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Research letter

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Caroline Stridsman, Lowie E.G.W. Vanfleteren, Jon R. Konradsen, Sten Axelsson Fisk, Christophe Pedroletti, Yvonne Sjöö, Jörgen Syk, Therese Sterner, Anne Lindberg, Alf Tunsäter, Fredrik Nyberg, Ann Ekberg-Jansson, Johanna Karlsson Sundbaum

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Predictors of severe COVID-19 in a registry-based Swedish cohort of patients with chronic obstructive pulmonary disease (COPD)

Stridsman Caroline[1], Vanfleteren Lowie E.G.W.[2,3], Konradsen Jon R[4], Axelsson Fisk Sten[5], Pedroletti Christophe[6], Sjöö Yvonne[7], Syk Jörgen[6,8,9], Sterner Therese[10], Lindberg Anne[1], Tunsäter Alf[11], Nyberg Fredrik[12], Ekberg-Jansson Ann[3], Karlsson Sundbaum Johanna[13]

[1]Department of Public Health and Clinical Medicine, Division of Medicine/The OLIN-unit, Umeå University, Umeå, Sweden.
[2]COPD Center, Department of Respiratory Medicine and Allergology, Sahlgrenska University Hospital, Gothenburg, Sweden.
[3]Department of Internal Medicine and Clinical Nutrition, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden.
[4]Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden.
[5]Department of clinical sciences Lund, Obstetrics and gynaecology, Lund University and Ystad Hospital, Sweden.
[6] Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden.
[7]The Swedish National Airway Register, Gothenburg, Sweden.
[8]Academic primary health care centre, Stockholm, Sweden.
[9]Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden.
[10]Department of Occupational and Environmental Dermatology, Skåne University Hospital, Lund University, Malmö, Sweden.
[11]Department of Respiratory Medicine and Allergology, Skåne University Hospital, Lund University, Lund, Sweden.
[12]School of Public Health and Community Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden.
[13]Department of Health, Education and Technology, Luleå University of Technology, Luleå, Sweden.

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To the Editor:

It is unclear if patients with chronic obstructive pulmonary disease (COPD) are at increased risk of becoming infected with SARS-CoV-2 [1,2]. However, after contracting SARS-CoV-2, patients with COPD are at high risk of severe COVID-19, a condition associated with morbidity and mortality [3,4]. Although studies have described COVID-19 cohorts and investigated COPD as a risk factor, studies investigating patients with COPD in relation to risks of COVID-19 remain rare. Approved by the Swedish Ethical Review Authority (2020-02777), the current study was based on the Swedish National Airway Register (SNAR), which includes a large, well-characterised cohort of patients with COPD [5]. In the cohort, patients who have been hospitalised or died from COVID-19 were identified, which afforded a unique opportunity to study predictors of severe COVID-19 in COPD.

Launched in 2013, SNAR comprises data on patients with a physician-diagnosis of COPD from primary and secondary care (ICD-10 J44) [5]. On 1 February 2020, 68,902 living patients with COPD were identified in SNAR. Severe COVID-19 was defined as inpatient care (primary discharge diagnosis) or death (the underlying cause of death) due to COVID-19. To identify these patients, data from SNAR were linked with the statistical databases of the Swedish National Board of Health and Welfare, the National Patient Register (NPR) for inpatient care and the Swedish Cause of Death Register (SCDR). Those registers provide data about COVID-19 based on ICD-10 U07.1 and U07.2. Data from both NPR and SCDR were collected until 11 September 2020, and additional data from NPR until 9 December 2020.

Clinical data from SNAR, including body mass index (BMI) (9.3% missing), forced expiratory volume in one second (FEV_1%) of predicted value (33.2% missing), smoking habits (10.4% missing) and COPD Assessment Test (CAT) scores (36.2% missing), were

used, and the most recent observation for each patient was identified. CAT was used as a binary categorical variable with cut-offs at ≥10 and ≥18, respectively [6]. Data regarding level of education were retrieved from Statistics Sweden. Medication-treated comorbidities were identified by Anatomical Therapeutic Chemical codes for dispensed pharmacy medications between 1 January 2019 and 28 February 2020. These data were retrieved from the Swedish Prescribed Drug Register and classified as cardiovascular disease (C01-03, C08, C09), diabetes (A10A, A10B) and depression (N06A). COPD treated in inpatient or secondary care in 2019 was used as a proxy for COPD morbidity, and data were retrieved from NPR (ICD-10 J44 as primary diagnosis).

Odds ratios (OR) and 95% confidence intervals (CI) were generated using multivariable logistic models, with severe COVID-19 as a dependent variable. Clinical data from SNAR were included, and missing values were handled in two ways: missing as a separate category (Models 1 and 4) and a complete case analysis (Model 2) [7]. The impact of comorbidities was studied using complete register data (Models 3 and 5). Models 1-3 had follow-up terminated on 9 December 2020, and Models 4 and 5 on 11 September 2020.

Of the 68,902 COPD patients registered in SNAR on 9 December 2020, 991 (1.4%) met the definition of severe COVID-19 (98.3% U07.1). Of them, 683 (66%) were identified by inpatient care and 308 (34%) by death certificates, and up to 11 September, 449 were identified by inpatient care and 308 by death certificates. Male sex (50.7% vs. 42.8%, $p<0.001$), older age (mean 78.4 vs. 73.3, $p<0.001$), and a lower FEV_1% of predicted (mean 57.2 vs. 60.7, $p<0.001$) were more common among patients with severe COVID-19 than without. Primary level of education was more common in severe COVID-19 (73.0% vs. 70.6%, $p=0.021$), while current smoking was less common (23.0% vs. 34.7%, $p<0.001$).

Patients with severe COVID-19 had a higher mean CAT score than those without (14.6 vs. 13.0, $p<0.001$), and a higher proportion had a CAT score ≥18 (31.5% vs. 22.2%, $p<0.001$), whereas those with CAT scores ≥10 did not differ significantly. Medication-treated cardiovascular disease (80.6% vs. 69.0%, $p<0.001$), diabetes (22.2% vs. 16.2%, $p<0.001$), depression (35.4% vs. 25.5%, $p<0.001$), and COPD treated in inpatient or secondary care in 2019 (25.3% vs. 13.1%, $p<0.001$) were more common conditions among patients with severe COVID-19 than ones without.

Clinical data from SNAR showed that older age, male sex, primary education, secondary education, underweight, obesity, FEV_1% of predicted <50, and a CAT score ≥18 were all associated with severe COVID-19, while current smoking was inversely associated (Model 1). The results were similar in the complete case analysis, except that level of education and BMI lost significance (Model 2). Cardiovascular disease, diabetes and depression remained independent predictors of severe COVID-19 when adjusted for covariates (Model 3). The pattern was similar when the follow-up was limited to 11 September (Models 4 and 5).

To date, it is well-known that older age, male sex, obesity, cardiovascular disease, diabetes and low socioeconomic status are risk factors for severe COVID-19 in the general population [1,8,9]. To that list, decreased lung function, higher CAT score, underweight, depression and prior COPD treated in inpatient or secondary care can be added as factors predicting severe COVID-19 in patients with COPD. According to guidelines, these factors should be considered throughout the management of COPD [10], and as highlighted in our result, also when identifying patients at risk for severe illness from COVID-19. When the risk of transmitting COVID-19 needs to be minimised, follow-up visits can be conducted by remote

consultations (online, phone and/or video links). If airflow limitation requires confirmation during the consultation, personal portable spirometry can be used, supported by video conference technology [11].

Surprisingly, current smoking was an inverse predictor in our study. However, it can be an age-related finding. The mean age in our cohort was above 70, and in another study, smokers more than 69 years old were not at any higher risk of COVID-19 than never-smokers, whereas the opposite was observed among younger individuals [12]. Even so, evidence strongly suggests the negative effects of smoking on COVID-19 at all ages [13,14], and the unexpected result requires further investigation.

A major strength of our study was the possibility to examine a large cohort of patients with COPD during a pandemic. Nonetheless, register studies have certain limitations, including the use of physician-diagnosed COPD for inclusion, the relatively crude definition of severe COVID-19, the lack of data regarding pharmacological COPD treatment and exacerbations and a variable amount of missing data. We handled missing data by using 1) missing as a separate category, to maintain statistical power; 2) a complete case analysis, which resulted in a loss of statistical power; and 3) a model including complete register data. When using missing as a separate category, the associations between severe COVID-19 and missing data on lung function and CAT indicate a selection bias. The delay in the delivery of data regarding death certificates from SCDR contributed to a different follow-up time for the combined outcome. Nevertheless, the Swedish COVID-19 strategy resulted in a rapid increase in cases and deaths during both endpoints [15] and our multivariable analyses were reassuringly similar when using 11 September as follow-up termination for both NPR and SCDR.

In conclusion, all clinical factors identified as predictors of severe COVID-19 in our study are important to monitor when managing patients with COPD. Beyond that, those patients need to be prioritised for vaccination.

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CONFLICTS OF INTEREST STATEMENT

CS has received personal fees from AstraZeneca, Boehringer-Ingelheim and Novartis for lectures at sponsored meetings. LV has received grants and personal fees from AstraZeneca and personal fees from GSK, Novartis, Boehringer-Ingelheim, Menarini, Resmed, Chiesi, AGA Linde, Zambon and Pulmonx. JS reports consulting fees paid to their employer from Orion Pharma. TS has received personal fees from ALK Abello for lectures at sponsored meetings. AL has received personal fees AstraZeneca, Novartis, Boehringer-Ingelheim and GlaxoSmithKline for advisory boards and/or lectures at sponsored meetings. AT has received

personal fees from AstraZeneca, Novartis, Boehringer-Ingelheim and GlaxoSmithKline for advisory boards and/or lectures at sponsored meetings. FN was an employee of AstraZeneca until 2019, and holds some AstraZeneca shares. JRK, SAF, CP, YS, AEJ and JKS have no conflicts of interest.

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Table 1. Multivariable Logistic Models: Independent predictors of severe COVID-19 based on clinical data from the Swedish National Airway Register (SNAR) (models 1, 2 and 4), and register data (models 3 and 5).

	Follow-up terminated on 9 December OR (95% CI)			**Follow-up terminated on 11 September OR (95% CI)**	
	Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 5**
Older age[1]	**1.06 (1.05-1.07)**	**1.05 (1.04-1.07)**	**1.06 (1.05-1.07)**	**1.06 (1.05-1.07)**	**1.06 (1.05-1.07)**
Male sex	**1.44 (1.26-1.64)**	**1.38 (1.13-1.69)**	**1.45 (1.27-1.65)**	**1.49 (1.28-1.73)**	**1.51 (1.30-1.75)**
Level of education					
Primary education	**1.23 (1.03-1.48)**	1.11 (0.85-1.45)	**1.20 (1.00-1.44)**	**1.23 (1.00-1.51)**	1.20 (0.97-1.47)
Secondary education	**1.32 (1.03-1.69)**	1.17 (0.81-1.70)	**1.31 (1.02-1.67)**	1.31 (0.99-1.74)	1.31 (0.99-1.73)
Tertiary education	Reference	Reference	Reference	Reference	Reference
Body Mass Index (BMI)					
Underweight	**1.56 (1.20-2.03)**	1.44 (0.96-2.17)		**1.53 (1.14-2.07)**	
Normal weight	Reference	Reference		Reference	
Overweight	0.91 (0.76.1.08)	0.93 (0.72-1.18)		0.87 (0.72-1.07)	
Obesity	**1.32 (1.10-1.57)**	1.23 (0.95-1.59)		**1.27 (1.04-1.55)**	
Missing data: BMI	0.89 (0.69-1.15)			0.84 (0.63-1.12)	
COPD severity based on spirometry[2]					
FEV_1% of predicted ≥80	Reference	Reference		Reference	
FEV_1% of predicted 50-79	1.22 (0.92-1.63)	1.30 (0.94-1.82)		1.22 (0.88-1.70)	
FEV_1% of predicted 30-49	**1.64 (1.21-2.23)**	**1.46 (1.02-2.02)**		**1.56 (1.10-2.22)**	
FEV_1% of predicted <30	1.29 (0.80-2.08)	1.19 (0.69-2.05)		1.16 (0.66-2.03)	
Missing data: FEV_1% of predicted	**1.98 (1.48-2.64)**			**1.99 (1.43-2.77)**	
Smoking habits					
Non-smoker	Reference	Reference		Reference	
Current smoker	**0.71 (0.57-0.88)**	**0.59 (0.42-0.84)**		**0.74 (0.58-0.94)**	
Ex-smoker	0.96 (0.80-1.15)	1.01 (0.76-1.34)		0.94 (0.77-1.16)	
Missing data: Smoking habits	0.97 (0.76-1.24)			0.98 (0.74-1.29)	
COPD Assessment Test (CAT)					
CAT score ≥18	**1.57 (1.30-1.90)**	**1.56 (1.25-1.94)**		**1.72 (1.38-2.13)**	
Missing data: CAT scores	**1.35 (1.14-1.59)**			**1.45 (1.20-1.76)**	

Comorbidities				
Cardiovascular disease		**1.26 (1.07-1.49)**		**1.35 (1.11-1.63)**
Diabetes		**1.36 (1.16-1.59)**		**1.28 (1.07-1.54)**
Depression		**1.58 (1.38-1.81)**		**1.67 (1.44-1.95)**
COPD inpatient/secondary care in 2019		**2.01 (1.74-2.33)**		**2.03 (1.72-2.40)**

[1]Entered as continuous variable. [2]According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD). Models 1 and 4: missing as a separate category. Model 2: complete cases analysis (n=35,948). Models 3 and 5: complete register data analysis. BMI (kg/m^2) = Underweight (BMI<19), normal weight (BMI 19-25), overweight (BMI 26-30) and obesity (BMI>30). FEV_1 = Forced expiratory volume in one second.