Clinically important deterioration in a mild–moderate COPD population

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Shareable abstract (@ERSpublications)
Population-based studies are needed to understand better the predictors of decline in mild–moderate COPD to develop suitable clinical tools for a "reach-out early" strategy to support better those susceptible to declining rapidly https://bit.ly/3DEevq6

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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 COPD clinical populations. We assessed whether 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 over 18 months for CID, and over the next 18 months for outcomes. Their association was then examined: 1) defined into threshold-based binary variables, the declines in forced expiratory volume in 1 s (FEV_1), health status and dyspnoea, using logistic regression models; 2) time to moderate/severe exacerbation and rates of moderate/severe exacerbations using Cox proportional hazards and Poisson regression, respectively.

Results Out of 420 participants, 252 (60%) demonstrated CID (definition 1, St George's Respiratory Questionnaire (SGRQ)). Presence of CID at 18 months showed association with future moderate/severe exacerbation (not statistically significant), worsening health status (COPD Assessment Test (CAT) score), and dyspnoea. As a component, FEV_1 was found to be less informative, compared with exacerbation for health status outcome (OR 4.31, 95% CI 1.29–14.41 for ⩾8-unit increase in SGRQ) alongside future exacerbation, and SGRQ health status component, for future health status decline (OR 0.33, 95% CI 0.17–0.66 for ⩾4-unit increase in SGRQ and OR 0.53, 95% CI 0.30–0.94 for ⩾2-unit increase CAT score).

Discussion Our finding of informative CID components seems to support recommendations of emphasis on 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 mild–moderate COPD populations.

Introduction

Heterogeneity of presentation and progression is a well-established concept in the understanding of COPD. Emerging new knowledge indicate potential multiple underlying pathophysiological mechanisms and risk factors [1–6], trajectories and treatment responses across patients with COPD. Thus, to differentiate those likely worsen *versus* stabilise [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 that are susceptible to experience rapid clinical deterioration continues to be a challenge to clinicians aiming to provide a personalised care plan 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 (BD) forced expiratory volume in 1 s (FEV_1) 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: 1) deterioration of lung function (⩾100 mL change in post-BD FEV_1 [10]); 2) 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 3) moderate–severe exacerbations (⩾ 1 moderate (requiring treatment with oral corticosteroids and/or antibiotics) or severe (requiring hospitalisation 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 eight-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 patient-level, two units of change in CAT score has been found to correspond with the MCID of four 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 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 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 dyspnoea worsening at 18 months. The secondary objective was to assess the impact of including biomarkers in the models. The exploratory objective was to assess for existing subgroups 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 non-institutionalised participants from nine cities aged 40 years or older at recruitment (2005–2009) registered at ClinicalTrials.gov (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 24–84 months) across three 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. A moderate or severe acute worsening of COPD was included as an exacerbation.

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 1) decrease of ⩾100 mL in post-BD FEV_1; and/or (2) increase of ⩾4 units in SGRQ score; and/or (3) incidence of a moderate/severe exacerbation. The analysis from a second CID definition using increase of ⩾2 units in CAT score instead of SGRQ [15], CID-D2, has been included in the supplementary material (supplementary figure S1 and supplementary tables S2–S5).

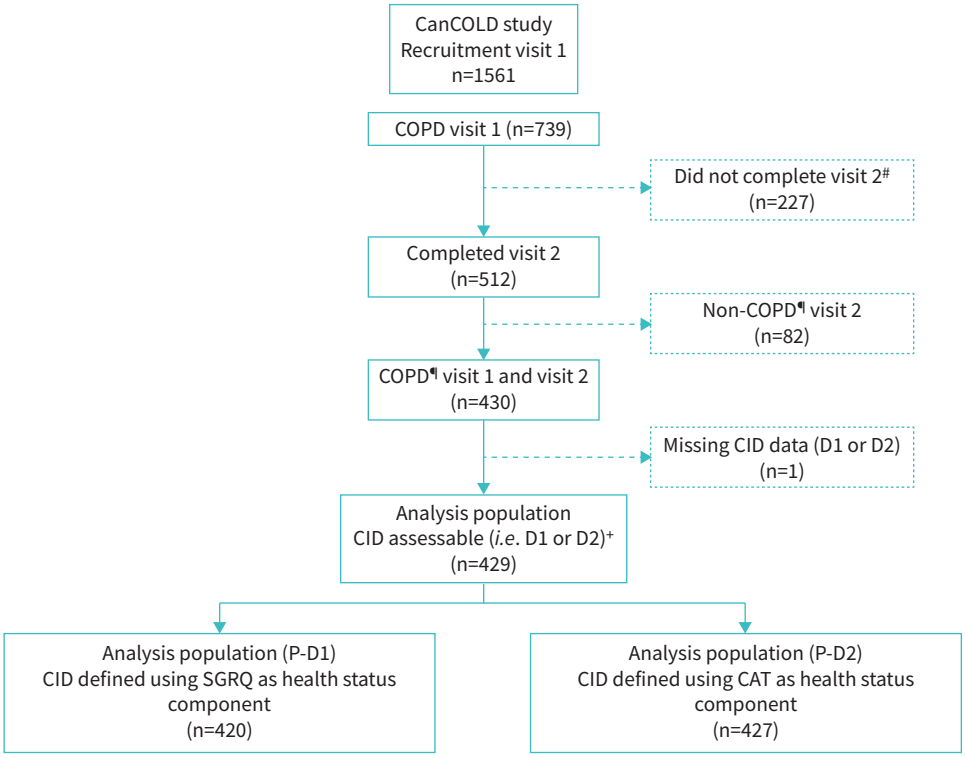


FIGURE 1 Study population participant flow diagram. CanCOLD: Canadian Cohort of Obstructive Lung Disease; CID: clinically important deterioration; SGRQ: St George's Respiratory Questionnaire; CAT: COPD Assessment Test. D1: Composite CID defined with SGRQ score as the health status component; D2: Composite CID defined with CAT score as the health status component. #: Administrative decision for restricted number of participants at visit 2. ¶: COPD is defined by spirometry as: post-bronchodilator forced expiratory volume in 1 second (FEV_1)/forced vital capacity <0.70. Those with asthma and COPD were not excluded. +: c1D-Dl: Composite CID defined with HRQoL components as SGRQ score; CID-D2: Composite CID defined with HRQoL components as CAT score.

Outcome variables

Changes between visits 2 and 3 were used to assess outcomes. Health status decline outcome was defined as increase of: ⩾4 units and ⩾8 units using SGRQ score; or ⩾2 units and ⩾4 units using CAT score. Decline in FEV_1 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. Increase in dyspnoea was defined as a ⩾1-unit increase in Medical Research Council (MRC) score.

Baseline variables included age, sex, body mass index (BMI) (calculated from measured height and weight using a standard protocol), self-reported cigarette smoking status (as current, former or never-smokers), and self-reported pack-years (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 objectives of presence of any cardiovascular disease (CVD) and absolute blood eosinophil (EOS) counts. Other biomarkers considered were C-reactive protein (CRP) and fibrinogen.

Statistical analysis

Descriptive analysis was reported. Differences between groups were analysed using chi-squared and Fisher's exact test for categorical variables, 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 FEV_1, changes in health status and dyspnoea were examined using logistic regression models and odds ratios were reported with 95% CI. Cox proportional hazards models were used for outcome of time to a new moderate/severe exacerbation from visit 2 and hazard ratios (95% CI) were reported. Finally, the incident rates of moderate/severe exacerbations between visit 2 and visit 3 were also

TABLE 1 Baseline characteristics of CanCOLD mild–moderate COPD population analysed and excluded

	COPD subjects (n=739)			
	Total n=739	Analysis population n=429	Population excluded n=310	p-value
Age, years	67.5±10.1	67.1±9.9	67.9±10.3	0.227
Sex, male	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				
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 dyspnoea scale score ⩾3/5	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*
SGRQ 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				
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 or 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 count				
Absolute count·μL^{-1}	0.23±0.17	0.23±0.17	0.25±0.18	0.203
<150·μL^{-1}	237 (37.1)	140 (37.9)	97 (36.1)	0.627
150 to <300·μL^{-1}	234 (36.7)	134 (36.3)	100 (37.2)	0.824
⩾300·μL^{-1}	167 (26.2)	95 (25.7)	72 (26.8)	0.772
EOS, %	5.2±3.8	5.2±3.9	5.3±3.7	0.679
CRP, mg·L^{-1}	2.50±3.29	2.42±3.41	2.62±3.11	0.758
Fibrinogen, g·L^{-1}	3.04±0.69	3.00±0.63	3.10±0.76	0.387

Data are presented as n (%) or mean±SD. CanCOLD: Canadian Cohort of Obstructive Lung Disease; BMI: body mass index ; FEV_1: forced expiratory volume in 1 s; SGRQ: St George's Respiratory Questionnaire; CAT: COPD assessment test; SF36: 36-Item short form; SABD: short-acting bronchodilator; LABA: long-acting β2 receptor agonist; LAMA: long-acting muscarinic antagonist; ICS: inhaled corticosteroid; EOS: eosinophils; CRP: C-reactive protein.

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 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 analysis as these are not confounders. Two models were employed: model 1 adjusted for baseline age, sex, BMI and smoking pack-years and model 2 additionally adjusted for any CVD and absolute EOS count. For the proposed exploratory objective, based on repeated measurements of FEV_1 at visits 1, 2 and 3, group-based trajectory modelling was carried out to assess for potential subgroups to describe their characteristics. Statistical analyses were performed using SAS (v.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±SD age of 67.1±9.9 years, was overweight (BMI of 27.7±5.3 kg·m^{-2}), 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 FEV_1% predicted. The excluded group had the highest mean FEV_1% predicted.

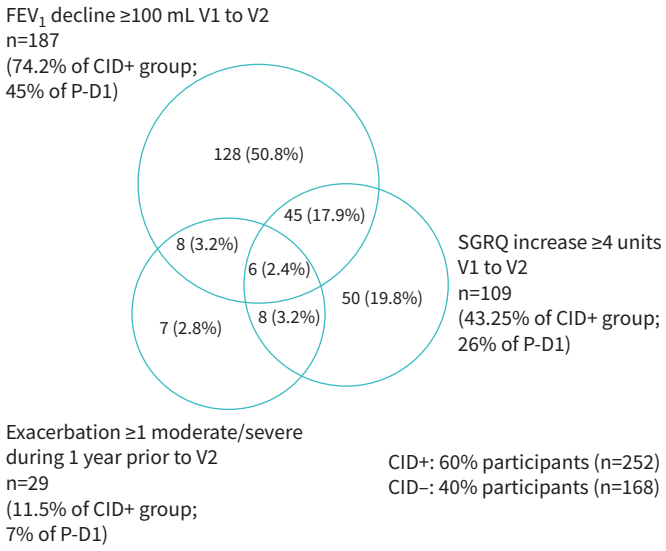


FIGURE 2 Individual components of the short-term clinically important deterioration (CID) assessed between visit 1 (V1) and visit 2 (V2) using St George's Respiratory Questionnaire (SGRQ) as health-related quality of life component to define CID. FEV_1: forced expiratory volume in 1 s; CID+: those demonstrating short-term clinically important deterioration; CID–: those not demonstrating short-term clinically important deterioration.

TABLE 2 Association of short-term composite CID-D1 (composite of decrease of ⩾100 mL in post-BD FEV_1; increase of ⩾4 units in SGRQ score; and incidence of a moderate/severe exacerbation) with outcomes over 18 months of follow-up

	COPD population					
	CID-D1 (composite of decrease of ⩾100 mL in post-BD FEV_1; increase of ⩾4 units in SGRQ score; and incidence of a moderate/severe exacerbation)					
	Composite CID+	Composite CID–	Composite CID+ *versus* CID– (model 1)		Composite CID+ *versus* CID– (model 2)	
	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 FEV_1[#]	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 FEV_1[#]	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[#]	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[#]	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[#]	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[#]	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[#]	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[¶], n per 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[¶], n per 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[§]	42 (21.2)	22 (16.8)	1.20 (0.88–1.62)	0.248	1.28 (0.92–1.78)	0.14

Data are presented as n (%) and OR/HR/RR (95% CI) unless specified otherwise. CID: clinically important deterioration; CID-D1: composite CID defined with SGRQ score as the health-related-quality of life components; BD: bronchodilator; BMI: body mass index; FEV_1: forced expiratory volume in 1 s; SGRQ: St George's respiratory questionnaire; OR: odds ratio; HR: hazard ratio; RR: rate ratio; CID+: those demonstrating the composite short-term CID-D1; CID–: those not demonstrating the composite short-term CID-D1; V2: visit 2; V3: visit 3; CAT: COPD assessment test; MRC: Medical Research Council score. [#]: ORs were calculated using a logistic regression model. [¶]: Moderate/severe exacerbation incident rate between V2 to V3 or follow-up 1 year after V2, and RR (95% CI) were calculated using a Poisson regression model. [§]: A new moderate/severe exacerbation from V2, and HR (95% CI) were calculated using a Cox model. Model 1 was adjusted for baseline age, sex, BMI and smoking pack-years. Model 2 was adjusted for baseline age, sex, BMI and smoking pack-years, any cardiovascular disease and absolute eosinophil count. *: p-value statistically significant (p<0.05).

TABLE 3 Association of exacerbation component of short-term CID-D1 (composite of decrease of ⩾100 mL in post-BD FEV_1; 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 +	CID component −	CID component+ *versus* CID component− (model 1)		CID Component+ *versus* CID Component− (model 2)	
	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 FEV_1[#]	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 FEV_1[#]	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[#]	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[#]	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[#]	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[#]	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[#]	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[¶], n per 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[¶], n per 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[§]	14 (53.8)	50 (16.5)	2.54 (1.62–4.00)	<0.001*	2.56 (1.55–4.23)	<0.001*

Data are presented as n (%) and OR/HR/RR (95% CI) unless specified otherwise. FEV_1: forced expiratory volume in 1 s; CID: clinically important deterioration; CID-D1: composite CID defined with SGRQ score as the health-related-quality of life components; SGRQ: St George's respiratory questionnaire; OR: odds ratio; HR: hazard ratio; RR: rate ratio; CID component +: those demonstrating the short-term CID-D1 component of exacerbation; CID−: those not demonstrating the short-term CID-D1 component of exacerbation; V2: visit 2; V3: visit 3; CAT: COPD assessment test; MRC: Medical Research Council score. [#]: OR were calculated using logistic regression model. [¶]: Moderate/severe exacerbation incident rate between V2 to V3 or follow-up 1 year after V2, and RR (95% CI) were calculated using a Poisson regression model. [§]: A new moderate/severe exacerbation from V2 and HR (95% CI) were calculated using a Cox model. Model 1 was adjusted for baseline age, sex, BMI and smoking pack-years. Model 2 were adjusted for baseline age, sex, BMI and smoking pack-years, any cardiovascular disease and absolute eosinophil count. *: p-value statistically significant (p<0.05).

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 (supplementary table S1). 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 the corresponding model 2 over the following 18 months.

In the analysis population, compared with those without CID, those with CID were observed to be significantly less likely for FEV_1 decline outcomes. Though statistically not significant, the following were observed: 1) A decreased odds for decline in health status outcomes defined with changes in SGRQ total scores while showing increased odds for decline in health status when using changes in CAT total scores. Increased odds (not statistically significant) were seen for increasing dyspnoea. 2) The direction of the associations was maintained in the corresponding model 2. 3) For exacerbation outcomes, compared with those without CID, those with CID showed: 1) elevated rate of moderate/severe exacerbations over 12 months and during the follow-up period; and 2) elevated risk of a moderate/severe exacerbation within 12 months (table 2).

Components of CID

Tables 3–5 present the association of each of the CID components with the outcomes in population. One or more moderate/severe exacerbation in the year preceding visit 2 was present in 11.5% of those with CID (figure 2) and was significantly associated with increased risk and rate of future exacerbations over the following year. This association was also seen in the corresponding model 2. However, for health status outcomes, it was significantly associated with increased odds of decline defined as a ⩾8-unit increase in SGRQ total score among those with CID in model 2. Though not statistically significant, the following

TABLE 4 Association of health status component of short-term CID-D1 (composite of decrease of ⩾100 mL in post-BD FEV_1; increase of ⩾4 units in SGRQ score; and incidence of a moderate/severe exacerbation) with outcomes over 18 months of follow-up

	COPD population					
	Health status component (SGRQ)					
	CID component +	CID component −	CID component+ *versus* CID component− (model 1)		CID component+ *versus* CID component− (model 2)	
	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 FEV_1[#]	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 FEV_1[#]	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[#]	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[#]	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[#]	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[#]	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[#]	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[¶], n per 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[¶], n per 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[§]	23 (27.1)	41 (16.8)	1.34 (0.98–1.82)	0.067	1.33 (0.96–1.86)	0.089

Data are presented as n (%) and OR/HR/RR (95% CI) unless specified otherwise. FEV_1: forced expiratory volume in 1 s; CID: clinically important deterioration; CID-D1: composite CID defined with SGRQ score as the health-status component; SGRQ: St George's respiratory questionnaire; OR: odds ratio; HR: hazard ratio; RR: rate ratio; CID component +: those demonstrating the short-term CID-D1 component of health-status SGRQ; CID−: those not demonstrating the short-term CID-D1 component of health-status SGRQ; V2: visit 2; V3: visit 3; CAT: COPD assessment test; MRC: Medical Research Council score. [#]: OR were calculated using logistic regression model. [¶]: Moderate/severe exacerbation incident rate between V2 to V3 or follow-up 1 year after V2, and RR (95% CI) were calculated using Poisson regeression model. §: A new moderate/severe exacerbation from V2, and HR (95% CI) were calculated using Cox model. Model 1 was adjusted for baseline age, sex, body mass index and smoking pack-years. Model 2 was adjusted for baseline age, sex, body mass index and smoking pack-years, any cardiovascular disease and absolute eosinophil count. *: p-value statistically significant (p<0.05).

were observed: 1) CID component of exacerbation showed increased odds of decline in health status outcomes measured using CAT score as well as for increased dyspnoea; and 2) reduced odds for decline in FEV_1 and for the outcome of a ⩾4-unit increase in SGRQ total score (table 3).

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 a ⩾4-unit increase in SGRQ total score and of a ⩾2-unit increase in CAT total score. Though not statistically significant, health status decline component of CID showed increased odds for increasing dyspnoea and future exacerbation, while showing decreased odds for FEV_1 decline and the remaining health status decline outcomes (table 4).

The FEV_1 decline was observed in 74.2% of those with CID (figure 2) and was significantly associated with decreased odds of study-defined medium-term FEV_1 declines. Though not statistically significant, decreased odds for health status decline outcomes of ⩾8-unit and ⩾4-unit increases in SGRQ score (model 2), and for increased dyspnoea was observed. The FEV_1 decline component was not indicative of future rate or risk of exacerbation (table 5).

Exploratory findings from group-based trajectory modelling

Based on FEV_1 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 6. The trajectories of group 1 *versus* group 2 demonstrated steady linear decline while the slopes remained parallel (figure 3). The group with the higher baseline FEV_1, group 2, was significantly younger, predominantly male, had a lower absolute eosinophil count, milder COPD severity with higher percentage of predicted FEV_1, and better health status by SGRQ score and Short-form 36 physical component. This group comprised of lower proportions of participants reporting experiences of at least one moderate/severe exacerbation in the preceding year, and those on respiratory medications (namely, short-acting bronchodilator (SABD) and inhaled corticosteroids (ICS) combined with long-acting β2 receptor agonist/

TABLE 5 Association of FEV_1 decline component of short-term CID-D1 (composite of decrease of ⩾100 mL in post-BD FEV_1; increase of ⩾4 units in SGRQ score; and incidence of a moderate/severe exacerbation) with outcomes over 18 months of follow-up

	COPD population					
	FEV_1 decline component					
	CID component +	CID component −	CID component+ *versus* CID component− (model 1)		CID component+ *versus* CID component− (model 2)	
	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 FEV_1[#]	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 FEV_1[#]	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[#]	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[#]	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[#]	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[#]	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[#]	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[¶], 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[¶], 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[§]	29 (19.9)	35 (19.1)	1.02 (0.76–1.36)	0.906	1.14 (0.83–1.56)	0.419

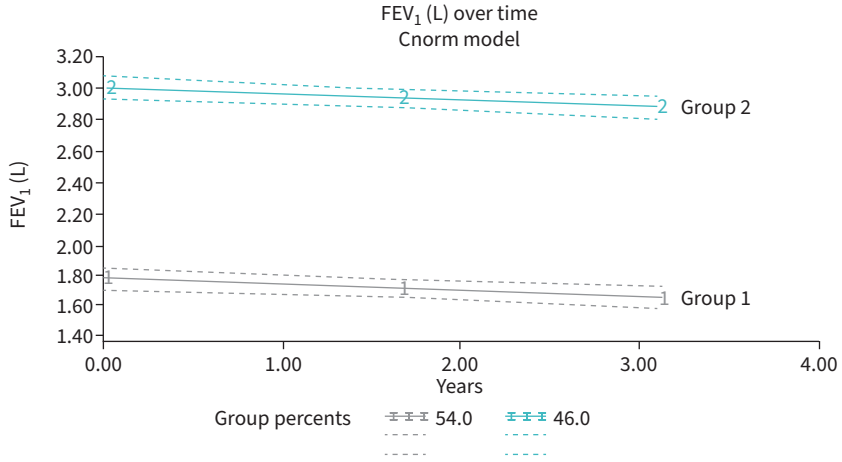
Data are presented as n (%) and OR/HR/RR (95% CI) unless specified otherwise. FEV_1: forced expiratory volume in 1 s; CID: clinically important deterioration; CID-D1: composite CID defined with SGRQ score as the health-status component; SGRQ: St George's respiratory questionnaire; OR: odds ratio; HR: hazard ratio; RR: rate ratio; CID component +: those demonstrating the short-term CID-D1 component of FEV1 decline; CID−: those not demonstrating the short-term CID-D1 component of FEV_1 decline; V2: visit 2; V3: visit 3; CAT: COPD assessment test; MRC: Medical Research Council score. [#]: OR were calculated using logistic regression model. [¶]: Moderate/severe exacerbation incident rate between V2 to V3 or follow-up 1-year after V2, and RR (95% CI) were calculated using a Poisson regression model. [§]: A new moderate/severe exacerbation from V2, and HR (95% CI) were calculated using a Cox model. Model 1 was adjusted for baseline age, sex, body mass index and smoking pack-years. Model 2 was adjusted for baseline age, sex, body mass index and smoking pack-years, any cardiovascular disease and absolute eosinophil count. *: p-value statistically significant (p<0.05).

long-acting muscarinic antagonist (LABA/LAMA)) in the previous year (table 6). 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 two groups are included in supplementary figure S2.

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 generalisability 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. As per *post hoc* power analysis, with proportion of FEV_1 decline (>100 mL decrease in FEV_1) in the reference group of around 57.8%, adjusted for four potential covariates (model 1), a total of 420 participants, translates to >85% power to estimate the odds ratio of 0.3 for CID to predict future FEV_1 decline (α=0.05, two-tailed test).

Consistent with current evidence, short-term CID and its exacerbation component was 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 existing literature, compared with the three-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].



	COPD		
FEV_1 (no missing data for the three points; n=366)	Group 1 (linear)	Group 2 (linear)	p-value for parameter comparison between group 1 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 modelling using forced expiratory volume in 1 s (FEV_1) trajectory over visit 1 (V1), visit 2 (V2) and visit 3 (V3). *: p-value statistically significant (p<0.05).

Short-term CID was not indicative of future decline in FEV_1, 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, inclusion of FEV_1 decline did not contribute to composite CID's capacity to differentiating in treatment effects [22]. Significant FEV_1 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 FEV_1 trajectories [34] and supportive of re-assessment of definition of FEV_1 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 FEV_1 decline, which has informed current MCID thresholds [35]. In a recent review, the authors contemplate the need for explorations of alternate definitions and thresholds for CID [36].

Emerging knowledge indicates prevalence of individuals with reduced FEV_1. 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 [40]) and/or external factors (*e.g.* smoking [2], ambient pollution [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 early disease stage [41]. In our analysis using GTBM, on the one hand the findings are consistent with subgroups at different baseline FEV_1 levels, however, over 37 months of study observation period these two groups were found to decline similarly.

In a nutshell, in a population diagnosed with mild–moderate COPD, short-term worsening captured as presence of CID, is likely to be associated with less lung function worsening over the immediately following 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 with advanced stages. The GOLD committee has persistently revised recommendations [8, 42] to draw attention of clinicians to symptom burden and exacerbation frequency over a singular focus on spirometry in their patient care management decisions [43–45].

TABLE 6 Baseline characteristics of groups identified based on FEV_1 trajectories

	COPD subjects (n=366)			
	Total n=366	Group 1 n=199	Group 2 n=167	p-value
Age, years	66.5±9.5	68.3±9.0	64.5±9.7	<0.001*
Sex, male	218 (59.6)	70 (35.2)	148 (88.6)	<0.001*
BMI, $kg \cdot m^{-2}$	27.2±5.4	27.3±6.3	27.1±4.0	0.78
Smoking status				
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 dyspnoea scale score ⩾3/5	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*
SGRQ 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				
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, $count \cdot \mu L^{-1}$	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
FEV_1 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+ (FEV_1, SGRQ and exacerbation)	217 (60.3)	125 (63.5)	92 (56.4)	0.195
Any CID+ (FEV_1, CAT and exacerbation)	224 (61.2)	125 (62.8)	99 (59.3)	0.49

Data are presented as n (%) or mean±SD. FEV_1: forced expiratory volume in 1 s; BMI: body mass index; CAT: COPD assessment test; CID+: those demonstrating short-term clinically important deterioration; EOS: eosinophils; ICS: inhaled corticosteroid; LABA: long-acting β2 receptor agonist; LAMA: long-acting muscarinic antagonist; MRC: Medical Research Council score; SABD: short-acting bronchodilator; SF36: 36-Item short form; SGRQ: St George's Respiratory Questionnaire. *: p-value statistically significant (p<0.05).

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 with 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 end-points for the assessment of treatment effect in this populations. 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 smaller sample size, though comparison of those excluded do not indicate bias, this weakness can be overcome in analysis upon the availability of future visit data. Thirdly, these findings need to 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 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. Our findings highlight the challenges of primary care teams. Detecting COPD at the mild–moderate severity stages will be encouraged by developing novel therapeutics needed to arrest

progression and potentially reverse the condition. In view of the looming mortality and morbidity challenge of COPD [46, 47], further examinations are needed in larger cohorts of patients with mild–moderate COPD. A validation study protocol in the primary care database of the UK Clinical Practice Research Datalink has been approved recently (protocol ID 21_000688). This will help to continue understanding trajectories and define generalisable holistic indicators of future deterioration in this population.

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 decision. 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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