Respiratory Medicine 206 (2023) 107064

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Original Research

Risk of hospitalization in a sample of COVID-19 patients with and without chronic obstructive pulmonary disease

Laura C. Myers [a,b,*], Richard Murray [c], Bonnie Donato [d], Vincent X. Liu [a,b], Patricia Kipnis [a,b], Asif Shaikh [e], Jessica Franchino-Elder [d]

[a] The Permanente Medical Group, Kaiser Permanente Northern California, Oakland, CA, USA
[b] Division of Research, Kaiser Permanente Northern California, Oakland, CA, USA
[c] Spire Health, San Francisco, CA, USA
[d] Health Economics and Outcomes Research, Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, USA
[e] Clinical Development and Medical Affairs, Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, USA

ARTICLE INFO

Keywords:
COVID-19
COPD
Pneumonia
Healthcare resource use

ABSTRACT

Background and objective: Patients with chronic obstructive pulmonary disease (COPD) may have worse coronavirus disease-2019 (COVID-19)–related outcomes. We compared COVID-19 hospitalization risk in patients with and without COPD.

Methods: This retrospective cohort study included patients ≥40 years, SARS-CoV-2 positive, and with Kaiser Permanente Northern California membership ≥1 year before COVID-19 diagnosis (electronic health records and claims data). COVID-19–related hospitalization risk was assessed by sequentially adjusted logistic regression models and stratified by disease severity. Secondary outcome was death/hospice referral after COVID-19.

Results and discussion: Of 19,558 COVID-19 patients, 697 (3.6%) had COPD. Compared with patients without COPD, COPD patients were older (median age: 69 vs 53 years); had higher Elixhauser Comorbidity Index (5 vs 0) and more median baseline outpatient (8 vs 4), emergency department (2 vs 1), and inpatient (2 vs 1) encounters. Unadjusted analyses showed increased odds of hospitalization with COPD (odds ratio [OR]: 3.93; 95% confidence interval [CI]: 3.40–4.60). After full risk adjustment, there were no differences in odds of hospitalization (OR: 1.14, 95% CI: 0.93–1.40) or death/hospice referral (OR: 0.96, 95% CI: 0.72–1.27) between patients with and without COPD. Primary/secondary outcomes did not differ by COPD severity, except for higher odds of hospitalization in COPD patients requiring supplemental oxygen versus those without COPD (OR: 1.84, 95% CI: 1.02–3.33).

Conclusions: Except for hospitalization among patients using supplemental oxygen, no differences in odds of hospitalization or death/hospice referral were observed in the COVID-19 patient sample depending on whether they had COPD.

1. Introduction

Chronic lung conditions are risk factors for respiratory complications and community-acquired pneumonia [1]. For example, patients with chronic obstructive pulmonary disease (COPD) have a >4-fold increased risk of pneumonia [2] and often have more severe outcomes [3]. This is believed to be related to abnormal lung architecture, chronic inflammation, and an immunocompromised state [4]. Whether or not this is also applicable to patients with coronavirus disease-2019 (COVID-19) and COPD remains uncertain.

There is conflicting evidence about whether patients with COPD have a higher risk of COVID-19–related hospitalization, mortality, and other adverse outcomes [5–9]. Several meta-analyses have suggested that patients with COPD are at an increased risk of severe disease or death from COVID-19 [5–8]. However, many of the studies in these meta-analyses were small, including <200 patients each. One

Abbreviations: ACE-2, angiotensin-converting enzyme-2; BMI, body mass index; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease-2019; GOLD, Global Obstructive Lung Disease; HRU, healthcare resource use; IQR, interquartile ranges; Kaiser Permanente Northern California, KPNC; LAPS2, Laboratory Acute Physiology Score, version 2; N3C, National COVID Cohort Collaboration; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

* Corresponding author. Division of Research, Kaiser Permanente Northern California Oakland, CA, 94612, USA.
E-mail address: Laura.c.myers@kp.org (L.C. Myers).

https://doi.org/10.1016/j.rmed.2022.107064
Received 27 May 2022; Received in revised form 21 November 2022; Accepted 23 November 2022
Available online 26 November 2022

propensity score–matched analysis of hospitalized patients did not show any differences in mortality or need for invasive mechanical ventilation related to a history of COPD [9]. A brief report from an analysis of the National COVID Cohort Collaboration (N3C) suggested an increased risk of mortality in patients with COPD, but despite a large sample size, this study was not able to account for several important clinical factors such as smoking status or baseline supplemental oxygen use [10].

The body of literature describing various outcomes of COVID-19 is growing [11,12], but there are still gaps in the risk of hospitalization in patients with COPD who develop COVID-19. Although the pathophysiological mechanisms contributing to poor outcomes in COPD patients with COVID-19 remain unclear, it has been proposed to be because of interacting factors [13]. Patients with COPD have a higher expression of angiotensin-converting enzyme-2 (ACE-2), the receptor in the lung epithelium that is required for the entry of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) into the body [14,15]. Watson et al. showed that as forced expiratory volume in 1 s decreases, ACE-2 expression increases [16]. As ACE-2 expression seems to contribute to the morbidity and severity of COVID-19 infection, we aimed at assessing whether hospitalization risk is higher for patients who have a history of COPD compared with those without. A better understanding of the risk of hospitalization for COPD patients could help prioritize and implement healthcare policies for this population, such as aggressive preventive measures (e.g., non-pharmacologic interventions to mitigate the risk of infection) and proactive COVID-19 vaccination.

2. Materials and methods

This study was approved by the Kaiser Permanente Northern California (KPNC) Institutional Review Board (1659946-3). A waiver for informed consent was obtained.

2.1. Cohort formation

Adults (aged ≥18 years) with a positive result for SARS-CoV-2 in the first nasopharyngeal swab sample tested using a polymerase chain reaction were identified in the KPNC healthcare system between 2/2/2020 and 9/30/2020. KPNC is an integrated healthcare delivery system serving 4.3 million members, which represents 36% of the insured adult population of Northern California [17]. KPNC members are similar to the general population in the United States [17]. Among the initially identified subjects, only those aged ≥40 years were included. We also required that the subjects have a continuous KPNC membership for ≥1 year before COVID-19 diagnosis (or if < 1 year, have a <3-month gap in membership or received a healthcare service during the month in which they were not a documented member, which is the usual KPNC membership criteria). This age cutoff has been used in prior studies to identify patients with COPD rather than asthma [18], and because age is associated with worse clinical outcomes in COVID-19 [19,20].

Patients who had ≥2 COPD-related healthcare encounters of any of the following types: outpatient, emergency department, or inpatient, were flagged as having COPD using a 3-year lookback period before COVID-19 diagnosis. The International Classification of Diseases, Tenth Revision [ICD-10] codes used to define COPD included J40, J41.0, J41.1, J41.8, J42, J43.0, J43.1, J43.2, J43.8, J43.9, J44.0, J44.1, and J44.9. At least two diagnosis codes were required to increase the specificity of identifying patients with COPD [21]. A 3-year lookback period was feasible because KPNC data contain longitudinal information with stable membership over time (69% retention at 5 years).

2.2. Data extraction

Patient characteristics were assessed using sociodemographic and clinical variables in the overall population and among patients with or without COPD. The neighborhood deprivation index (NDI) was used as a measure of socioeconomic status, with higher values associated with lower socioeconomic status [22,23]. Individual Elixhauser comorbidities were extracted, and the Elixhauser Comorbidity Index was calculated. The Elixhauser Comorbidity Index includes 30 variables and is significantly associated with in-hospital mortality and post-discharge all-cause mortality [24]. Respiratory-specific variables included a history of lung cancer, pneumonia, dyspnea, sarcoid, bronchiectasis, use of supplemental oxygen in the year before COVID-19 diagnosis, and number of COPD-related healthcare encounters in the year before COVID-19 diagnosis (outpatient, emergency department, or inpatient). Characteristics of patients were also summarized based on whether patients were treated for COVID-19 in the outpatient or inpatient setting by COPD history.

For the subset of patients admitted to the hospital, clinical variables were extracted from the electronic health record for the first hospitalization after the COVID-19 diagnosis. The variables included vital signs, laboratory values, code status (advanced directive), the highest level of respiratory support required, receipt of intensive care, length of hospital stay, death during inpatient stay, discharge disposition (home, skilled nursing facility, or hospice), need for supplemental oxygen at discharge, and nonelective, any-cause, 30-day readmissions. Readmission was defined as any hospitalization (inpatient or observation-related hospitalization) in which the patient was admitted through the emergency department per previous KPNC studies [25], as all nonelective inpatient admissions must pass through the emergency department. This study also captured the Laboratory Acute Physiology Score, version 2 (LAPS2), which was developed at KPNC to describe illness severity for inpatients using vital signs, neurologic status, and 15 laboratory test values [26]. LAPS2 has been validated externally in multiple settings and has demonstrated high performance in predicting mortality relative to other severity of illness scores [27–29].

2.3. Outcomes

The primary outcome was COVID-19–related hospitalization, defined using combinations of administrative codes recommended by the Centers for Disease Control and Prevention (full definition in Table E1) [30,31]. The positive SARS-CoV-2 polymerase chain reaction test had to be in the 3 weeks before admission or during hospitalization to be considered a COVID-19–related hospitalization. The secondary outcome was a composite of any-cause death or referral to hospice care within 30 days after COVID-19 diagnosis. Death data were extracted on 5/31/2021 to ensure at least 6 months of follow-up, as death cases take time to be entered into our research databases if occurring in the outpatient setting. Referral to hospice care was used as a composite outcome to capture as many outpatient deaths as possible, as has been done previously [32].

2.4. Missing data

Missing data were limited to laboratory values of hospitalized patients, such as hemoglobin A1c, lactate, D-dimer, and arterial blood gas, which are not checked in every patient, as well as derived vital signs (oxygen saturation/fraction of inspired oxygen ratio), which require a higher level of respiratory support to be recorded. Table E2 shows the missingness of these variables among the subset of patients admitted to the hospital. These variables were not used in modeling; thus, imputation was not necessary.

2.5. Statistical analysis

Categorical variables were summarized as numbers and percentages, and continuous variables as medians with interquartile ranges (IQRs). The risk of hospitalization was evaluated using logistic regression analysis. Unadjusted and adjusted odds ratios (ORs) were reported with 95% confidence intervals (CIs). Three models were developed that incrementally included more risk adjustment variables to control for

confounding: Model 1 adjusted for age, sex, race, and NDI; Model 2 adjusted for the covariates used in Model 1 plus Elixhauser Comorbidity Index and individual Elixhauser comorbidities common in COPD and shown to increase the risk of COVID-19–related hospitalization [33–36]; and Model 3 adjusted for the covariates used in Models 1 and 2 plus body mass index (BMI), smoking, month of positive COVID-19 test, and the number of healthcare encounters in the previous year. In addition, a *post hoc* sensitivity analysis was conducted by removing the number of prior healthcare encounters in the previous year from Model 3 to compare the model fit (Akaike Information Criterion [37]) with and without this variable.

Stratified analyses were performed to compare patients with severe or nonsevere COPD with those without COPD. COPD severity was defined using two measures: 1) supplemental oxygen use and 2) frequency of COPD exacerbations in the 1 year before COVID-19. COPD patients with frequent COPD exacerbations (≥2) were severe and COPD patients with infrequent exacerbations (0 or 1) were nonsevere. Medical encounters and pharmacy data were combined to identify COPD exacerbations using a published algorithm (**eMethods**) [38,39].

Unadjusted and age-adjusted survival over time was displayed according to the history of COPD. Patients who lost KPNC membership after the COVID-19 diagnosis were censored. Survival probabilities were compared using log-rank tests.

All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC). All statistical significance thresholds used a two-tailed alpha value of 0.05.

3. Results

3.1. Patient characteristics

Among >4.3 million adults in the KPNC population, 36,137 adults with a positive SARS-CoV-2 test result were identified during the study period, of whom 19,558 were aged ≥40 years and included in the analysis. Of the 19,558 subjects, 697 (3.6%) had COPD and 18,861 (96.4%) did not have COPD (Table 1). The test-positivity rate was similar between patients with COPD (1.0%) and without COPD (0.9%).

Patients with COPD were older than those without COPD (median [IQR] age: 69 [59–78] and 53 [46–61] years, respectively). Patients with COPD had a higher median Elixhauser Comorbidity Index (5 [IQR: 1–14]) than those without COPD (0 [0–2]) and were more likely to be former or current smokers (former, 56.4%; current, 8.5%) than those without COPD (21.3% and 4.1%, respectively). There was no difference in BMI between patients with or without COPD. Compared with patients without COPD, those with COPD had more outpatient encounters (median: 8 [IQR: 3–15] vs 4 [IQR: 2–7]), emergency department encounters (median: 2 [IQR: 1–4] vs 1 [IQR: 1–2]), and inpatient encounters (median: 2 [IQR: 1–3] vs 1 [IQR: 1–1]) in the year before COVID-19 diagnosis.

Overall, a few patients (n = 28; 0.1%) had a history of lung cancer in the year before COVID-19 diagnosis, which was similar between patients with and without COPD (Table 2). Compared with patients without COPD, more patients with COPD had a diagnosis of pneumonia (49.0% vs 18.4%), dyspnea (71.1% vs 20.5%), or bronchiectasis (5.5% vs 0.4%), and were prescribed supplemental oxygen (11.6% vs 2.0%) in the year before COVID-19. Patients with COPD had a median of 7 (IQR: 2–20) COPD-related encounters in the 3 years before COVID-19 diagnosis.

Characteristics of patients with and without COPD were compared according to whether they required inpatient treatment for COVID-19 (Table E3 for patients treated as outpatient and Table E4 for patients treated as inpatients). Patients with COPD were older, had a higher comorbidity burden, and were more likely to be smokers than those without COPD, regardless of whether or not they were treated in the outpatient or inpatient setting. Patients with COPD had a higher median number of healthcare encounters in the year before COVID-19 diagnosis compared with those without COPD, regardless of whether or not they

Table 1
Demographic and clinical characteristics of patients with COVID-19 overall and by history of COPD.

Variable	All COVID+ (n = 19,558)	With COPD (n = 697)	Without COPD (n = 18,861)	P value
Age at diagnosis, years	53 (46–62)	69 (59–78)	53 (46–61)	<0.0001
Sex, male	9432 (48.2)	309 (44.3)	9123 (48.4)	0.04
Race/ethnicity				
Hispanic	9014 (46.1)	176 (25.3)	8838 (46.9)	<0.0001
White	5065 (25.9)	309 (44.3)	4756 (25.2)	
Asian	2526 (12.9)	49 (7.0)	2477 (13.1)	
Other	1544 (7.8)	81 (11.6)	1463 (7.8)	
African American	1409 (7.2)	82 (11.8)	1327 (7.0)	
Neighborhood deprivation index[a]	0.04 (−0.54 to 0.78)	0.00 (−0.57 to 0.73)	0.04 (−0.54 to 0.79)	0.20
Body mass index, kg/m^2	29.6 (26.0–34.1)	29.9 (25.5–34.9)	29.7 (26.0–34.0)	0.47
Smoking				
Never	13,803 (70.6)	242 (34.7)	13,561 (71.9)	<0.0001
Former	4415 (22.6)	393 (56.4)	4022 (21.3)	
Current	831 (4.3)	59 (8.5)	772 (4.1)	
Number of healthcare encounters in the year before COVID-19				
Inpatient	1 (1–2)	2 (1–3)	1 (1–1)	<0.0001
Emergency department	1 (1–2)	2 (1–4)	1 (1–2)	<0.0001
Outpatient	4 (2–7)	8 (3–15)	4 (2–7)	<0.0001
Virtual visit	4 (2–7)	4 (2–8)	4 (2–7)	<0.0001
Elixhauser Comorbidity Index	0 (0–2)	5 (1–14)	0 (0–2)	<0.0001
Diabetes with and without complications	5323 (27.2)	408 (58.5)	4918 (26.1)	<0.0001
Hypertension	4775 (24.4)	411 (59.0)	4364 (23.1)	<0.0001
Peripheral vascular disease	2448 (12.5)	399 (57.3)	2049 (10.9)	<0.0001
Obesity	1918 (9.8)	173 (24.8)	1745 (9.3)	<0.0001
Renal failure	1032 (5.3)	168 (24.1)	864 (4.6)	<0.0001
Hypothyroidism	993 (5.1)	104 (14.9)	889 (4.7)	<0.0001
Psychosis	819 (4.2)	136 (19.5)	683 (3.6)	<0.0001
Blood loss anemia	824 (4.2)	111 (15.9)	713 (3.8)	<0.0001
Depression	794 (4.1)	105 (15.1)	689 (3.7)	<0.0001
Neurodegenerative disorders	773 (4.0)	117 (16.8)	656 (3.5)	<0.0001
Liver disease	715 (3.7)	68 (9.8)	647 (3.4)	<0.0001
Fluid/electrolyte disorder	490 (2.5)	92 (13.2)	398 (2.1)	<0.0001
Congestive heart failure	482 (2.5)	143 (20.5)	339 (1.8)	<0.0001
Solid tumor with or without metastases	455 (2.3)	40 (5.7)	415 (2.2)	<0.0001
Rheumatoid arthritis/collagen vascular disorder	374 (1.9)	39 (5.6)	335 (1.8)	<0.0001
Paralysis	225 (1.2)	26 (3.7)	199 (1.1)	<0.0001
Weight loss	213 (1.1)	43 (6.2)	170 (0.9)	<0.0001
Alcohol or drug abuse	205 (1.1)	35 (5.0)	170 (0.9)	<0.0001
Valvular disease	178 (0.9)	41 (5.9)	137 (0.7)	<0.0001
Coagulopathy	181 (0.9)	31 (4.5)	150 (0.8)	<0.0001
Lymphoma	73 (0.4)	8 (1.1)	65 (0.3)	<0.0001
Pulmonary circulation disorders	49 (0.3)	15 (2.2)	34 (0.2)	<0.0001
Peptic ulcer disease	38 (0.2)	6 (0.9)	32 (0.2)	<0.0001
Acquired immunodeficiency disorder	43 (0.2)	6 (0.9)	37 (0.2)	<0.0001

Continuous variables are expressed as median (interquartile range). Categorical variables are expressed as n (%).
COPD = chronic obstructive pulmonary disease, COVID-19 = coronavirus disease-2019.
[a] The scale ranges from −1.8 to 3.72, with higher values indicating worse socioeconomic status.

Table 2
Respiratory variables describing patients with COVID-19 by history of COPD.

Variable	All COVID+ (n = 19,558)	With COPD (n = 697)	Without COPD (n = 18,861)	P value
History of lung cancer	28 (0.1)	7 (1.0)	21 (0.1)	0.0006
History of pneumonia	3812 (19.5)	342 (49.0)	3470 (18.4)	<0.0001
History of dyspnea	4360 (22.3)	496 (71.1)	3864 (20.5)	<0.0001
History of sarcoid	34 (0.4)	<5	32 (0.2)	0.69
History of bronchiectasis	120 (1.5)	38 (5.5)	82 (0.4)	<0.0001
History of interstitial lung disease	260 (1.3)	43 (6.2)	217 (3.0)	<0.0001
Supplemental oxygen in 1 year before COVID-19 diagnosis	450 (2.3)	81 (11.6)	369 (2.0)	<0.0001
Number of COPD-related encounters in the 3-year look back period from positive test	n/a	7 (2–20)	n/a	n/a

Continuous variables are expressed as median (interquartile range). Categorical variables are expressed as n (%).
COPD = chronic obstructive pulmonary disease, COVID-19 = coronavirus disease-2019, n/a = not applicable.

were treated in the inpatient or outpatient setting (Table E3).

3.2. Characteristics of COVID-19–related hospitalizations by history of COPD

Of the 19,558 COVID-19 patients included in the study, 2885 (14.8%) required hospitalization. A greater proportion of patients with COPD were hospitalized for COVID-19 compared with patients without COPD (38.7% vs 13.9%). There were only a few differences in the initial vital signs between patients depending on their history of COPD (Table 3), although patients with COPD had a slightly higher severity of illness on admission compared with those without COPD (LAPS2 score: median [IQR] 87 [67–109] vs 76 [56–100]). The proportion of patients treated in the intensive care unit was similar between patients with and without COPD (22.2% vs 23.7%). More patients with COPD received noninvasive ventilation or high-flow oxygen compared with patients without COPD (35.9% vs 23.9%). In addition, more patients with COPD had a limitation of life-sustaining therapy care directive (do not intubate, do not resuscitate, partial code) compared with patients without COPD both at 1 h of hospitalization (25.2% vs 9.2%) and as the last logged (43.3% vs 19.3%). There were no differences in the highest lactate level, need for vasopressors, first pH logged, and length of hospital stay between patients with and without COPD (Table 3).

A greater proportion of patients with COPD died during the hospital stay compared with those without COPD (17.8% vs 11.8%, Table 3). Compared with patients without COPD, fewer patients with COPD were discharged home (64.1% vs 79.7%), whereas more patients with COPD were discharged to a skilled nursing facility (16.7% vs 7.3%) and experienced nonelective, any-cause, 30-day readmissions (19.6% vs 9.1%). There were no differences in the length of hospital stay or need for supplemental oxygen at the time of discharge.

3.3. Logistic regression analyses

Unadjusted analyses showed that patients with COPD had greater odds of hospitalization than those without COPD (OR: 3.93; 95% CI: 3.40–4.60; Table 4A). After adjusting for baseline demographics and comorbidities (Model 2), the odds of hospitalization for patients with COPD decreased but were still higher compared with patients without COPD (OR: 1.51; 95% CI:1.25–1.83). Only after full risk adjustment accounting for other factors, including healthcare resource use (HRU) (Model 3; Table 4A) was there no difference in the odds of

Table 3
Hospitalization characteristics of patients with COVID-19 by history of COPD.

Variable	All COVID+ (n = 2885)	With COPD (n = 270)	Without COPD (n = 2615)	P value
Initial vital signs				
Heart rate, beats per minute	101 (89–113)	99 (87–113)	101 (89–113)	0.22
Systolic blood pressure, mmHg	112 (101–123)	111 (101–125)	112 (101–123)	0.86
Respiratory rate, breaths per minute	27 (22–32)	25 (22–30)	27 (22–33)	0.0002
Oxygen saturation, %	91 (88–94)	92 (89–94)	91 (88–94)	0.24
LAPS2[a]	77 (57–101)	87 (67–109)	76 (56–100)	<0.0001
Highest level of respiratory support				
None	464 (16.1)	40 (14.8)	424 (16.2)	0.0006
Nasal cannula	1187 (41.1)	93 (34.4)	1094 (41.8)	
Face mask	112 (3.9)	10 (3.7)	102 (3.9)	
Noninvasive ventilation or high-flow oxygen	721 (25.0)	97 (35.9)	624 (23.9)	
Invasive mechanical ventilation	401 (13.9)	30 (11.1)	371 (14.2)	
Received intensive care unit level of care	679 (23.5)	60 (22.2)	619 (23.7)	0.59
Required vasopressors	378 (13.1)	29 (10.7)	349 (13.4)	0.22
First saturation/ FiO_2 ratio	144 (99–240)	165 (104–325)	141 (99–232)	0.006
First PaO_2/FiO_2 ratio	112 (74–208)	155 (88–252)	111 (74–200)	0.04
Lowest PaO_2/FiO_2 ratio	80 (57–142)	88 (63–197)	78 (56–137)	0.11
First PCO_2, mmHg	36 (32–42)	40 (34–50)	36 (32–41)	<0.0001
First pH	7.43 (7.38–7.47)	7.43 (7.34–7.47)	7.44 (7.39–7.47)	0.34
First bicarbonate, mmol/L	25 (23–27)	26 (23–28)	25 (23–27)	0.0006
Highest lactate, mmol/L	1.5 (1.1–2.1)	1.5 (1.1–2.1)	1.5 (1.1–2.1)	0.88
Highest D-dimer, mg/L	1.2 (0.7–2.3)	1.5 (0.8–2.7)	1.2 (0.7–2.2)	0.002
Most recent HbA1c, %	6.0 (5.6–7.3)	6.0 (5.6–7.2)	6.0 (5.6–7.4)	0.64
Most recent eosinophil count, %	1 (0–3)	2 (0–4)	1 (0–3)	0.002
Advanced care directive at 1 h				
Full code	2569 (89.1)	202 (74.8)	2367 (90.5)	<0.0001
Limitation of life-sustaining therapies	310 (10.7)	68 (25.2)	242 (9.2)	
Comfort care	6 (0.2)	<5	6 (0.2)	
The last advanced care directive logged				
Full code	2250 (78.0)	150 (55.6)	2100 (80.3)	<0.0001
Limitation of life-sustaining therapies[b]	623 (21.6)	117 (43.3)	506 (19.3)	
Comfort care	12 (0.4)	<5	9 (0.3)	
Supplemental oxygen order at discharge	1158 (40.1)	101 (37.4)	1057 (40.4)	<0.0001
Length of hospital stay as a continuous measure, days	5.5 (3.0–10.5)	5.8 (3.3–12.5)	5.4 (3.0–10.3)	0.05
Discharge disposition (other than death)				
Home	2257 (78.2)	173 (64.1)	2084 (79.7)	<0.0001
Skilled nursing facility	237 (8.2)	45 (16.7)	192 (7.3)	<0.0001
Hospice	28 (1.0)	<5	25 (1.0)	0.80
Death while inpatient	357 (12.3)	48 (17.8)	309 (11.8)	0.005

(continued on next page)

Table 3 (*continued*)

Variable	All COVID+ (n = 2885)	With COPD (n = 270)	Without COPD (n = 2615)	P value
Death inpatient or after discharge	505 (17.5)	72 (26.7)	433 (16.6)	<0.0001
Nonelective, any-cause, 30-day readmission	289 (10.0)	52 (19.6)	237 (9.1)	<0.0001

Continuous variables are expressed as median (interquartile range). Categorical variables are expressed as n (%).
CI = confidence interval, COPD = chronic obstructive pulmonary disease, COVID-19 = coronavirus disease-2019; HbA1c = Hemoglobin A1c; LAPS2 = Laboratory Acute Physiology Score, version 2, PaO_2/FiO_2 = ratio of partial pressure of arterial oxygen and fraction of inspired oxygen, PCO_2 = partial pressure of carbon dioxide, pH = potential of hydrogen, saturation/FiO_2 ratio = simple predictor of noninvasive positive pressure ventilation failure in critically ill patients.
[a] LAPS2 is a score (range: 0 to 414) to describe the severity of illness for inpatients that use vital signs, neurologic status, and 16 laboratory tests. The univariate relationship between LAPS2 and 30-day mortality was 1.0% for scores 0 to 59, 5.0% for scores 60 to 109, and 13.7% for scores ≥110. After adjusting for age, sex, and comorbid conditions, the adjusted odds ratio for inpatient mortality for an increase in LAPS2 of 5 points is 1.134 (95% CI, 1.133 to 1.135) [25].
[b] Includes do not intubate, do not resuscitate, and partial code.

Table 4A
The OR of hospitalization or death/hospice referral in COVID-19 for patients with COPD vs patients without COPD.

COPD vs no COPD	OR for hospitalization (95% CI)	OR for death or hospice referral (95% CI)
Unadjusted	3.93 (3.40–4.60)	5.59 (4.50–6.91)
Model 1*	1.96 (1.65–2.33)	1.45 (1.13–1.87)
Model 2†	1.51 (1.25–1.83)	1.04 (0.79–1.36)
Model 3‡	1.14 (0.93–1.40)	0.96 (0.72–1.27)

hospitalization for patients with COPD versus patients without COPD (OR: 1.14; 95% CI: 0.93–1.40).

Similar results were seen for the composite secondary outcome of death or hospice referral. There was no difference in death or hospice referral for patients with COPD compared with patients without COPD after full risk adjustment (Model 3) (Table 4A).

The sensitivity analysis showed that removing the number of healthcare encounters in the previous year from Model 3 resulted in higher odds of hospitalization for patients with COPD compared with patients without COPD but with a higher Akaike Information Criterion (Table E5).

3.4. Stratified analyses by COPD severity

Of the 697 patients with COPD, 616 (88.4%) had no supplemental oxygen use before COVID-19 diagnosis, whereas 81 (11.6%) had prior use. After full risk adjustment (Model 3), there was no difference in odds of hospitalization between patients with COPD not on prior supplemental oxygen and patients without COPD (Table 4B). Similar results were seen in the composite outcome of death or hospice referral. However, COPD patients with prior supplemental oxygen use had greater odds of hospitalization after full risk adjustment (Model 3, Table 4C), but not death or hospice referral compared with patients without COPD.

Of the 697 patients with COPD, 406 (58.2%) had infrequent exacerbations, and 291 (41.8%) had frequent exacerbations. After full risk adjustment (Model 3), there was no difference in the odds of hospitalization between patients with infrequent COPD exacerbations and those without COPD (Table 4D). Similar results were seen for the composite outcome of death or hospice referral. There were no differences in the odds of hospitalization, death, or hospice referral comparing COPD patients with a history of frequent exacerbations with patients without COPD after full adjustment (Table 4E).

3.5. Survival analysis

Unadjusted and age-adjusted survival curves for patients with and without COPD are shown in Fig. 1A and **1B,** respectively. Very few (<1%) patients lost their KPNC membership within 30 days. The probability of survival at 30 days was 0.90 in patients with COPD and 0.98 in those without COPD. For 90-day survival, the corresponding values were 0.88 and 0.97. After adjusting for age, the log-rank test showed no statistical significance in survival probability over time between patients with and without COPD (P = 0.73).

4. Discussion

This study investigated the odds of COVID-19–related hospitalization in patients with a history of COPD versus those without COPD. Patients with a history of COPD were older and had a higher comorbidity burden than those without COPD. While unadjusted analyses showed greater odds of hospitalization and the composite outcome of death/hospice referral for those with COPD, a fully adjusted model accounting for sociodemographic characteristics, comorbid conditions, and other factors such as HRU showed no differences in these outcomes. We showed that all three sets of variables were important to understanding the relationship between COPD and the outcomes, as a statistically significant association remained after adjusting for sociodemographic characteristics and comorbidity burden (Model 2). We interpret this to mean that while the presence of COPD itself did not increase the risk of hospitalization for COVID-19, many factors must be accounted for to fully address for confounding.

The longitudinal and detailed nature of the claims and electronic health records from KPNC facilitated an in-depth examination of confounding factors. However, we acknowledge that there were significant differences in patient populations between groups. For instance, the COPD group was older than the non-COPD group. This finding has been previously reported [10,40], and could be related to older patients with COPD delaying seeking medical help or more comorbidities and severe COPD exacerbations not manageable at home than younger patients [41]. In order to address the differences among groups, we leveraged multifactor adjustment, which included age in all logistic regression models tested and comorbid diseases in Models 2 and 3. Variables

Table 4B
Stratified analysis comparing patients with COPD not requiring supplemental oxygen before COVID-19 to patients without COPD.

COPD not requiring supplemental oxygen vs no COPD	OR for hospitalization (95% CI)	OR for death or hospice referral (95% CI)
Unadjusted	3.28 (2.76–3.89)	4.53 (3.56–5.76)
Model 1*	1.66 (1.37–2.00)	2.04 (2.03–2.05)
Model 2†	1.36 (1.11–1.66)	0.93 (0.69–1.25)
Model 3‡	1.08 (0.87–1.35)	0.88 (0.65–1.19)

Table 4C
Stratified analysis comparing patients with COPD requiring supplemental oxygen before COVID-19 to patients without COPD.

COPD requiring supplemental oxygen vs no COPD	OR for hospitalization (95% CI)	OR for death or hospice referral (95% CI)
Unadjusted	14.75 (9.14–23.80)	16.43 (10.40–25.96)
Model 1*	6.74 (4.04–11.25)	3.58 (2.11–6.07)
Model 2†	3.55 (2.09–6.04)	1.76 (1.01–3.08)
Model 3‡	1.84 (1.02–3.33)	1.47 (0.82–2.63)

Table 4D
Stratified analysis comparing patients with infrequent COPD exacerbations before COVID-19 to patients without COPD.

COPD with infrequent exacerbations[§] vs no COPD	OR for hospitalization (95% CI)	OR for death or hospice referral (95% CI)
Unadjusted	2.54 (2.05–3.12)	3.66 (2.67–5.00)
Model 1*	1.56 (1.23–1.97)	1.39 (0.96–2.00)
Model 2[†]	1.38 (1.08–1.77)	1.21 (0.83–1.76)
Model 3[‡]	1.18 (0.91–1.53)	1.22 (0.84–1.79)

Table 4E
Stratified analysis comparing patients with frequent COPD exacerbations before COVID-19 to patients without COPD.

COPD with frequent exacerbations[§] vs no COPD	OR for hospitalization (95% CI)	OR for death or hospice referral (95% CI)
Unadjusted	6.79 (5.34–8.58)	8.68 (6.55–11.50)
Model 1*	2.57 (2.00–3.31)	1.50 (1.09–2.07)
Model 2[†]	1.70 (1.29–2.24)	0.92 (0.65–1.30)
Model 3[‡]	1.09 (0.80–1.49)	0.78 (0.54–1.12)

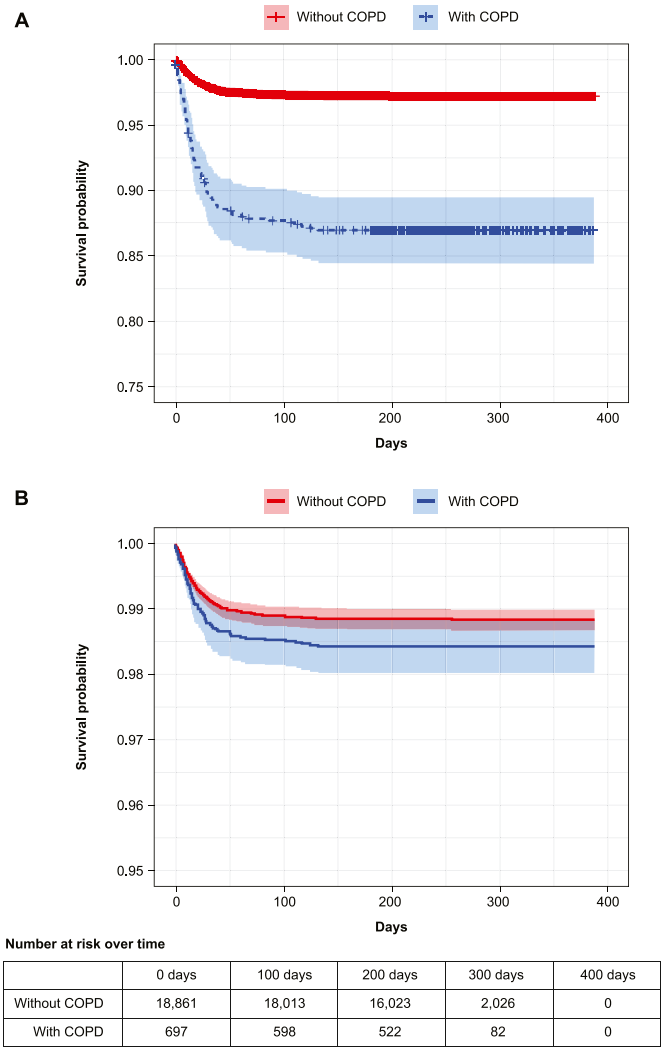
CI = confidence interval, COPD = chronic obstructive pulmonary disease, COVID-19 = coronavirus disease-2019, OR = odds ratio.

* Adjusted for the following demographics: age, sex, race, neighborhood deprivation index.

† Adjusted for the covariates in Model 1 plus Elixhauser Comorbidity Index and the following individual comorbidities: hypertension, diabetes, renal failure, congestive heart failure, peripheral vascular disease, liver disease, anemia, neurologic disease, hypothyroidism, electrolyte disorder, weight loss, depression, drug use disorder, valvular disease, cancer, arthritis, coagulation disorder, pulmonary circulation disease, lymphoma, and peptic ulcer disease.

‡ Adjusted for the covariates in Model 2 plus body mass index, smoking, month of positive COVID-19 test, and the number of prior healthcare encounters in the previous year.

§ Infrequent COPD exacerbations were defined as 0–1 exacerbation; frequent COPD exacerbations were defined as >1 exacerbation.



Number at risk over time

	0 days	100 days	200 days	300 days	400 days
Without COPD	18,861	18,013	16,023	2,026	0
With COPD	697	598	522	82	0

Fig. 1. Survival curve of patients with COVID-19 by the history of COPD A) Unadjusted analysis, B) Age-adjusted analysis. Time starts from the first COVID-19-positive test. Death could occur as inpatient or outpatient. Patients were censored on the date of the last known membership, which is denoted by hash marks on the unadjusted survival curve. Log-rank test values were $P < 0.0001$ for unadjusted analysis and $P = 0.73$ for age-adjusted analysis. COPD = chronic obstructive pulmonary disease, COVID-19 = coronavirus disease-2019.

included in Model 3 led to the dissolution of the association between COPD and hospitalization. The sensitivity analysis shows that the removal of a single set of variables in Model 3 (HRU) makes the association resume significance. However, the simultaneous rise of the Akaike Information Criterion [37] indicates that the original model including HRU had a better fit. While few studies have examined the risk of hospitalization in COPD and COVID-19 [9], none has included this important variable in risk adjustment. We believe HRU is a relevant confounder in the association because patients with COPD could have a lower threshold to seek care, or they may require hospital-level care for reasons not captured in the Elixhauser Comorbidity Index or individual comorbidity variables. The Elixhauser is not exhaustive, is not tailored to the COPD patient population, and does not take into account comorbidity severity. Anxiety, for example, is a common comorbidity in patients with COPD, increases with COPD severity, and could change one's threshold for seeking care; however, it is not included in the Elixhauser Comorbidity Index [42].

Our findings were generally consistent in stratified analyses comparing patients who were or were not on supplemental oxygen, and who had frequent versus infrequent exacerbation histories. These categories were used as a proxy for COPD severity before COVID-19 diagnosis in the absence of pulmonary function test results and categorization according to the Global initiative for chronic Obstructive Lung Disease (GOLD) [41]. Higher odds of hospitalization were observed among patients with COPD requiring pre–COVID-19 supplemental oxygen compared with patients without COPD, even after full risk adjustment with HRU. Although not specifically studied during the COVID-19 pandemic, previous studies have identified long-term oxygen therapy as a predictor of admission to an intensive care unit and of mortality in patients with COPD exacerbations who visit emergency departments [43,44]. This could mean that the sickest COPD patients on home supplemental oxygen at baseline may be at a higher risk for hospitalization, which would be unsurprising given their poor reserve, especially for overcoming respiratory infections. However, this observation could also be explained by confounders that we did not adjust for, such as poor nutritional status and frailty that are associated with both need for supplemental oxygen and an increased risk of hospitalization [45–47].

Although several studies and meta-analyses have reported higher mortality rates among patients with COVID-19 who have COPD compared with those without COPD, these observations have generally been based on small sample sizes [6,8,48–50]. A propensity score–matched study was used to evaluate mortality, invasive mechanical ventilation, intensive care unit admission, and hospital length-of-stay among patients hospitalized for COVID-19 with or without COPD/emphysema using electronic health record data [9]. They used imaging findings, history of tobacco use, or long-acting bronchodilator prescription to flag a diagnosis of COPD/emphysema [9]. After matching for age, BMI, and serologic data correlated with the severity of COVID-19 disease (c-reactive protein, lactate dehydrogenase, interleukin-6, D-dimer, and ferritin), no significant differences in

outcomes were observed between patients with or without COPD/emphysema. Our fully adjusted findings are consistent with this publication and extend this work by reporting not only mortality but also hospitalization risk. A pooled analysis of 11 epidemiological studies from China and the United States reported lower COVID-19 hospitalization rates in patients with COPD [51]. Our study has the advantage of accessing and using important variables such as smoking status, supplemental oxygen use before COVID-19 diagnosis, and the number of COPD exacerbations before COVID-19 diagnosis.

A brief report from a large study using electronic health records from the United States N3C reported increased mortality among patients with COVID-19 and COPD (n = 7449 and 15% mortality) versus those without COPD (n = 273,963 and 4% mortality) [10]. The increased odds of mortality for patients with COPD remained significant after adjusting for age, sex, diabetes, hypertension, chronic kidney disease, and obesity (OR: 2.10; 95% CI: 1.96–2.26). While the N3C study had a large sample size, the lack of risk adjustment for smoking, the need for supplemental oxygen, and previous healthcare encounters limit their study. We believe our study more completely adjusts for COPD complexity, which explains the differences in results. In addition, we chose hospitalization as the primary outcome because it is more proximal than mortality.

The strength of our study was that the study cohort was derived from a large population of patients within an integrated health system. KPNC members are followed longitudinally with little turnover in membership and have similar healthcare access at any of our 21 hospitals. The availability of both inpatient and outpatient data over time was a notable strength for performing robust risk adjustment, stratified analyses, and survival analysis. In addition, SARS-CoV-2 test positivity was similar between patients with and without COPD, which is reassuring that positive testing was not differentially higher in patients with COPD. Finally, according to the US COVID-NET database (Coronavirus Disease 2019-Associated Hospitalization Surveillance Network), COPD prevalence among those hospitalized with COVID-19 between March 2020 and December 2020 (the timeframe of our study) varied between 6.2% and 13% and increased to 18.2% by June 2022 [52]. The fact that the COPD prevalence among hospitalized patients with COVID-19 was higher than the age-adjusted COPD prevalence in California in 2020 (prevalence = 5.1%, 95% CI: 4.3%–6.0%) [53], suggests that individuals with underlying COPD are at higher risk of SARS-CoV-2 infection. However, our study could not confirm this because it was focused on a denominator of patients with COVID-19, not the general population [54].

Our findings should also be interpreted in the context of certain limitations. First, COPD was identified using administrative codes, which can have a sensitivity of <30% [55,56]. However, our requirement for patients to have multiple codes for COPD over time has been shown to have better sensitivity (85%), which was the approach we employed [21]. Moreover, the inclusion of broad ICD-10 COPD diagnosis (i.e., including bronchitis, not specified as acute or chronic, simple and mucopurulent chronic bronchitis, and unspecified chronic bronchitis) may have diluted the cohort from being true COPD patients [57]. For instance, the proportion of never smokers with COPD in our study (34.7%) was higher than that anticipated from a US COPD population (3.2% in 2018) [58]. This could reflect the inclusion of COPD patients exposed to passive smoke or non-smoking associated COPD (e.g. occupational exposure to dust, fumes or air pollution) [59–61]. However, it is reassuring that the percent of COPD in patients with COVID-19 in our study was 3.6%, which was at least not more than the prevalence of COPD in Northern California (5.1%) [53], suggesting that COPD was drastically not over-represented. Further, we examined a population of KPNC-insured patients. While KPNC-insured patients typically represent insured adults in Northern California and the United States, we did not study the uninsured, whose different sociodemographic characteristics may put them at different risk for COVID-19-related hospitalization [62]. Moreover, pulmonary function testing is not reliably available electronically in KPNC and might have led to the under-diagnosis of COPD in our population. Second, there may have been under-reporting of COVID-19 because patients tested outside of the KPNC healthcare system could not have been captured in our analysis; this is thought to be limited, however, as testing availability was amply available at KPNC early in the pandemic. Third, there may have been under-reporting of outpatient deaths. KPNC captures outpatient deaths, but some death reports come from the state with a delay in reporting. We were able to overcome this by using hospice referral as a composite outcome with death and ensuring there were at least 6 months of follow-up in the survival analysis to capture as many deaths, or anticipated deaths, as possible. Using hospice referral as a proxy has been done in a previous COVID-19–related study as a way to capture patients at the end of their life who are highly likely to die [32]. Fourth, it was not possible to include Modified Medical Research Council scores, COPD Assessment Test scores, GOLD class, or spirometry results because these are not routinely collected electronically at KPNC. However, we included prior supplemental oxygen use and some pre–COVID-19 COPD exacerbations as proxies for COPD severity, which many published studies have not included [9,10,50]. Lastly, some patients with COPD, potentially those with more severe disease, may have followed strict social distancing behavior and remained at home. If this were the case, our sample may represent a less-severe COPD patient population, which could underestimate outcome risk. Therefore, future research is needed to further understand the qualitative aspects of COPD patients' behavior during the pandemic [63,64].

In conclusion, this study did not detect a difference in the odds of hospitalization or the composite of death/hospice referral for patients with COVID-19 by the history of COPD after full risk adjustment with variables such as HRU except in patients who were on supplemental oxygen prior to COVID-19. We believe our use of longitudinal data and our analytic approach of building sequential models, assessing both clinical and statistical contribution of information, and performing stratified analyses make our findings robust. The insights reported in this manuscript might help clinicians communicate the potential risks associated with COVID-19 to their patients with COPD and better inform prevention and treatment plans for these patients.

CRediT authorship contribution statement

Laura Myers had full access to all the data in the study and takes complete responsibility for the project administration, supervision, validation, and formal analysis. Authors were either employees of or received support from BI and actively engaged in the conceptualization, methodology, formal analysis, validation, and interpretation of the data; writing – original draft, writing – review, and editing of the manuscript.

Funding

This study was funded by Boehringer Ingelheim (BI) Inc. The study lead was Laura Myers, MD, MPH of Kaiser Permanente Northern California. The medical writing support was provided by Claire Line, Ph.D., of Cactus Life Sciences (part of Cactus Communications).

Notation of prior abstract publication/presentation

The results presented herein have been submitted to the American Thoracic Society (ATS) International Conference, San Francisco, May 12–18, 2022.

Declaration of competing interest

Dr. Bonnie Donato, Dr. Asif Shaikh, and Dr. Jessica Franchino-Elder are employees of BI. Dr. Richard Murray is the Chief Medical Officer of Spire Health and reports receiving consulting fees from BI; he serves as the Chairman of the Board for the Allergy and Asthma Foundation of America. Dr. Vincent Liu, Dr. Laura Myers, and Dr. Patricia Kipnis

received funding from BI to perform the study.

Acknowledgments

Medical writing support was provided by Claire Line, Ph.D., at Cactus Life Sciences (part of Cactus Communications).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2022.107064.

References

[1] M.I. Restrepo, O. Sibila, A. Anzueto, Pneumonia in patients with chronic obstructive pulmonary disease, Tuberc. Respir. Dis. 81 (3) (2018) 187–197.
[2] C. Janson, G. Johansson, B. Stallberg, K. Lisspers, P. Olsson, D.L. Keininger, et al., Identifying the associated risks of pneumonia in COPD patients: ARCTIC an observational study, Respir. Res. 19 (1) (2018) 172.
[3] A. Liapikou, E. Polverino, S. Ewig, C. Cilloniz, M.A. Marcos, J. Mensa, et al., Severity and outcomes of hospitalised community-acquired pneumonia in COPD patients, Eur. Respir. J. 39 (4) (2012) 855–861.
[4] T.A. Bhat, L. Panzica, S.G. Kalathil, Y. Thanavala, Immune dysfunction in patients with chronic obstructive pulmonary disease, Ann. Am. Thorac. Soc. 12 (Suppl 2) (2015) S169–S175.
[5] G. Lippi, B.M. Henry, Chronic obstructive pulmonary disease is associated with severe coronavirus disease 2019 (COVID-19), Respir. Med. 167 (2020), 105941.
[6] G. Rabbani, S.M. Shariful Islam, M.A. Rahman, N. Amin, B. Marzan, R.C. Robin, et al., Pre-existing COPD is associated with an increased risk of mortality and severity in COVID-19: a rapid systematic review and meta-analysis, Expet Rev. Respir. Med. 15 (5) (2021) 705–716.
[7] Q. Zhao, M. Meng, R. Kumar, Y. Wu, J. Huang, N. Lian, et al., The impact of COPD and smoking history on the severity of COVID-19: a systemic review and meta-analysis, J. Med. Virol. 92 (10) (2020) 1915–1921.
[8] F.M. Reyes, M. Hache-Marliere, D. Karamanis, C.G. Berto, R. Estrada, M. Langston, et al., Assessment of the association of COPD and asthma with in-hospital mortality in patients with COVID-19. A systematic review, meta-analysis, and meta-regression analysis, J. Clin. Med. 10 (10) (2021) 2087.
[9] R.M. Marron, M. Zheng, G. Fernandez Romero, H. Zhao, R. Patel, I. Leopold, et al., Impact of chronic obstructive pulmonary disease and emphysema on outcomes of hospitalized patients with coronavirus disease 2019 pneumonia, chronic, Obstr. Pulm. Dis. 8 (2) (2021) 255–268.
[10] D. Meza, B. Khuder, J.I. Bailey, S.R. Rosenberg, R. Kalhan, P.A. Reyfman, Mortality from COVID-19 in patients with COPD: a US study in the N3C data enclave, Int. J. Chronic Obstr. Pulm. Dis. 16 (2021) 2323–2326.
[11] K. Dorjee, H. Kim, E. Bonomo, R. Dolma, Prevalence and predictors of death and severe disease in patients hospitalized due to COVID-19: a comprehensive systematic review and meta-analysis of 77 studies and 38,000 patients, PLoS One 15 (12) (2020), e0243191.
[12] A. Izcovich, M.A. Ragusa, F. Tortosa, M.A. Lavena Marzio, C. Agnoletti, A. Bengolea, et al., Prognostic factors for severity and mortality in patients infected with COVID-19: a systematic review, PLoS One 15 (11) (2020), e0241955.
[13] M. Fekete, Z. Szarvas, V. Fazekas-Pongor, A. Feher, N. Dosa, A. Lehoczki, et al., COVID-19 infection in patients with chronic obstructive pulmonary disease: from pathophysiology to therapy, Mini-review, Physiol. Int. (2022).
[14] J.M. Leung, C.X. Yang, A. Tam, T. Shaipanich, T.L. Hackett, G.K. Singhera, et al., ACE-2 expression in the small airway epithelia of smokers and COPD patients: implications for COVID-19, Eur. Respir. J. 55 (5) (2020), 2000688.
[15] A. Agusti, O. Sibila, S. Casas-Recasens, N. Mendoza, L. Perea, A. Lopez-Giraldo, et al., Molecular interactions of SARS-CoV-2 in lung tissue of patients with chronic obstructive pulmonary disease, Ann. Am. Thorac. Soc. 18 (11) (2021) 1922–1924.
[16] A. Watson, L. Oberg, B. Angermann, C.M. Spalluto, M. Huhn, H. Burke, et al., Dysregulation of COVID-19 related gene expression in the COPD lung, Respir. Res. 22 (1) (2021) 164.
[17] N. Gordon, T. Lin, The kaiser Permanente northern California adult member health survey, Perm. J. 20 (4) (2016) 15–225.
[18] P.K. Lindenauer, M.S. Shieh, M.S. Stefan, K.A. Fisher, S.D. Haessler, P.S. Pekow, et al., Hospital procalcitonin testing and antibiotic treatment of patients admitted for chronic obstructive pulmonary disease exacerbation, Ann. Am. Thorac. Soc. 14 (12) (2017) 1779–1785.
[19] F.E. Lithander, S. Neumann, E. Tenison, K. Lloyd, T.J. Welsh, J.C.L. Rodrigues, et al., COVID-19 in older people: a rapid clinical review, Age Ageing 49 (4) (2020) 501–515.
[20] Geriatric Medicine Research Collaborative, Covid Collaborative, C. Welch, Age and Frailty Are Independently Associated with Increased Mortality in COVID-19: Results of an International Multi-Centre Study, SSRN, 2020.
[21] A.S. Gershon, C. Wang, J. Guan, J. Vasilevska-Ristovska, L. Cicutto, T. To, Identifying individuals with physcian diagnosed COPD in health administrative databases, COPD 6 (5) (2009) 388–394.
[22] L.C. Messer, B.A. Laraia, J.S. Kaufman, J. Eyster, C. Holzman, J. Culhane, et al., The development of a standardized neighborhood deprivation index, J. Urban Health 83 (6) (2006) 1041–1062.
[23] M.R. Andrews, K. Tamura, S.E. Claudel, S. Xu, J.N. Ceasar, B.S. Collins, et al., Geospatial analysis of neighborhood deprivation index (NDI) for the United States by county, J. Maps 16 (1) (2020) 101–112.
[24] C. van Walraven, P.C. Austin, A. Jennings, H. Quan, A.J. Forster, A modification of the Elixhauser comorbidity measures into a point system for hospital death using administrative data, Med. Care 47 (6) (2009) 626–633.
[25] G.J. Escobar, C. Plimier, J.D. Greene, V. Liu, P. Kipnis, Multiyear rehospitalization rates and hospital outcomes in an integrated health care system, JAMA Netw. Open 2 (12) (2019), e1916769.
[26] G.J. Escobar, M.N. Gardner, J.D. Greene, D. Draper, P. Kipnis, Risk-adjusting hospital mortality using a comprehensive electronic record in an integrated health care delivery system, Med. Care 51 (5) (2013) 446–453.
[27] D.C. Ashana, G.L. Anesi, V.X. Liu, G.J. Escobar, C. Chesley, N.D. Eneanya, et al., Equitably allocating resources during crises: racial differences in mortality prediction models, Am. J. Respir. Crit. Care Med. 204 (2) (2021) 178–186.
[28] M.A.F. Pimentel, O.C. Redfern, J. Malycha, P. Meredith, D. Prytherch, J. Briggs, et al., Detecting deteriorating patients in the hospital: development and validation of a novel scoring system, Am. J. Respir. Crit. Care Med. 204 (1) (2021) 44–52.
[29] T. Lagu, P.S. Pekow, M.S. Shieh, M. Stefan, Q.R. Pack, M.A. Kashef, et al., Validation and comparison of seven mortality prediction models for hospitalized patients with acute decompensated heart failure, Circ. Heart Fail. 9 (8) (2016), https://doi.org/10.1161/CIRCHEARTFAILURE.1115.002912e002912.
[30] S.S. Kadri, J. Gundrum, S. Warner, Z. Cao, A. Babiker, M. Klompas, et al., Uptake and accuracy of the diagnosis code for COVID-19 among US hospitalizations, JAMA 324 (24) (2020) 2553–2554.
[31] Centers for Disease Control and Prevention, New ICD-10-CM code for the 2019 novel coronavirus (COVID-19), december 3, 2020, Atlanta, Georgia, https://www.cdc.gov/nchs/data/icd/Announcement-New-ICD-code-for-coronavirus-19-508.pdf. (Accessed 27 July 2021).
[32] D.A. Asch, M.N. Islam, N.E. Sheils, Y. Chen, J.A. Doshi, J. Buresh, et al., Patient and hospital factors associated with differences in mortality rates among black and white US medicare beneficiaries hospitalized with COVID-19 infection, JAMA Netw. Open 4 (6) (2021), e2112842.
[33] J.A.W. Gold, K.K. Wong, C.M. Szablewski, P.R. Patel, J. Rossow, J. da Silva, et al., Characteristics and clinical outcomes of adult patients hospitalized with COVID-19 - Georgia, March 2020, MMWR Morb. Mortal. Wkly. Rep. 69 (18) (2020) 545–550.
[34] J.Y. Ko, M.L. Danielson, M. Town, G. Derado, K.J. Greenlund, P.D. Kirley, et al., Risk Factors for COVID-19-Associated Hospitalization: COVID-19-Associated Hospitalization Surveillance Network and Behavioral Risk Factor Surveillance System, Cold Spring Harbor Laboratory, 2020.
[35] C.M. Petrilli, S.A. Jones, J. Yang, H. Rajagopalan, L. O'Donnell, Y. Chernyak, et al., Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study, BMJ 369 (2020) m1966. –m1966.
[36] P.R. Rosenbaum, D.B. Rubin, The central role of the propensity score in observational studies for causal effects, Biometrika 70 (1) (1983) 41–55.
[37] S. Portet, A primer on model selection using the Akaike Information Criterion, Infect. Dis. Model. 5 (2020) 111–128.
[38] D. Singer, L.G.S. Bengtson, C. Elliott, A.R. Buikema, J. Franchino-Elder, Healthcare resource utilization, exacerbations, and readmissions among medicare patients with chronic obstructive pulmonary disease after long-acting muscarinic antagonist therapy initiation with soft mist versus dry powder inhalers, Int. J. Chronic Obstr. Pulm. Dis. 15 (2020) 3239–3250.
[39] S.R. Palli, M. Frazer, M. DuCharme, A.R. Buikema, A.J. Anderson, J. Franchino-Elder, Differences in real-world health and economic outcomes among patients with COPD treated with combination tiotropium/olodaterol versus triple therapy, J. Manag. Care Spec. Pharm. 26 (10) (2020) 1363–1374.
[40] D.A. Puebla Neira, A. Watts, J. Seashore, A. Duarte, S.P. Nishi, E. Polychronopoulou, et al., Outcomes of patients with COPD hospitalized for coronavirus disease 2019, chronic, Obstr. Pulm. Dis. 8 (4) (2021) 517–527.
[41] J.Y. So, N.N. O'Hara, B. Kenaa, J.G. Williams, C.L. deBorja, J.F. Slejko, et al., Population decline in COPD admissions during the COVID-19 pandemic associated with lower burden of community respiratory viral infections, Am. J. Med. 134 (10) (2021) 1252–1259, e1253.
[42] A. Pooler, R. Beech, Examining the relationship between anxiety and depression and exacerbations of COPD which result in hospital admission: a systematic review, Int. J. Chronic Obstr. Pulm. Dis. 9 (2014) 315–330.
[43] J.M. Quintana, C. Esteban, A. Unzurrunzaga, S. Garcia-Gutierrez, N. Gonzalez, I. Barrio, et al., Predictive score for mortality in patients with COPD exacerbations attending hospital emergency departments, BMC Med. 12 (1) (2014) 66.
[44] J.M. Quintana, C. Esteban, A. Unzurrunzaga, S. Garcia-Gutierrez, N. Gonzalez, I. Lafuente, et al., Prognostic severity scores for patients with COPD exacerbations attending emergency departments, Int. J. Tubercul. Lung Dis. 18 (12) (2014) 1415–1420.
[45] R. Hallin, G. Gudmundsson, C. Suppli Ulrik, M.M. Nieminen, T. Gislason, E. Lindberg, et al., Nutritional status and long-term mortality in hospitalised patients with chronic obstructive pulmonary disease (COPD), Respir. Med. 101 (9) (2007) 1954–1960.
[46] E. Chailleux, J.P. Laaban, D. Veale, Prognostic value of nutritional depletion in patients with COPD treated by long-term oxygen therapy: data from the ANTADIR observatory, Chest 123 (5) (2003) 1460–1466.
[47] R. Bernabeu-Mora, G. Garcia-Guillamon, E. Valera-Novella, L.M. Gimenez-Gimenez, P. Escolar-Reina, F. Medina-Mirapeix, Frailty is a predictive factor of readmission within 90 days of hospitalization for acute exacerbations of chronic obstructive pulmonary disease: a longitudinal study, Ther. Adv. Respir. Dis. 11 (10) (2017) 383–392.

[48] D. Graziani, J.B. Soriano, C. Del Rio-Bermudez, D. Morena, T. Diaz, M. Castillo, et al., Characteristics and prognosis of COVID-19 in patients with COPD, J. Clin. Med. 9 (10) (2020) 3259.
[49] J.S. Alqahtani, T. Oyelade, A.M. Aldhahir, S.M. Alghamdi, M. Almehmadi, A. S. Alqahtani, 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 15 (5) (2020), e0233147.
[50] P. Aveyard, M. Gao, N. Lindson, J. Hartmann-Boyce, P. Watkinson, D. Young, et al., Association between pre-existing respiratory disease and its treatment, and severe COVID-19: a population cohort study, Lancet Respir. Med. 9 (8) (2021) 909–923.
[51] P. Rogliani, D. Lauro, N. Di Daniele, A. Chetta, L. Calzetta, Reduced risk of COVID-19 hospitalization in asthmatic and COPD patients: a benefit of inhaled corticosteroids? Expet Rev. Respir. Med. 15 (4) (2021) 561–568.
[52] Centers for Disease Control and Prevention (CDC), COVID-NET: COVID-19-Associated hospitalization surveillance Network. https://gis.cdc.gov/grasp/COVIDNet/COVID19_3.html. (Accessed 27 August 2022).
[53] Centers for Disease Control and Prevention (CDC), Chronic obstructive pulmonary disease (COPD). Data and statistics. https://www.cdc.gov/copd/data-and-statistics/state-estimates.html. (Accessed 27 August 2022).
[54] F.V. Gerayeli, S. Milne, C. Cheung, X. Li, C.W.T. Yang, A. Tam, et al., COPD and the risk of poor outcomes in COVID-19: a systematic review and meta-analysis, EClinicalMedicine 33 (2021).
[55] Y. Lacasse, J.M. Daigle, S. Martin, F. Maltais, Validity of chronic obstructive pulmonary disease diagnoses in a large administrative database, Can. Respir. J. 19 (2) (2012) e5–9.
[56] B.D. Stein, A. Bautista, G.T. Schumock, T.A. Lee, J.T. Charbeneau, D.S. Lauderdale, et al., The validity of International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis codes for identifying patients hospitalized for COPD exacerbations, Chest 141 (1) (2012) 87–93.
[57] S.H. Chu, E.S. Wan, M.H. Cho, S. Goryachev, V. Gainer, J. Linneman, et al., An independently validated, portable algorithm for the rapid identification of COPD patients using electronic health records, Sci. Rep. 11 (1) (2021), 19959.
[58] American Lung Association, Trends in Lung Disease. COPD Risk Factors and Patient Characteristics, 2018. https://www.lung.org/research/trends-in-lung-disease/copd-trends-brief/copd-risk-factors. (Accessed 26 August 2022).
[59] R.E. Jordan, K.K. Cheng, M.R. Miller, P. Adab, Passive smoking and chronic obstructive pulmonary disease: cross-sectional analysis of data from the Health Survey for England, BMJ Open 1 (2) (2011), e000153.
[60] S.S. Salvi, P.J. Barnes, Chronic obstructive pulmonary disease in non-smokers, Lancet 374 (9691) (2009) 733–743.
[61] D. Adeloye, P. Song, Y. Zhu, H. Campbell, A. Sheikh, I. Rudan, Global, regional, and national prevalence of, and risk factors for, chronic obstructive pulmonary disease (COPD) in 2019: a systematic review and modelling analysis, Lancet Respir. Med. 10 (5) (2022) 447–458.
[62] N. Gordon, Similarity of Adult Kaiser Permanente Members to the Adult Population in Kaiser Permanente's Northern California Service Area: Comparisons Based on the 2017/2018 Cycle of the California Health Interview Survey, Report prepared for the Kaiser Permanente Division of Research, Oakland, CA, November 8, 2020. https://divisionofresearch.kaiserpermanente.org/projects/memberhealthsurvey/SiteCollectionDocuments/compare_kp_ncal_chis2017-18.pdf. (Accessed 26 August 2022).
[63] E. Pleguezuelos, A. Del Carmen, E. Moreno, P. Ortega, X. Vila, L. Ovejero, et al., The experience of COPD patients in lockdown due to the COVID-19 pandemic, Int. J. Chronic Obstr. Pulm. Dis. 15 (2020) 2621–2627.
[64] H. McAuley, K. Hadley, O. Elneima, C.E. Brightling, R.A. Evans, M.C. Steiner, et al., COPD in the time of COVID-19: an analysis of acute exacerbations and reported behavioural changes in patients with COPD, ERJ Open Res 7 (1) (2021), 00718–02020.