGE in the overall study population and the COPD group ($r_{\text{packyears smoked-total}} = -0.21$, p-value $=0.015$; $r_{\text{packyears smoked-COPD}} = -0.295$, p-value$=0.049$).

sRAGE has been reported to be positively correlated with FEV1 in COPD patients ($r = 0.235$, $p = 0.032$) [41,48] as well as for DLCO ($r = 0.308$, $p = 0.006$). We observed negative correlations for FEV1 in the overall population and the 3 groups. In the at-risk groups, this was statistically significant ($r = -0.508$, p-value$= 0.026$). Similarly negative correlations were observed FVC in the overall population and the 3 groups where this was statistically significant for at-risk and

COPD groups ($r_{at\text{-}risk}$ = -0.561, p-value = 0.012; r_{COPD} = -0.314, p-value=0.036). The authors of a multi-cohort study, Klont et al., observed inconsistency in the association between baseline sRAGE and emphysema progression or COPD [49], also noting that an individual's genotype potentially influences the detected levels. While airway limitation is integral to COPD, the severity of emphysema is variable across individuals with similar FEV1. Our finding of negative correlation of sRAGE with emphysema score ($r_{emphysema\ score\text{-}total}$=-0.221, p-value=0.017) is consistent with reported associations of sRAGE observed at baseline [39] and with decline of lung density over time [50]. Klont et al. suggested that sRAGE may be a non-specific marker of loss of lung epithelium (similar to DLCO) [49] in view of lower levels among those with idiopathic pulmonary fibrosis [51]. For DLCO, a not statistically significant weak positive correlation was observed ($r_{DLCO\text{-}COPD}$ = 0.015, p-value=0.92).

A positive correlation (statistically significant) with LAA-950 was noted with serum AGE for the overall study population and the COPD group. A negative correlation (statistically significant) with emphysema score was noted with serum sRAGE for the overall study population. However, the ratio of AGE/sRAGE, in both the overall population and the at-risk group, showed a positive correlation with packyears of cigarette smoked and LAA-950. Also, showing positive correlation in the over all population for emphysema score and in the at-risk group showed positive correlations FEV1 and FVC.

Strengths and limitations

This is the first study to our knowledge that is well-defined for known confounders, drawn from a well characterised longitudinal cohort established with the primary care patient population in

mind. The study findings add to existing understanding of the serum levels of the individual biomarkers and their ratio across 3 groups: the healthy, smokers without COPD, and those with COPD. We also present the correlations with important variables reported in the literature as observed in our study population for the individual biomarkers of AGE and sRAGE and/sRAGE, recently proposed by us as a potential index of disease activity in individuals with COPD. The study groups of smokers and COPD comprise those belonging to the highest and lowest quartiles for FEV1 annual decline between visits 1 and 3 for an opportunity to study those showing the highest airflow deterioration against relatively stable individuals in the groups. There is an emerging interest in the AGE-RAGE axis in COPD [52-54] and encouraging reports of early intervention among those with mild-moderate COPD, making this study timely [55]. Among important findings, this study contributes clarifications to the ongoing discussions for the potential biomarker serum sRAGE along with serum AGE, and the ratio helps support the role of the ratio proposed as the informative marker. Among studies investigating AGEs in COPD, skin autofluorescence (SAF) levels are used while we have assessed both AGE and sRAGE levels in serum.

Along with these strengths, this study has limitations as well. The baseline levels of the biomarkers were not obtained from analysis performed at baseline. For the current study, we evaluated the biomarker levels in biobanked samples from visit 1. This may be acceptable since the current study's goal was not to report on absolute values for these levels. Given the goal of our study, we did not assess the same samples using other kits for the values obtained. While this study was to assess the biomarkers in the predominantly mild-moderate COPD cohort and present the findings of the ratio of AGE/sRAGE in this population, a larger study population is needed to validate the findings reported. Also, we did not delve into sub-analysis due to the

limited sample size. Lastly, though an acute temporary impact of smoking on sRAGE levels has been proposed, we could not assess our findings against the duration of sample collection from the last cigarette smoked amongst the current smokers.

CONCLUSION

In the current environment with an active focus on the early stages of COPD for detection and treatment, our findings bring important feedback from a relatively mild-moderate population-based cohort perspective highlighting the role the ratio can play as an informative variable towards assessing a holistic impression of disease activity in personalized care strategy where the individual presents a unique progression influenced by comorbidities over the heterogeneity of the disease itself. Carefully designed cohorts, in the light of available knowledge, need to be evaluated for cross-sectional as well as longitudinal data to understand the potential of this proposed marker, AGE/sRAGE (index of AGE-RAGE stress), for further clinically correlated evidence. The data suggests the potential for AGE/sRAGE as a promising new biomarker in mild-moderate COPD. However, further evaluations are needed to explore correlations with available markers of COPD.

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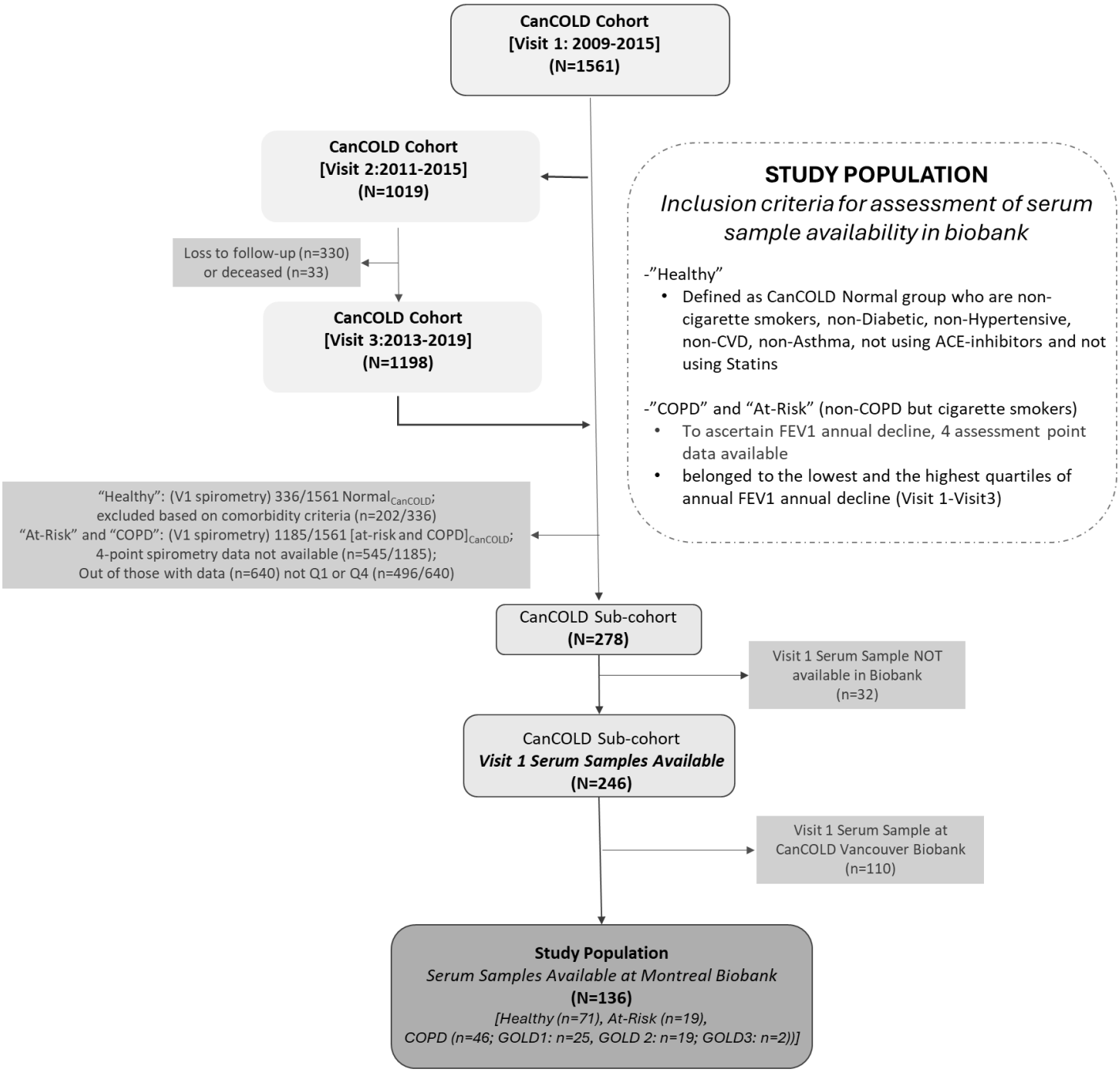


Figure1. Flow diagram showing identification of study population

CanCOLD: Canadian Cohort Obstructive Lung Disease; COPD: Chronic Obstructive Pulmonary Disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease; ACE: Angiotensin-Converting Enzyme; CVD; FEV1: Forced Expiratory Volume in the first second

Table 1. Baseline characteristics of the study population

	TOTAL	HEALTHY	AT RISK¶	COPD	OVERALL p-VALUE
	n=136	**n=71**	**n=19**	**n=46**	
AGE, IN YEAR	63.7 ± 9.4	63.3 ± 9.6	65.0 ± 8.4	63.7 ± 9.8	0.786
SEX, MALE GENDER, n (%)	78 (57.4)	35 (49.3)	9 (47.4)	34 (73.9)	0.018*
BMI, kg/m^2	26.4 ± 4.7	25.4 ± 3.6	28.5 ± 7.1	27.2 ± 4.7	0.066
SMOKING STATUS, n (%)					
NEVER	82 (60.3)	71 (100.0)	0 (0.0)	11 (23.9)	<0.001*
FORMER	41 (30.1)	0 (0.0)	17 (89.5)	24 (52.2)	<0.001*
CURRENT	13 (9.6)	0 (0.0)	2 (10.5)	11 (23.9)	<0.001*
PACK-YEARS OF CIGARETTES	12.4 ± 23.7	0.0 ± 0.0	11.5 ± 13.1	31.9 ± 31.4	<0.001*
MRC DYSPNEA SCALE SCORE ≥ 3/5, n (%)	4 (3.0)	0 (0.0)	1 (5.6)	3 (6.8)	0.051
$FEV_{1,}$ L	2.8 ± 0.9	3.0 ± 0.9	2.9 ± 0.8	2.5 ± 0.8	0.004*
FEV_1, % PREDICTED	99.0 ± 20.7	107.7 ± 15.5	105.2 ± 15.7	83.1 ± 20.3	<0.001*
EMPHYSEMA SCORE	0.8 ± 1.7	0.2 ± 0.9	0.4 ± 1.0	1.6 ± 2.2	<0.001*
LAA-950	4.1 ± 4.4	3.1 ± 4.0	2.7 ± 3.0	5.9 ± 4.8	<0.001*
HTN (NO DIABETES), n (%)	16 (11.8)	0 (0.0)	4 (21.1)	12 (26.1)	<0.001*
HTN & DIABETES, n (%)	5 (3.7)	0 (0.0)	1 (5.3)	4 (8.7)	0.03*
CVD (NO HTN), n (%)	15 (11.0)	0 (0.0)	3 (15.8)	12 (26.1)	<0.001*
ASTHMA (EVER), n (%)	21 (15.4)	0 (0.0)	5 (26.3)	16 (34.8)	<0.001*
DIABETES & NO HTN, n (%)	1 (0.7)	0 (0.0)	1 (5.3)	0 (0.0)	0.14
STATIN USE, n (%)	18 (13.2)	0 (0.0)	5 (26.3)	13 (28.3)	<0.001*
ACE-INHIBITOR, n (%)	8 (5.9)	0 (0.0)	1 (5.3)	7 (15.2)	0.002*

¶*: Cigarette or pipe/cigar smoking (non-COPD);*

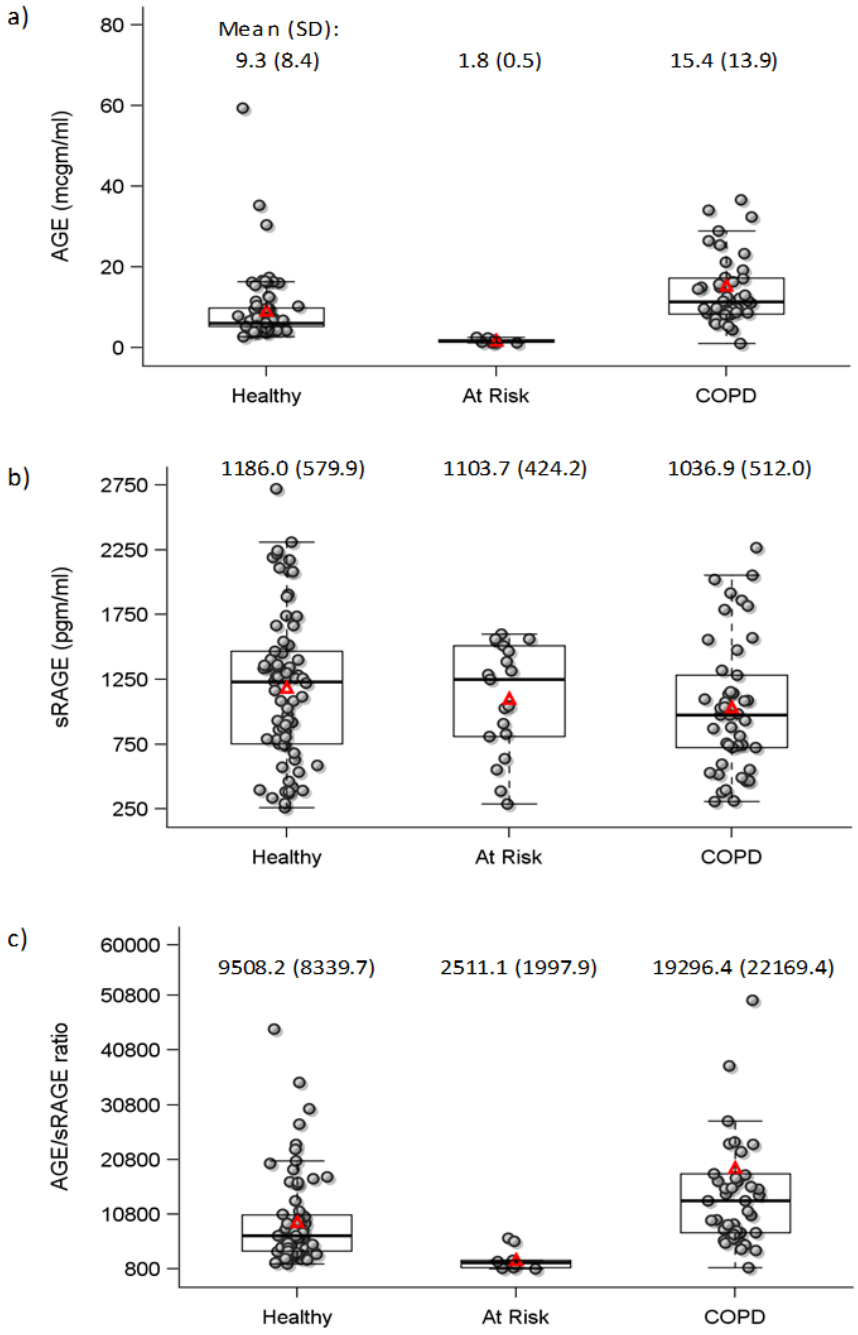
BMI: Body Mass Index; MRC: Medical Research Council; FEV1: Forced Expiratory Volume in the first second; FVC: Forced Vital Capacity; LAA-950: Low Attenuation Areas less than a threshold of -950 Hounsfield units; HTN: Hypertension; ACE: Angiotensin-Converting Enzyme

Table 2: The distribution of AGE, sRAGE and AGE/sRAGE ratio

AGE, (mcgm/ml)	***Total (n=123)***	***Healthy (n=69)***	***At Risk (n=10)***	***COPD (n=44)***	***Overall P-value***
median (Q1, Q3)	*7.7 (5.4, 12.8)*	*6.2 (5.4, 9.8)[a]*	*1.7 (1.4, 2.0)[a]*	*11.4 (8.4, 17.3)[a]*	*<0.001**
sRAGE, (pgm/ml)	***Total (n=134)***	***Healthy (n=70)***	***At Risk ((n=19)***	***COPD (n=45)***	***Overall P-value***
median (Q1, Q3)	*1085.7 (739.2, 1465.1)*	*1228.4 (753.3, 1468.5)*	*1248.7 (808.0, 1508.1)*	*973.9 (724.4, 1284.6)*	*0.347*
AGE/sRAGE Ratio	***Total (n=121)***	***Healthy (n=68)***	***At Risk (n=10)***	***COPD (n=43)***	***Overall P-value***
median (Q1, Q3)	*7439.5 (4431.7, 15589.5)*	*6874.3 (4089.9, 10679.2)[a]*	*1893.8 (993.3, 2432.0)[a]*	*13252.9 (7439.5, 18202.6)[a]*	*<0.001**

¶: Cigarette or pipe/cigar smoking (non-COPD);
AGEs: Advanced Glycation End products; sRAGE, soluble Receptor of AGE; mcgm/ml: microgram/ milliliter; pgm/ml: picogram/ milliliter; Q1: First Quartile; Q3: 3rd quartile
"a" indicates statistically significant difference (p<0.05) in the two group comparisons

Figure 2: Box plots showing the distributions for AGE, sRAGE and AGE/ sRAGE ratio



Red triangle indicates mean value;
AGEs: Advanced Glycation End products; sRAGE, soluble Receptor of AGE; mcgm/ml: microgram/ milliliter; pgm/ml: picogram/ milliliter

Table3: Correlation between AGE, sRAGE and ratio of AGE/sRAGE for selected variables

		Total		Healthy		At Risk¶		COPD	
Variable1	**Variable2**	**Pearson correlation coefficient (r)**	**p-value**	**Pearson correlation coefficient (r)**	**p-value**	**Pearson correlation coefficient (r)**	**p-value**	**Pearson correlation coefficient (r)**	**p-value**
AGE	Age	-0.051	0.573	0.101	0.409	0.566	0.088	-0.228	0.136
AGE	Pack-years smoked¶	0.108	0.234	-	-	0.234	0.515	-0.118	0.447
AGE	FEV_1, L	-0.065	0.473	0.11	0.366	0.136	0.708	-0.055	0.722
AGE	FEV_1, % predicted	**-0.189**	**0.036**	0.084	0.495	0.282	0.431	-0.129	0.402
AGE	FVC, L	0.086	0.343	0.095	0.436	0.167	0.644	0.054	0.728
AGE	DLCO	0.096	0.293	0.019	0.877	-0.071	0.846	0.233	0.129
AGE	Emphysema Score	0.075	0.441	-0.113	0.41	0.44	0.203	-0.124	0.429
AGE	LAA-950	**0.326**	**<.001**	0.179	0.199	0.079	0.84	**0.324**	**0.042**
sRAGE	Age	-0.013	0.88	0.043	0.726	0.178	0.465	-0.154	0.313
sRAGE	Pack-years smoked¶	**-0.21**	**0.015**	-	-	-0.171	0.483	**-0.295**	**0.049**
sRAGE	FEV_1, L	-0.106	0.224	-0.024	0.846	-0.508	0.026	-0.257	0.089
sRAGE	FEV_1, % predicted	-0.103	0.234	-0.157	0.195	-0.2	0.412	-0.275	0.067
sRAGE	FVC, L	-0.152	0.08	0.026	0.831	**-0.561**	**0.012**	**-0.314**	**0.036**
sRAGE	DLCO	-0.044	0.612	-0.062	0.614	-0.35	0.142	0.015	0.92
sRAGE	Emphysema Score	**-0.221**	**0.017**	-0.14	0.313	-0.088	0.72	-0.245	0.109
sRAGE	LAA-950	-0.102	0.282	0.089	0.522	-0.279	0.262	-0.236	0.137
AGE/sRAGE	Age	-0.041	0.654	-0.011	0.931	-0.097	0.789	-0.089	0.568
AGE/sRAGE	Pack-years smoked¶	**0.208**	**0.022**	-	-	**0.697**	**0.025**	0.018	0.907
AGE/sRAGE	FEV_1, L	-0.047	0.607	0.122	0.321	**0.747**	**0.013**	0.007	0.967
AGE/sRAGE	FEV_1, % predicted	-0.151	0.098	0.105	0.392	0.258	0.472	-0.005	0.974
AGE/sRAGE	FVC, L	0.105	0.252	0.076	0.535	**0.813**	**0.004**	0.091	0.561
AGE/sRAGE	DLCO	0.046	0.616	0.018	0.884	0.489	0.151	0.113	0.471
AGE/sRAGE	Emphysema Score	**0.209**	**0.032**	-0.049	0.727	-0.243	0.499	0.078	0.625
AGE/sRAGE	LAA-950	**0.212**	**0.035**	-0.015	0.915	**0.699**	**0.036**	0.187	0.255

¶: Cigarette or pipe/cigar smoking; At risk group comprise of those without COPD.

AGEs: Advanced Glycation End products; sRAGE, soluble Receptor of AGE; mcgm/ml: microgram/ milliliter; pgm/ml: picogram/ milliliter; FEV1: Forced Expiratory Volume in the first second; FVC: Forced Vital Capacity; DLCO: diffusing capacity for carbon monoxide; LAA-950: Low Attenuation Areas less than a threshold of -950 Hounsfield units; HTN: Hypertension;

Figure 3: Correlation of serum levels of AGE in the study population

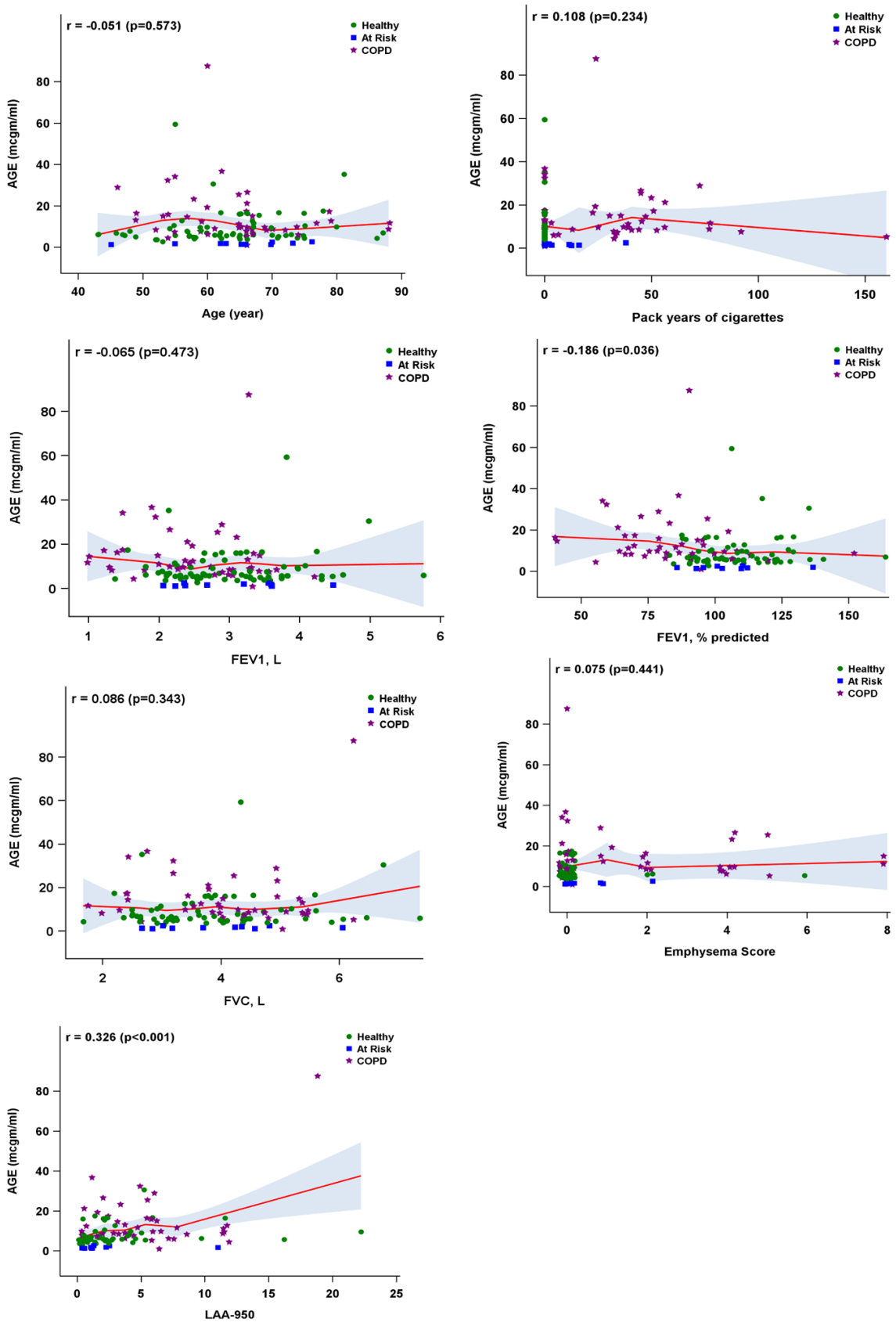


Figure 4: Correlation of serum levels of sRAGE in the study population

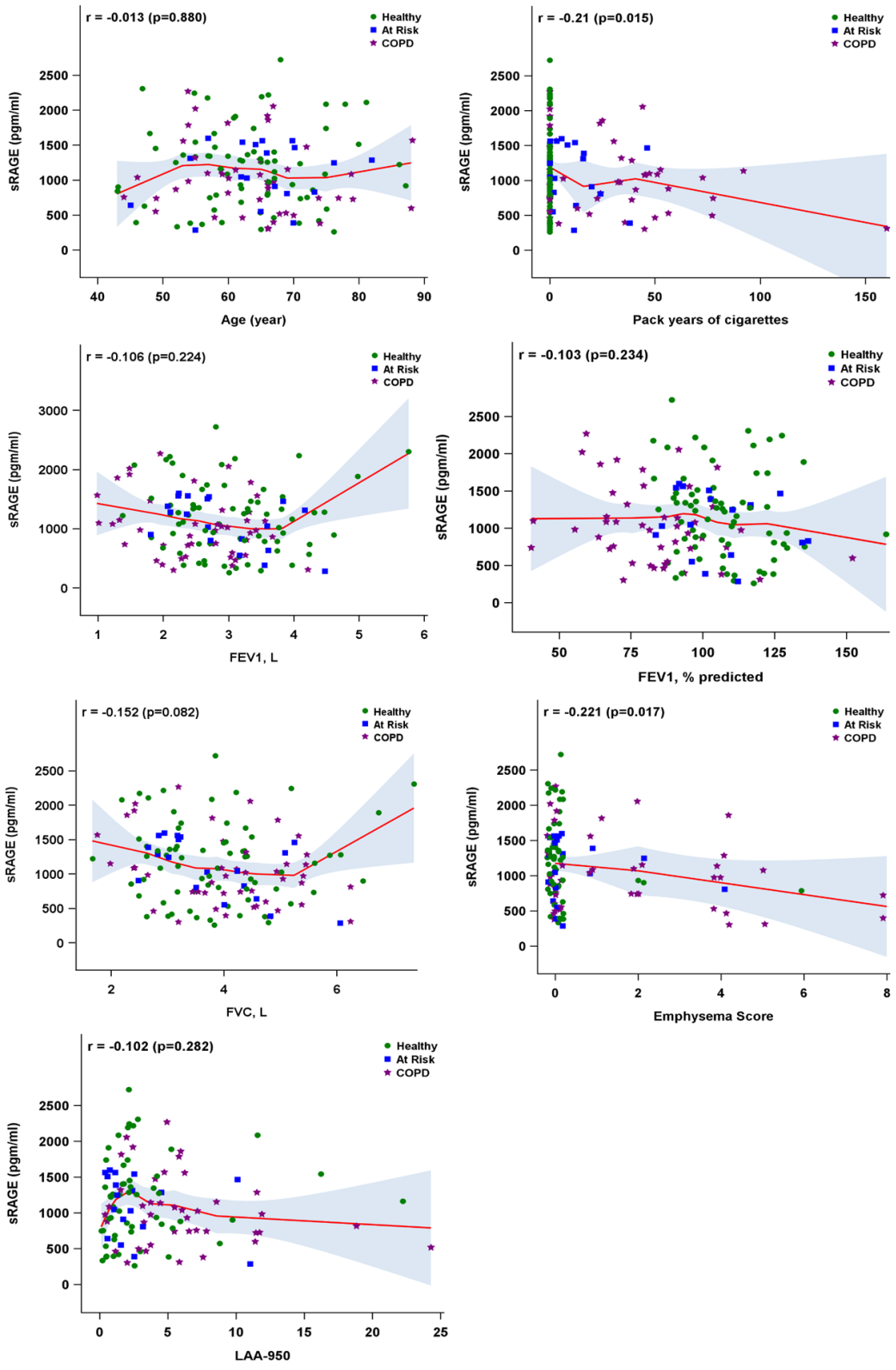
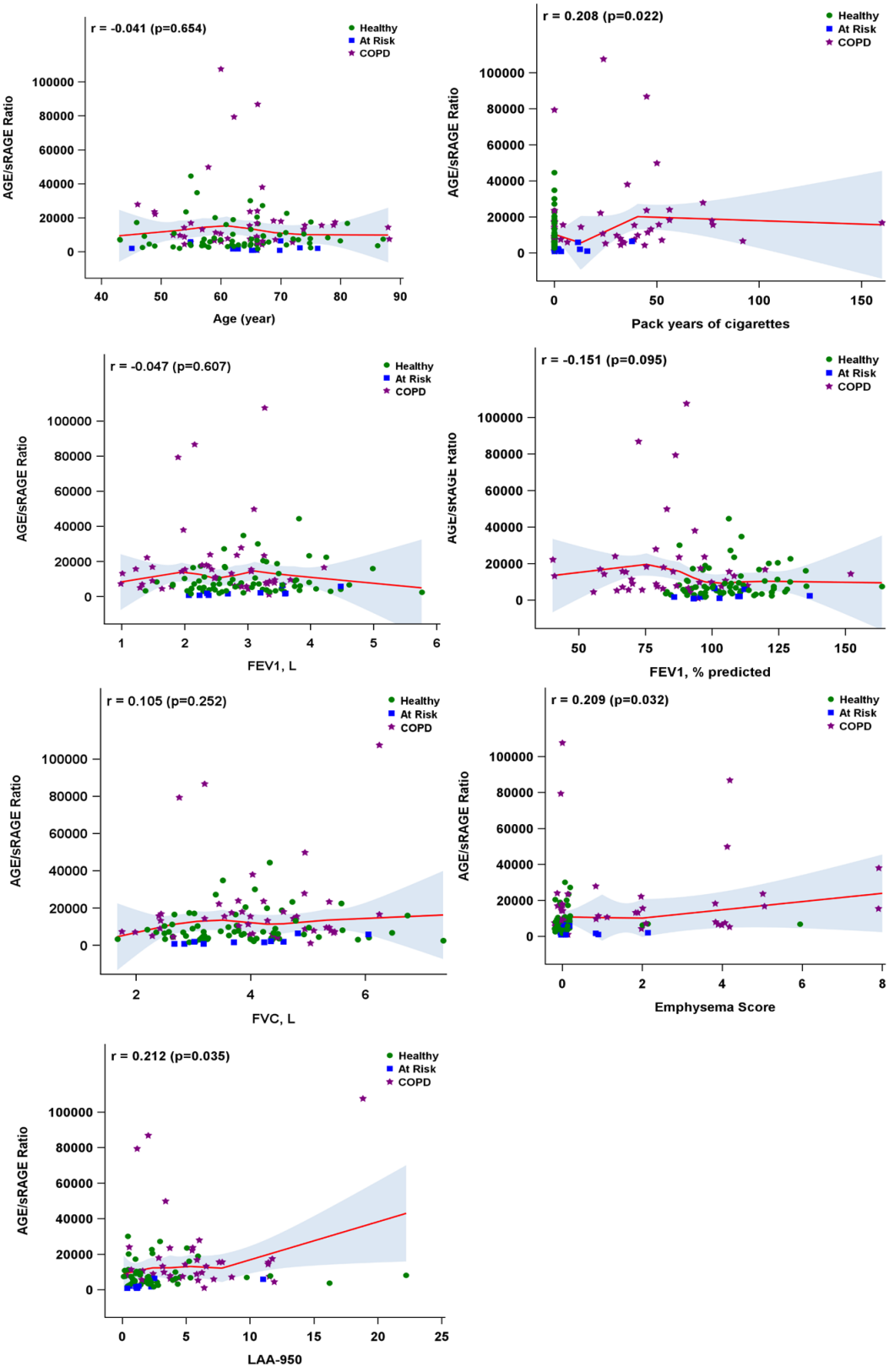


Figure 5: Correlation of serum levels of AGE/ sRAGE ratio in the study population



8. Discussion

8.1 Summary of Findings

Current literature on COPD is built around studying those with moderate-severe disease, especially since diagnoses at earlier stages were not commonplace. A sense of paucity of treatment options in these cases, alongside a low uptake of performing spirometry in primary care settings, has been observed. In view of the burden on human quality of life and the healthcare system from COPD and future projections of increases in this burden, coupled with the emerging understanding of the phenotypic heterogeneity of the disease, it has become important to bridge the knowledge gaps to support prognostication and prediction in the mild-moderate COPD population considering family-medicine practices. This would, in turn, support the identification of high-risk groups and the ability to assess clinically meaningful outcomes and thresholds to guide treatment as well as develop therapeutics ranging from those to arrest declines to preventative interventions in the future. These are important elements for individualized treatment, given the diversity of presentation and progression of the disease.

After reviewing the evolving concepts and management strategies (described in Chapter 3) potential tools and models were considered. Short-term clinically important deterioration (CID) and Acute COPD Exacerbation Prediction Tool (ACCEPT) 2.0 proposed for prediction of future exacerbations in current literature were identified for further investigation in the mild-moderate COPD patient population. A suitable cohort was identified (described in Chapter 4) to undertake the evaluations.

CID is a practical clinical tool to assess clinically important deterioration using observed changes on 3 components to inform 'change' in the patient's trajectory. The components are namely: FEV1decline (disease severity component), exacerbation (disease activity component), and deterioration of health status (disease impact component). Short-term CID was developed as a composite surrogate outcome measure to assess treatment efficacy in trials. Following this, it has been used as a predictor of future exacerbation. This tool can be used to identify individuals, or groups of individuals, who may be experiencing 'change' at varying intensities based on the thresholds of the 3 components, I assessed it as a predictor of various outcomes of clinical significance including future exacerbations in a model scenario controlled age, sex, BMI and another scenario where the models were additionally controlled for comorbidity (any CVD) and biomarker (absolute eosinophil count; others assess: CRP and fibrinogen). My assessments of the tool, as defined currently, revealed that in the target patient population, exacerbation history and health status (SGRQ) components were more informative over the severity of airway obstruction in clinical assessments when using the tool to prognosticate. Two different definitions were investigated, based on the choice of health status measurement.

In the mild-moderate COPD population examined, short-term composite CID, as currently defined, is not informative of lung function decline over 18 months follow-up in either model, whether adjusted for age, sex, BMI, and smoking pack-years or additionally with clinically available variables of biomarker (absolute eosinophil count) and comorbidity (CVD). Given the prevalent consensus encouraging reliance on exacerbation and health status in assessing future disease worsening and treatment decisions, as reflected in the GOLD recommendation, while CID emerged as a promising tool in my investigations as described in Chapter 5, the need for further investigations in appropriate yet larger cohort emerged.

To validate the findings obtained in the Canadian cohort, a suitable larger cohort mindful of patients in the primary care setting was identified as described in Chapter 4. Assessments of interest include if short-term CID, as currently defined, is a suitable predictor of clinically significant outcomes, including exacerbation for a similar duration in the period following CID assessment, further investigated by varying the follow-up window and definitions of CID, along with trajectory analysis. The UK-CPRD is the database of patient electronic data from the UK's general practices under the NHS. Since the general practices are the nodes for referrals to secondary care hospitalization data is also available through linkages for patients in the database. This makes this database a suitable source cohort to replicate the CanCOLD cohort and identify the large validation cohort for further investigations and reporting. This work is currently ongoing, and the protocol is discussed in Chapter 5 under further research.

ACCEPT 2.0 which has been recently recalibrated for generalizability, was the prediction model identified for assessment of applicability in a mild-moderate COPD of CanCOLD. In my investigations, as described in Chapter 6, ACCEPT 2.0 performed better than the history of exacerbation in predicting future exacerbation outcomes in the CanCOLD cohort with a modified definition of the outcome variable in view of the characteristics of the mild-moderate COPD patients. While the discrimination was acceptable (AUC >.70) for outcomes of any exacerbation, of ≥ 1 moderate or severe exacerbation, and of ≥ 1 severe exacerbation or ≥2 moderate exacerbation, on calibration aspect, the model was limited in predicting exacerbations with accuracy when subjects with COPD had a very low annual rate such as any exacerbation < 0.4. Future research may consider a re-assessment of the results reported here in larger cohorts of individuals with mild-moderate COPD representative of the real-life primary-care/family medicine practice patient population.

Risk prediction tools inclusive of biomarkers with risk predictors are increasingly being proposed for use to support care management decisions to assess suitability for an intervention [195-197]. In COPD, biomarker panels have been proposed to increase model accuracy for prediction of all-cause mortality in moderate to very severe COPD [174]. A biomarker can be an important tool for allowing inferences such as the presence of pre-disease conditions, disease, its progression, and response to treatment. Biomarkers can act as informative variables in a prediction model, impacting its discrimination and/or calibration accuracies. I present the role of stressor-antistressor imbalance in the pathophysiology of COPD, which is triggered by AGE binding with its membrane-bound receptor, RAGE, in an environment of reduced availability of the soluble RAGE, sRAGE, which is a decoy since it binds with AGE does not promote inflammation. My goal was to highlight that the ratio of AGE/sRAGE is a potential informative variable for COPD disease activity, in view of the heterogeneity and influence of comorbidities in the disease population. In chapter 7, after presenting the pathophysiology, I measure and report findings from a sub-cohort of CanCOLD identified for the study. The study population included 3 groups: “healthy” (CanCOLD participants of the “Normal” group who are non-cigarette smokers, non-diabetic, non-hypertensive, non-CVD, non-asthma, not using ACE-inhibitors and not using Statins), “at-risk” (CanCOLD participants of the “Normal” group who are cigarette, pipe or cigar smokers) and “COPD” (largely CanCOLD participants with mild-moderate COPD). Apart from their differences in smoking and comorbidities, which were part of the selection criteria, the COPD group had more male participants. The groups were similar in age and BMI. The ratio of AGE/sRAGE was significantly elevated in the COPD group. Investigating its relationship with variables of smoking, lung function, emphysema, and gas diffusion in the overall population, the ratio showed a positive correlation with packyears of

cigarette smoked and emphysema (LAA-950 and emphysema score). In the at-risk group showed positive correlations with FEV1, FVC, and LAA-950. The ratio emerges as a potential disease activity marker for the mild-moderate disease populations. Future research may assess the reproducibility of the reported findings in suitable larger cohorts and perform further sub-group analysis, for instance, based on specific combinations of comorbidities in a strata of smoking status, etc., to generate deeper insight in this patient population.

8.2 Strengths and Limitations

Study-specific strengths and limitations have been discussed in the respective manuscripts. Overall, the strengths of the studies in this thesis include the selection of an appropriate cohort to identify the study population with the primary care COPD patient population in mind. The studies in this thesis are the first ones, to our knowledge, to examine CID (a composite measure of deterioration) and ACCEPT 2.0 (model for predicting risk of future exacerbation) in a population-based mild-moderate COPD population. assessments of the applicability in the target population allows the opportunity to continue to add to the existing knowledge from COPD populations where these have previously been assessed in. This continuum allows for observations of nuances given the heterogeneity of the target population. Also, for the disease activity marker (AGE/sRAGE ratio) study, the carefully selected healthy control group and the availability of detailed characterization of comorbidities in the cohort make the study findings important for the clarity they add to the existing literature. Also, serum levels were measured for both biomarkers in the study. The follow-up periods available in the cohort allowed for further definition of inclusion criteria. To summarise, the findings from the studies in this thesis add clinically significant knowledge to support future research on making personalized care from mild-moderate stages of COPD a reality.

While there are several strengths, there are limitations of the studies in this thesis, which can be summarised to study population size due to which validation studies in larger cohorts need to be undertaken; one such study has already been initiated using the UK-CPRD, and the protocol is discussed here. The initiation of this study was significantly affected by Coronavirus disease 2019 (COVID-19). The travel bans and prolonged uncertainties needed a complete overhaul of

the logistics of undertaking the study, including finding new funds to support an application for a single study license from CPRD, obtaining 'new client' approval from the data custodians in the UK for data access from the Research Institute of McGill University Health Centre location. Delays due to ascertainment of legalities rising from the disparities in definitions of roles of parties to the contract, among others, led to significant wait periods before the data access process commencement for the approved protocol. Secondly, the ACCEPT 2.0 I evaluated had been recalibrated for generalizability but not specifically for mild-moderate COPD. Also, due to the impact of COVID-19, the start of the fourth visit was significantly delayed and is scheduled to be completed only in 2024- early 2025. As a result, a longer follow-up period could not be used for outcome definition. Thirdly, along with sample size, using biobank samples and analyzing using one method/kit type as advisable for serum level assessments respectively in the case of each biomarker of the ratio may be seen as a limitation, and potentially the availability of corresponding levels from other tissue or other compartments in these participants would have helped a further nuanced understanding. The study population size was affected by COVID-19, and the analysis had to be re-scheduled in view of laboratory closures and uncertainties. Once the facilities were re-opened, analysis had to be restricted to those available at the Montreal biobank for analysis at the Meakins Meakins-Christie Laboratories of the Centre for Respiratory Research at McGill University and the Research Institute of the McGill University Health Centre. My goal in the current study was to assess the evidence in this population to inform future studies.

8.3 Clinical Implications and Opportunities for Future Research

This thesis was developed and aimed at contributing new knowledge towards supporting efforts in personalized care in COPD aligned with a philosophy of early detection and intervention for the prevention of rapid disease progression such as rapid decline and/or future exacerbations. The importance of assessing disease early on and knowing who, from mild to moderate disease, will have rapid disease progression will have major implications and applications in clinical practice and future designing and recruitment of new intervention RCTs.

Three aspects of these multidimensional efforts were identified for this thesis and as mentioned in the thesis structure.

- identification of patients with COPD, early on, who are susceptible to experiencing rapid disease progression both in real-world and trial settings;
- identification and better characterizing the validity of tools to indicate a clinically meaningful change in an outcome such as or particularly future exacerbation which is clinically implementable for future treatment decision-making making which in trial settings can help assess the efficacy of investigational treatment;
- identification and exploration of a new and informative biomarker suitable in a patient population manifesting heterogeneity due to diversity of pathogenesis and influence of co-morbidities.

The studies in this thesis add to our understanding of the applicability of CID (a composite measure of deterioration) and ACCEPT 2.0 (future exacerbation risk prediction model) among those with mild-moderate COPD. This can, on the one hand, be used for prognostication, while

on the other hand, the characteristics of the individuals can inform the identification of different susceptible groups, thus enabling the development of personalized care. The characteristics of individuals demonstrating susceptibility to rapid decline could guide inclusion criteria for clinical trials developing targeted interventions. The study on CID (manuscript 1) shows that CID, as currently defined, may not be applicable in the mild-moderate COPD population. These observations led to a larger study where we are re-assessing and examining suitable definitions in this population.

Findings from the study on ACCEPT2.0 will stimulate future research to adapt a version of the model for the mild-moderate COPD population. The identified UK-CPRD database can also support this study.

The findings from the ratio of serum AGE/sRAGE study conducted in a defined sub-cohort of CanCOLD is being considered for a cohort-wide assessment and evaluation for baseline and subsequently at other follow-up visits to create longitudinal observations. Feasibility for studies including genetic predisposition [genome-wide association (GWAS)] and lung anatomy (dysanapsis) data of the CanCOLD cohort will help further the understanding of the proposed pathophysiology involving AGE-RAGE stress.

The studies discussed in this thesis, under the three themes, have large clinical implications, and these findings are timely in the light of shifting focus towards early intervention philosophy in COPD, creating opportunities for collaborative multidisciplinary studies to continue bridging the knowledge gaps.

8.4 Conclusions

“An ounce of prevention is worth more than a pound of cure” is not only a popular proverb, it is also a guiding philosophy of healthcare that has stood the test of time. This is a fundamental principle in modern medicine and consistent for infectious diseases as for non-communicable diseases. Bridging knowledge gaps, especially at the developmental and early manifestation stages is essential to this philosophy. Among chronic conditions, COPD is a global challenge for healthcare systems and the health experience of individuals affected due to its prevalence, management at severe stages or during crisis episodes, and mortality [1-3]. A growing body of knowledge in COPD has revealed it to be an “umbrella term” for a disease, which is as if a syndrome constituted of multiple disease subtypes involving different biological mechanisms [198,199] where commodities further modify presentation and progression at an individual level. While traditionally initial efforts have been focused on alleviating the distress of those affected severely, deeper understanding has evolved the understanding of this condition, and studies demonstrating the benefits of efforts for early identification at the community level and pulmonologist-directed treatment encourage studies among those with mild-moderate COPD, such as those in this thesis, with a goal to develop targeted care for this patient population to prevent exacerbation episodes that are known to significantly accelerate deterioration. Findings from this thesis add knowledge on a composite outcome measure or a clinical tool for a measure of clinically meaningful deterioration, a risk prediction model for future exacerbations, and a marker of disease activity which is a ratio of two biomarkers, towards efforts in developing treatment strategy and therapeutic options which are equally essential in this population.

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Appendix 1

Supplementary Material: Manuscript 1

List of Figures

SN	Figure No.	Title
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2	S2	Plots of trajectories of SGRQ (a), CAT (b) and exacerbation (c) between group 1 and group 2 as identified by Group Based Trajectory Modeling using FEV1 trajectory over Visit-1 (V1), Visit-2 (V2) and Visit-3 (V3).

List of Tables

SN	Table No.	Title
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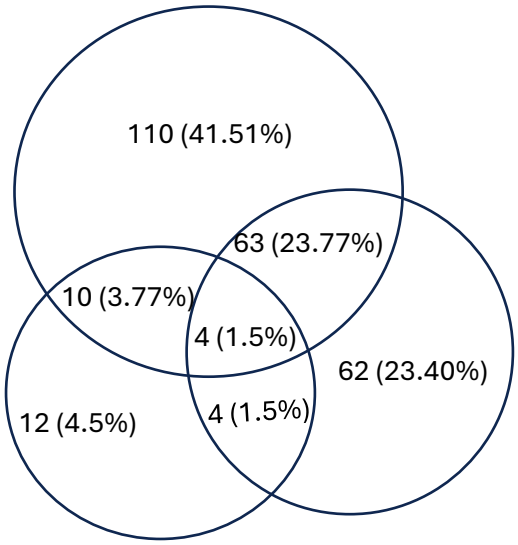
2	S2	Association of short-term composite CID-D2 (composite of decrease of ≥100 mL in post-BD FEV1; increase of ≥2 units in CAT score; and incidence of a moderate/severe exacerbation) with outcomes over 18 months of follow-up
3	S3A	Association of exacerbation component of short-term CID-D2 (composite of decrease of ≥100 mL in post-BD FEV1; increase of ≥2 units in CAT score; and incidence of a moderate/severe exacerbation) with outcomes over 18 months of follow-up
4	S3B	Association of health status component of short-term CID-D2 (composite of decrease of ≥100 mL in post-BD FEV1; increase of ≥2 units in CAT score; and incidence of a moderate/severe exacerbation) with outcomes over 18 months of follow-up
5	S3C	Association of FEV1 decline component of short-term CID-D2 (composite of decrease of ≥100 mL in post-BD FEV1; increase of ≥2 units in CAT score; and incidence of a moderate/severe exacerbation) with outcomes over 18 months of follow-up

FEV1 decline ≥100 mL V1 to V2
n=187
(70.57% of CID+ group;
43.79% of P-D2)



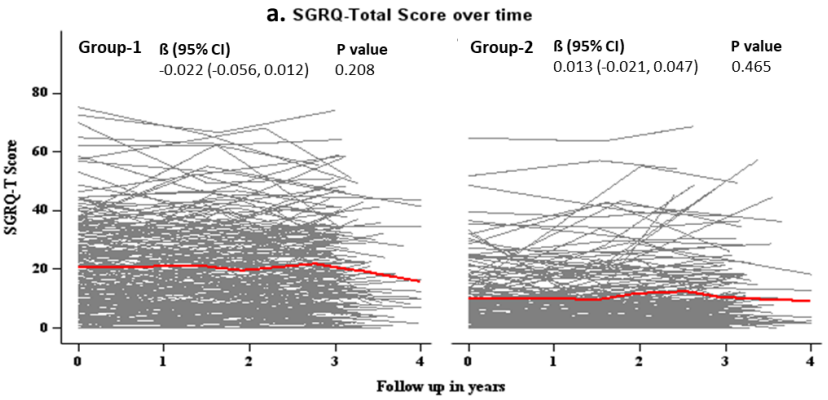
CAT increase ≥2-units V1 to V2
n=133
(50.19% of CID+ group;
31.15% of P-D2)

Exacerbation ≥1 moderate/severe during 1year prior to V2
n=30
(11.32% of CID+ group;
7.03% of P-D2)

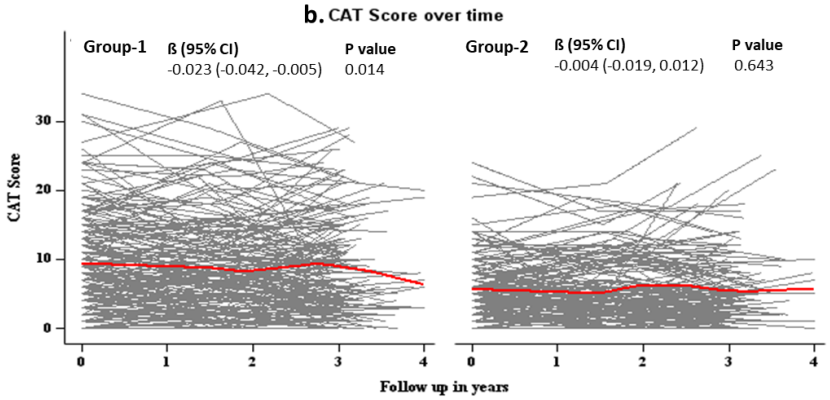
CID*+: 62% participants (n=265)
CID*-: 38% participants (n=162)

Analysis population n=427
**CID defined using CAT as HRQoL component*
CID+= group demonstrating short-term Clinically Important Deterioration

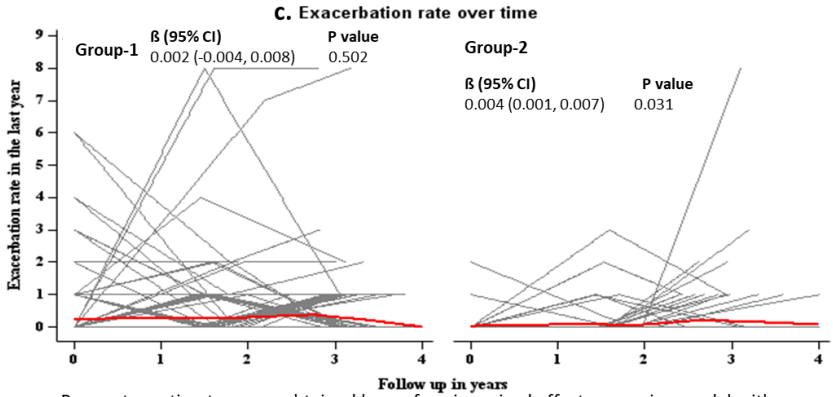
Figure S1: Individual components of the short-term CID assessed between visit1 (V1) and visit 2 (V2) using CAT as HRQoL component to define CID (CID-D2).



Parameter estimates were obtained by performing mixed effect regression model with random intercept accounting for the correlation with repeated measures



Parameter estimates were obtained by performing mixed effect regression model with random intercept accounting for the correlation with repeated measures



Parameter estimates were obtained by performing mixed effect regression model with random intercept accounting for the correlation with repeated measures

Figure S2. Plots of trajectories of SGRQ (a), CAT (b) and exacerbation (c) between group 1 and group 2 as identified by Group Based Trajectory Modeling using FEV1 trajectory over Visit-1 (V1), Visit-2 (V2) and Visit-3 (V3).

Supplement Table S1. Comparison of baseline characteristics of study participants by CID definitions: CID-D1 (HRQoL component: ≥4 units SGRQ) and CID-D2 (HRQoL component: ≥2 units CAT) where CID is a composite of decrease of ≥100 mL in post-BD FEV1; HRQoL component; and incidence of a moderate/severe exacerbation

	COPD subjects (n=739)							
	CID-D1			CID-D2			CID-D1 vs D2	
	CID+	CID-	P value	CID+	CID -	P value	Comparing P-values	
	N=252	N=168		N=265	N=162		CID+	CID-
Age, in year	66.4 ± 9.6	68.1 ± 10.3	0.092	67.2 ± 9.7	66.8 ± 10.2	0.715	0.3	0.245
Sex, male gender, n (%)	146 (57.9)	105 (62.5)	0.362	154 (58.1)	101 (62.3)	0.417	1	1
BMI	27.5 ± 6.0	27.5 ± 4.8	0.855	27.6 ± 5.9	27.3 ± 4.8	0.546	0.766	0.627
Smoking status, n (%)								
Never	61 (24.2)	52 (31.0)	0.127	68 (25.7)	53 (32.7)	0.116	0.703	0.731
Former	122 (48.4)	98 (58.3)	0.046*	130 (49.1)	89 (54.9)	0.238	0.884	0.534
current	69 (27.4)	18 (10.7)	<0.001 *	67 (25.3)	20 (12.3)	0.001*	0.588	0.643
Pack-years of cigarettes	26.2 ± 25.8	17.9 ± 20.5	0.002*	25.6 ± 25.5	16.9 ± 20.6	<0.001 *	0.801	0.583
MRC Dyspnea scale Score ≥ 3/5, n (%)	18 (7.5)	14 (8.6)	0.683	21 (8.3)	11 (7.0)	0.635	0.732	0.598
$FEV_{1,}$ L	2.3 ± 0.8	2.3 ± 0.8	0.5	2.3 ± 0.8	2.3 ± 0.8	0.632	0.852	0.994
FEV_1, % predicted	79.9 ± 19.7	81.6 ± 17.2	0.379	81.2 ± 19.6	79.8 ± 17.3	0.456	0.475	0.343
SGRQ-Total	17.3 ± 16.0	15.4 ± 14.6	0.299	17.7 ± 16.1	14.5 ± 14.1	0.043*	0.705	0.557
CAT score	8.4 ± 6.6	7.0 ± 6.4	0.01*	8.1 ± 6.6	7.4 ± 6.3	0.291	0.432	0.454
SF36 Physical component scale	49.3 ± 9.7	51.9 ± 7.2	0.035*	49. (among 5 ± 9.6	51.8 ± 7.2	0.072	0.816	0.932
SF36 Mental component scale	50.1 ± 8.8	50.2 ± 9.8	0.561	49.8 ± 9.5	50.6 ± 8.5	0.515	0.95	0.995
Respiratory medications reported in the past 12 months, n (%)								
SABD	20 (7.9)	10 (6.0)	0.439	18 (6.8)	12 (7.4)	0.809	0.618	0.596
LABA or LAMA	2 (0.8)	5 (3.0)	0.121	2 (0.8)	5 (3.1)	0.11	1	0.953
ICS alone	21 (8.3)	15 (8.9)	0.831	20 (7.5)	16 (9.9)	0.401	0.741	0.768
ICS combined with LABA/LAMA	58 (23.0)	28 (16.7)	0.114	55 (20.8)	32 (19.8)	0.803	0.534	0.467
Any above medications	101 (40.1)	58 (34.5)	0.25	95 (35.8)	65 (40.1)	0.376	0.322	0.293

	COPD subjects (n=739)							
	CID-D1			CID-D2			CID-D1 vs D2	
	CID+	CID-	P value	CID+	CID -	P value	Comparing P-values	
	N=252	N=168		N=265	N=162		CID+	CID-
EOS (biobank sample)								
Absolute count, count/ microliter	0.22 ± 0.18	0.23 ± 0.15	0.112	0.22 ± 0.17	0.24 ± 0.17	0.1	0.948	0.972
<150 Eos/microliter	86 (40.4)	51 (34.5)	0.255	89 (40.1)	51 (35.2)	0.343	0.952	0.898
150 to <300 Eos count/ microliter	73 (34.3)	57 (38.5)	0.409	84 (37.8)	50 (34.5)	0.514	0.439	0.474
≥300 Eos count/ microliter	54 (25.4)	40 (27.0)	0.721	49 (22.1)	44 (30.3)	0.075	0.421	0.53
Percentage, %	5.0 ± 4.2	5.4 ± 3.5	0.052	4.9 ± 4.0	5.5 ± 3.7	0.029*	0.893	0.89
CRP	2.63 ± 3.96	2.12 ± 2.49	0.153	2.54 ± 3.78	2.23 ± 2.77	0.141	0.976	0.999
Fibrinogen	3.01 ± 0.58	3.01 ± 0.69	0.415	2.99 ± 0.57	3.02 ± 0.71	0.726	0.756	0.877

BMI= Body Mass Index; CAT= COPD Assessment Test; CID+= group demonstrating short-term Clinically Important Deterioration; EOS= Eosinophil Count; FEV1= Forced expiratory volume in 1 second; ICS= inhaled corticosteroids; HRQoL= Health-related quality of life; LAMA= long-acting anti-muscarinic antagonist; LABA=long-acting β2 receptor agonist; MRC=Medical Research Council score; SABD= Short-acting bronchodilator; SF-36= 36-Item Short Form Health Survey; SGRQ= St. George respiratory Questionnaire score

Table S2. Association of short-term composite CID-D2 with outcomes over 18 months of follow-up

	COPD population					
	CID-D2 (composite of decrease of ≥100 mL in post-BD FEV1; increase of ≥2 units in CAT score; and incidence of a moderate/severe exacerbation)					
	Composite CID + n (%)	Composite CID- n (%)	Composite CID+ vs. Composite CID- (model1) OR /HR/RR (95% CI)	P value	Composite CID+ vs. Composite CID- (model2) OR /HR/RR (95% CI)	P value
Outcome (change from V2 to V3)						
≥100 mL decrease in FEV1[a], n (%)	78 (35.1)	87 (61.3)	0.32 (0.20-0.50)	<0.001*	0.30 (0.18-0.49)	<0.001*
≥200 mL decrease in FEV1[a], n (%	41 (18.5)	46 (32.4)	0.41 (0.24-0.69)	<0.001*	0.40 (0.23-0.70)	0.001*
≥4-unit increase in SGRQ[a], n (%)	50 (22.4)	38 (27.0)	0.75 (0.45-1.23)	0.254	0.68 (0.40-1.15)	0.146
≥8-unit increase in SGRQ[a], n (%)	23 (10.3)	21 (14.9)	0.63 (0.33-1.21)	0.163	0.63 (0.32-1.24)	0.182
≥2-unit increase in CAT[a], n (%)	64 (28.4)	46 (31.7)	0.76 (0.48-1.22)	0.256	0.73 (0.44-1.21)	0.229
≥4-unit increase in CAT[a], n (%)	35 (15.6)	28 (19.3)	0.68 (0.39-1.20)	0.183	0.69 (0.38-1.26)	0.223
≥1-unit increase in MRC[a], n (%)	32 (15.8)	20 (14.7)	0.81 (0.42-1.55)	0.517	0.86 (0.43-1.75)	0.682
Event-based exacerbation rate between V2 to V3[b], no./patient-year	0.27	0.24	0.96 (0.67 - 1.37)	0.819	0.98 (0.67 - 1.43)	0.921
Event-based exacerbation rate in 1-year follow-up from V2[b], no./patient-year	0.33	0.27	1.07 (0.70 - 1.63)	0.767	1.04 (0.67 - 1.62)	0.871
Event-based exacerbation in 1-year follow-up from V2[c], n (%)	42 (20.3)	22 (17.3)	0.94 (0.70 - 1.27)	0.696	1.04 (0.75 - 1.42)	0.83

a. OR were calculated using logistic regression model.

b. moderate/sever exacerbation incident rate between V2 to V3 or follow-up 1-year after V2, and RR (95% CI) were calculated using Poisson regression model.

c. a new moderate/sever exacerbation from V2, and HR (95% CI) were calculated using Cox model.

Model1 were adjusted for baseline age, sex, BMI, and smoking pack-years.

Model2 were adjusted for baseline age, sex, BMI, and smoking pack-years, any CVD, and Absolute EOS count.

Composite CID +: Those demonstrating CID (positive for at least one of the 3 components of the composite).

Table S3 A. Association of exacerbation component of short-term CID-D2 with outcomes over 18 months of follow-up

	COPD population					
			Exacerbation Component			
	CID Component +	CID Component -	CID Component + vs. CID Component- (model1)		CID Component + vs. CID Component- (model2)	
	n (%)	n (%)	OR /HR/RR (95% CI)	P value	OR /HR/RR (95% CI)	P value
Outcome (change from V2 to V3)						
≥100 mL decrease in FEV1[a], n (%)	7 (29.2)	158 (46.5)	0.60 (0.23-1.55)	0.295	0.55 (0.20-1.55)	0.259
≥200 mL decrease in FEV1[a], n (%	4 (16.7)	83 (24.4)	0.77 (0.24-2.44)	0.657	0.61 (0.17-2.28)	0.466
≥4-unit increase in SGRQ[a], n (%)	5 (21.7)	83 (24.3)	0.78 (0.27-2.25)	0.647	1.16 (0.38-3.52)	0.789
≥8-unit increase in SGRQ[a], n (%)	5 (21.7)	39 (11.4)	2.58 (0.84-7.94)	0.098	4.28 (1.28-14.31)	0.018*
≥2-unit increase in CAT[a], n (%)	8 (34.8)	102 (29.4)	1.17 (0.46-2.97)	0.745	1.40 (0.51-3.88)	0.515
≥4-unit increase in CAT[a], n (%)	5 (21.7)	58 (16.7)	1.18 (0.40-3.48)	0.771	1.66 (0.53-5.18)	0.381
≥1-unit increase in MRC[a], n (%)	4 (18.2)	48 (15.1)	1.11 (0.32-3.85)	0.866	1.59 (0.43-5.80)	0.485
Event-based exacerbation rate in 1-year follow-up from V2[b], no./patient-year	1.11	0.23	4.12 (2.56 - 6.63)	<0.001*	4.11 (2.46 - 6.86)	<0.001*
Event-based exacerbation rate between V2 to V3[b], no./patient-year	0.98	0.18	4.77 (3.12 - 7.28)	<0.001*	5.66 (3.55 - 9.03)	<0.001*
Event-based exacerbation in 1-year follow-up from V2[c], n (%)	14 (51.9)	50 (16.3)	2.47 (1.58 - 3.86)	<0.001*	2.41 (1.48 - 3.92)	<0.001*

CID component +: Among the CID positive group, those demonstrating the CID component reported in the table (FEV1 decline component).

CID-D2: composite of decrease of ≥100 mL in post-BD FEV1; an increase of ≥2 units in CAT score; and incidence of a moderate/severe exacerbation

a. OR were calculated using logistic regression model.

b. moderate/severe exacerbation incident rate between V2 to V3 or follow-up 1-year after V2, and RR (95% CI) were calculated using Poisson regression model.

c. a new moderate/severe exacerbation from V2 and HR (95% CI) was calculated using Cox model.

Model 1 series were adjusted for baseline age, sex, BMI, and smoking pack-years.

Model 2 series were adjusted for baseline age, sex, BMI, smoking pack-years, any CVD, and Absolute EOS count.

Table S3 B. Association of health status component of short-term CID-D2 with outcomes over 18 months of follow-up

	COPD population					
			Health status Component (CAT)			
	CID Component +	CID Component -	CID Component + vs. CID Component- (model1)		CID Component + vs. CID Component- (model2)	
	n (%)	n (%)	OR /HR/RR (95% CI)	P value	OR /HR/RR (95% CI)	P value
Outcome (change from V2 to V3)						
≥100 mL decrease in FEV1[a], n (%)	39 (36.4)	126 (49.0)	0.59 (0.37-0.96)	0.032*	0.61 (0.36-1.01)	0.055
≥200 mL decrease in FEV1[a], n (%	19 (17.8)	68 (26.5)	0.58 (0.32-1.04)	0.068	0.59 (0.32-1.11)	0.1
≥4-unit increase in SGRQ[a], n (%)	22 (20.4)	66 (25.8)	0.72 (0.42-1.25)	0.244	0.57 (0.31-1.05)	0.073
≥8-unit increase in SGRQ[a], n (%)	12 (11.1)	32 (12.5)	0.87 (0.43-1.76)	0.69	0.76 (0.35-1.65)	0.492
≥2-unit increase in CAT[a], n (%)	16 (14.8)	94 (35.9)	0.30 (0.16-0.54)	<0.001*	0.29 (0.15-0.55)	<0.001*
≥4-unit increase in CAT[a], n (%)	8 (7.4)	55 (21.0)	0.29 (0.13-0.63)	0.002*	0.29 (0.12-0.67)	0.004*
≥1-unit increase in MRC[a], n (%)	16 (16.3)	36 (14.9)	1.01 (0.51-1.98)	0.988	1.01 (0.49-2.12)	0.971
Event-based exacerbation rate in 1-year follow-up from V2[b], no./patient-year	0.27	0.32	0.79 (0.51 - 1.24)	0.309	0.81 (0.50 - 1.30)	0.381
Event-based exacerbation rate between V2 to V3[b], no./patient-year	0.21	0.25	0.81 (0.55 - 1.21)	0.308	0.77 (0.50 - 1.19)	0.241
Event-based exacerbation in 1-year follow-up from V2[c], n (%)	19 (19.2)	45 (19.1)	0.88 (0.64 - 1.21)	0.441	0.94 (0.67 - 1.32)	0.727

a. OR were calculated using logistic regression model.

b. moderate/severe exacerbation incident rate between V2 to V3 or follow-up 1-year after V2, and RR (95% CI) were calculated using Poisson regression model.

c. a new moderate/severe exacerbation from V2 and HR (95% CI) was calculated using Cox model.

Model 1 series were adjusted for baseline age, sex, BMI, and smoking pack-years.

Model 2 series were adjusted for baseline age, sex, BMI, smoking pack-years, any CVD, and Absolute EOS count.

CID component +: Among the CID positive group, those demonstrating the CID component reported in the table (FEV1 decline component).

CID-D2: composite of decrease of ≥100 mL in post-BD FEV1; an increase of ≥2 units in CAT score; and incidence of a moderate/severe exacerbation

Table S3 C. Association of FEV1 decline component of short-term CID-D2 with outcomes over 18 months of follow-up

	COPD population					
	FEV1 Decline Component					
	CID Component + n (%)	CID Component - n (%)	CID Component + vs. CID Component- (model1)		CID Component + vs. CID Component- (model2)	
			OR /HR/RR (95% CI)	P value	OR /HR/RR (95% CI)	P value
Outcome (change from V2 to V3)						
≥100 mL decrease in FEV1[a], n (%)	44 (28.4)	121 (57.9)	0.24 (0.15-0.39)	<0.001*	0.23 (0.13-0.38)	<0.001*
≥200 mL decrease in FEV1[a], n (%	22 (14.2)	65 (31.1)	0.29 (0.16-0.51)	<0.001*	0.26 (0.14-0.50)	<0.001*
≥4-unit increase in SGRQ[a], n (%)	38 (24.4)	50 (24.0)	1.01 (0.62-1.66)	0.962	0.94 (0.55-1.60)	0.824
≥8-unit increase in SGRQ[a], n (%)	16 (10.3)	28 (13.5)	0.71 (0.36-1.38)	0.307	0.71 (0.34-1.45)	0.341
≥2-unit increase in CAT[a], n (%)	53 (33.8)	57 (26.8)	1.29 (0.81-2.05)	0.278	1.28 (0.78-2.12)	0.333
≥4-unit increase in CAT[a], n (%)	29 (18.5)	34 (16.0)	1.12 (0.64-1.96)	0.693	1.04 (0.57-1.91)	0.892
≥1-unit increase in MRC[a], n (%)	24 (16.8)	28 (14.3)	0.94 (0.49-1.79)	0.846	0.98 (0.49-1.98)	0.955
Event-based exacerbation rate in 1-year follow-up from V2[b], no./patient-year	0.29	0.32	0.84 (0.57 - 1.26)	0.403	0.89 (0.58 - 1.36)	0.591
Event-based exacerbation rate between V2 to V3[b], no./patient-year	0.22	0.25	0.78 (0.54 - 1.12)	0.175	0.88 (0.60 - 1.31)	0.54
Event-based exacerbation in 1-year follow-up from V2[c], n (%)	0.22	0.25	0.78 (0.54 - 1.12)	0.175	0.88 (0.60 - 1.31)	0.54

a. OR were calculated using logistic regression model.

b. moderate/severe exacerbation incident rate between V2 to V3 or follow-up 1-year after V2, and RR (95% CI) were calculated using Poisson regression model.

c. a new moderate/severe exacerbation from V2 and HR (95% CI) was calculated using Cox model.

Model 1 series were adjusted for baseline age, sex, BMI, and smoking pack-years.

Model 2 series were adjusted for baseline age, sex, BMI, smoking pack-years, any CVD, and Absolute EOS count.

CID component +: Among the CID positive group, those demonstrating the CID component reported in the table (FEV1 decline component).

CID-D2: composite of decrease of ≥100 mL in post-BD FEV1; an increase of ≥2 units in CAT score; and incidence of a moderate/severe exacerbation

Appendix 2

Approved Protocol CPRD ID #21_000688

Medicines & Healthcare products Regulatory Agency

CPRD

1

General information

Protocol reference Id

21_000688

Study title

Short term clinically important deterioration as an indicator of medium and long-term Chronic Obstructive Pulmonary Disease progression: An external validation of Canadian population based longitudinal Cohort findings in the UK primary care population

Research Area

Disease Epidemiology

Does this protocol describe an observational study using purely CPRD data?

Yes

Does this protocol involve requesting any additional information from GPs, or contact with patients?

No

2 Research team

Role	Chief Investigator
Title	Professor
Full name	Jean Bourbeau
Affiliation/organisation	Research Institute of the McGill University Health Centre
Email	jean.bourbeau@mcgill.ca
Will this person be analysing the data?	No
Status	Confirmed

Role	Corresponding Applicant
Title	PhD candidate
Full name	Sharmistha Biswas
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Will this person be analysing the data?	Yes
Status	Confirmed

Role	Collaborator
Title	Professor
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Will this person be analysing the data?	Yes
Status	Confirmed

Role	Collaborator
Title	Research Associate
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Will this person be analysing the data?	No
Status	Confirmed

Role	Collaborator
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Will this person be analysing the data?	Yes
Status	Confirmed

Role	Collaborator
Title	Associate Professor
Full name	Benjamin Smith
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Will this person be analysing the data?	No
Status	Confirmed

3

Access to data

Sponsor

Research Institute of the McGill University Health Centre

Funding source for the study

Is the funding source for the study the same as Chief Investigator's affiliation?

Yes

Funding source for the study

Research Institute of the McGill University Health Centre

Institution conducting the research

Is the institution conducting the research the same as Chief Investigator's affiliation?

Yes

Institution conducting the research

Research Institute of the McGill University Health Centre

Method to access the data

Indicate the method that will be used to access the data

Study-specific dataset agreement

Is the institution the same as Chief Investigator's affiliation?

No

Institution name

Extraction by CPRD

Will the dataset be extracted by CPRD

Yes

CPRD query reference number

00108179

Multiple data delivery

This study requires multiple data extractions over its lifespan

No

Data processors

Data processor is	Same as the chief investigator's affiliation
Processing	Yes
Accessing	Yes
Storing	Yes
Processing area	Worldwide

4

Information on data

Primary care data

CPRD Aurum

Do you require data linkages

Yes

Patient level data

HES Accident and Emergency

HES Admitted Patient Care

HES Outpatient

NCRAS data

Covid 19 linkages

Area level data

Do you require area level data?

No

Practice level (UK)

Patient level (England only)

Withheld concepts

Are withheld concepts required?
No

Linkage to a dataset not listed

Are you requesting a linkage to a dataset not listed?
No

Patient data privacy

Does any person named in this application already have access to any of these data in a patient identifiable form, or associated with an identifiable patient index?
No

Lay Summary

Chronic Obstructive Pulmonary Disease (COPD) is a complex non-completely reversible respiratory condition which is emerging as a leading cause of mortality, globally. Nearly 70% of the patients go undiagnosed and diagnosis tends to happen at advanced stages of the disease. Since underlying disease process may vary significantly between COPD patients, diagnosis may present as a unique challenge. Early detection and targeted management are key concerns.
Only few studies collect detailed data, either patient-reported or observational data captured from health records, on 'flare-ups' (difficulty to breath upon exposure to smoke or pollution, among others, lasting for days to weeks requiring treatment and even hospitalization). The Canadian Cohort Obstructive Lung Disease (CanCOLD) is a unique urban population-based cohort with detailed follow-up data among those with early disease. Our preliminary analysis with CanCOLD suggests that indicators of deterioration observed may differ between those in early and advanced disease-stages. Here, primary-care data such as the Clinical Practice Research Datalink (CPRD) provides the opportunity to study individuals from early-stages, thus enabling us to validate findings from the CanCOLD cohort and in assessing the early disease trajectory of COPD.
Our aim is to focus attention on early detection and timely intervention strategies in COPD by contributing to bridging the gap in our understanding of early disease progression. By studying patient characteristics, we can develop care-pathways especially for those likely to experience a rapid decline. We believe this information is vital to developing new therapeutics and is also critical for healthcare systems in developing efficient care management.

Technical Summary

Chronic Obstructive Pulmonary Disease (COPD) is a complex disease marked by partly irreversible airflow obstruction from an interplay of multiple pathological processes in an individual, making prognosis and management challenging. COPD has emerged among the leading causes of mortality globally. The current understanding of the heterogeneity of the disease and evolutions in patient management is largely based on the body of knowledge from moderate to severe patients. However, our understanding of early disease is limited, and tailored treatment approaches aimed at those susceptible to decline rapidly are needed.
Our goal is to assess the role of recently proposed clinically important deterioration (CID), in predicting future trajectory in the early disease population. COPD-patients are largely identified at advanced disease stages with 70% remaining undiagnosed.
We have assessed CID and its components in the population-based longitudinal Canadian Cohort Obstructive Lung Disease (CanCOLD) study population. This unique well- defined milder disease cohort provides a comprehensive real-life observation of disease progression not available through existing severe disease clinical study populations.
Since COPD patients are largely managed in primary care, the primary care Clinical Practice Research Database (CPRD) provides a large representative clinical cohort to validate CanCOLD findings. The Hospital Episode Statistics (HES) database containing details of all admissions including emergency attendances and outpatient appointments would permit evaluation of COPD exacerbations, an important indicator of deterioration. Association of CID and the outcomes of future disease progression will be assessed for: 1) decline in lung function and health status using logistic regression models; 2) new moderate/severe exacerbations using Cox Proportional Hazards models; and 3) the incidence of these exacerbations using Poisson regression models. This will aid the development of i) an understanding of characteristics of susceptible patients, and ii) CID definition for the milder disease population towards effective care pathways and future tailored clinical trial designs.

Outcomes to be measured

Primary outcome: Medium-term (up to 24 months) deterioration in lung function [using measured forced expiratory volume in one second (FEV1); Medical Research Council (MRC) Dyspnea Scale score; COPD Assessment Test (CAT) score and exacerbations].

Objectives, specific aims & rationale

Research objectives: The general objective is to replicate the population-based CanCOLD cohort using the primary care CPRD database to inform the development of a CID in the mild-moderate COPD population by:
• Examining the predictive nature of CID in a clinical population of mild- moderate COPD patients
• Comparing the results of the CPRD analysis with the findings from the CanCOLD cohort
• Modifying and validating the CID tool suited to milder COPD subjects

Primary objective: To determine whether the short-term CID, as currently defined in literature, is a predictor of medium and long-term outcomes (FEV1, MRC score, CAT score and exacerbations) in mild-moderate COPD patients by replicating population-based CanCOLD cohort in the external validation general practice CPRD cohort.

Secondary objective: To assess the current definition of CID in mild-moderate COPD subjects from a population-based sample in CanCOLD compared to a convenient sample in a family medicine practice (CPRD-derived clinical cohort).

Exploratory objectives: The base cohort (validation cohort is a subset of this cohort) will be used for exploratory analysis. This cohort will include those 40 years or older with minimum 1 spirometry available at or after the age of 40 years and follow-up data available for at least 3 years from this spirometry. Past records will include any spirometry available prior to the age of 40 years, history of respiratory illness diagnosis (COPD and asthma) and use of medications (bronchodilators and Inhaled corticosteroids (ICS). Having a base-cohort will support sensitivity and further exploratory analysis. Some of these assessments might include:
i. Assessing trajectory with different categories of outcome assessment periods (e.g. 18 months, 24 months, 36 months, 5 years, 10 years etc. based on available cohort data)
ii. Assessing modified CID definitions for mild-moderate COPD population exploring CID definition period categories (e.g.,12 months, 18 months, 24 months, 5 years, 10 years etc. based on available cohort data)
iii. Assessing existing and new CID components for mild-moderate COPD population
iv. Assessment of trajectory among those in the base-cohort with additional spirometry beyond the 3 required for validation study-cohort (which reflect CanCOLD visits 1,2 and 3) to allow evaluation of CanCOLD findings from anticipated visit 4 (longer outcome duration between visits 2 and 4)
v. Evaluating population with biomarker results and assessing CID definition in the mild-moderate population with and without biomarkers.

Rationale of the study:
Current knowledge highlights COPD as a multidimensional disease and assessing single outcomes fail to evaluate the complexity of the patient experience. Also, the progression of COPD varies among patients making it crucial to identify those susceptible to decline rapidly at an early stage for efficient patient care management. This need has led to the development of a multidimensional clinical tool, CID. However, this toll has been developed in more severe clinical populations. We first assessed this tool in the mild-moderate CanCOLD cohort population. We propose to replicate the milder COPD population of the CanCOLD cohort using the CPRD clinical population to compare and to validate our findings from this population-based cohort, to assess and modify the CID tool towards its application in the mild-moderate COPD population in detecting ‘rapid decliner’. The knowledge from this research will facilitate future treatment developments, augment patient care and enable clinicians to deploy appropriate interventions to slow disease progression.

Well-structured and well-phenotyped population based longitudinal studies like CanCOLD have provided the opportunity to study real-life disease trajectory in the milder disease categories of COPD. External validation of findings is important in a clinical population of patients with mild to moderate COPD in the family medicine practice. Given the global public health challenge we face in COPD, findings from the proposed study will aid in informing natural history of COPD as well as in guiding clinical and therapeutic research and resource allocation for targeted early management of those at higher risk of rapid disease progression.

Study background

Chronic Obstructive Pulmonary Disease (COPD) is the fourth leading cause of mortality, globally, estimated to become the third by 2020 (GOLD, 2020). The disease burden is projected to continue to rise globally through the decades with population aging along with persistent exposure to COPD risk factors. It remains to be a complex non completely reversible chronic respiratory condition with heterogenous underlying pathophysiologies associated with significant morbidity, mortality and burden of care. The true prevalence of COPD is underestimated, largely due to underdiagnosis from a lack of awareness of the widespread presence of COPD among physicians and patients. It is among the chronic diseases associated with advanced age, largely due to our current understanding where progression to significant symptom burden triggers investigation and detection. This has focused attention to disease management for severe stages. It is reported that nearly 70% patients in the early-disease stages remain undiagnosed (Bourbeau et al., 2014). The latest update from a large meta-analysis was conducted using data from 60 publications across various World Health Organization (WHO) regions which included 30 studies from the European Region, 13 from the Western Pacific Region, 10 from the Region of the Americas, 4 from the Eastern Mediterranean Region, 2 studies each from African and South-East Asia Regions, and 1 international-level study (Varmaghani et al., 2019). Among 127 598 subjects included in the study, 44.16% were reported with mild COPD (GOLD 1), 44.22% with moderate COPD (GOLD 2), and the remaining 11.6% with severe COPD (GOLD 3) based on post-bronchodilator COPD assessment. By age-group, the authors report highest prevalence of COPD of 21.38% (18.42–25.40) in the 60 years and above age-group and the lowest prevalence of 5.28% (4.08–6.49) in the below 50 years age-group. A prevalence of 10.16% (7.94–12.37) was reported in the 50 to 59 years age-group.

From their meta-analysis, the authors report the worldwide prevalence of COPD to be 12.16% (10.91–13.40%) with stage I (7.06%) as the most prevalent while stages III and IV as the least (1.61%). Most clinical trials to date have studied patients with severe and very severe disease, GOLD III-IV. Assessing mild disease requires population-based studies and studies done in primary care.

The ability to predict disease activity and recognize individuals who are at high risk of having faster disease progression is another important challenge in COPD research. In recent COPD literature a composite outcome index comprising of lung function decline and patient reported outcomes, Clinically Important Deterioration (CID), has been proposed to identify individuals who are at higher risk of having important changes in disease-course (Singh et al., 2016). It has been used as outcome measure (Singh et al., 2017) as well as short-term predictor of change over longer duration (Naya et al., 2018). However, these assessments have been conducted largely among patients with more severe disease stages and in selective clinical cohorts or trials and it remains to be evaluated in mild COPD. We have recently assessed short-term CID, as currently defined in literature, in a population-based study, the Canadian Cohort Obstructive Lung Disease (CanCOLD). CanCOLD cohort expands over 9 cities, with detailed data collection at 3 timepoints (over a median follow up of 3 years). COPD participants in the CanCOLD cohort were generally milder (in majority GOLD 1 and 2) and often without a clinical diagnosis of COPD. Demographic, anthropometric, risk factor (smoking, occupational and biomass exposure, ambient air quality among others), comorbidities, respiratory symptoms, detailed exacerbation history (patient reported outcome-PRO) and prospective 3-monthly information, quality of life assessments (CAT, SGRQ, HAD, mMRC) are available along with detailed pharmacological treatment, biomarkers, and imaging information. Follow-up allows for short term CID assessment (at median 18 months follow-up between visits 1 and 2) as well as longitudinal follow-up for medium-term (visit 3 currently available, long-term would include visit 4) outcome assessment. Using data from visits 1,2 and 3, our findings suggest that in these individuals CID is not able to predict FEV1 and PRO decline in the period of visit 2 to visit 3 based on the short-term assessment between visit 1 and 2 interval. However, the composite index and its component of exacerbations is able to predict high risk exacerbations, i.e., those who have frequent exacerbations. Thus, we are unable to confirm findings from past studies on individuals with more advanced disease stages.

We would like to assess the validity of these findings from CanCOLD to be able to determine if short term FEV1 and PRO changes have limited capacity in early and mild disease to predict

medium and long-term COPD trajectory. This could be done by accessing the family physician practice United Kingdom Clinical Practice Research Datalink-CPRD.

The CPRD covers about 15% of the population of the United Kingdom (UK) and contains anonymized data from general practices that have agreed to share patient data. In the UK National Health Service (NHS), a general practitioner (GP) refers patients to diagnostic test and secondary care and over 98% of the population has been reported to be registered with a GP practice in England (NHS Digital, 2018). The CRPD is the combined database of two similarly structured complementary databases: CPRD GOLD and CPRD AURUM. Practices contribute to the CPRD through either of these based on the patient management software system provider used: Vision® software system (CRPD GOLD database) or the EMIS® software system (CPRD AURUM database) (Herrett et al., 2015). A majority of these practices have consented to participate in the CPRD linkage scheme and provide patient-level information.

Wolf et.al described the September 2018 CPRD Aurum database reporting over 19 million patients in England, of whom 7 million were included as alive and currently contributing and representative of approximately 13% of the population of England (Wolf et. al., 2019). Considering a period between 1995 and September 2018, the study reported a median follow-up of 4.2 years (IQR: 1.5–11.4) for all patients and 9.1 years (IQR: 3.3–20.1) for current patients. Additional practices from Northern Ireland have been added since the review and with the combined coverage, CPRD currently includes 35 million patient lives, including 11 million reported currently registered patients (NIHR, 2019).

CPRD reports Aurum linkage data as inclusive of patients from 890 practices in England representing a coverage of approximately 99% of CPRD Aurum practices and 28,618,186 patients as currently eligible for linkage as available in the August 2019 build (NIHR, 2021). Data from patients from all practices in CPRD Aurum can be linked to a range of health-related data sources including secondary care, disease registries and death registration records. NHS Digital, a trusted third party, uses an NHS number, exact date of birth, sex and patient residence postcode (Padmanabhan et al., 2018) to link CPRD Aurum to other patient-level health data making available only de-identified data through the CPRD.

The Hospital Episode Statistics (HES) datasets are of primary interest to the proposed study. It contains details of all admissions to, or attendances at English NHS healthcare providers, including all patients treated in NHS hospitals and treatment centers (including the independent sector) funded by the NHS. HES includes details such as dates, specialty, clinical diagnosis and procedures across: Admitted Patient Care (APC) data; Outpatient (OP) records of outpatient care in England; Accident and Emergency (A&E) care records in England; Diagnostic Imaging Dataset (DID) taken from NHS radiological information systems; and Patient Reported Outcome Measures (PROM).Diagnostic data is recorded using the International Classification of Diseases version 10 (ICD10) coding frame and procedure information is coded using the UK Office of Population, Census and Surveys classification (OPCS) 4.6. (NIHR, 2021).

The CPRD database has been used to study COPD (Rebordosa et al., 2019) with reported availability of good-quality spirometry, investigation, hospitalization, prescription and mortality records. Given that this is a GP database, we expect to have the opportunity to access a sizable proportion of COPD patients with mild or moderate disease through this database. Additionally, the General Medical Services (GMS) contract Quality and Outcomes Framework (QOF) of the National Health Services (NHS) included COPD indicators in April 2004, to incentivize high quality care and use of a standardized reporting system. The guidelines include provision of spirometry assessments among symptomatic patients as a positive evaluator for quality of physician services. Medical Research Council-MRC dyspnea grade has been routinely collected in the annual review of patients with COPD since April 2009 [(Gruffydd-Jones & Jones, 2011); (NICE guideline [NG115], 2018) (Primary Care Strategy and NHS Contracts Group, 2019); (The NHS Information Centre, Prescribing and Primary Care Services, 2010)]. This makes CRPD a potential source of good quality longitudinal data on COPD patients with repeat spirometry and MRC Dyspnea Scale evaluations along with exacerbation information.

The evaluation proposed in current study has not been conducted previously using the CPRD data where repeated measurements for spirometry, quality of life and exacerbation data is required at 3 time points to include: baseline (defined at study-entry), at about 18 months (6 months grace period) from study-entry defined baseline and at another point at least 18 months (6 months grace period) beyond this point amounting to minimum 3 years follow-up from study-entry. Age of 40 years or above with minimum one spirometry assessment at or after the age of 40 years, active status in the CPRD will be used to define entry into base cohort. Those with available medical history will be assessed for COPD diagnosis, diagnosis of asthma, treatment history of ICS and bronchodilators, moderate-severe exacerbations and minimum one additional spirometry prior to entry spirometry. Deaths within the minimum 3 years follow-up as well as in the extended period up to one additional spirometry beyond the 3 years analysis study period will not be excluded from base-cohort. Eligible patients from this base-cohort will be considered for

proposed replication and validation analysis. The inclusion criteria for this analysis cohort, referred to as the study-cohort here, aims to replicate CanCOLD observation timepoints and validate CanCOLD findings.

Study type

Hypothesis testing study type for external validation of findings from a population-based study among milder COPD cohort using primary care clinical cohort CPRD data.
[Appendix 1 a.- Figure 1: Base-study and CanCOLD replication (Validation) study cohort timeline visualization]

Study design

The proposed study is a retrospective secondary database cohort study of patients with COPD aged 40 years or older between September 2009 and September 2019.

While cross-sectional studies have helped capture the ground-realities in COPD, well-structured population based detailed longitudinal studies like CanCOLD provide the opportunity to study real-life disease trajectory in the milder disease categories of COPD. External validation of findings is especially important since longitudinal studies of disease progression in milder disease population in general population cohorts are lacking. Given the global public health challenge we face in COPD, findings from the proposed study will aid in informing natural history of COPD as well as guide identifying cohort-characteristics for the future development of targeted care molecules and strategy [illustrated in Appendix 1 b. -Figure 2 Diagrammatic representation of study design and analysis flow].

The proposed study uses the CPRD data to replicate the CanCOLD cohort to assess validity of findings in a convenient clinical cohort. A vast majority of studies among COPD patients are carried out in selective moderate-severe disease populations which are not conducive to the study early disease progression aimed at identifying rapid decliners to develop early and targeted intervention strategies. Being a primary care database, the CPRD provides the opportunity to observe patients from early disease stages.

For the analysis of replicability of CanCOLD findings patients in the CPRD cohort who meet all of the following criteria will be entered into the validation study: aged 40 years with diagnosed COPD, with available COPD questionnaire data including the COPD Assessment Test (CAT) and Medical Research Council-MRC Dyspnea Scale, and at least 3 years of continuous clinical records containing 3 concurrent assessments of spirometry and COPD questionnaires to enable assessment of clinically important deterioration (CID) using first two evaluations at about 18 months intervals (grace period will be included) and outcome at minimum interval of about 18 months (grace period will be included) from CID assessment measurement. Analysis to evaluate CID as a predictor of medium and long-term deterioration will follow the analysis implemented in CanCOLD cohort.

Feasibility counts

Feasibility assessment included review of published literature and discussion with scientists with experience of working with CPRD in the area of COPD.

Studies have assessed the availability of spirometry and symptoms data in the CPRD among those 40 years or older with COPD. Rebordosa et al. reported availability of relevant information for COPD severity assessment among 75% of the 63 900 identified patients who were new users of 1 or more COPD medication of interest (Rebordosa et al., 2019). From literature, out of 539 643 patients treated with a first-line treatment of long-acting 2 agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) between 2002–2015, there were 41540 who have been identified having met the criteria of age 55 years or above with a diagnosis of COPD and being initiated on the treatments (Suissa et al., 2008). Moderate and severe exacerbations were the outcomes assessible in these patients. In another study assessing COPD control, total of 14,173 patients were identified having linked Electronic Medical Records-EMRs and COPD questionnaire data from the linked OPCRD. A quarter of these patients comprised of ever-smokers patients aged 40 years or older with diagnosed COPD with available CAT assessment and minimum 15 months of continuous clinical records (Nibber et al., 2017).

In view of inclusion criteria for identifying analysis study-cohort for the proposed replication of CanCOLD findings, we expect to have a similar, to comparatively smaller sample for final analysis but adequately large to allow exploration of study questions and sensitivity analysis with opportunity for sub-group analysis.

Through a feasibility assessment discussion with scientists with experience in COPD research using the CPRD Aurum data, we anticipate roughly 200,000 COPD patient data with 30-40% having more than 3 spirometry assessments and 40-50% with MRC assessments. The spirometry and MRC assessments are likely to be recorded within one week. The repeat assessments are anticipated to be roughly one year apart. Aligned with published literature, CAT score is available in a smaller population where 3 assessments are anticipated in roughly 15-20% COPD patients. AECOPD data will be extracted using published algorithms (Rothnie et al., PLoS One. 2016; Rothnie et al., Clin Epidemiol. 2016). Given the large primary care cohort of the CPRD Aurum data, this discussion builds confidence that the proposed study is feasible in an adequately large sample size for investigation of the proposed study objectives.

Sample size considerations

The primary objective of this study is to evaluate the presence of Clinically Important Deterioration (CID) assessed over a duration of 18-24 month and examine its association with the decline in FEV1 and deterioration in health status at 3-years. Based on current literature, CID is defined as a composite (presence of at least one criteria) measure of: i. Lung function [decline of 100 mL from baseline in post-bronchodilator FEV1]; ii. Deterioration in health status: CAT [increase of 2 units in CAT score]; iii. Acute exacerbation of COPD [incidence of a moderate/severe exacerbation (acute worsening of COPD requiring oral corticosteroids, antibiotics, emergency department treatment, or hospitalization) Based on the available information derived from CanCOLD cohort, among those with COPD, the prevalence of CID at 18-months is about 60% . If 30% of those with COPD show decline in FEV1 and deterioration in health status, a sample size of 1000 participants is needed to detect an OR of less than 0.6 (with alpha=0.05) adjusted for 4 covariates (age, sex, BMI, smoking status) with more than 95% power. In view of inclusion criteria for identifying analysis study-cohort for the proposed replication of CanCOLD findings, and based on feasibility assessments, we expect to have a similar, to comparatively smaller sample for final analysis but adequately large (N= about 10,000- 15,000 assuming that the validation cohort will comprise of at least about 50 % of individuals with available 3+ CAT measurements) to allow exploration of study questions and sensitivity analysis with opportunity for sub-group analysis. Preliminary feasibility assessment summary (conducted for 2013-2019) in included in Table 1 [Appendix 1 c.- Table1: Summary of Patient Counts by Time Period in CPRD Aurum Database].

Planned use of linked data and benefit to patients in England and Wales

The study will use HES (Hospital Episode Statistics) linked data [HES Accident and Emergency (A&E), HES Admitted Patient Care (APC) and HES Outpatient (OP)], for the base and validation cohorts.

The study will obtain data on demographics, comorbidities, smoking history and current status, previous diagnosis of asthma, Spirometry, CAT score, MRC score, the values of biomarkers (Eosinophil and C-Reactive Protein) and treatment from the primary care records.

Identification and classification of episodes/instances of Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) is crucial to the study. AECOPD event categories of interest are: Moderate (acute worsening of COPD requiring oral corticosteroids, antibiotics, emergency department treatment) and severe (acute worsening of COPD requiring hospitalization). The proposed study will follow the identification and extraction algorithms for moderate and severe AECOPD as described in literature (Rothnie et al., PLoS One. 2016; Rothnie et al., Clin Epidemiol. 2016).

The HES-APC and HES-A&E linkages will allow the study to ascertain critical information towards moderate exacerbation resulting in A&E attendance and severe exacerbation (resulting in hospitalized). The HES-OP data will provide further information on attendance at secondary care outpatient clinics to further describe severity (e.g., recent secondary care outpatient visit to the respiratory physician) which is required to describe patient severity and to contextualize the findings.

Impact of the proposed study on patients in England and Wales:

Based on data between 2001-2010, currently available statistics form the British Lung Foundation (BLF) ranks UK 12th globally, and third in Europe for COPD mortality (British Lung Foundation, 2018). Loss of life due to COPD has been on the rise since 2008. In 2012 COPD was listed as a leading cause of mortality in the UK with 29,776 death, which was 26.1% of deaths from lung disease or 5.3% of total deaths reported. Between 2008-2012, parts of England (the North East and the North West) and Wales registered higher than overall UK COPD mortality rates. Rate of emergency hospital admission among COPD patients was higher than overall UK rates for parts of England (the North East, the North West, and Yorkshire and the Humber) and Wales in this period. Those living with diagnosed COPD were 40 years of age or older, with proportions rising with age.

The total costs of all respiratory illness were estimated to be £11.1 billion (£165 billion including intangible costs) which represented 0.6% of UK's Gross Domestic Product (GDP) in 2014. Within respiratory illness, the total cost associated with COPD was 29%, which was in the vicinity of trachea, bronchus and lung cancers at 28%. In the published report "Estimating the economic burden of respiratory illness in the UK" commissioned by the BLF, around 1.2 million people are estimated to be living with diagnosed COPD, the second commonest lung disease in the UK (after asthma), with a significant cost burden to the NHS. Cost to the NHS is estimated to be around £1·9 billion each year (British Lung Foundation, 2017).

The "battle for breath" campaign of the BLF has been continuing to draw the nation's attention to lung diseases-UK's third 'biggest killer', to support NHS in the field of lung health. The Taskforce for Lung Health's five-year plan was launched about 2 years ago to improve lung health in England. Efforts are ongoing for plans for improvements in Wales and Scotland as well. The goal is the betterment of care management, with an eye on efficient measures to find the 'missing million' (Nacul et al., 2010) undiagnosed COPD patients. There is a growing urgency for early detection and intervention, pharmacological as well as non-pharmacological, to target better management at milder disease stages to get ahead of the current trend of COPD detection at advanced age and disease stages upon emergency hospitalization. Along with raising public and medical community's awareness, it is equally important to develop appropriate tools and intervention strategies. While early detection is important, it needs to be supplemented with a better understanding of milder disease and disease activity progression to inform research and development into targeted interventions, especially focused on those susceptible for rapid decline. Efficient COPD care management built around improving quality of life experience is a pressing need for population in the UK, especially those in England and Wales, while also being imperative

for nations such as Canada with a strong public health system. Studies to identify rapid decliners in early stages, such as the present study, are key to gathering knowledge to efficiently and effectively address this global leading cause of mortality and public health challenge.

Definition of the study population

For the analysis of replicability of CanCOLD findings in an external clinical cohort, patients in the CPRD cohort who meet all of the following criteria will be entered into the validation study cohort: aged 40 years with/ without diagnosed COPD, with available COPD questionnaire data including the CAT and Medical Research Council-MRC Dyspnea Scale, and at least 3 years of continuous clinical records containing 3 concurrent assessments of spirometry and COPD questionnaires to enable assessment of CID using first two evaluations at about 18 months intervals (grace period will be included) and outcome at minimum interval of about 18 months (grace period will be included) from CID assessment measurement. Date of diagnosis will not be the entry/ baseline for current analysis cohort. The first spirometry at or after age of 40 years will be the baseline, and patients will be categorised by COPD severity based on this assessment. The 3 measurements of spirometry are as follows: 1st (entry) spirometry; 1st repeat spirometry within 18 months from entry spirometry; and 2nd repeat spirometry up to 24 months from 18-24 months measurement. Measurements for assessment of CID, outcome and confounders will be extracted. Moderate and severe exacerbation data will be defined and extracted from hospitalization and prescription linked data as in literature (Rothnie et al., PLoS One. 2016; Rothnie et al., Clin Epidemiol. 2016). Patients in whom spirometry and health status measurements are not available at the 3 minimum required time-points will be excluded from the proposed study-cohort [Appendix 1 d.- Figure 3: CanCOLD replication study-cohort definition from identification of base-cohort]. In view of COVID-19 pandemic, we will exclude data after March 2020.

For secondary approach, all patients with mid-moderate disease at diagnosis and in whom spirometry, CAT, MRC and exacerbation evaluations are available to enable CID will be considered. The following secondary analysis will be considered: (i) restricting analysis to smoker 10 pack-years (current and ex-smokers); (ii) evaluating CID assessment over shorter duration (3, 6 or 12 months); (iii) assessing outcome over longer duration (beyond 3 years). Base cohort would contribute to sensitivity analysis among those with: at least 1 spirometry recording prior to the study-entry spirometry and minimum 1 spirometry beyond to proposed outcome assessment to evaluate persistent cases; records will be evaluated for record of first bronchodilator use with or without a diagnosis of COPD, records will be evaluated for available blood eosinophil concentration measure prior to study-entry [Appendix 1 a.-Figure 1]. Those eligible, will be assessed for presence of 1 spirometry pre and post validation study cohort description of 3 consecutive spirometry count and under relaxed consideration of interval between consecutive spirometry to assess disease trajectories over follow-ups longer than available with CanCOLD]. However, in view of COVID-19 pandemic, we will exclude data after March 2020.

Selection of comparison groups/controls

Not Applicable

Exposures, outcomes and covariates

Independent variable (variables of interest):
Short-term (over a duration of 18-24 months) clinically important deterioration (CID) evaluated as a composite measure of:
i. Lung function [decline of 100 mL from baseline in post-bronchodilator FEV1]
ii. Deterioration in health status: CAT [increase of 2 units in CAT score]
iii. Acute exacerbation of COPD [incidence of a moderate/severe exacerbation (acute worsening of COPD requiring oral corticosteroids, antibiotics, emergency department treatment, or hospitalization) in short-term CID assessment period]
Components of the CID will also be assessed individually
Dependent variable (Outcome):
Lung function [FEV1 decline of 100 mL, 200 mL]
Deterioration in health status: MRC score [2, 3] and CAT [2 units, 4 units]
Acute exacerbation of COPD [moderate/severe exacerbation (acute worsening of COPD requiring oral corticosteroids, antibiotics, emergency department treatment, or hospitalization in the post CID assessment period]
Duration of outcome assessment would be up to 24 months for post-CID assessment period. The validation cohort will closely align with the CanCOLD analysis. Changes are in the post-CID assessment period. In the exploratory analysis, longer outcome durations will be included.
Dependent and independent variables have been studied using the CPRD and present study will use published algorithms for these variables.
Covariates:
Age, sex, BMI, smoking status, comorbidities, and treatment medication (binary variable).
Exploratory analysis will evaluate assessment with biomarkers of blood eosinophil levels, C-reactive protein (CRP) levels.
GOLD report 2020 classification will be used to identify severity of airflow limitation in COPD using post-bronchodilator FEV1 percent of predicted value among those with a ratio of forced expiratory volume in 1 s (FEV1) to forced vital capacity (FVC) below 0.07.

Available labeled code-lists are submitted.

Data/statistical analysis

Demographic characteristics of the validation cohort will be described along with characteristics of the at risk, COPD GOLD I, II, III and IV subpopulations.
For primary objective, outcomes of decline in FEV1 (100 mL, 200 mL), deterioration in health status using CAT score (increase of 2 units, 4 units) and MRC score (2, 3) will be analysed using logistic regression model and Odds Ratio will be reported for CID as composite and subsequently the components as independent variables in the validation cohort. For secondary objective, the models will be assessed by COPD sub-populations based on GOLD categories of the validation cohort. Cox Proportional Hazards models will be used for outcome of a new moderate/severe exacerbation in the post CID assessment period and Hazard Ratio (95% CI) will be reported. Finally, incident rate of moderate/severe exacerbations in the post-CID assessment period will be analysed using Poisson regression models and Rate Ratios (95% CI) will be reported. All models will be adjusted for baseline age, sex, BMI, and smoking status. These models will be assessed with and without biomarker blood eosinophil and CRP as a covariate (in exploratory analysis)
For exploratory objective, the base-cohort will be used instead of the validation cohort to understand decline trajectory, among those with additional spirometry beyond the 3 required for validation cohort to assess CID definitions and if these are predictive of decline in longer periods.
i) Assessing trajectory in the subpopulations with different categories of outcome assessment periods (e.g., 18 months, 24 months, 36 months etc. based on available cohort data)
ii) Assessing new CID definitions for mild-moderate COPD population exploring CID definition period categories (e.g.,12 months, 18 months, 24 months etc. based on available cohort data)
iii) Assessing new CID components for mild-moderate COPD population
iv) Assessment of trajectory among those in the base-cohort with additional spirometry beyond the 3 required for validation study-cohort (which reflect CanCOLD visits 1,2 and 3) to allow evaluation of CanCOLD findings from anticipated visit 4 [longer outcome duration (median duration of 8.6 years assuming visit 4 in 2022) between visits 2 and 4] as well as longer follow-ups
v) Evaluating population with biomarker results and assessing CID definition in the mild-moderate population with and without biomarkers.

Plan for addressing confounding

The models assessing short-term CID as predictor of medium and long-term outcomes among mild-moderate COPD patients in the proposed study will be adjusted for baseline age, sex, BMI, and smoking status.

Plans for addressing missing data

The study will use complete case analysis for its primary analysis.
Missing data will be considered likely to be dependent on the value of the missing variable and will not be imputed.

Patient or user group involvement

The proposed study will identify a comparable cohort using existing data in the CPRD as an external validation cohort to examine findings from CanCOLD study. As a result, patient will not be contacted as a part of the proposed study. The study team will include feedback from the scientific community involved in studying COPD using the CPRD to fine-tune proposed implementation plan and sensitivity analysis to ensure quality of knowledge generated from this undertaking.
The CanCOLD study has been developed with patient and user group involvement during its planning and design stages.

Plans for disseminating & communicating

The study findings will be disseminated through:
i. manuscript submitted to a high impact medical journal (e.g., JAMA, Lancet Resp, AJRCCM, ERJ) for publication,
ii. submitted to conferences dedicated to respiratory diseases for presentation, and
iii. findings will be discussed at institution's seminars and conferences.

In all publications, the following acknowledgement will be included:
• This study is based in part on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data is provided by patients and collected by the NHS as part of their care and support. The interpretation and conclusions contained in this study are those of the author/s alone.
• Copyright © [YEAR], re-used with the permission of The Health & Social Care Information Centre. All rights reserved.

We will report our findings following the principles outlined in the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) (Vandenbroucke et al.,2014) and REporting of studies Conducted using Observational Routinely collected health Data (RECORD) statement (Benchimol et al., 2015)

Conflict of interest statement

Competing interests: This study is partly supported by Research Institute of McGill University Health Centre and GlaxoSmithKline. SB is supported by Fonds de recherche du Québec – Santé Doctoral Training award. JB holds a Distinguished Scientist Award, McGill University, Feb 1, 2020-Jan 31, 2025.
JB reports grants from CIHR, Canadian Respiratory Research Network (CRRN) and Foundation of the MUHC, grants and personal fees from AstraZeneca, Boehringer Ingelheim, Grifols, GlaxoSmithKline, Novartis, Trudell, outside the submitted work.
DD: The Canadian Cohort Obstructive Lung Disease (CanCOLD; NCT00920348) study is currently funded by the Canadian Respiratory Research Network, the Canadian Institutes of Health Research (CIHR; CIHR/Rx&D Collaborative Research Program Operating Grants- 93326), and the following industry partners: AstraZeneca Canada Ltd; Boehringer Ingelheim Canada Ltd; GlaxoSmithKline (GSK) Canada Ltd; and Novartis.

Limitations of study design

The CPRD data provides an ideal opportunity to validate findings from a population-based longitudinal COPD cohort focused on studying early disease progression. However, there are certain challenges in replicating a cohort with regular planned follow-up as part of study design. Based on your feasibility assessments, we believe that we will be able to identify a validation cohort of comparable sample size.

In the CanCOLD cohort, non-COPD smokers (current or ex-smokers) at study entry form the 'at-risk' sub-population. COPD diagnosis being based on baseline spirometry at study-entry in this cohort. A comparable 'at-risk' population with sequential spirometry and required concomitant assessments will not be available in the CPRD data among 40 years or older non-COPD individuals. This will prevent a complete replication of the CanCOLD cohort. As a result, the proposed study will evaluate findings from mild-moderate COPD population from CanCOLD cohort.

Availability of biomarker assessments and clinical quantification of smoking in pack years of cigarette smoked data in the CPRD could limit inclusion of these covariates in primary analysis.

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Appendices

appendix-1_isac-submission_cprd-cid-validation-study-protocol-july2022_0.pdf

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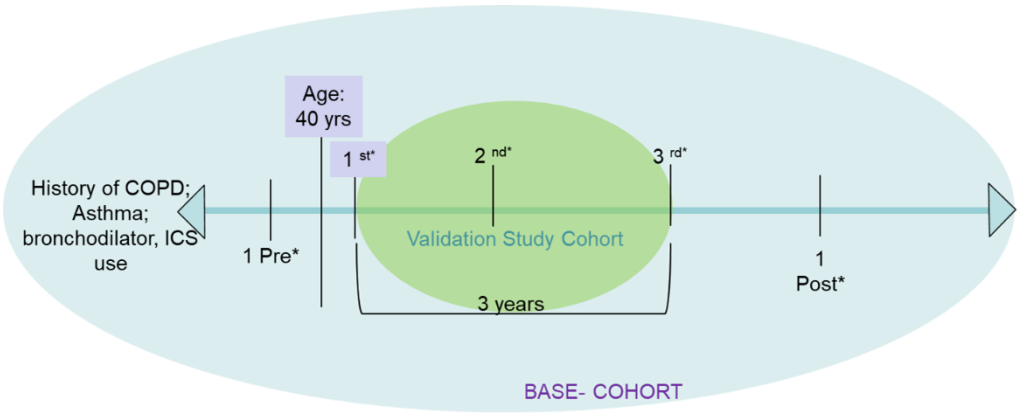
Short term clinically important deterioration as an indicator of medium and long-term COPD progression in the UK primary care population: An external validation of findings from the Canadian population based CanCOLD Cohort.

APPENDIX 1: Figures and Tables

Appendix #	Title	Protocol section reference
Appendix 1 a.	Figure1. Base-study and CanCOLD replication (Validation) study cohort timeline visualization	Study Type
Appendix 1 b.	Figure 2: Diagrammatic representation of study design and analysis flow	Study Design
Appendix 1 c.	Table1: Summary of Patient Counts by Time Period in CPRD Aurum Database	Sample size considerations
Appendix 1 d.	Figure 3: CanCOLD replication study-cohort definition from identification of base-cohort	Definition of the Study population

Appendix 1 a.

Figure 1: *Base-study and CanCOLD replication (Validation) study cohort timeline visualization*



Base- cohort Eligibility:	Validation study- cohort Eligibility:
• Age ≥ 40 yrs; • min 1 spirometry available at or after age of 40 yrs (study-entry spirometry); • follow-up data available for min 3 yrs from this spirometry	• Age ≥ 40 yrs; • Study-entry spirometry+ 2 follow-up spirometry evaluations at required intervals and within 3 yrs of study-entry spirometry

** Spirometry*

Base cohort*:*

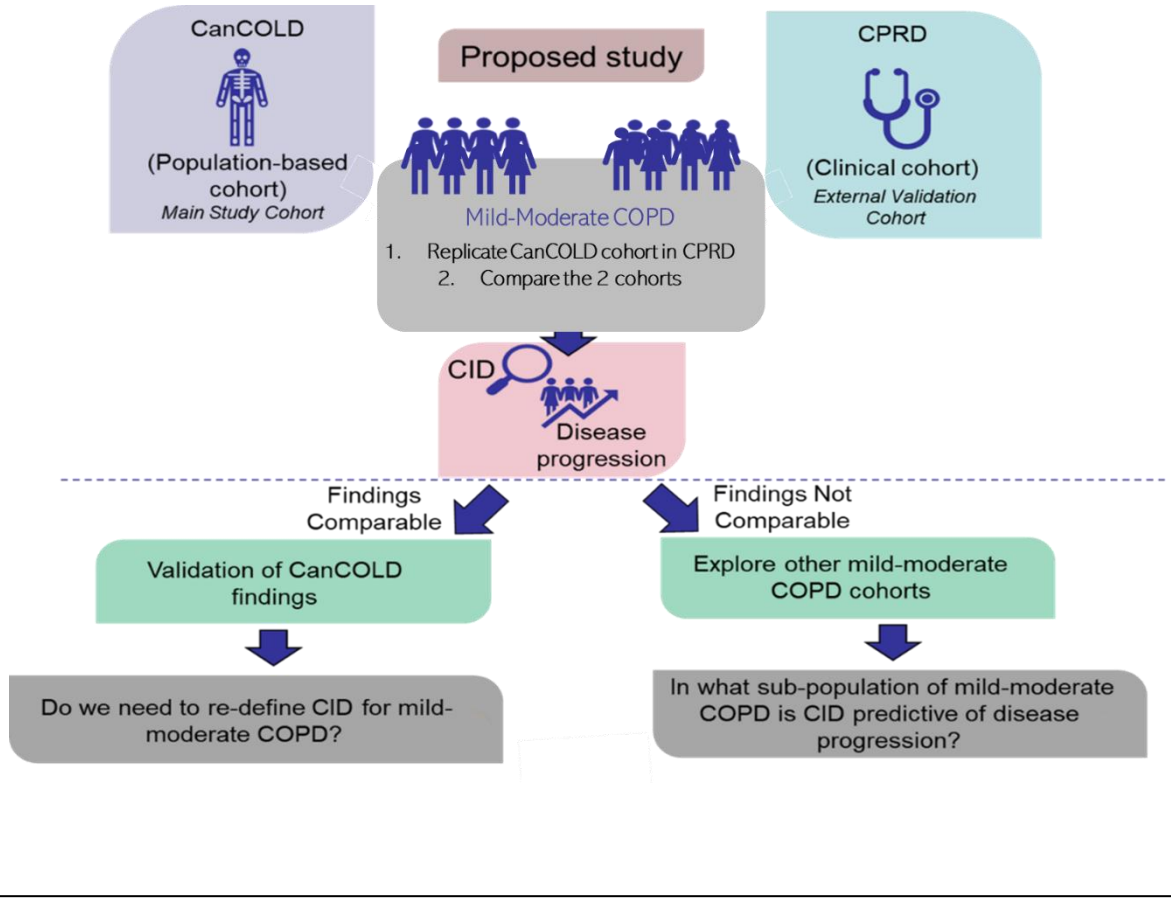
- *Those eligible, will be assessed for presence of ≥ 1 spirometry pre and post validation study cohort description of 3 consecutive spirometry count and under relaxed consideration of interval between consecutive spirometry to assess disease trajectories over follow-ups longer than available with CanCOLD*
- *Will exclude data after March 2020*

Validation cohort:

- *Study-entry spirometry required to be completed between November 2009 and August 2015 (at or after the age of 40 years)*
- *Will exclude data after March 2020*

Appendix 1 b.

***Figure 2**: Diagrammatic representation of study design and analysis flow*



Appendix 1 c.

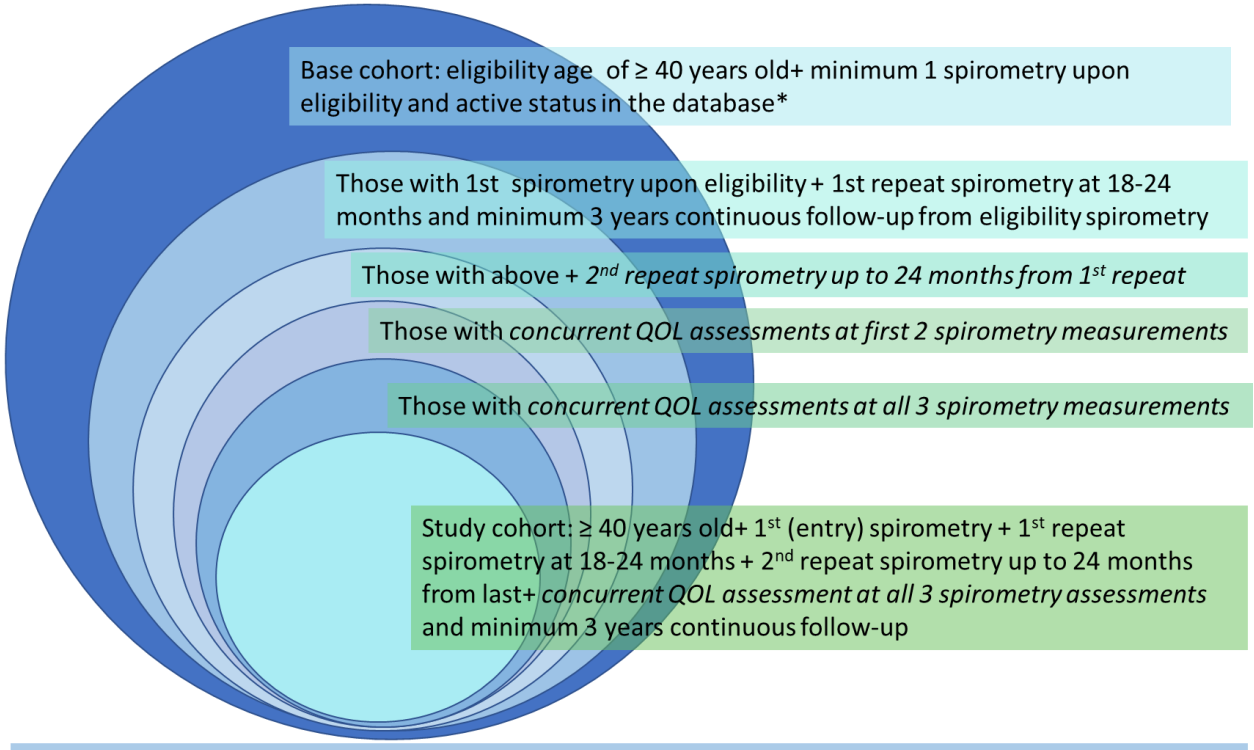
Table 1: *Summary of Patient Counts by Time Period in CPRD Aurum Database*

	Sep 2013 - Sep 2016	**Sep 2016 - Sep 2019**
Number of patients with COPD diagnosis and continuous enrolment	243814	209905
Number (%) of patients with at least one record of FEV1	161420 (66%)	177385 (85%)
Number (%) of patients with at least one record of MRC Score	156875 (64%)	184340 (88%)
Number (%) of patients with at least one record of CAT-Total Score	49252 (20%)	86475 (41%)
Number (%) patients with 3+ FEV1 measurement	67150 (42%)	72512 (41%)
Number (%) patients with 3+ MRC measurement	85042 (54%)	95650 (52%)
Number (%) patients with 3+ CAT measurement	10892 (22%)	19930 (23%)

** Note: Same patients can contribute to both time periods if they continue to be enrolled for full length during both time periods.*

Appendix 1 d.

***Figure 3**: CanCOLD replication study-cohort definition from identification of base-cohort*



* *Those with medical history, will be assessed for childhood diagnosis of asthma, history of physician-confirmed COPD diagnosis, treatment history of ICS and bronchodilators and moderate-severe exacerbations*

Those eligible for base cohort, will be assessed for presence of 1 spirometry pre and post validation study cohort

Appendix 3

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