Check for updates

RESEARCH ARTICLE

REVISED Characteristics and outcomes of COVID-19 patients with COPD from the United States, South Korea, and Europe [version 3; peer review: 2 approved]

David Moreno-Martos [iD][1], Katia Verhamme[2], Anna Ostropolets [iD][3], Kristin Kostka[4,5], Talita Duarte-Sales[6], Daniel Prieto-Alhambra[7], Thamir M Alshammari[8], Heba Alghoul [iD][9], Waheed-Ul-Rahman Ahmed[7,10], Clair Blacketer[2,11], Scott DuVall[12], Lana Lai[13], Michael Matheny[14,15], Fredrik Nyberg [iD][16], Jose Posada [iD][17], Peter Rijnbeek[2], Matthew Spotnitz [iD][3], Anthony Sena[2,11], Nigam Shah[17], Marc Suchard [iD][18,19], Seng Chan You [iD][20], George Hripcsak[3], Patrick Ryan[3,11], Daniel Morales [iD][1,21]

[1]Population Health and Genomics, University of Dundee, Dundee, UK
[2]Medical Informatics, Erasmus MC, Rotterdam, The Netherlands
[3]Biomedical Informatics, Columbia University Medical Center, New York, USA
[4]Real World Solutions, IQVIA, Cambridge, MA, USA
[5]OHDSI Center at The Roux Institute, Northeastern University, Portland, ME, USA
[6]Fundació Institut Universitari per a la recerca a l'Atenció Primaria de Salut Jordi Gol i Gurina (IDIAPJGol), IDIAPJGol, Barcelona, Spain
[7]Nuffield Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences, University of Oxford, Oxford, UK
[8]College of Pharmacy, Riyadh Elm University, Riyadh, Saudi Arabia
[9]Faculty of Medicine, Islamic University of Gaza, Gaza, Palestinian Territory
[10]College of Medicine and Health, University of Exeter, Exeter, UK
[11]Janssen Research and Development, Janssen Research and Development, Titusville, NJ, USA
[12]VA Informatics and Computing Infrastructure, University of Utah, Salt Lake City, UT, USA
[13]Department of Medical Sciences, University of Manchester, Manchester, UK
[14]Geriatrics Research Education and Clinical Care Service & VINCI, Tennessee Valley Healthcare System VA, nashville, TN, USA
[15]Department of Biomedical Informatics, Vanderbilt University Medical Center, Nashville, TN, USA
[16]School of Public Health and Community Medicine, University of Gothenburg, Gothenburg, Sweden
[17]Department of Medicine, Stanford University, Redwood City, CA, USA
[18]Department of Biostatistics UCLA Fielding School of Public Health, University of California, Los Angeles, Los Angeles, CA, USA
[19]Department of Computational Medicine David Geffen School of Medicine at UCLA,, University of California, Los Angeles, Los Angeles, CA, USA
[20]Department of Preventive Medicine, Yonsei University, Seoul, South Korea
[21]Department of Public Health, University of Southern Denmark, Odense, Denmark

Open Peer Review

Approval Status ✔✔

	1	2
version 3		✔ view

Abstract
Background: Characterization studies of COVID-19 patients with

chronic obstructive pulmonary disease (COPD) are limited in size and scope. The aim of the study is to provide a large-scale characterization of COVID-19 patients with COPD.

Methods: We included thirteen databases contributing data from January-June 2020 from North America (US), Europe and Asia. We defined two cohorts of patients with COVID-19 namely a 'diagnosed' and 'hospitalized' cohort. We followed patients from COVID-19 index date to 30 days or death. We performed descriptive analysis and reported the frequency of characteristics and outcomes among COPD patients with COVID-19.

Results: The study included 934,778 patients in the diagnosed COVID-19 cohort and 177,201 in the hospitalized COVID-19 cohort. Observed COPD prevalence in the diagnosed cohort ranged from 3.8% (95%CI 3.5-4.1%) in French data to 22.7% (95%CI 22.4-23.0) in US data, and from 1.9% (95%CI 1.6-2.2) in South Korean to 44.0% (95%CI 43.1-45.0) in US data, in the hospitalized cohorts. COPD patients in the hospitalized cohort had greater comorbidity than those in the diagnosed cohort, including hypertension, heart disease, diabetes and obesity. Mortality was higher in COPD patients in the hospitalized cohort and ranged from 7.6% (95%CI 6.9-8.4) to 32.2% (95%CI 28.0-36.7) across databases. ARDS, acute renal failure, cardiac arrhythmia and sepsis were the most common outcomes among hospitalized COPD patients.

Conclusion: COPD patients with COVID-19 have high levels of COVID-19-associated comorbidities and poor COVID-19 outcomes. Further research is required to identify patients with COPD at high risk of worse outcomes.

Keywords
COPD, SARS-CoV-2, coronavirus, COVID, epidemiology.

	1	2
(revision) 10 Jan 2023		⚠
version 2 (revision) 24 Mar 2022	✓ view	? view
version 1 24 Jan 2022	? view	

1. **Marta A. Kisiel**, Uppsala University, Uppsala, Sweden

2. **Laurie Tomlinson** (iD), London School of Hygiene & Tropical Medicine, London, UK

Any reports and responses or comments on the article can be found at the end of the article.

Corresponding author: Daniel Morales (d.r.z.morales@dundee.ac.uk)

Author roles: Moreno-Martos D: Formal Analysis, Investigation, Project Administration, Software, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Verhamme K**: Data Curation, Investigation, Methodology, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing; **Ostropolets A**: Conceptualization, Data Curation, Investigation, Methodology, Software, Visualization, Writing – Review & Editing; **Kostka K**: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Duarte-Sales T**: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Prieto-Alhambra D**: Conceptualization, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Writing – Review & Editing; **Alshammari TM**: Conceptualization, Investigation, Methodology, Supervision, Writing – Review & Editing; **Alghoul H**: Investigation, Methodology, Writing – Review & Editing; **Ahmed WUR**: Investigation, Methodology, Writing – Review & Editing; **Blacketer C**: Data Curation, Investigation, Methodology, Project Administration, Resources, Software, Validation, Writing – Review & Editing; **DuVall S**: Data Curation, Investigation, Methodology, Project Administration, Resources, Software, Validation, Writing – Review & Editing; **Lai L**: Formal Analysis, Investigation, Methodology, Writing – Review & Editing; **Matheny M**: Data Curation, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Writing – Review & Editing; **Nyberg F**: Investigation, Methodology, Supervision, Writing – Review & Editing; **Posada J**: Data Curation, Investigation, Methodology, Project Administration, Writing – Review & Editing; **Rijnbeek P**: Conceptualization, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Validation, Visualization, Writing – Review & Editing; **Spotnitz M**: Investigation, Methodology, Writing – Review & Editing; **Sena A**: Data Curation, Formal Analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – Review & Editing; **Shah N**: Investigation, Methodology, Project Administration, Resources, Supervision, Writing – Review & Editing; **Suchard M**: Conceptualization, Data Curation, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Visualization, Writing – Review & Editing; **Chan You S**: Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Software, Visualization, Writing – Review & Editing; **Hripcsak G**: Conceptualization, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project

Administration, Resources, Software, Supervision, Visualization, Writing – Review & Editing; **Ryan P**: Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Visualization, Writing – Review & Editing; **Morales D**: Conceptualization, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing

How to cite this article: Moreno-Martos D, Verhamme K, Ostropolets A *et al.* **Characteristics and outcomes of COVID-19 patients with COPD from the United States, South Korea, and Europe [version 3; peer review: 2 approved]** Wellcome Open Research 2023, **7**:22 https://doi.org/10.12688/wellcomeopenres.17403.3

First published: 24 Jan 2022, **7**:22 https://doi.org/10.12688/wellcomeopenres.17403.1

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected over 200 million patients and resulted in more than 4.2 million deaths worldwide as of April 2021[1]. Coronavirus disease 2019 (COVID-19) can lead to severe lung injury and pneumonia, acute kidney injury, cardiovascular complications, and death. The symptoms and complications of COVID-19 early in the pandemic have been compared to seasonal influenza resulting in national policy measures classifying chronic obstructive pulmonary disease (COPD) patients as high risk and advising them to take additional protective measures[2]. The prevalence of COPD among COVID-19 patients has ranged from 0.8% to 38% during the first wave of the pandemic depending upon the cohort studied[3]. Whilst some studies suggested that the prevalence of COPD among COVID-19 patients during the first wave of the pandemic may be lower than the prevalence of COPD in the general population COPD was still considered a risk factor for severe COVID-19 disease[4].

Estimates for the prevalence of COPD among COVID-19 patients from the first wave of the pandemic typically came from small, single-centre hospitalised cohorts and examined a limited range of patient characteristics and outcomes[3]. Larger comparisons from geographically diverse cohorts that also include patients with milder COVID-19 illness provide a more compelling picture and improve generalisability. Viral respiratory tract infections are common triggers for exacerbations resulting in increased morbidity and mortality yet it is uncertain how often people with COPD with COVID-19 present with exacerbations[5,6].

The aim of this study was to perform a large-scale, federated network, descriptive characterization study reporting the demographics, comorbidities, and outcomes of COPD patients with COVID-19 during the first wave of the pandemic at the point of diagnosis and hospitalisation.

Methods

Ethical approval

All the data partners received Institutional Review Board (IRB) approval or exemption. STARR-OMOP had approval from IRB Panel #8 (RB-53248) registered to Leland Stanford Junior University under the Stanford Human Research Protection Program (HRPP). The use of VA data was reviewed by the Department of Veterans Affairs Central Institutional Review Board (IRB), was determined to meet the criteria for exemption under Exemption Category 4(3), and approved for Waiver of HIPAA Authorization. The research was approved by the Columbia University Institutional Review Board as an OHDSI network study. The use of SIDIAP was approved by the Clinical Research Ethics Committee of the IDIAPJGol (project code: 20/070-PCV). The use of CPRD was approved by the Independent Scientific Advisory Committee (ISAC) (protocol number 20_059RA2). The use of IQVIA OpenClaims and IPCI was exempted from IRB approval for COVID-19 research.

Study design

The Characterizing Health Associated Risks and Your Baseline Disease In SARS-COV-2 (CHARYBDIS) study is a multinational cohort study using retrospective electronic health records and claims data on COVID-19 patients from three continents during the first wave of the pandemic, the North America (US), Europe, and Asia[7]. All data for were standardized to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM)[8,9]. The Charybdis protocol and source code is available via open access (https://github.com/ohdsi-studies/Covid19Charac-terizationCharybdis)[10].

Data sources

Of the nineteen databases available on 28th November 2020, 13 that had a minimum sample size of 140 COVID-19 patients with COPD were included. This minimum threshold was considered appropriate to estimate the prevalence of a previous condition or 30-day risk of an outcome affecting 10% of the study population. Supplementary Figure S1 presents the database selection process for this study[11].

Data from the United States included: the University of Colorado Anschuz Medical Campus Health Data Compass (CU-AMC HDC), the Columbia University Irving Medical Center data warehouse (CUIMC), HealthVerity, Stanford Medicine Research Data Repository (STARR-OMOP), IQVIA Open Claims, Optum de-identified Electronic Health Record Dataset and the United States Department of Veterans Affairs (VA-OMOP). Data from South Korea included the Health Insurance Review & Assessment Service (HIRA) database. Data from Europe included the Spanish Information System for Research in Primary Care (SIDIAP) database; the Dutch Integrated Primary Care Information (IPCI) database, LPD (Longitudinal Patients Database) France, LPD Italy and the UK Clinical Practice Research Datalink (CPRD). Further information about databases considered for inclusion is contained in Appendix 1[11].

Study participants and follow-up

COVID-19 cohorts: Two non-mutually exclusive cohorts were defined (Appendix 2)[11]. COVID-19 patients in the *diagnosed* cohort were defined as patients during the first wave of the pandemic having a clinical diagnosis and/or positive test for SARS-CoV-2 from outpatient or inpatient records. In the diagnosed cohort, the index date was the earliest date of COVID-19

diagnosis or a first positive test. COVID-19 patients in the *hospitalized* cohort were defined as patients during the first wave of the pandemic with a hospitalization episode and a clinical diagnosis of COVID-19 or positive SARS-CoV-2 test within 21 days prior to admission and up to the end of hospitalization. This time window was chosen to include patients with a diagnosis prior to hospitalization and to allow for delays in recording of test results. In the hospitalized cohort, the index date was the day of hospitalization.

All patients were required to have at least a year of observation time prior to index date. Patients were followed from the index date to the earliest of the studied outcome, end of follow-up (30 days after index date), end of data capture, or death.

COPD definition: COPD was defined as either: a) an occurrence of a COPD diagnosis code any time on or before the COVID-19 index date or b) a prescription or administration of COPD medications within the year prior to index date in patients older than or equal to 55 years (Appendix 3)[11]. We excluded patients with a diagnosis of asthma prior to the COPD diagnosis to avoid misclassification with asthma. Codes used to define these cohorts have been previously described[12,13] and are included in the Appendix[11].

Baseline characteristics

Conditions and procedures were identified within 1 to 365 to days prior to the index date using Systematized Nomenclature of Medicine (SNOMED CT) codes with all descendent codes included codes mapped from local source vocabularies. We report pre-specified demographics and conditions related to COPD and COVID-19. Other conditions analysed as part of the larger CHARYBDIS project are reported here (https://data.ohdsi.org/Covid19CharacterizationCharybdis/).

COPD exacerbation was defined by a COPD exacerbation code at index date in databases with disease codes for exacerbation. The following medications were identified within 1 to 30 days prior to index date to characterise how patients were recently managed prior to the COVID-19 index date: systemic corticosteroids, inhaled corticosteroids (ICS), short-acting beta2-agonists (SABA), long-acting beta2-agonists (LABA), short-acting muscarinic antagonists (SAMA), long-acting antimuscarinic antagonists (LAMA), methylxanthines, mucolytics, oxygen therapy, antibiotics (beta-lactam penicillins, macrolides, fluoroquinolones), acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids. Medication use was calculated using drug eras that began starting on the date of the first drug exposure and ended on the observed end date of the last concatenated medication record, with a grace period of 30 days between medication records which allowed for sequential medication records to be considered as a continuous drug era.

Outcomes

We identified the following outcomes within 30 days following the index date: death, use of intensive services (identified as a recorded invasive mechanical ventilation and/or a tracheostomy and/or extracorporeal membrane oxygenation procedure), acute respiratory distress syndrome (ARDS), acute renal failure syndrome (ARFS), cardiac arrhythmia, heart failure, pulmonary oedema, myocardial infarction, sepsis, bleeding, venous thromboembolism (VTE), pulmonary embolism (PE) and stroke (ischaemic and haemorrhagic).

Analysis

A common analytical code for CHARYBDIS was run locally in each database. Only aggregate results from each database were then shared. We report the number and proportion by socio-demographics, history of comorbidities, and commonly used medications in each population with 95% confidence intervals (CI) calculated using the Wilson score method. Standardised mean differences (SMD) were calculated to aid comparison between study cohorts. We used R version 3.6.0 for data visualization. All the data partners obtained Institutional Review Board (IRB) approval or exemption to conduct this study, as required.

Results

Prevalence of COPD

The study included 934,778 COVID-19 patients from the first wave of the pandemic in the diagnosed cohort (84.0% from US and 16.0% from European databases) and 177,201 COVID-19 patients in the hospitalized cohort (87.5% from US, 8.8% from European and 3.7% from South Korean databases). The observed prevalence of COPD in the diagnosed cohort ranged from 3.8% (95%CI 3.5-4.1) in data from France to 22.7% (95%CI 22.4-23.0) in the US (overall median 7.7%) (Table 1) during the first wave of the pandemic. The observed prevalence of COPD in COVID-19 patients in the hospitalized cohort ranged from 1.9% (95%CI 1.6-2.2) in data from South Korea to 44.0% (95%CI 43.1-45.0) in the US (overall median 20.9%) during the first wave of the pandemic. Among databases contributing to both COVID-19 cohorts, the prevalence of COPD was greater in hospitalized than in the diagnosed COVID-19 cohorts. COPD exacerbation at presentation ranged from <0.8% to 6.4% (95%CI 4.8-8.5) in the *diagnosed* cohort (median 4.1%), and from 1.3% (95%CI 0.6-2.8) to 12.0% (95%CI 8.8-16.2) amongst those in the *hospitalized* cohort (median 7.7%) (Table 2).

Demographics

In the *hospitalized* cohort, COPD patients with COVID-19 were more commonly male (range 46.8% to 58.5%, overall median 54.5%) (Supplementary Table S1)[11]. However, there was less consistent sex difference amongst patients in the *diagnosed* cohort (Supplementary Table S2)[11]. Whilst in VA-OMOP 96.7% of hospitalized patients and 94.6% of diagnosed patients were male, this was expected due to the population demographics with data predominantly originating from male veterans. In both cohorts, COPD patients with COVID-19 had a similar distribution of age and were more commonly older than 65 years (Supplementary Figure S2 and S3)[11].

Table 1. Prevalence of COPD in COVID-19 patients from 26 database cohorts in 7 countries.

Cohort	US CU-AMC	US CUIMC	US HealthVerity	US IQVIA OpenClaims	US Optum EHR	US STARR-OMOP	US VA-OMOP	KR HIRA	UK CPRD	NL IPCI	ES SIDIAP	FR LPD France	IT LPD Italy
Diagnosed COVID-19	7270	8519	114173	466191	129512	3328	55557	-	3372	3047	122141	17180	4488
COPD (n)	692	770	6500	68262	11056	218	12610	-	261	200	15803	648	340
Prevalence (%), 95%CI	9.5 8.9-10.2	9.0 8.4-9.7	5.7 5.6-5.8	14.6 14.5-14.7	8.5 8.4-8.7	6.6 5.8-7.4	22.7 22.4-23.0	-	7.7 6.9-8.7	6.6 5.7-7.5	12.9 12.8-13.1	3.8 3.5-4.1	7.6 6.8-8.4
Hospitalized COVID-19	1434	2600	7581	133091	22024	-	10471	7599	-	-	18202	-	-
COPD (n)	299	447	1649	30917	4504	-	4611	145	-	-	4843	-	-
Prevalence (%), 95%CI	20.9 18.8-23.0	17.2 15.8-18.7	21.8 20.8-22.7	23.2 23.0-23.5	20.5 19.9-21.0	-	44.0 43.1-45.0	1.9 1.6-2.2	-	-	26.6 26.0-27.3	-	-

Grey =US database. Pink=South Korean database. Yellow=European database. US=United States. KR=South Korea. UK=United Kingdom. NL=Netherlands. ES=Spain. (n) = number. NA= not applicable for that cohort.

Table 2. Prevalence of COPD exacerbation in COVID-19 patients.

Cohort	US CU-AMC	US CUIMC	US HealthVerity	US IQVIA OpenClaims	US Optum EHR	US STARR-OMOP	US VA-OMOP	KR HIRA	UK CPRD	ES SIDIAP	FR LPD France
Diagnosed COVID-19 Prevalence (%), 95%CI	6.4 4.8-8.5	1.9 1.1-3.1	3.7 3.3-4.2	5.0 4.8-5.2	6.2 5.8-6.7	4.1 2.2-7.6	2.9 2.6-3.2	-	<1.9	1.8 1.6-2.0	<0.8
Hospitalized COVID-19 Prevalence (%), 95%CI	12.0 8.8-16.2	1.3 0.6-2.8	8.6 7.3-10.1	7.7 7.4-8.0	10.8 9.9-11.7	-	5.5 4.9-6.2	<3.4	-	3.2 2.7-3.7	-

*No data on COPD exacerbations recorded for IPCI and LDP Italy. Grey =US database. Pink=South Korean database. Yellow=European database. US=United States. KR=South Korea. UK=United Kingdom. NL=Netherlands. ES=Spain.

Baseline comorbidities

In the *diagnosed* COPD cohort, the most prevalent comorbidities included obesity (median 49.1%), cardiovascular disease (median 63.2%), hypertension (median 72.4%), chronic kidney disease (CKD) (median 29.8%) and type 2 diabetes mellitus (T2DM) (median 35.9%) (Table 3). Compared to those in the diagnosed cohort, the *hospitalized* COPD cohort had a greater prevalence of cardiovascular comorbidities, T2DM and CKD although these differences were typically modest (Table 4, Figure 1, Supplementary Figure S3)[11].

Medication use

Systemic corticosteroid use in the 30 days prior to index date ranged from 5.1% (95%CI 3.7-7.1) to 26.4% (95%CI 21.4-32.1) in the *diagnosed* cohort, and from 7.5% (95%CI 6.3-8.9) to 28.4% (95%CI 23.6-33.8) in the *hospitalized* cohort (Table 5 and Supplementary Table S3)[11]. Corresponding numbers for inhaled corticosteroid (ICS) use ranged from 5.3% (95%CI 3.4-8.27.7) to 44.8% (95%CI 38.9-50.9), and from 7.6% (95%CI 5.5-10.4) to 33.7% (95%CI 32.4-35.0) respectively (Figure 2). LABA use was more frequent than LAMA use. Macrolides were the most commonly prescribed antibiotics in the 30 days before index date in the US, French, and Italian databases while beta-lactam penicillins were more frequently prescribed in the South Korean, UK, Spanish and Dutch databases. Acetaminophen and NSAIDs were commonly prescribed to COPD patients, with use of both being more prevalent in the *hospitalized* cohort.

Outcomes

The proportion of hospitalized COVID-19 patients during the first wave of the pandemic requiring intensive services varied from 5.5% (95%CI 4.5-6.7) to 30.8% (95%CI 25.8-36.2) (median 17.7%). Amongst hospitalized COPD patients with COVID-19 during the first wave of the pandemic, the most common 30-day outcomes included ARDS (median 45.9%), ARFS (median 45.9%), cardiac arrhythmia (median 29.6%), heart failure (median 14.6%) and sepsis (median 16.9%). Outcomes

were more common in the hospitalised cohort than the diagnosed patients (Figure 3). (Table 6 and Supplementary Table S4)[11]. Among COPD patients with COVID-19 in the hospitalized cohort, 30-day mortality during the first wave of the pandemic ranged from 7.6% (95%CI 6.9-8.4) to 32.2% (95%CI 28.0-36.7) (medium 21.4%), whilst in the diagnosed cohort 30-day mortality ranged from 3.7% (95%CI 3.4-4.1) to 24.9% (95%CI 20.0-30.5) (median 15.6%) (Table 7).

Discussion

COPD prevalence among patients with COVID-19 from the first wave of the pandemic was 1.5- to 3-fold greater among those hospitalized than among those in the diagnosed cohort. Studies from China at the time reported the lowest observed COPD prevalence in COVID-19 patients with rates as low of 0.8%[3]. In contrast, COPD prevalence from the first wave appeared greater in European and US COVID-19 study populations. We similarly observed a low COPD prevalence among COVID-19 patients from the first wave in South Korea compared to other countries, which may reflect differences in the baseline prevalence of COPD in each country. However, it could also relate to differences in how health care systems responded to the pandemic, for example whether people with COPD were considered high risk and given advice on risk reduction measures and shielding. The differential response between countries during the first wave of the pandemic could therefore have influenced the prevalence measures.

COVID-19 patients with COPD from the first wave of the pandemic in both cohorts had a similar age distribution with the proportion of men being consistently higher in the hospitalized cohort. Increasing age, male gender and a history of cardiovascular disease are established risk factors for severe COVID-19[14–20]. We similarly observed a high prevalence of cardiometabolic comorbidities among COPD patients with COVID-19 from both cohorts. This included arrythmia, which may be related to atrial fibrillation being prevalent within patients with COPD.

Table 3. Prevalence of comorbidity in COPD patients in the diagnosed COVID-19 cohort.

|	CU-AMC HDC % (95%CI)	CUIMC % (95%CI)	HealthVerity % (95%CI)	IQVIA-OpenClaims % (95%CI)	OptumEhr % (95%CI)	STARR-OMOP % (95%CI)	VA-OMOP % (95%CI)	CPRD % (95%CI)	IPCI % (95%CI)	SIDIAP % (95%CI)	LPD-FRANCE % (95%CI)	LPDItaly % (95%CI)
Anxiety	16.6 (14.0-19.6)	11.4 (9.3-13.8)	15.7 (14.8-16.6)	15.9 (15.6-16.2)	18.6 (17.9-19.3)	21.1 (16.2-27.0)	33.5 (32.7-34.3)	<1.9	8.0 (5.0-12.6)	26.3 (25.6-27.0)	11.6 (9.4-14.3)	10.3 (7.5-14.0)
Atrial fibrillation	16.3 (13.7-19.2)	16.2 (13.8-19.0)	13.8 (13.0-14.7)	17.5 (17.2-17.8)	17.0 (16.3-17.7)	17.4 (12.9-23.0)	17.9 (17.2-18.6)	4.2 (2.4-7.4)	9.5 (6.2-14.4)	15.1 (14.5-15.7)	<0.8	12.4 (9.3-16.3)
Autoimmune condition	18.6 (15.9-21.7)	33.9 (30.6-37.3)	13.7 (12.9-14.6)	37.4 (37.0-37.8)	19.9 (19.2-20.6)	18.8 (14.2-24.5)	32.6 (31.8-33.4)	13.8 (10.1-18.5)	27.5 (21.8-34.1)	12.0 (11.5-12.5)	18.5 (15.7-21.7)	22.4 (18.3-27.1)
Bronchiectasis	<1.4	2.9 (1.9-4.3)	1.1 (0.9-1.4)	1.4 (1.3-1.5)	1.5 (1.3-1.7)	5.5 (3.2-9.4)	0.8 (0.7-1.0)	<1.9	<2.5	4.1 (3.8-4.4)	1.2 (0.6-2.4)	<1.5
Cancer*	28.2 (25.0-31.7)	37.4 (34.1-40.9)	12.9 (12.1-13.7)	30.3 (30.0-30.6)	29.5 (28.7-30.4)	47.2 (40.7-53.8)	37.3 (36.5-38.1)	14.9 (11.1-19.7)	28.0 (22.2-34.6)	19.0 (18.4-19.6)	9.6 (7.6-12.1)	27.1 (22.7-32.1)
Cardiac arrhythmia	28.5 (25.3-32.0)	24.4 (21.5-27.6)	18.9 (18.0-19.9)	25.6 (25.3-25.9)	28.0 (27.2-28.8)	28.0 (22.5-34.3)	25.6 (24.9-26.4)	4.6 (2.6-7.9)	11.0 (7.4-16.1)	26.4 (25.7-27.1)	5.7 (4.2-7.8)	19.1 (15.3-23.6)
Cerebrovascular disease	6.6 (5.0-8.7)	10.8 (8.8-13.2)	7.3 (6.7-8.0)	10.4 (10.2-10.6)	9.0 (8.5-9.6)	7.3 (4.5-11.5)	8.5 (8.0-9.0)	4.6 (2.6-7.9)	6.5 (3.8-10.8)	4.0 (3.7-4.3)	4.0 (2.7-5.8)	10.9 (8.0-14.7)
Chronic Liver Disease	3.0 (2.0-4.6)	3.6 (2.5-5.2)	2.3 (2.0-2.7)	2.5 (2.4-2.6)	3.2 (2.9-3.5)	9.6 (6.4-14.2)	7.2 (6.8-7.7)	-	-	2.2 (2.0-2.4)	<0.8	3.5 (2.0-6.0)
CKD*	29.8 (26.5-33.3)	39.5 (36.1-43.0)	21.6 (20.6-22.6)	40.0 (39.6-40.4)	36.0 (35.1-36.9)	33.9 (27.9-40.4)	36.3 (35.5-37.1)	26.1 (21.1-31.8)	23.0 (17.7-29.3)	23.0 (22.4-23.7)	3.5 (2.3-5.2)	11.2 (8.3-15.0)
Depression	15.6 (13.1-18.5)	14.3 (12.0-17.0)	10.7 (10.0-11.5)	12.8 (12.6-13.1)	14.9 (14.2-15.6)	19.3 (14.6-25.0)	21.2 (20.5-21.9)	6.9 (4.4-10.6)	3.0 (1.4-6.4)	18.2 (17.6-18.8)	11.9 (9.6-14.6)	8.8 (6.2-12.3)
Heart disease*	63.2 (59.5-66.7)	80.0 (77.0-82.7)	47.4 (46.2-48.6)	81.4 (81.1-81.7)	67.7 (66.8-68.6)	65.6 (59.1-71.6)	77.2 (76.5-77.9)	44.8 (38.9-50.9)	49.5 (42.6-56.4)	43.7 (42.9-44.5)	18.7 (15.9-21.9)	46.5 (41.3-51.8)
Heart failure	18.2 (15.5-21.2)	22.6 (19.8-25.7)	19.9 (19.0-20.9)	26.8 (26.5-27.1)	21.2 (20.4-22.0)	19.7 (15.0-25.5)	20.4 (19.7-21.1)	4.6 (2.6-7.9)	8.5 (5.4-13.2)	12.3 (11.8-12.8)	2.0 (1.2-3.4)	5.3 (3.4-8.2)
Hypertension*	72.4 (69.0-75.6)	86.9 (84.3-89.1)	58.8 (57.6-60.0)	90.0 (89.8-90.2)	79.1 (78.3-79.8)	75.2 (69.1-80.5)	89.1 (88.5-89.6)	30.7 (25.4-36.5)	49.5 (42.6-56.4)	39.0 (38.2-39.8)	43.1 (39.3-46.9)	66.8 (61.6-71.6)
Interstitial lung disease	1.6 (0.9-2.8)	2.5 (1.6-3.9)	2.1 (1.8-2.5)	2.6 (2.5-2.7)	2.4 (2.1-2.7)	4.1 (2.2-7.6)	1.6 (1.4-1.8)	<1.9	-	0.5 (0.4-0.6)	<0.8	<1.5
Myocardial infarction	12.6 (10.3-15.3)	8.6 (6.8-10.8)	4.6 (4.1-5.1)	6.3 (6.1-6.5)	10.7 (10.1-11.3)	10.6 (7.2-15.4)	6.7 (6.3-7.1)	<1.9	6.0 (3.5-10.2)	2.7 (2.5-3.0)	<0.8	3.5 (2.0-6.0)
Obesity	47.5 (43.8-51.2)	57.3 (53.8-60.8)	20.1 (19.1-21.1)	35.8 (35.4-36.2)	60.7 (59.8-61.6)	49.1 (42.5-55.7)	55.2 (54.3-56.1)	50.6 (44.6-56.6)	33.0 (26.9-39.8)	52.1 (51.3-52.9)	14.4 (11.9-17.3)	25.6 (21.2-30.5)
Sleep apnea	21.5 (18.6-24.7)	9.6 (7.7-11.9)	10.9 (10.2-11.7)	9.8 (9.6-10.0)	14.4 (13.8-15.1)	23.4 (18.3-29.4)	30.6 (29.8-31.4)	<1.9	<2.5	6.0 (5.6-6.4)	1.2 (0.6-2.4)	2.1 (1.0-4.2)
T2DM*	34.5 (31.0-38.1)	50.4 (46.9-53.9)	35.9 (34.7-37.1)	57.6 (57.2-58.0)	40.6 (39.7-41.5)	40.8 (34.5-47.4)	54.5 (53.6-55.4)	24.9 (20.0-30.5)	34.0 (27.8-40.8)	21.6 (21.0-22.2)	18.2 (15.4-21.4)	20.6 (16.6-25.2)

*Prevalent conditions measured any time in the past, others within the previous year. Grey =US database. Yellow=European database. Pink=South Korean database. CKD=Chronic kidney disease. T2DM=type 2 diabetes mellitus.

Table 4. Prevalence of comorbidity in hospitalized COVID-19 patients with COPD.

	CU-AMC HDC % (95%CI)	CUIMC % (95%CI)	HealthVerity % (95%CI)	IQVIA-OpenClaims % (95%CI)	OptumEhr % (95%CI)	VA-OMOP % (95%CI)	HIRA % (95%CI)	SIDIAP % (95%CI)
Anxiety	17.1 (13.3-21.8)	10.1 (7.6-13.2)	21.4 (19.5-23.4)	15.3 (14.9-15.7)	17.0 (15.9-18.1)	32.3 (31.0-33.7)	20.0 (14.3-27.3)	23.3 (22.1-24.5)
Atrial fibrillation	19.1 (15.0-23.9)	17.0 (13.8-20.8)	23.7 (21.7-25.8)	20.5 (20.0-21.0)	20.0 (18.9-21.2)	22.3 (21.1-23.5)	<3.4	16.7 (15.7-17.8)
Autoimmune condition	16.7 (12.9-21.3)	36.7 (32.4-41.3)	17.3 (15.6-19.2)	40.0 (39.5-40.6)	19.1 (18.0-20.3)	36.9 (35.5-38.3)	20.7 (14.9-28.0)	12.7 (11.8-13.7)
Bronchiectasis	<3.3	3.4 (2.1-5.5)	1.6 (1.1-2.3)	1.7 (1.6-1.8)	1.5 (1.2-1.9)	0.8 (0.6-1.1)	<3.4	5.0 (4.4-5.7)
Cancer*	26.4 (21.7-31.7)	35.3 (31.0-39.8)	15.1 (13.5-16.9)	32.5 (32.0-33.0)	28.8 (27.5-30.1)	40.3 (38.9-41.7)	20.0 (14.3-27.3)	22.4 (21.2-23.6)
Cardiac arrhythmia	31.8 (26.8-37.3)	25.5 (21.7-29.7)	31.6 (29.4-33.9)	31.1 (30.6-31.6)	33.3 (31.9-34.7)	31.9 (30.6-33.3)	9.7 (5.9-15.6)	29.6 (28.3-30.9)
Cerebrovascular disease	7.4 (4.9-10.9)	11.4 (8.8-14.7)	11.0 (9.6-12.6)	12.4 (12.0-12.8)	9.2 (8.4-10.1)	9.8 (9.0-10.7)	13.1 (8.6-19.6)	3.8 (3.3-4.4)
Chronic Liver Disease	4.3 (2.5-7.2)	4.7 (3.1-7.1)	4.1 (3.2-5.2)	3.1 (2.9-3.3)	3.4 (2.9-4.0)	9.1 (8.3-10.0)	10.3 (6.3-16.3)	1.9 (1.6-2.3)
CKD*	34.4 (29.2-40.0)	47.7 (43.1-52.3)	36.7 (34.4-39.1)	47.7 (47.1-48.3)	40.8 (39.4-42.2)	47.3 (45.9-48.7)	17.2 (11.9-24.2)	25.2 (24.0-26.4)
Depression	18.4 (14.4-23.2)	17.0 (13.8-20.8)	14.6 (13.0-16.4)	12.7 (12.3-13.1)	14.1 (13.1-15.2)	19.7 (18.6-20.9)	6.9 (3.8-12.2)	14.8 (13.8-15.8)
Heart disease*	66.9 (61.4-72.0)	83.4 (79.7-86.6)	66.3 (64.0-68.5)	86.1 (85.7-86.5)	70.7 (69.3-72.0)	83.0 (81.9-84.1)	38.6 (31.1-46.7)	49.6 (48.2-51.0)
Heart failure	22.7 (18.3-27.8)	27.1 (23.2-31.4)	35.8 (33.5-38.1)	33.2 (32.7-33.7)	26.4 (25.1-27.7)	28.4 (27.1-29.7)	15.2 (10.3-21.9)	14.0 (13.1-15.0)
Hypertension*	75.9 (70.7-80.4)	90.8 (87.8-93.1)	75.3 (73.2-77.3)	93.0 (92.7-93.3)	79.9 (78.7-81.0)	93.0 (92.2-93.7)	55.9 (47.8-63.7)	41.1 (39.7-42.5)
Interstitial lung disease	<3.3	3.1 (1.8-5.1)	3.5 (2.7-4.5)	4.6 (4.4-4.8)	3.2 (2.7-3.8)	2.1 (1.7-2.6)	<3.4	0.8 (0.6-1.1)
Myocardial infarction	17.1 (13.3-21.8)	11.9 (9.2-15.2)	8.8 (7.5-10.3)	9.1 (8.8-9.4)	14.3 (13.3-15.3)	9.8 (9.0-10.7)	<3.4	3.6 (3.1-4.2)
Obesity	50.5 (44.9-56.1)	58.2 (53.6-62.7)	25.7 (23.6-27.9)	38.8 (38.3-39.3)	58.3 (56.9-59.7)	55.0 (53.6-56.4)	-	57.7 (56.3-59.1)
Sleep apnea	22.1 (17.8-27.1)	9.2 (6.9-12.2)	13.5 (11.9-15.2)	11.6 (11.2-12.0)	13.9 (12.9-14.9)	29.7 (28.4-31.0)	-	8.3 (7.6-9.1)
T2DM*	40.5 (35.1-46.2)	58.8 (54.2-63.3)	48.6 (46.2-51.0)	63.0 (62.5-63.5)	44.6 (43.1-46.1)	61.6 (60.2-63.0)	57.2 (49.1-65.0)	25.6 (24.4-26.9)

*Prevalent conditions measured any time in the past, others within the previous year. Grey =US database. Yellow=European database. Pink=South Korean database. CKD=Chronic kidney disease. T2DM=type 2 diabetes mellitus.
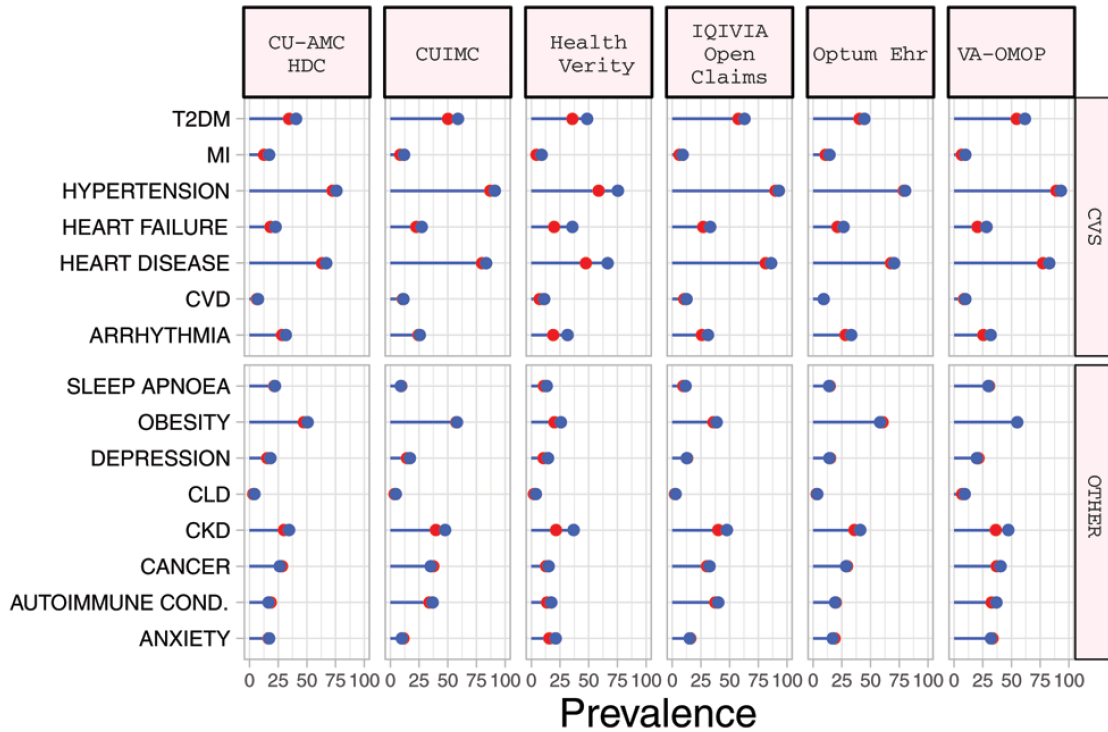
Figure 1. Prevalence of comorbidities among COPD patients with COVID-19 who have been diagnosed (red) and hospitalized (blue). *Databases contributing patients to both the diagnosed and hospitalized cohorts. T2DM=Type 2 diabetes mellitus. MI=myocardial infarction. CVD=Cerebrovascular disease. CLD=chronic liver disease. CKD=chronic kidney disease. Autoimmune Cond.=autoimmune conditions. CVS=Cardiovascular.

Although exacerbation at presentation was recorded more commonly among hospitalized patients, overall exacerbation prevalence among COVID-19 patients with COPD during the first wave of the pandemic was relatively low. Further studies are required to formally assess to what degree typical exacerbations of COPD are a presenting feature of COVID-19 in people with COPD.

There have been safety concerns over the role of ICS with reports of worse COVID-19 outcomes associated with ICS use[21,22]. Whilst our study was not designed to formally assess this, we saw no large differences in ICS use between the cohorts as might be expected if use was associated with a large risk. Indeed, early clinical trials suggest that use of inhaled budesonide use may be beneficial[23]. The increased use of acetaminophen, opioids and NSAIDs among hospitalized patients also suggests greater symptomatic illness. Whilst similar safety concerns with NSAID use also emerged early in the pandemic, more recent studies have not found them to be harmful[24,25].

The most common 30-day outcomes were ARDS, ARFS, arrhythmia, sepsis and heart failure suggesting that a multi-organ approach was required for COVID-19 clinical management during the first wave of the pandemic. As

expected, hospitalized COPD patients had a higher prevalence of poor health outcomes. However, it is useful to understand this risk among a cohort that includes milder cases at an earlier stage of the illness despite having similar levels of baseline comorbidity.

Strength and limitations

A strength of this study is the federated analysis allowing large numbers of patients to be characterized between countries, which overcomes some of the limitations of smaller single centre studies and inevitable heterogeneity that can occur by applying different study designs and methods of analysis. Furthermore, information on a large number of additional patient characteristics relating to conditions and treatment are also available online beyond what has been presented here. The study has several limitations, however. First, the study is dependent upon the quality and extent of data captured by each database that could underestimate the prevalence of some characteristics. For conditions and treatments, the assumption was made that patients did not have the health condition or treatment if it were not captured in the database. A specific example of this is prior systemic corticosteroid use that ranged from 7.5% to 28.4% in the COVID-19 hospitalized cohort and 5.1% to 26.4% in the diagnosed cohort. The prevalence of systemic corticosteroid use was slightly higher than the prevalence of an exacerbation

Table 5. Prevalence of treatments in patients with COPD in the 30 days before COVID-19 hospitalization.

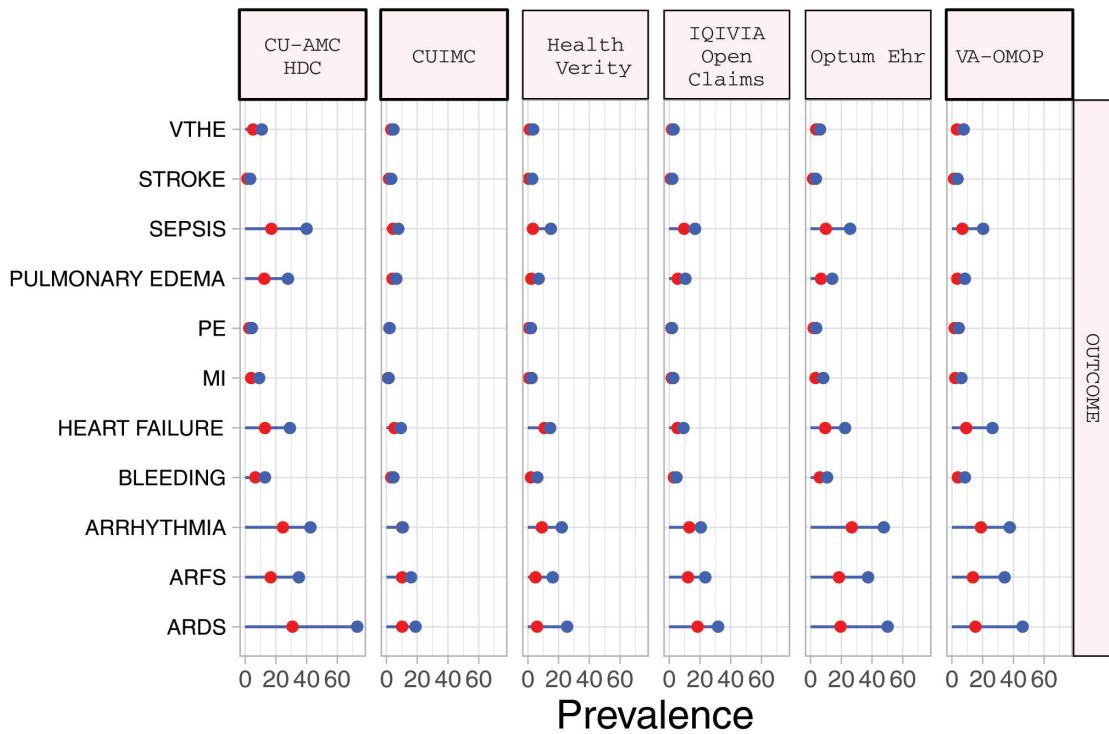|	CU-AMC HDC % (95%CI)	CUIMC % (95%CI)	HealthVerity % (95%CI)	IQVIA-OpenClaims % (95%CI)	OptumEhr % (95%CI)	VA-OMOP % (95%CI)	HIRA % (95%CI)	SIDIAP % (95%CI)
Systemic corticosteroids	28.4 (23.6-33.8)	13.4 (10.5-16.9)	7.5 (6.3-8.9)	12.7 (12.3-13.1)	16.1 (15.1-17.2)	16.1 (15.1-17.2)	23.4 (17.2-30.9)	17.9 (16.9-19.0)
Inhaled corticosteroid	25.8 (21.2-31.0)	7.6 (5.5-10.4)	9.6 (8.3-11.1)	14.0 (13.6-14.4)	14.4 (13.4-15.5)	26.5 (25.2-27.8)	<6.8	33.7 (32.4-35.0)
SABA	33.4 (28.3-38.9)	13.0 (10.2-16.4)	9.5 (8.2-11.0)	14.4 (14.0-14.8)	20.6 (19.4-21.8)	26.9 (25.6-28.2)	<3.4	14.3 (13.3-15.3)
SAMA	17.1 (13.3-21.8)	6.0 (4.2-8.6)	4.1 (3.2-5.2)	4.9 (4.7-5.1)	11.1 (10.2-12.0)	10.8 (9.9-11.7)	<3.4	22.4 (21.2-23.6)
LABA	19.7 (15.6-24.6)	5.1 (3.4-7.6)	7.1 (6.0-8.4)	10.6 (10.3-10.9)	10.9 (10.0-11.8)	18.4 (17.3-19.5)	4.1 (1.9-8.7)	30.4 (29.1-31.7)
LAMA	7.4 (4.9-10.9)	1.3 (0.6-2.8)	3.8 (3.0-4.8)	6.4 (6.1-6.7)	7.2 (6.5-8.0)	13.8 (12.8-14.8)	<3.4	19.3 (18.2-20.4)
Mucolytics	<3.3	<1.1	0.8 (0.5-1.4)	0.2 (0.2-0.3)	1.3 (1.0-1.7)	1.5 (1.2-1.9)	71.0 (63.1-77.8)	12.4 (11.5-13.4)
Beta-lactam penicillins	7.0 (4.6-10.5)	4.7 (3.1-7.1)	3.3 (2.5-4.3)	4.0 (3.8-4.2)	5.9 (5.2-6.6)	5.9 (5.3-6.6)	13.1 (8.6-19.6)	11.7 (10.8-12.6)
Fluoroquinolones	4.7 (2.8-7.7)	4.7 (3.1-7.1)	2.8 (2.1-3.7)	4.3 (4.1-4.5)	3.7 (3.2-4.3)	2.8 (2.4-3.3)	9.7 (5.9-15.6)	10.0 (9.2-10.9)
Macrolides	11.4 (8.3-15.5)	9.4 (7.0-12.5)	6.1 (5.0-7.4)	8.9 (8.6-9.2)	9.1 (8.3-10.0)	7.5 (6.8-8.3)	9.7 (5.9-15.6)	10.6 (9.8-11.5)
Acetaminophen	34.4 (29.2-40.0)	19.5 (16.1-23.4)	3.9 (3.1-5.0)	8.4 (8.1-8.7)	24.2 (23.0-25.5)	30.3 (29.0-31.6)	45.5 (37.6-53.6)	60.4 (59.0-61.8)
NSAIDs	54.2 (48.5-59.8)	7.4 (5.3-10.2)	3.5 (2.7-4.5)	19.7 (19.3-20.2)	7.8 (7.0-8.6)	48.8 (47.4-50.2)	27.6 (21.0-35.4)	9.2 (8.4-10.1)
Opioids	28.8 (24.0-34.2)	8.3 (6.1-11.2)	5.3 (4.3-6.5)	9.0 (8.7-9.3)	13.7 (12.7-14.7)	12.5 (11.6-13.5)	48.3 (40.3-56.4)	17.6 (16.6-18.7)
Oxygen	7.7 (5.2-11.3)	<1.1	2.8 (2.1-3.7)	2.4 (2.2-2.6)	2.5 (2.1-3.0)	1.4 (1.1-1.8)	4.8 (2.3-9.6)	<0.1

Grey =US database. Pink=South Korean database. Yellow=European database. SABA=short-acting beta-agonist. SAMA=short-acting muscarinic-antagonist. LABA=long-acting beta-agonist. LAMA=Long-acting muscarinic-antagonist. NSAIDs=non-steroidal anti-inflammatory drugs.
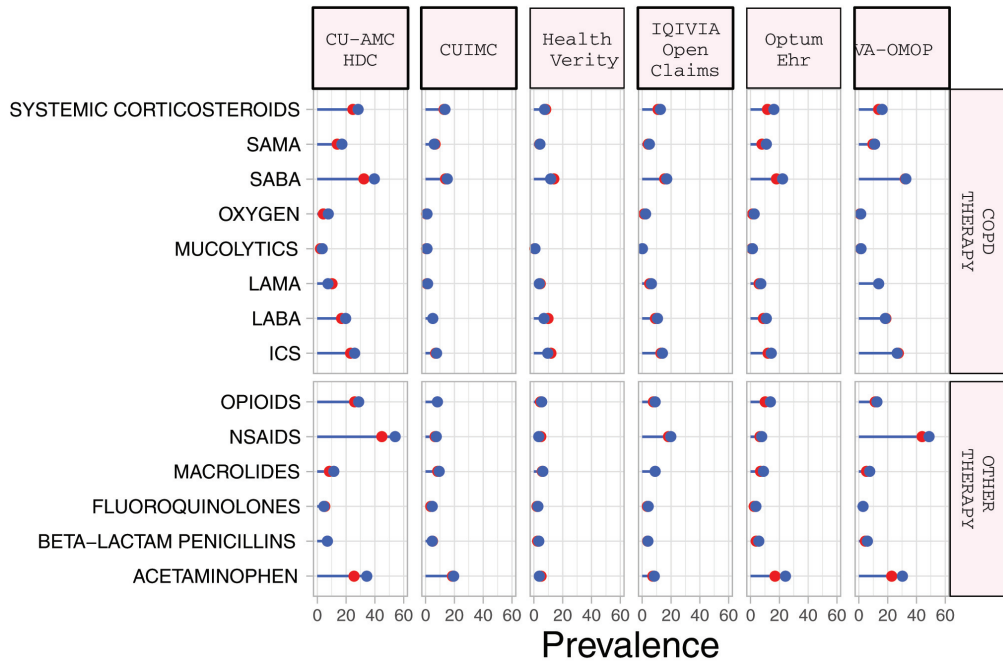
Figure 2. Prevalence of treatments among COPD patients with COVID-19 who have been diagnosed (red) and hospitalized (blue). *Databases contributing patients to both the diagnosed and hospitalized cohorts. SAMA=short-acting muscarinic antagonist. SABA=short-acting beta2-agonist. LAMA=Long-acting muscarinic antagonist. LABA=Long-acting beta2-agonist. ICS=inhaled corticosteroids. NSAIDs=non-steroidal anti-inflammatory drugs.

Figure 3. Prevalence of outcomes among COPD patients with COVID-19 who have been diagnosed (red) and hospitalized (blue). *Databases contributing patients to both the diagnosed and hospitalized cohorts. VTHE=venous thromboembolism. PE=pulmonary edema. MI=myocardial infarction. ARFS=Acute renal failure syndrome. ARDS=Acute respiratory distress syndrome.

Table 6. Prevalence of outcomes in hospitalized COVID-19 patients with COPD.

	CU-AMC HDC % (95%CI)	CUIMC % (95%CI)	HealthVerity % (95%CI)	IQVIA-OpenClaims % (95%CI)	OptumEhr % (95%CI)	VA-OMOP % (95%CI)	HIRA % (95%CI)
Intensive services	30.8 (25.8-36.2)	NA	5.5 (4.5-6.7)	9.9 (9.6-10.2)	17.7 (16.6-18.8)	18.4 (17.3-19.5)	9.7 (5.9-15.6)
ARDS	72.9 (67.6-77.6)	19.0 (15.6-22.9)	25.6 (23.5-27.8)	31.7 (31.2-32.2)	50.2 (48.7-51.7)	45.9 (44.5-47.3)	<3.4
ARFS	35.1 (29.9-40.7)	16.1 (13.0-19.8)	16.3 (14.6-18.2)	23.5 (23.0-24.0)	37.4 (36.0-38.8)	34.4 (33.0-35.8)	<3.4
Cardiac arrhythmia	48.2 (42.6-53.8)	14.8 (11.8-18.4)	15.5 (13.8-17.3)	14.9 (14.5-15.3)	37.4 (36.0-38.8)	37.8 (36.4-39.2)	7.6 (4.3-13.1)
Heart failure	29.1 (24.2-34.5)	9.4 (7.0-12.5)	14.6 (13.0-16.4)	9.3 (9.0-9.6)	22.4 (21.2-23.6)	26.4 (25.1-27.7)	4.8 (2.3-9.6)
Pulmonary edema	27.8 (23.0-33.1)	6.5 (4.6-9.2)	7.0 (5.9-8.3)	10.5 (10.2-10.8)	14.2 (13.2-15.2)	8.3 (7.5-9.1)	4.1 (1.9-8.7)
Myocardial infarction	9.0 (6.3-12.8)	1.3 (0.6-2.8)	2.4 (1.8-3.3)	2.6 (2.4-2.8)	8.3 (7.5-9.1)	6.1 (5.4-6.8)	<3.4
Sepsis	40.1 (34.7-45.8)	7.6 (5.5-10.4)	14.9 (13.3-16.7)	16.9 (16.5-17.3)	25.8 (24.5-27.1)	20.3 (19.2-21.5)	5.5 (2.8-10.5)
Bleeding	13.0 (9.7-17.3)	4.5 (2.9-6.8)	6.2 (5.1-7.5)	4.8 (4.6-5.0)	10.9 (10.0-11.8)	8.3 (7.5-9.1)	6.2 (3.3-11.4)
VThE	10.7 (7.7-14.7)	4.5 (2.9-6.8)	3.5 (2.7-4.5)	2.8 (2.6-3.0)	6.3 (5.6-7.0)	7.6 (6.9-8.4)	-
PE	4.3 (2.5-7.2)	2.0 (1.0-3.8)	2.0 (1.4-2.8)	1.9 (1.8-2.1)	3.8 (3.3-4.4)	4.5 (3.9-5.1)	-
Stroke	3.3 (1.8-6.0)	3.1 (1.8-5.1)	2.9 (2.2-3.8)	2.0 (1.8-2.2)	3.4 (2.9-4.0)	3.6 (3.1-4.2)	<3.4

Grey =US database. Pink=South Korean database. Yellow=European database. SABA=short-acting beta-agonist. ARDS=acute respiratory distress syndrome. ARFS=acute renal failure syndrome. VThe=venous thromboembolic disease. PE=pulmonary embolism.

Table 7. Death within 30 days of COVID-19 diagnosis or hospitalization.

Cohort	CU-AMC % (95%CI)	CUIMC % (95%CI)	Optum EHR % (95%CI)	VA-OMOP % (95%CI)	HIRA % (95%CI)	CPRD % (95%CI)	IPCI % (95%CI)	SIDIAP % (95%CI)
Diagnosed COVID-19	11.6 (9.4-14.2)	18.8 (16.2-21.7)	3.7 (3.4-4.1)	8.3 (7.8-8.8)	-	24.9 (20.0-30.5)	23.5 (18.2-29.8)	15.6 (15.0-16.2)
Hospitalized COVID-19	25.8 (21.2-31.0)	32.2 (28.0-36.7)	7.6 (6.9-8.4)	17.6 (16.5-18.7)	16.6 (11.4-23.5)	-	-	21.4 (20.3-22.6)

Grey =US database. Pink=South Korean database. Yellow=European database

diagnosis. Whilst this suggests that some underestimation in exacerbation recording may have occurred, other indications for systemic corticosteroid in patients with COPD exist that could also explain the higher systemic corticosteroids use. Second, despite using a standardized data structure and method of analysis, heterogeneity between databases was still observed and it was not possible to determine whether this related to differences in clinical care compared to differences in the type of database. In this regard databases were a mixture between electronic health records and administrative claims capturing

Table 8. Database information.

ID	Name	Description	Terms of Use	Terms and conditions for the access
CPRD	Clinical Practice Research Datalink	The Clinical Practice Research Datalink (CPRD) is a governmental, not-for-profit research service, jointly funded by the NHS National Institute for Health Research (NIHR) and the Medicines and Healthcare products Regulatory Agency (MHRA), a part of the Department of Health, United Kingdom (UK). CPRD consists of data collected from UK primary care for all ages. This includes conditions, observations, measurements, and procedures that the general practitioner is made aware of in addition to any prescriptions as prescribed by the general practitioner. In addition to primary care, there are also linked secondary care records for a small number of people. The major data elements contained within this database are outpatient prescriptions given by the general practitioner (coded with Multilex codes) and outpatient clinical, referral, immunization or test events that the general practitioner knows about (coded in Read or ICD10 or LOINC codes). The database also contains the patients' year of births and any date of deaths.	1) Please allow for 2 weeks lead time for all publications using these results to go through internal review process. 2) The results are considered fit-for-use and were generated for this specific protocol. Derivations from the intent of this protocol are not validated by our institution.3) Our institution expects all authors to comply with all applicable personal data protection rules (such as the European Data Protection Regulation 2016/679, of April 27, 2016). 4) Our institution reserves the right to request to omit our results from a drafted publication if the findings could inflict reputational or institutional harm.	https://www.cprd.com/
CU-AMC HDC	U of Colorado Anschuz Medical Campus Health Data Compass (CU-AMC HDC)	Health Data Compass (HDC) is a multi-institutional data warehouse. HDC contains inpatient and outpatient electronic medical data including patient, encounter, diagnosis, procedures, medications, laboratory results from two electronic medical record systems (UCHealth and Children's Hospital of Colorado), state-level all-payers claims data, and the Colorado death registry. Acknowledgement statement: Supported by the Health Data Compass Data Warehouse project (healthdatacompass.org).	1) Please allow for 2 weeks lead time for all publications using these results to go through internal review process. 2) When using our results, you must always use this specific name when referring to our database. No other labels should be used in presenting our results. 3) The results are considered fit-for-use and were generated for this specific protocol. Derivations from the intent of this protocol are not validated by our institution. 4) Our institution reserves the right to request to omit our results from a drafted publication if the findings could inflict reputational or institutional harm.	https://www.healthdatacompass.org/
CUIMC	Columbia University Irving Medical Center	The clinical data warehouse of NewYork-Presbyterian Hospital/Columbia University Irving Medical Center, New York, NY, based on its current and previous electronic health record systems, with data spanning over 30 years and including over 6 million patients	Our institution reserves the right to request to omit our results from a drafted publication if the findings could inflict reputational or institutional harm. The results are specific to a study and should not be reused in other studies without review from our institution. For consistency, the Columbia database should be referred to as CUIMC.	https://www.cuimc.columbia.edu/about-us/explore-cuimc/contact-cuimc gh13@columbia.edu

ID	Name	Description	Terms of Use	Terms and conditions for the access
HealthVerity	HealthVerity	This HealthVerity derived data set contains de-identified patient information with an antibody and/or diagnostic test for COVID-19 linked to all available Medical Claims and Pharmacy Data from select private data providers participating in the HealthVerity marketplace.	1) Please allow for 2 weeks lead time for all publications using these results to go through internal review process. 2) The results are considered fit-for-use and were generated for this specific protocol. Derivations from the intent of this protocol are not validated by our institution.3) Our institution expects all authors to comply with all applicable personal data protection rules (such as the European Data Protection Regulation 2016/679, of April 27, 2016). 4) Our institution reserves the right to request to omit our results from a drafted publication if the findings could inflict reputational or institutional harm.	https://healthverity.com/license-healthcare-data-healthverity-marketplace/
HIRA	Health Insurance Review & Assessment Service	National claim data from a single insurance service from South Korea. It contains the observational medical records (including both inpatient and outpatient) of a patient while they are qualified to get the national medical insurance.	Review & Assessment service and the Ministry of Health and Welfare jointly release nationwide COVID-19 patient's de-identified data and do cooperation research together with the most prestigious academies and government organizations. Because raw data are owned in the organization so that cohort data are managed by result value sharing method with implementing analysis code without personal information leakage.	https://www.hira.or.kr/eng/main.do
IPCI	Integrated Primary Care Information	The Integrated Primary Care Information (IPCI) database is collected from EHR records of patients registered with 391 GPs throughout the Netherlands. The database contains records from approximately 2.6 million patients out of a Dutch population of 17M (8.2%) starting in 1996.	1) Results can only be used in the intent of a study that is approved by our governance board. Additional derived studies from large-scale analysis therefore require approval. 2) Inclusion of IPCI researchers is required for these derived studies to provide the proper context and interpretation of these results.	https://www.ipci.nl/
IQVIA-OpenClaims	IQVIA Open Claims	A United States database of open, pre-adjudicated claims from January 2013 to May 2020. Data are reported at anonymized patient level collected from office-based physicians and specialists via office management software and clearinghouse switch sources for the purpose of reimbursement. A subset of medical claims data have adjudicated claims.	Inclusion of IQVIA researchers is required in manuscripts using IQVIA data.	https://www.iqvia.com/solutions/real-world-evidence/real-world-data-and-insights
LPD-FRANCE	LPD FRANCE	LPD France is a computerised network of physicians including GPs who contribute to a centralised database of anonymised patient EMR. Currently, >1200 GPs from 400 practices are contributing to the database covering 7.8M patients in France. The database covers a time period from 1994 through the present. Observation time is defined by the first and last consultation dates. Drug information is derived from GP prescriptions. Drugs obtained over the counter by the patient outside the prescription system are not reported.	Inclusion of IQVIA researchers is required in manuscripts using IQVIA data.	https://www.iqvia.com/solutions/real-world-evidence/real-world-data-and-insights

ID	Name	Description	Terms of Use	Terms and conditions for the access
LPDItaly	IQVIA LPD Italy	LPD Italy is comprised of anonymised patient records collected from software used by GPs during an office visit to document patients' clinical records. Data coverage includes over 2M patient records with at least one visit and 119.5M prescription orders across 900 GP practices. Dates of service include from 2004 through present. Observation time is defined by the first and last consultation dates. Drugs are captured as prescription records with product, quantity, dosing directions, strength, indication and date of consultation.	Inclusion of IQVIA researchers is required in manuscripts using IQVIA data.	https://www.iqvia.com/solutions/real-world-evidence/real-world-data-and-insights
OptumEhr	Optum© de-identified Electronic Health Record Dataset	Optum© de-identified Electronic Health Record Dataset is derived from dozens of healthcare provider organizations in the United States (that include more than 700 hospitals and 7,000 Clinics treating more than 103 million patients) receiving care in the United States. The medical record data includes clinical information, inclusive of prescriptions as prescribed and administered, lab results, vital signs, body measurements, diagnoses, procedures, and information derived from clinical Notes using Natural Language Processing (NLP).	1) Please allow for 2 weeks lead time for all publications using these results to go through internal review process. 2) The results are considered fit-for-use and were generated for this specific protocol. Derivations from the intent of this protocol are not validated by our institution.3) Our institution expects all authors to comply with all applicable personal data protection rules (such as the European Data Protection Regulation 2016/679, of April 27, 2016). 4) Our institution reserves the right to request to omit our results from a drafted publication if the findings could inflict reputational or institutional harm.	https://www.optum.com/business/solutions/life-sciences/real-world-data/ehr-data.html ?
SIDIAP	Information System for Research in Primary Care (SIDIAP)	The Information System for Research in Primary Care (SIDIAP; www.sidiap.org) is a primary care records database that covers approximatly 80% of the population of Catalonia, North-East Spain. Healthcare is universal and tax-payer funded in the region, and primary care physicians are gatekeepers for all care and responsible for repeat prescriptions.	1) When using our results, you must always use this specific name and this citation when referring to our database. No other labels should be used in presenting our results: Information System for Research in Primary Care (SIDIAP). 2) The results are considered fit-for-use and were generated for this specific protocol. Derivations from the intent of this protocol are not validated by our institution. 3) Our institution expects all authors to comply with all applicable personal data protection rules (such as the European Data Protection Regulation 2016/679, of April 27, 2016). 4) Our institution reserves the right to request to omit our results from a drafted publication if the findings could inflict reputational or institutional harm.	https://www.sidiap.org/index.php/en
STARR-OMOP	STARR-OMOP	STAnford medicine Research data Repository, a clinical data warehouse containing live Epic data from Stanford Health Care, the Stanford Children's Hospital, the University Healthcare Alliance and Packard Children's Health Alliance clinics and other auxiliary data from Hospital applications such as radiology PACS. STARR platform is developed and operated by Stanford Medicine Research IT team and is made possible by Stanford School of Medicine Research Office. https://arxiv.org/abs/2003.10534	1) When using our results, you must always use this specific name and this citation when referring to our database. No other labels should be used in presenting our results. 2) The results are considered fit-for-use and were generated for this specific protocol. Derivations from the intent of this protocol are not validated by our institution. 3) Our institution expects all authors to comply with all applicable personal data protection rules 4) Our institution reserves the right to request to omit our results from a drafted publication if the findings could inflict reputational or institutional harm.	https://med.stanford.edu/starr-omop.html

ID	Name	Description	Terms of Use	Terms and conditions for the access
VA-OMOP	Department of Veterans Affairs	VA OMOP data reflects the national Department of Veterans Affairs health care system, which is the largest integrated provider of medical and mental health services in the United States. Care is provided at 170 VA Medical Centers and 1,063 outpatient sites serving more than 9 million enrolled Veterans each year.	1) Please allow for 2 weeks lead time for all publications using these results to go through internal review process. 2) When using our results, you must always use this specific name and this citation when referring to our database. No other labels should be used in presenting our results. We would like to have the name and description of the database standardized.3) The results are considered fit-for-use and were generated for this specific protocol. Derivations from the intent of this protocol are not validated by our institution. 4) Our institution expects all authors to comply with all applicable personal data protection rules (such as the European Data Protection Regulation 2016/679, of April 27, 2016). 5) Our institution reserves the right to request to omit our results from a drafted publication if the findings could inflict reputational or institutional harm. In line with item 3, we would like to make sure that data created and validated with one use case in mind still fits for other use cases. We do not anticipate examples where data would produce such harm (outside of some data quality issue / need for retraction), but if that were the case, we would need to alert VA leadership and ensure the wording was objective. 6) We need to acknowledge our funding using language like: "This work was supported using resources and facilities of the Department of Veterans Affairs (VA) Informatics and Computing Infrastructure (VINCI), VA HSR RES 13–457." This can be shortened and arranged in the acknowledgement section with others. 7) We need a disclaimer such as: "The views expressed are those of the authors and do not necessarily represent the views or policy of the Department of Veterans Affairs or the United States Government." This can be shorted and combined with other institutions' disclaimers.	https://www.data.va.gov/

data from different health care settings. The definition of our hospitalized cohort meant that patients with hospital-acquired COVID-19 may have been included. These patients may have had a different disease course compared with community-acquired COVID-19 who were hospitalised due to developing severe COVID-19. We excluded patients with an asthma diagnosis prior to their index date. Despite this it is possible that some misclassification of asthma patients could still have occurred in older patients who were defined as having COPD using medications and age, if they were not previously coded as having asthma. In this regard, patients with asthma and COVID-19 may have a lower prevalence of comorbidities and differences in survival[26]. Our study analysed data specifically from the first wave of the COVID-19 pandemic. Since then, several COVID-19 variants have emerged with different severities and results may not be generalisable. Lastly, our study was descriptive in nature with the aim of being hypothesis generating and informing healthcare resource use. It was not designed to examine causal associations or to establish causal inference in relation to differences in COVID-19 outcomes that may result from differences in patient characteristics such as comorbidity that would require specialized study designs and regression analyses. However, this type of evidence has still contributed to support the understanding COVID-19 in patients in many settings and could be useful as hypothesis generating for future studies in patients with COPD[27].

Conclusions

COVID-19 patients with COPD in the first wave of the pandemic were a vulnerable group with a high prevalence of other risk factors for severe COVID-19. No large differences in ICS use were seen between COPD patients with milder and more severe COVID-19 during the first wave of the pandemic although further studies are required to confirm or refute this. COPD patients experienced a high morbidity and mortality from COVID-19 during the first wave of the pandemic suggesting a multi-organ approach to clinical management was required.

Data availability

Underlying data

Raw data from each database cannot be shared due to data privacy and governance requirements but raw data could be accessed according to the terms and conditions of each data source. The data source information including the terms and conditions for data access can be found in Table 8. Analyses were performed locally in compliance with all applicable data privacy laws. All aggregate data has been made freely available for public inquiry (https://data.ohdsi.org/Covid19CharacterizationCharybdis/).

All analytic code and result sets have been made available (https://github.com/ohdsi-studies/Covid19Characterization-Charybdis).

Archived analysis code as at time of publication: https://doi.org/10.5281/zenodo.5779264[28]. Code is available under the terms of the Apache License 2.0.

Extended data

Zenodo: Characteristics and outcomes of COVID-19 patients with COPD from the United States, South Korea, and Europe - Supplementary Materials. https://doi.org/10.5281/zenodo.5729423[11].

This project contains the following extended data:

- **Supplementary Table S1**. Age and gender distribution of hospitalized COVID-19 patients with COPD.

- **Supplementary Table S2**. Age and gender distribution of diagnosed COVID-19 patients with COPD.

- **Supplementary Table S3**. Prevalence of treatments in patients with COPD in the 30 days before COVID-19 diagnosis.

- **Supplementary Table S4**. Prevalence of outcomes in diagnosed COVID-19 patients with COPD with 95%CI.

- **Supplementary Figure S1**. Flow chart showing database selection.

- **Supplementary Figure S2**. Prevalence of age and gender among COPD patients with COVID-19 who have been diagnosed and hospitalized.

- **Supplementary Figure S3**. Comparison of characteristics between COPD patients with COVID-19 in the diagnosed and hospitalized cohorts by SMD.

- **Appendix 1**. Overview of Data Sources Screened for Eligibility and Contributing Results

- **Appendix 2**. Definitions and codes used to identify COVID-19

- **Appendix 3**. Definitions and codes used to identify COPD patients

Data are available under the terms of the Creative Commons Attribution 4.0 International Public License (Attribution 4.0 International).

References

1. Worldometer: **COVID-19 CORONAVIRUS PANDEMIC.** [cited 2021 Apr 20].
   Reference Source

2. British Thoracic Society: **BTS guidance for health care professionals in relation to shielding.** [cited 2020 Sep 20].
   Reference Source

3. Leung JM, Niikura M, Yang CWT, et al.: **COVID-19 and COPD.** Eur Respir J. 2020; **56**(2): 2002108.
   PubMed Abstract | **Publisher Full Text** | **Free Full Text**

4. Alqahtani JS, Oyelade T, Aldhahir AM, et al.: **Prevalence, Severity and Mortality associated with COPD and Smoking in patients with COVID-19: A Rapid Systematic Review and Meta-Analysis.** PLoS One. 2020; **15**(5): e0233147.
   PubMed Abstract | **Publisher Full Text** | **Free Full Text**

5. Wark PA, Tooze M, Powell H, et al.: **Viral and bacterial infection in acute asthma and chronic obstructive pulmonary disease increases the risk of readmission.** Respirology. 2013; **18**(6): 996–1002.
   PubMed Abstract | **Publisher Full Text** | **Free Full Text**

6. Ko FW, Chan PK, Chan RWY, et al.: **Molecular detection of respiratory pathogens and typing of human rhinovirus of adults hospitalized for exacerbation of asthma and chronic obstructive pulmonary disease.** Respir Res. 2019; **20**(1): 210.
   PubMed Abstract | **Publisher Full Text** | **Free Full Text**

7. Prieto-Alhambra D, Kostka K, Duarte-Salles T, et al.: **Unraveling COVID-19: a large-scale characterization of 4.5 million COVID-19 cases using CHARYBDIS.** Res Sq. 2021; rs.3.rs-279400.
   PubMed Abstract | **Publisher Full Text** | **Free Full Text**

8. Voss EA, Makadia R, Matcho A, et al.: **Feasibility and utility of applications of the common data model to multiple, disparate observational health databases.** J Am Med Inform Assoc. 2015; **22**(3): 553–64.
   PubMed Abstract | **Publisher Full Text** | **Free Full Text**

9. Hripcsak G, Duke JD, Shah NH, et al.: **Observational Health Data Sciences and Informatics (OHDSI): Opportunities for Observational Researchers.** Stud Health Technol Inform. 2015; **216**: 574–8.
   PubMed Abstract | **Free Full Text**

10. Sena A, Kostka K, Schuemie M, et al.: **ohdsi-studies/ Covid19CharacterizationCharybdis: Charybdis v1.1.1 - Publication Package (Version v1.1.1).** Zenodo. 2020; [cited 2020 Sep 16].
    Publisher Full Text

11. Moreno-Martos D, Morales DR: **Characteristics and outcomes of COVID-19 patients with COPD from the United States, South Korea, and Europe - Supplementary Materials.** Zenodo. 2021; [cited 2021 Dec 14].
    http://www.doi.org/10.5281/zenodo.5729423

12. Duarte-Salles T, Vizcaya D, Pistillo A, et al.: **Baseline characteristics, management, and outcomes of 55,270 children and adolescents diagnosed with COVID-19 and 1,952,693 with influenza in France, Germany, Spain, South Korea and the United States: an international network cohort study.** medRxiv. 2020; 2020.10.29.20222083.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

13. Kohler J, Kostka K, Makadia R, et al.: **Using Real World Data to Understand HIV and COVID-19 in the U.S.A. and Spain: Characterizing Co-Infected Patients Across the Care Cascade.** medRxiv. 2020; 2020.11.10.20229401.
    Publisher Full Text

14. Du RH, Liang LR, Yang CQ, et al.: **Predictors of Mortality for Patients with COVID-19 Pneumonia Caused by SARS-CoV-2: A Prospective Cohort Study.** Eur Respir J. 2020; **55**(5): 2000524.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

15. Verity R, Okell LC, Dorigatti I, et al.: **Estimates of the severity of coronavirus disease 2019: a model-based analysis.** Lancet Infect Dis. 2020; **20**(6): 669–677.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

16. Richardson S, Hirsch JS, Narasimhan M, et al.: **Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area.** JAMA. 2020; **323**(20): 2052–2059.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

17. Yang X, Yu Y, Xu J, et al.: **Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study.** Lancet Respir Med. 2020; **8**(5): 475–481.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

18. Yancy CW: **COVID-19 and African Americans.** JAMA. 2020; **323**(19): 1891–1892.
    PubMed Abstract | **Publisher Full Text**

19. Rimmer A: **Covid-19: Two thirds of healthcare workers who have died were from ethnic minorities.** BMJ. 2020; **369**: m1621.
    PubMed Abstract | **Publisher Full Text**

20. Burn E, You SC, Sena AG, et al.: **Deep phenotyping of 34,128 adult patients hospitalised with COVID-19 in an international network study.** Nat Commun. 2020; **11**(1): 5009.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

21. Schultze A, Walker AJ, MacKenna B, et al.: **Risk of COVID-19-related death among patients with chronic obstructive pulmonary disease or asthma prescribed inhaled corticosteroids: an observational cohort study using the OpenSAFELY platform.** Lancet Respir Med. 2020; **8**(11): 1106–1120.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

22. Aveyard P, Gao M, Lindson N, et al.: **Association between pre-existing respiratory disease and its treatment, and severe COVID-19: a population cohort study.** Lancet Respir Med. 2021; **9**(8): 909–923.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

23. Ramakrishnan S, Nicolau DV Jr, Langford B, et al.: **Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial.** Lancet Respir Med. 2021; **9**(7): 763–772.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

24. Lund LC, Kristensen KB, Reilev M, et al.: **Adverse outcomes and mortality in users of non-steroidal anti-inflammatory drugs who tested positive for SARS-CoV-2: A Danish nationwide cohort study.** PLoS Med. 2020; **17**(9): e1003308.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

25. Wong AY, MacKenna B, Morton CE, et al.: **Use of non-steroidal anti-inflammatory drugs and risk of death from COVID-19: an OpenSAFELY cohort analysis based on two cohorts.** Ann Rheum Dis. 2021; **80**(7): 943–951.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

26. Morales DR, Ostropolets A, Lai L, et al.: **Characteristics and outcomes of COVID-19 patients with and without asthma from the United States, South Korea, and Europe.** J Asthma. 2022; **11**: 1–11.
    PubMed Abstract | **Publisher Full Text**

27. Halpin DMG, Criner GJ, Papi A, et al.: **Global Initiative for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease. The 2020 GOLD Science Committee Report on COVID-19 and Chronic Obstructive Pulmonary Disease.** Am J Respir Crit Care Med. 2021; **203**(1): 24–36.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

28. Sena A, Kostka K, Schuemie M, et al.: **DavidMorenoMartos/ Covid19CharacterizationCharybdis: v1.4.3 (v1.4.3).** Zenodo. 2021; [cited 2021 Dec 14].
    http://www.doi.org/10.5281/zenodo.5779264

Open Peer Review

Current Peer Review Status: ✅ ✅

Version 3

Reviewer Report 13 January 2023

https://doi.org/10.21956/wellcomeopenres.20813.r54044

✅ **Laurie Tomlinson** [iD]

Department of Non-Communicable Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK

The authors have addressed the minor issues I commented on previously - many thanks.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pharmacoepidemiology and clinical epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 2

Reviewer Report 14 December 2022

https://doi.org/10.21956/wellcomeopenres.19703.r52973

❓ **Laurie Tomlinson** [iD]

Department of Non-Communicable Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK

This is a powerful multi-database, multi-country study that carefully describes the demographics of COVID-19 patients with COPD during the first wave of the pandemic. It carefully describes the

data sources and methods, and does not over interpret the causal significance of their findings.

I have a few minor points that I think can be easily addressed.
1. I think the definition of hospital cases will include those who caught COVID-19 while in hospital. These people tended to have a different disease course and may not represent the patients who were admitted with COVID-19. This could be pointed out as a limitation.

2. There is likely to be some misclassification of asthmatics who were classified through medication use and were asthma had not been coded. These people may have fewer comorbidities than those with COPD: again this is simply a minor limitation.

3. The section about hydroxychloroquine and azithromycin is now historic and could be removed – or clarified that this will only relate to a small % of people in analyses of Wave 1.

4. A key limitation is the differences in prevalence and timing of Wave 1 in these countries in relation to the period of data capture, as well as the healthcare response in each country. This is likely to impact on between country differences, particularly mortality. This should be highlighted at least in the discussion.

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pharmacoepidemiology and clinical epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 31 March 2022

https://doi.org/10.21956/wellcomeopenres.19703.r49458

✔ **Marta A. Kisiel**

Department of Medical Sciences, Environmental and Occupational Medicine, Uppsala University, Uppsala, Sweden

I have read the current version of manuscript and it is improved, the authors responded to all my questions. I have no more questions at this moment and I would recommend the manuscript for indexing.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

- -

Version 1

Reviewer Report 31 January 2022

https://doi.org/10.21956/wellcomeopenres.19241.r48211

?   **Marta A. Kisiel**

Department of Medical Sciences, Environmental and Occupational Medicine, Uppsala University, Uppsala, Sweden

This study addressed an important topic, investigating COVID-19 patients with COPD. The study is based on several databases from different countries. The main conclusion was that there were more COPD patients in the hospitalised COVID-19 group than in the diagnosed COVID-19 group. The authors highlighted the limitation of heterogenicity of the cohorts. Also, the accuracy of COPD diagnosis in all included cohorts might be a limitation that should be added. The authors show other comorbidities like obesity, cardiovascular diseases and diabetes. It might be that association of COPD and hospitalised COVID-19 should be adjusted by other comorbidities.
The information on different cohorts is hard to find among all supplementary tables and might be organised in a more available form. As the authors should extend the list of study limitations.

The study should undergo a minor revision before it can be accepted.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Asthma, Occupational Lung Disease, Smal airways, Post covid

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 18 Mar 2022
David Moreno Martos, University of Dundee, Dundee, UK

We thank the reviewer for their time in reviewing the manuscript. We agree it is entirely possible that some of the differences in outcomes between COVID-19 diagnosed and hospitalised patients may be as a result of other comorbidities. However, this study is descriptive in nature and hypothesis generating rather than intended to provide causal inference, which would be beyond the scope of the current study. We have now expanded the study limitations in the Discussion. Journal requirements preclude us to include supplementary material here although we have re-formatted the supplementary material document to improve clarity.

Competing Interests: No competing interests were disclosed.