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Short title: The Groningen severe COPD Cohort

Jorine E. Hartman, PhD[1,2], Pauline J.M. Kuks, MD[1,2], Maarten van den Berge. MD PhD[1,2], Nick H.T. ten Hacken, MD PhD[1,2], Jorrit B.A. Welling, MD PhD[1,2], Karin Klooster, PhD[1,2], Marieke C. van der Molen, MD[1,2], Simon D. Pouwels, PhD[1,2,3], Dirk-Jan Slebos, MD PhD[1,2]

[1.] Department of Pulmonary Diseases, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.

[2.] Groningen Research Institute for Asthma and COPD, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.

[3.] Department of Pathology and Medical Biology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Corresponding author

J.E. Hartman, PhD

Department of Pulmonary diseases AA11

University Medical Centre Groningen

PO Box 30001, 9700 RB Groningen

The Netherlands

Tel : +31 503612357, E-mail: j.hartman@umcg.nl

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ABSTRACT

The projection is that the prevalence and burden of chronic obstructive pulmonary disease (COPD) will increase in the coming decades. Consequently, the group of patients with severe, often end-stage, COPD will also increase. In the last decade, multiple new treatment modalities became available. However, due to the heterogeneity and complexity of end-stage COPD, these treatments can be best provided by identifying the phenotype or endotype of the patient and consequently selecting the right treatment for the right patient. Our hospital is an expertise center for severe COPD. We have been active in developing bronchoscopic lung volume reduction techniques and other experimental bronchoscopic treatments. This has led to a constant large flow of nationwide referrals of patients with severe COPD, which gave us the unique opportunity to set up “the Groningen Severe COPD Cohort (GSCC)”. The main aim of the GSCC cohort is to identify clinical phenotypes and endotypes in patients with severe COPD and to investigate the contribution of (epi)genomics. In total, the cohort included 1030 patients of whom 121 also underwent a bronchoscopy with collection of lung biopsies, lung brushes and nosh brush samples. In the future, the findings of this cohort may lead to earlier identification of subjects at risk for severe COPD, better clinical characterisation of established COPD, and a more tailored treatment of this subgroup. This manuscript describes the Groningen Severe COPD cohort, providing an overview of the cohort design, the collected data, a description of the cohort characteristics, future plans and possibilities for collaboration.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is highly prevalent with an estimated global prevalence of 11.7% and was the third leading cause of death in 2019 according to the World Health Organization (WHO) [1,2]. The projection is that the prevalence and burden of COPD will increase even further in the coming decades due to aging of the world's population and continued exposure to COPD risk factors [3].

Consequently, the group of patients with severe, often end-stage, COPD will increase. In the last decade, multiple new treatment modalities became available for these patients [4]. However, due to the heterogeneity and complexity of end-stage COPD, these treatments can be best provided by identifying the phenotype or endotype of the patient and consequently selecting the right treatment for the right patient [4]. As the phenotype or endotype is important for treatment selection and success, more insight and identification of the different subgroups of patients with severe COPD would be useful. Even more, because there still is a large group of severe COPD patients who could benefit from new therapies aimed at reducing symptoms despite the increase in treatment modalities.

The classical clinical phenotypes of COPD are small airway disease, emphysema and chronic bronchitis but this distinction seems not sufficient to optimally characterize COPD patients to target their treatment. Furthermore, there is significant overlap between these phenotypes and there is a lot of heterogeneity even between patients within one of these phenotypes [5]. A proposed definition of a phenotype is '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, rate of disease progression or death)' [6]. The observable structural and functional characteristics that constitute a phenotype are determined by the combined influence of environmental and genetic factors.

Subgroups of patients can also be defined based on an endotype. The advantage of endotyping is that it defines subtypes of a given disease based on distinct functional or pathobiological mechanisms. Next to improved selection of specific subgroups, e.g. who benefit the most from a given therapy, endotyping also leads to novel insights on the biological mechanisms driving these subgroups thus providing new targets for improved personalized treatment [7]. Gaining more insight in new phenotypes and endotypes based on e.g. lung function, clinical, radiologic, systemic, pathological, immunological and even genetic parameters in patients with severe COPD could lead to a more personalized approach in the management of severe COPD, and contribute to the understanding of the multifactorial pathophysiology of COPD.

The University Medical Center Groningen in the Netherlands is an expertise center for severe COPD. Next to other treatment options such as lung transplantation, non-invasive ventilation and pulmonary rehabilitation, we have been active in developing bronchoscopic lung volume reduction (BLVR) techniques and other experimental bronchoscopic treatments. This has led to a constant large flow of nationwide referrals of patients with severe COPD [8], which gave us the unique opportunity to set up “the Groningen Severe COPD Cohort- GSCC”.

The main aim of the GSCC cohort is to identify clinical phenotypes and endotypes in patients with severe COPD and to investigate the contribution of (epi)genomics to these pheno- and endotypes. In the future, the findings of this cohort may lead to earlier identification of subjects at risk for severe COPD, better clinical characterisation of established COPD, and a more tailored treatment of this subgroup.

This manuscript describes the Groningen Severe COPD cohort, providing an overview of the cohort design, the collected data, a description of the cohort characteristics, future plans and possibilities for collaboration.

COHORT DESCRIPTION

This cohort had an observational cross-sectional study design with 2 phases. The aim was to include 1000 patients with severe COPD who were referred to our hospital for bronchoscopic lung volume reduction (BLVR) treatment evaluation. During the physical consultation in our hospital an extensive panel of study measurements were performed (Phase A). A subgroup of patients who were eligible for a BLVR treatment and underwent a bronchoscopy were asked for phase B, in which, during the therapeutic bronchoscopy procedure nose brushes, bronchial brushes and bronchial biopsies were collected. Patients were included between 18-8-2014 and 10-7-2019.

DATA COLLECTION

The included study measures and outcomes are shown in table 1.

Samples: Blood samples have been collected from 924 subjects of the Groningen Severe COPD cohort. From all these subjects serum, plasma and peripheral blood DNA has been isolated and stored at -80 °C until further use. Serum and plasma can be used to assess a wide range of inflammatory markers, cytokines and other biomarkers, while peripheral blood DNA can be used for whole-genome sequencing.

From a subset of 121 subjects additional samples have been collected, including bronchial brushes, nose brushes and lung tissue biopsies (Phase B). RNA has been isolated from bronchial and nose brushes and whole genome sequencing has been performed to analyse gene expression levels.

FOLLOW-UP

This is an observational cross-sectional cohort. We did verify the vital status of the patients with the Dutch government personal record database at 3-4-2021 and whether patients underwent a bronchoscopic treatment or not. This verification could be repeated in the future.

PARTICIPANT CHARACTERISTICS

In total 1030 patients were included of whom 677 were female (66%). Patient characteristics are shown in table 2. In 121 patients who also underwent a bronchoscopy, lung biopsies, lung brush and nose brush samples were collected. At the verification date of vital status on 3-4-2021, 274 of the patients (27%) had died with a median of 857 days (range 2-2245) after their physical consultation in our hospital.

ETHICS

This cohort was approved by the ethics committee of the UMCG, Groningen, The Netherlands and all patients provided written informed consent (ECnumber:2014/102). Furthermore, the trial is registered at clinicaltrials.gov: NCT04023409.

FINDINGS TO DATE

So far, one paper was published including data from this cohort. In this paper, we combined this cohort with a previous dataset of patients who visited us for a consultation visit. We investigated the survival rate in patients who were evaluated for BLVR treatment and whether the survival rate differed between patients who underwent BLVR treatment and patients who did not [9]. In total 1471 patients were included of whom the median survival was approximately 7.4 years. The median survival time of patients who were treated with BLVR

was significantly longer than in patients who were not and furthermore undergoing BLVR was found to be an independent predictor of survival. Our results suggest that bronchoscopically reducing lung volume in patients with severe hyperinflation may lead to a survival benefit in a population with a severely reduced life expectancy.

STRENGHTS AND LIMITATIONS

A strength of this cohort is the large sample size of severe COPD patients and the fact that all measurements were performed in one hospital with the same equipment and protocols. A limitation of this cohort is that it only includes patients who were referred for a bronchoscopic lung volume reduction treatment and therefore is a specific subset of patients which might not be representative of the complete severe COPD population. On the other hand it is a rather homogeneous group of patients. Another limitation of the cohort is that it is cross-sectional and does not include follow up.

COLLABORATION / ONGOING ACTIVITIES AND FUTURE PLANS

Currently, multiple analyses are being performed to investigate specific subgroups in an effort to identify potential new phenotypes of severe COPD. One example is a comparison between patients with severe early onset COPD versus 'normal' onset COPD. And another analysis aims to identify the frequency of genetic variants in genes known to cause COPD in this patient group with severe COPD.

Currently, the SHERLOCK/P4O2 project [NCT04263961] is being executed in our hospital. In this study also severe COPD patients are included who undergo a bronchoscopy in which samples are collected. In addition, both ex- and current smokers with mild-to-moderate COPD and those without airflow obstruction are included. The combination of both cohorts in the

future enables us to identify which phenotypes and endotypes are present in COPD in general and which are specific to those who develop severe end-stage disease with extensive emphysema. To this end, amongst others RNA-sequencing and proteomics analyses will be performed in bronchial biopsies. In addition, extensive clinical characterization and sample collection (blood, urine, stool, sputum, bronchial and nasal brushes and bronchial wash) will be performed for future analyses yet to be defined. Next to the 121 severe COPD of whom already airway samples were collected in the GSCC cohort, this cohort aims to include before the end of 2024 a total of 433 patients: 100 patients with severe COPD and 333 participants with either mild-to-moderate COPD or without airflow obstruction.

We are open to collaborations and proposals for new research questions by contacting the corresponding author.

Contributorship statement

JEH and DJS: substantial contributions to the conception and design of the cohort, the acquisition, analysis and interpretation of data for the work; AND drafting the manuscript AND final approval of the version to be published; AND agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

NHTtH and MvdB: substantial contributions to the conception and design of the cohort, the acquisition, and interpretation of data for the work; AND revising the manuscript critically for important intellectual content; AND final approval of the version to be published; AND agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

PJMK, JBAW, KK, MCvdM and SDP**:** substantial contributions to data acquisition AND revising the manuscript critically for important intellectual content; AND Final approval of the version to be published; AND Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding declaration

The authors received no specific funding for this work.

Competing interest statement

The authors have declared that no competing interests exist.

Data sharing statement

The data obtained from the cohort described in this manuscript can be shared for collaborations or proposals. Data are available on reasonable request.

We have provided the following statement in the manuscript: "We are open to collaborations and proposals for new research questions by contacting the corresponding author."

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TABLES

Table 1: Overview of study measures

Variable	***Measures***
Demographics	Gender, age, birthweight, gestational age, smoking status, packyears. Physical therapy status, pulmonary rehabilitation status, use of pulmonary medications and long term oxygen therapy (LTOT)
Exacerbation status	Number in past year, hospital admissions in past year
Body composition	BMI, hip-waist ratio, bio-impedance
Pulmonary function measures	Spirometry Body plethysmography Diffusion capacity
	Annual lung function decline before visit (spirometry)
Lab regular	Arterial blood gas, complete blood count, basic chemistry, fibrinogen, alpha-1-anitrypsine
Additional blood samples	Serum, plasma, peripheral blood DNA
CT-scan	*Quantification LungQ software (Thirona, Nijmegen, The Netherlands):* Per lung and lobes: volumes and emphysema scores. Air trapping score, fissure integrity and Pi10.
Questionnaires	*mMRC:* Dyspnea
	CAT: Quality of life
	SGRQ: Quality of life
	CCQ: COPD control
	EQ5D: Quality of life
	BHQ: Bronchial hyperresponsiveness
	SQUASH: Physical activity
	Comorbidities: Self-reported
	Family history of pulmonary diseases: Self-reported
***Subset** (patients who underwent a bronchoscopy)*	
Nose brushes	RNA from nose brushes
Bronchial brushes	RNA from bronchial brushes
Bronchial biopsies	Paraffin-embedded
Follow-up	
Vital status	Verified with Dutch government personal records database on 3-4-2021
BLVR treatment status	Treated with a bronchoscopic lung volume reduction treatment

Table 2: Patient characteristics

Gender, *female (%)*		677 (65.7%)
Age, *years*		61 ± 7.5
mMRC, *score*		3 (0-4)
Current smokers, *number (%)*		20 (2%)
Packyears, *years*		40 ± 19
Use of	Maintenance Antibiotics	212 (21%)
	Maintenance Prednisolon	169 (16%)
	Any ICS	896 (87%)
	LTOT in rest	183 (18%)
	LTOT during exercise	266 (26%)
FEV_1, *liter*		0.82 ± 0.32
FEV_1, *% of predicted*		30.9 ± 10.6
Annual FEV_1, decline before participation, *liter /year*		-0.07 ± 0.05
FVC, *liter*		2.99 ± 10.2
RV, *liter*		4.62 ± 1.11
RV, *% of predicted*		219 ± 47
TLC, *liter*		7.62 ± 1.49
DLCO, *mmol/min*kPa*		2.59 ± 1.00
RV/TLC, *ratio*		0.61 ± 0.09
PaCO2, *kPa*		5.33 ± 0.73
PaO2, *kPa*		9.02 ± 1.24
Exacerbation in past year, *number*		2 (0-15)
Hospitalizations for exacerbation in past year, *number*		0 (0-11)
EBV treatment, *yes (%)*		220 (21%)
Coil treatment, *yes (%)*		46 (5%)
CAT, *total score*		22.4 ± 6.3
SGRQ, *total score*		58.8 ± 13.4
CCQ, *total score*		3.17 ± 0.98
EQ-5D, *VAS 0-100*		49 ± 17
BHQ, *mean score*		2.63 ± 0.99
Emphysema score, *%voxels <-950 HU*		36.7 ± 8.5
Total lung capacity inspiratory on CT, *liter*		6.97 ± 1.44
Pi10, *mm*		2.65 ± 0.31

Data are presented as n(%), mean ± standard deviation or median (range).

mMRC: modified Medical Research Council scale, ICS: inhaled corticosteroids, LTOT: long term oxygen therapy, FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, RV: residual volume, TLC: total lung capacity, DLCO: diffusing capacity for carbon monoxide, PaCO2: Partial pressure of carbon dioxide, PaO2: Partial pressure of oxygen, EBV: endobronchial valve, CAT: COPD assessment test, SGRQ: St. George's Respiratory Questionnaire, CCQ: COPD control questionnaire, EQ-5D: EuroQol-5 dimensions, VAS: visual analogue scale (0-100), BHQ: bronchial hyperresponsiveness questionnaire, Pi10:the square root of wall area at airways with a perimeter of 10mm, CT: computed tomography, HU: Hounsfield units, mm: millimetre.