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

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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, KPMC; LAP52, Laboratory Acute Physiology Score, version 2; N3C, National COVID Cohort Collaboration; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

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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. Admission 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
comorbidity burden, and were more likely to be smokers than those
number of healthcare encounters in the year before COVID-19 diagnosis
outpatient or inpatient setting. Patients with COPD had a higher median
treated as inpatients). Patients with COPD were older, had a higher
according to whether they required inpatient treatment for COVID-19
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: 3–20)
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

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-positive 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 (me-
dian: 2 [IQR: 1–4] vs 1 [IQR: 1–2]), and inpatient encounters (me-
dian: 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: 3–20)
COPD-related encounters in the 3 years before COVID-19 diagnosis.

Continuous variables are expressed as median (interquartile range). Categorical
variables are expressed as n (%).
COPD = chronic obstructive pulmonary disease, COVID-19 = coronavirus dis-
ease-2019. * The scale ranges from −1.8 to 3.72, with higher values indicating worse
socioeconomic status.
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 (LAPSO 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 intu-
bate, 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 hos-
ital 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: 3.40–4.68; 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 2
Respiratory variables describing patients with COVID-19 by history of COPD.

| Variable | All COVID+ (n = 19,558) | With COPD (n = 18861) | P value |
|----------|-------------------------|-----------------------|---------|
| History of lung cancer | 28 (0.1) | 7 (0.1) | 0.0006 |
| History of pneumonia | 3812 (19.5) | 3470 (18.4) | <0.0001 |
| History of dyspnea | 4360 (22.3) | 4986 (26.0) | <0.0001 |
| History of sarcoid | 34 (0.4) | 32 (0.2) | 0.69 |
| History of bronchiectasis | 120 (1.5) | 82 (0.4) | <0.0001 |
| History of interstitial lung disease | 260 (1.3) | 217 (1.3) | <0.0001 |
| Supplemental oxygen in 1 year before COVID-19 diagnosis | 450 (2.3) | 369 (2.0) | <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, n/a = not applicable.

### 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 | 99 (87–113) | 101 (89–113) | 0.22 |
| Systolic blood pressure, mmHg | 112 | 111 | 112 | 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 |
| LAPSO<sup>a</sup> | 77 (57–101) | 87 (67–109) | 76 (56–100) | <0.0001 |
| Highest level of respiratory support | 464 (14.1) | 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 | 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<sub>2</sub> ratio | 144 (40.5) | 165 (47.2) | 141 (49-232) | 0.006 |
| First PaO<sub>2</sub>/FiO<sub>2</sub> ratio | 112 (45.2) | 155 (58.6) | 111 (74-200) | 0.04 |
| Lowest PaO<sub>2</sub>/FiO<sub>2</sub> ratio | 80 (34.0) | 88 (36.3) | 78 (56-137) | 0.11 |
| First PaCO<sub>2</sub>, mmHg | 36 (32–40) | 40 (34–50) | 36 (32–41) | <0.0001 |
| First pH | 7.43 | 7.43 | 7.44 | 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 | 12.0 (7.2–8.3) | 1.5 (0.8–7.2) | 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 c-reactive protein count, % | 1 (0–3) | 2 (0–4) | 1 (0–3) | 0.002 |
| Advanced care directive at 1 h | 2569 (89.1) | 202 (74.8) | 2367 (90.5) | <0.0001 |
| Full code | | | | |
| 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 | 2250 (78.0) | 150 (55.6) | 2100 (80.3) | <0.0001 |
| Full code | 623 (21.6) | 117 (43.3) | 506 (19.3) | |
| Limitation of life-sustaining therapies | | | | |
| 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) | 2257 (78.2) | 173 (64.1) | 2084 (79.7) | <0.0001 |
| Home | 237 (8.2) | 45 (16.7) | 192 (7.3) | <0.0001 |
| Skilled nursing facility | 28 (1.0) | <5 | 25 (1.0) | 0.80 |
| Hospice | 357 (12.3) | 48 (17.8) | 309 (11.8) | 0.005 |

(continued on next page)
Participants with a history of frequent exacerbations with patients 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 [18,46], 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 including age were included in all models to control for differences in patient populations between groups.
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)                         |

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.

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 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.
§ Adjusted for the covariates in Model 3 plus body mass index, smoking, month of positive COVID-19 test, and the number of prior healthcare encounters in the previous year.
* Frequent COPD exacerbations were defined as >1 exacerbation.

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.

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].
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 macropurulent 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 (3.6%) 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.

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Notation of prior abstract publication/presentation

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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...
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