Long-term impact of SARS-CoV-2 on recurrent COPD exacerbations

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Summary

Background SARS-CoV-2 infection could increase the long-term risk of recurrent chronic obstructive pulmonary disease (COPD) exacerbations. This study investigated the long-term risk of COPD exacerbations following SARS-CoV-2 infection, with comparisons by hospitalisation status.

Methods We conducted a retrospective cohort study using data from a large urban academic health system (March 2020–February 2025). The final cohort comprised of 2268 hospitalised and 1471 non-hospitalised COVID-19 patients with pre-existing COPD, each matched 1:1 by propensity score with non-COVID controls. Adjusted hazard ratios (aHRs) were estimated using Andersen-Gill models, and adjusted incidence rate ratios (aIRRs) using negative binomial models. Cumulative hazards were derived from Nelson-Aalen curves. Secondary analyses evaluated socioeconomic factors and multiple sensitivity analyses assessed robustness.

Findings Among hospitalised patients, the incidence rate of COPD exacerbations was 35.7 per 100 person-years in the COVID-19 cohort, compared to 15.9 in controls (aIRR 1.81 [95% CI, 1.45–2.26]). Among non-hospitalised patients, rates were 13.7 vs 10.6 (aIRR 1.23 [0.88–1.73]). Hospitalised patients had a higher overall hazard of recurrent COPD exacerbations (aHR 1.69 [1.36–2.10]; $p < 0.001$), with risk persisting over four years post-infection. No significant difference was observed among non-hospitalised patients. Unmet social needs increased the risk by 53% among hospitalised patients, while Medicaid or Medicare coverage more than doubled the risk among non-hospitalised patients relative to private insurance. Findings were consistent across multiple sensitivity analyses.

Interpretation COVID-19 hospitalisation was associated with a sustained increased risk of recurrent COPD exacerbations, underscoring the need for long-term pulmonary follow-up and targeted interventions in this high-risk population.

Funding None.

Keywords: COPD exacerbation; Pulmonary infection; SARS-CoV-2; SDOH

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide, characterised by progressive airflow limitation and a heightened susceptibility to exacerbations.[1,2] Acute exacerbations of COPD are major events that contribute to accelerated lung function decline, increased healthcare utilisation, and mortality risk.[2,3] Viral respiratory infections, including influenza and coronaviruses, are well-recognised triggers of exacerbation, primarily through mechanisms of heightened systemic inflammation, impaired mucociliary clearance, and direct epithelial damage.[3]

The emergence of SARS-CoV-2 has introduced new concerns regarding its long-term impact on patients with pre-existing respiratory diseases, particularly COPD.[4] Early studies reported that individuals with COPD are at increased risk of severe COVID-19 outcomes, including hospitalisation, critical illness, and mortality.[4] Alqahtani et al. (2020) conducted a meta-analysis demonstrating that COPD patients had a fourfold increased risk of severe COVID-19 compared to those without COPD.[5] Lippi and Henry (2020) reported that COPD was one of the strongest predictors of poor COVID-19 prognosis, with significantly higher ICU admission and mortality rates.[6]

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Research in context

Evidence before this study

We searched PubMed (January 2020–January 2025) using terms related to COPD, COVID-19, exacerbations, and long-term outcomes. Prior studies suggested short-term increases in COPD exacerbations during or soon after COVID-19 illness, but no study evaluated the long-term burden of recurrent COPD exacerbations over multiple years. Evidence incorporating social determinants of health into post-COVID COPD outcomes has also been limited.

Added value of this study

Using a large, diverse urban health system and nearly five years of post-infection follow-up, we applied recurrent-event models in propensity-matched cohorts of hospitalised and non-hospitalised COPD patients with COVID-19 vs non-COVID controls. We found that COVID-19 hospitalisation was associated with a sustained increase in recurrent COPD exacerbations, whereas non-hospitalised infection showed no significant increase. Socioeconomic factors were strong independent predictors of recurrent COPD exacerbation.

Implications of all the available evidence

These findings indicate that severe COVID-19 identifies a vulnerable COPD subgroup whose risk of recurrent COPD exacerbation remains elevated long after acute recovery and is not explained by clinical severity markers alone. Incorporating COVID-19 hospitalisation history into COPD management and providing proactive, long-term pulmonary follow-up, while addressing social and economic barriers, may be essential to reducing the post-COVID exacerbation burden in this high-risk population.

However, less is known about the prolonged effects of SARS-CoV-2 infection on COPD disease progression. Given that severe COVID-19 is associated with persistent pulmonary inflammation, endothelial dysfunction, and fibrosis,[7,8] and the sheer number of individuals affected by COVID-19, there is growing concern that patients hospitalised with COVID-19 who have COPD may experience a sustained increase in the risk of recurrent COPD exacerbation. A few studies have indicated that viral-induced lung injury can result in long-term sequelae, including post-viral fibrosis and chronic airway inflammation, which may predispose patients to recurrent COPD exacerbations.[9,10] Evidence from post-severe acute respiratory syndrome (SARS) and post-Middle-East respiratory syndrome (MERS) studies suggests that coronavirus infections may have prolonged respiratory consequences, leading to impaired lung function and increased susceptibility to exacerbations in patients with underlying respiratory conditions.[11,12]

The goal of this study was to investigate whether COVID-19 is associated with long-term increases in risk of COPD exacerbations in a large urban health system. Our analysis is based on data from a large, predominant urban health system in the Bronx, which was among the early epicentres of the COVID-19 pandemic and experienced multiple waves of infections. Understanding the interplay between COVID-19 and COPD is crucial for developing effective long-term management strategies and mitigating the risk of disease progression in this vulnerable population.

Methods

Study design and data source

This retrospective cohort study utilised data from the Montefiore Health System (Bronx, New York City), which comprises multiple hospitals and numerous clinics serving a large, racially and ethnically diverse population in an urban setting. As New York City was an early epicentre of the COVID-19 pandemic and subsequent surges of infection, this is an ideal setting to provide early information on the longer-term impacts of SARS-CoV-2 infection among patients with COPD. Data were extracted from the electronic medical record and standardised using the OMOP common data model, which has been described previously.[13–22] The study was approved by the Einstein-Montefiore Institutional Review Board with an exemption for informed consent and a HIPAA waiver (IRB# 2021-13658).

Study population

The study cohort included adult patients with a documented diagnosis of COPD before the index date and at least 14 days of post–index follow-up. To reduce bias from differential healthcare utilisation, we also adjusted for patients with at least 1 year of documented healthcare encounters before the index encounter. Patients with COVID-19 were identified by polymerase chain reaction (PCR)-confirmed SARS-CoV-2 infection between March 2020 and February 2025. Patients hospitalised with COVID-19 were defined as those with a positive test and an inpatient admission within 14 days or during the same hospitalisation. For both hospitalised and non-hospitalised patients, the index date was the date of the positive PCR test. Patients in the control group without COVID-19 had no record of a positive SARS-CoV-2 test or COVID-19 diagnosis during the study period. Potential misclassification is discussed in the Limitation section.

We constructed two separate 1:1 propensity score-matched cohorts to compare (A) patients hospitalised with COVID-19 who had COPD with matched controls without COVID-19, and (B) non-hospitalised patients

with COVID-19 who had COPD with matched controls without COVID-19. Propensity scores were estimated using logistic regression, including demographic characteristics (age, sex, race, and ethnicity) and comorbidities (obesity, smoking, hypertension, diabetes, chronic kidney disease, liver disease, congestive heart failure, coronary artery disease, myocardial infarction, asthma, obstructive sleep apnoea, and pulmonary hypertension) and observation time.

Each patient with COVID-19 was 1:1 matched to a non-COVID-19 control without replacement using nearest-neighbour matching on the propensity score and observation time. Observation time was included in the propensity score to reduce bias from differential healthcare engagement, follow-up intensity, and censoring patterns between groups. Covariate balance between matched groups was assessed using standardised mean differences, with all matched covariates achieving an absolute standardised mean difference <0.1, indicating adequate balance. The final analytic sample included 2268 patients hospitalised with COVID-19 (one patient could not be matched within the calliper and was therefore excluded from the matched analysis) and 1471 non-hospitalised patients with COVID-19, and their matched non-COVID-19 controls in equal numbers.

Exposure and covariates

The primary exposure was SARS-CoV-2 infection, categorised into hospitalised COVID-19, non-hospitalised COVID-19, or non-COVID-19 controls. Baseline demographic characteristics, including age (calculated from birthdate to the index date), sex (obtained from electronic health record (EHR) records) race, and ethnicity, were tabulated, with race/ethnicity presented as Black, White, Hispanic, and Other. The "Other" category included patients who identified as Pacific Islander and American Indian/Alaska Native individuals, as well as patients whose race and/or ethnicity did not fall into the displayed Black, White, or Hispanic bins (including declined, other unspecified, or unknown). Comorbid conditions were identified using ICD-10 codes and documented at any time before the index date. These included obesity, smoking, hypertension, type 1 diabetes (T1D), type 2 diabetes (T2D), chronic kidney disease (CKD), liver disease, congestive heart failure (CHF), coronary artery disease (CAD), myocardial infarction (MI), asthma, obstructive sleep apnoea (OSA), and pulmonary hypertension (PHTN). Patients with a history of COPD encompassed a range of conditions, including chronic obstructive pulmonary disease, unspecified (J44.9), COPD with acute lower respiratory infection (J44.0), and COPD with (acute) exacerbation (J44.1), as well as emphysema (J43.x), excluding unilateral pulmonary emphysema (J43.0).

To investigate the potential contribution of social determinants of health (SDOH) to outcomes, we incorporated documented social needs, insurance coverage, and neighbourhood-level income. Since 2016, the Montefiore Health System has utilised a standardised SDOH screening instrument developed from the Health Leads Toolkit (https://healthleadsusa.org/). Patient participation in this screening was voluntary. Analyses incorporating SDOH variables were restricted to patients with available screening data, and we did not perform imputation given the relative stability of SDOH factors during the observation window. The screening tool evaluated eight domains of unmet social needs: housing stability, food security, utility access, healthcare transportation, medication affordability, childcare or eldercare requirements, legal services, and safety concerns. We dichotomised patients into those reporting no unmet social needs vs those reporting one or more unmet needs. Neighbourhood-level income was approximated using median household income at the patient's ZIP code level from the U.S. Census Bureau American Community Survey. Insurance status was defined as the most recent payer category (Medicaid, Medicare, private, or other) documented closest to the index date. Insurance status was available for most patients, with less than 1% missing across cohorts. ZIP code-linked median household income was similarly complete, with approximately 1% missing due to unavailable or invalid address data.

COVID-19 vaccination was defined as receipt of at least one vaccine dose before the index date. Vaccination data were sourced from the New York State Immunisation Information System (including New York City data), patient self-report, Care Everywhere data shared across Epic organisations, and vaccinations administered within the Montefiore Health System. This allowed for the capture of both in-system and external COVID-19 vaccinations. Frequent exacerbators were defined as having at least two COPD exacerbations in the year before the index. Reinfection was defined as a second positive PCR test ≥90 days after the first diagnosis in accordance with CDC guidelines.[23] and post–index influenza or respiratory syncytial virus (RSV) infections were identified using PCR-based diagnoses. Prior healthcare encounter was defined as having at least one documented clinical encounter within the health system ≥1 year before the index date, which was taken as a proxy for engagement with the healthcare system.

Outcomes

The primary outcome was the risk of recurrent COPD exacerbations over the study period. Exacerbations occurring within 7 days of each other were counted as a single episode. This interval was chosen to align with the Global Initiative for Chronic Obstructive Lung Disease 2025 recommendations, which describe a typical treatment duration of approximately 5 days for systemic corticosteroids and 5–7 days for antibiotics.[24]

In the primary analysis, COPD exacerbations were identified by an ICD-10 code of J44.1 and confirmed by evidence of pharmacologic treatment. For inpatient encounters, confirmation required administration of a short-acting beta-agonist, muscarinic antagonist, or systemic corticosteroid during hospitalisation. For outpatient encounters, confirmation required a prescription for one of these medications within 7 days of the diagnosis date. Encounters coded simultaneously for asthma and COPD exacerbation were excluded to minimise diagnostic misclassification.

Secondary analyses

To evaluate socioeconomic factors as predictors of COPD exacerbations, we examined insurance type, income tertile, and unmet social needs in multivariable models adjusting for COVID-19 status and baseline clinical characteristics.

Sensitivity analyses

We conducted multiple sensitivity analyses to assess the robustness of our findings under varied assumptions. First, we fit a multivariable Andersen-Gill model with full covariate adjustment in the unmatched cohort, following univariate analyses. Second, we implemented an Andersen-Gill model with inverse probability weighting (IPW) on the unmatched cohort. Third, in the match cohort, we fit a shared frailty model to account for within-person heterogeneity and unmeasured differences between patients. This approach allows for correlation between recurrent COPD exacerbation events within the same individuals, recognising that some patients may inherently have higher susceptibility to exacerbation even after adjusting for covariates, while treating death as non-informative censoring. Fourth, using our matched cohorts, we repeated analyses after excluding patients with post–index influenza or RSV infection to minimise confounding from other acute respiratory viral illnesses. Fifth, to isolate the association of the index COVID-19 event with subsequent COPD exacerbations, analyses were repeated after excluding individuals with documented SARS-CoV-2 reinfection during follow-up. The effect of COVID-19 reinfection was addressed through exclusion because subsequent reinfection lies on the causal pathway between the index COVID-19 event and subsequent COPD exacerbations. Further adjustment for reinfection would attenuate the total association between our main outcome of index COVID-19 severity and subsequent recurrent COPD exacerbations and introduce overadjustment bias. Sixth, we varied the minimum gap used to define distinct exacerbation events, repeating analyses using a 3-day gap. Seventh, we repeated analyses using a 14-day gap to apply a more conservative episode definition. Eighth, we fit a joint frailty model that simultaneously estimates recurrent COPD exacerbations and mortality, explicitly accounting for death as informative censoring through a shared patient-level frailty term. Ninth, to further assess the impact of potential misclassification of SARS-CoV-2 infection status among controls, we conducted a sensitivity analysis restricting the control group to patients with documented negative SARS-CoV-2 testing who remained negative throughout the study period. Finally, we calculated E-values to quantify the minimum strength of unmeasured confounding necessary to explain away the observed associations. All multivariable models included covariates as potential confounders, though these adjustments were not intended to support causal inference.

Statistical analysis

Descriptive statistics were used to summarise baseline characteristics. Continuous variables are reported as mean (SD). Distributional assumptions were assessed using graphical methods (including histograms and Q–Q plots), which showed no substantial deviations from approximate normality. Age and observation time were compared between groups using two-sample t-tests. Categorical variables are presented as counts (percentages) and were compared using chi-square or Fisher's exact tests, as appropriate.

Details of the propensity score models, including coefficients for all covariates, are provided in the Supplementary Table S1. The association between COVID-19 exposure and recurrent COPD exacerbations was modelled using the Andersen-Gill extension of the Cox proportional hazards model with a robust sandwich variance estimator, to account for within-person correlation of events. Tied event times were handled using the Breslow method, with right censoring at the end of follow-up. p values were derived from cluster-robust Wald tests.

The proportional hazards (PH) assumption was evaluated by testing an interaction between COVID-19 exposure and follow-up time within the Andersen–Gill model. Because standard Schoenfeld residual-based tests are not well suited to recurrent-event frameworks in which individuals can contribute multiple events, we used this time-interaction approach. No evidence of PH violations was observed in either the hospitalised or non-hospitalised cohorts (COVID-19 status × time interaction: all $p > 0.05$, cluster-robust Wald Test).

Although propensity score matching achieved adequate balance across all matched covariates, baseline vaccination status, which was not included in the matching algorithm, along with prespecified confounders, including prior frequent exacerbation history and baseline healthcare engagement, were adjusted for in all post-matching outcome models to reduce residual confounding. To compare COPD exacerbation rates across exposure groups, we fit a negative binomial regression model with log-transformed person-time as

an offset and reported adjusted incidence rate ratios (aIRRs). The Nelson-Aalen estimator was used to assess the cumulative hazard of COPD exacerbation. Separate curves were generated for patients hospitalised with COVID-19 and their matched non-COVID controls, and non-hospitalised patients with COVID-19 and their matched non-COVID controls. Sensitivity analyses used stabilised inverse probability weights (IPWs) to reduce confounding using the ATT (average treatment effect on the treated) method, and covariate balance was assessed using standardised mean differences. A joint frailty model with an Andersen-Gill formulation and death as a terminal event was used, incorporating a shared gamma-distributed frailty to account for informative censoring by mortality. All statistical analyses were conducted in Python and R.

Role of funders
There was no funding for this study.

Results

Study cohort

Among 1.9 million patients in the health system, 48,018 had a diagnosis of COPD. Of these, 5533 were diagnosed with COVID-19, and 42,485 had no documented COVID-19 diagnosis during the study period. After excluding patients without pre-existing COPD, those with fewer than two healthcare encounters, or with less than 14 days of post–index follow-up, 3742 patients with COVID-19 and pre-existing COPD and 15,952 patients without COVID-19 and with pre-existing COPD were eligible for analysis. The COVID-19 cohort was stratified by hospitalisation status into 2269 patients who were hospitalised and 1473 patients who were not hospitalised. Each subgroup was then matched 1:1 to non-COVID COPD controls using nearest-neighbour propensity score matching based on age, sex, race and ethnicity, obesity, smoking status, hypertension, diabetes, chronic kidney disease, liver disease, congestive heart failure, coronary artery disease, myocardial infarction, asthma, obstructive sleep apnoea, pulmonary hypertension, and observation time (Fig. 1). This resulted in final matched cohorts of 2268 hospitalised pairs and 1471 non-hospitalised pairs.

Baseline characteristics of the matched cohorts are presented in Table 1. After 1:1 propensity score matching, standardised mean differences were below 0.1 for all matched variables, indicating adequate balance. The patients in the hospitalised matched cohort (n = 2268 pairs) had a mean age of 73.4 years, was 45.0% male, 34.7% Black, and 16.9% White, with a high prevalence of hypertension (86.3%), type 2 diabetes (61.9%), chronic kidney disease (52.1%), and congestive heart failure (61.6%). At index, 6.1% required acute oxygen therapy, 3.7% required invasive mechanical ventilation, and 7.5% required non-invasive ventilation. The patients in the non-hospitalised matched cohort (n = 1471 pairs) was younger (mean age, 66.6 years), with lower comorbidity burden, including hypertension (77.0%), type

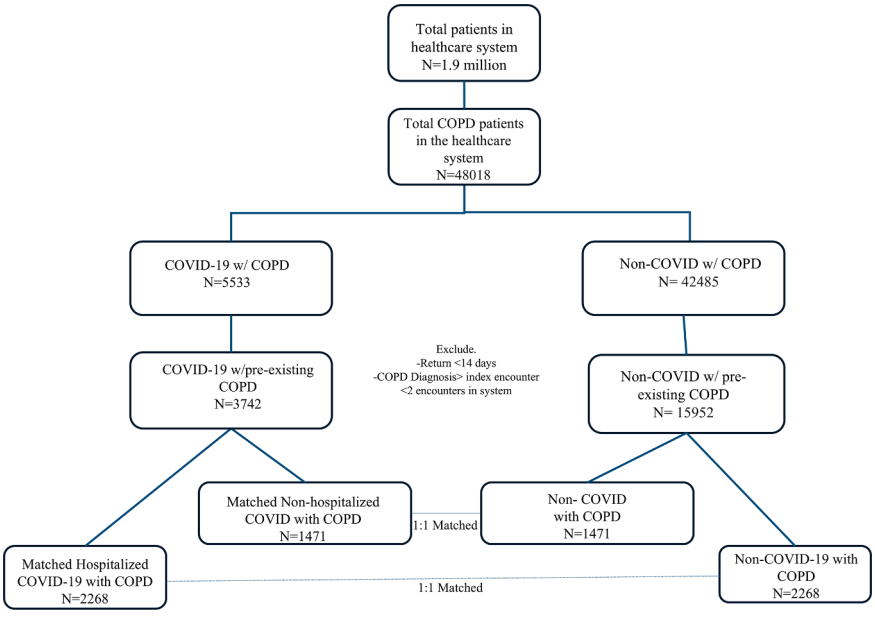

Fig. 1: Flowchart of study cohort selection.

Variable	A.Hospitalised vs Non-COVID			B. Non-hospitalised vs Non-COVID		
	COVID+ Hosp	Non-COVID	SMD[a]	COVID+ Non-Hosp	Non-COVID	SMD[a]
	(n = 2268)	(n = 2268)		(n = 1471)	(n = 1471)	
Observation Time, Mean (SD)	**23.49 (16.69)**	**22.63 (19.12)**	**0.048**	**26.5 (13.96)**	**25.4 (20.14)**	**0.065**
Demographics						
Age, Mean (SD)	73.4 (13.1)	73.7 (13.0)	0.025	66.6 (13.3)	67.0 (15.0)	0.035
Male	1020 (45.0%)	1047 (46.2%)	0.024	554 (37.7%)	589 (40.0%)	0.047
Female	1248 (55.0%)	1221 (53.8%)	0.024	917 (62.3%)	882 (60.0)%	0.047
Black	786 (34.7%)	811 (35.8%)	0.023	510 (34.7%)	501 (34.1%)	0.013
White	383 (16.9%)	392 (17.3%)	0.011	214 (14.5%)	234 (15.9%)	0.039
Hispanic	936 (41.3%)	893 (39.4%)	0.039	605 (41.1%)	575 (39.1%)	0.041
Other (Race/Ethnicity)	163 (7.2%)	172 (7.6%)	0.015	142 (9.7%)	161 (10.9%)	0.039
Comorbidities						
Obesity	1023 (45.1%)	977 (43.1%)	0.04	684 (46.5%)	661 (44.9%)	0.032
Smoking	1592 (70.2%)	1568 (69.1%)	0.024	1072 (72.9%)	1071 (72.8%)	0.002
Hypertension	1958 (86.3%)	1961 (86.5%)	0.006	1135 (77.2%)	1132 (77.0%)	0.005
Diabetes type 1	83 (3.7%)	76 (3.4%)	0.016	28 (1.9%)	26 (1.8%)	0.007
Diabetes type 2	1403 (61.9%)	1419 (62.6%)	0.014	702 (47.7%)	706 (48.0%)	0.006
Chronic kidney disease	1182 (52.1%)	1147 (50.6%)	0.03	460 (31.3%)	462 (31.4%)	0.002
Liver disease	164 (7.2%)	146 (6.4%)	0.032	39 (2.7%)	41 (2.8%)	0.006
Congestive heart failure	1397 (61.6%)	1358 (59.9%)	0.035	467 (31.7%)	480 (32.6%)	0.019
Coronary Artery disease	153 (6.7%)	155 (6.8%)	0.004	90 (6.1%)	86 (5.8%)	0.013
Myocardial Infarction	573 (25.3%)	529 (23.3%)	0.047	206 (14.0%)	215 (14.6%)	0.017
Asthma	1103 (48.6%)	1079 (47.6%)	0.02	869 (59.1%)	837 (56.9%)	0.045
Obstructive sleep apnoea	537 (23.7%)	500 (22.0%)	0.04	335 (22.8%)	312 (21.2%)	0.039
Pulmonary hypertension	572 (25.2%)	530 (23.4%)	0.042	195 (13.3%)	228 (15.5%)	0.063
Social and clinical factors						
≥1 unmet social need	228 (10.1%)	109 (4.8%)	0.202	183 (12.4%)	103 (7.0%)	0.182
Insurance						
Medicaid	603 (26.6%)	599 (26.4%)	0.005	425 (28.9%)	510 (34.7%)	0.125
Medicare	1125 (49.6%)	1102 (48.6%)	0.02	459 (31.2%)	558 (37.9%)	0.141
Private	515 (22.7%)	540 (23.8%)	0.026	538 (36.6%)	381 (25.9%)	0.231
Other	10 (0.4%)	7 (0.3%)	0.017	42 (2.9%)	10 (0.7%)	0.165
Baseline vaccination						
Vaccinated (Any)	807 (35.6%)	133 (5.9%)	0.732	745 (50.6%)	98 (6.7%)	0.971
Income (ZIP-level Median)						
Low tertile	911 (40.2%)	939 (41.4%)	0.024	477 (32.4%)	527 (35.8%)	0.072
Middle tertile	620 (27.3%)	586 (25.8%)	0.034	549 (37.3%)	460 (31.3%)	0.126
High tertile	713 (31.4%)	687 (30.3%)	0.024	421 (28.6%)	440 (29.9%)	0.029
Frequent exacerbator	174 (7.7%)	118 (5.2%)	0.102	53 (3.6%)	60 (4.1%)	0.026
Prior healthcare encounter	1834 (80.9%)	1885 (83.1%)	0.057	1255 (85.3%)	1208 (82.1%)	0.087
Hospitalisation severity						
Acute oxygen therapy	138 (6.1%)	–	–	–	–	–
Invasive mechanical ventilation	83 (3.7%)	–	–	–	–	–
Non-invasive ventilation	171 (7.5%)	–	–	–	–	–

[a]SMD: Standardise mean differences.

Table 1: **Baseline characteristics of hospitalised and non-hospitalised COVID-19 cohorts compared with Non-COVID controls after 1:1 propensity score.**

2 diabetes (48.0%), chronic kidney disease (31.4%), and congestive heart failure (32.6%). Demographic and clinical characteristics of the unmatched cohorts are presented in Supplementary Table S2.

Incidence of COPD exacerbations

Table 2 presents the incidence rates and adjusted incidence rate ratios (aIRRs) for recurrent COPD exacerbations comparing patients with COVID-19, stratified by hospitalisation status, with their matched patients without COVID-19. Among patients who were hospitalised, the incidence rate of recurrent COPD exacerbations was 35.7 per 100 person-years in the COVID-19 cohort compared with 15.9 per 100 person-years in matched controls (aIRR, 1.81 [95% CI, 1.45–2.26]). Among patients who were not hospitalised,

Category	Patients with ≥1 exacerbation (n, %)	# events	Person time (Years)	Exacerbation rate (/100 PY)	aIRR (95% CI)
A. Hospitalise vs Non COVID					
Hosp COVID+	470 (20.7%)	1584	4439.97	35.7	1.81 [1.45–2.26]
Non-COVID	262 (11.6%)	678	4276.54	15.9	1 (Ref)[a]
B. Non-hospitalised Vs Non COVID					
Non-hosp COVID+	185 (12.6%)	445	3261.10	13.7	1.23 [0.88–1.73]
Non-COVID	127 (8.63%)	329	3087.60	10.6	1 (Ref)[a]

aIRR: adjusted incidence rate ratio. PY: Person-Year. [a]Ref = reference group. aIRR model adjusted for frequent exacerbation history, baseline vaccination status, and healthcare system encounter at least 1 year before index date in addition to matched covariates.

***Table 2*: Exacerbation rates and adjusted incidence rate ratios for recurrent chronic obstructive pulmonary disease exacerbations among hospitalised and non-hospitalised COVID-19 patients compared with matched controls without COVID-19.**

the incidence rate was 13.7 per 100 person-years in the COVID-19 cohort compared with 10.6 per 100 person-years in matched controls (aIRR, 1.23 [95% CI, 0.88–1.73]). All models adjusted for baseline vaccination status, frequent exacerbation history, and baseline health care engagement.

Risk of COPD exacerbations

Time-stratified analyses revealed distinct risk patterns between patients with COVID-19 who were hospitalised and those who were not hospitalised (Table 3). Patients who were hospitalised exhibited significantly elevated risk of recurrent COPD exacerbation overall (aHR 1.69 [95% CI, 1.36–2.10]; $p < 0.001$) and in both time periods (0–24 months: aHR 1.56 [95% CI, 1.27–1.91]; $p < 0.001$; 24–48 months: aHR 1.57 [95% CI, 1.09–2.25]; $p = 0.016$), with this elevated risk persisting across early and late follow-up. In contrast, non-hospitalised patients showed no significant increase in risk overall (aHR 1.29 [95% CI, 0.92–1.80]; $p = 0.14$) or within either time period (0–24 months: aHR 1.26 [95% CI, 0.92–1.71]; $p = 0.15$; 24–48 months: aHR 0.80 [95% CI, 0.36–1.79]; $p = 0.59$). All p values reported using cluster-robust Wald tests.

Cumulative hazard of exacerbation

The Nelson-Aalen cumulative hazard estimates demonstrate differential risk of COPD exacerbations over 55 months of follow-up (Fig. 2). Patients with COVID-19 who were hospitalised (A) exhibited a higher cumulative hazard of exacerbations compared with their matched patients without COVID-19, with early and persistent separation of the curves. Patients with COVID-19 who were not hospitalised (B) showed a lower cumulative hazard than hospitalised patients, with initial overlap between the curves for non-hospitalised patients with COVID-19 and their matched patients without COVID-19, followed by modest separation later in follow-up.

Secondary and sensitivity analyses

To evaluate socioeconomic factors as predictors of COPD exacerbations, we examined insurance type, income tertile, and unmet social needs in multivariable models adjusting for COVID-19 status and baseline clinical characteristics (Supplementary Table S3). SDOH screening data were available for a subset of patients in the matched cohorts. In the hospitalised matched cohort, SDOH data were available for 1342 COVID-19 patients (59.2% of hospitalised COVID-19) and 600 non-COVID patients (26.5% of controls). In the non-hospitalised matched cohort, SDOH data were available for 945 COVID-19 patients (64.2% of non-hospitalised COVID) and 401 non-COVID patients (27.3% of controls). Approximately 1% of insurance status and income data were missing due to invalid or unavailable address data and were excluded from analyses.

Analysis	Hospitalised vs Non Covid			Non-hospitalised vs Non Covid		
	HR	95% CI	p-value	HR	95% CI	p-value
Overall[a]	1.69	1.36–2.09	<0.001	1.29	0.92–1.80	0.14
0–24 months[a]	1.56	1.27–1.91	<0.001	1.26	0.92–1.71	0.15
24–48 months[a]	1.57	1.09–2.25	0.016	0.80	0.36–1.79	0.59

HR: hazard ratio. [a]Models adjusted for frequent exacerbation history, baseline vaccination status, and healthcare system encounter at least 1 year before index date in addition to matched covariates.

***Table 3*: Time-stratified risk of recurrent COPD exacerbations comparing COVID-19 and matched Non-COVID controls using Andersen-Gill Adjusted HR Model.**

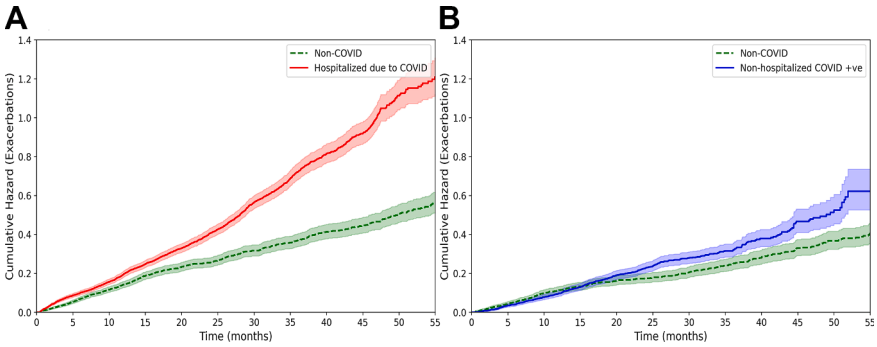

Fig. 2: Nelson–Aalen cumulative hazard estimates for recurrent COPD exacerbations in patients with pre-existing COPD. **A)** shows patients hospitalised with COVID-19 and their matched non-COVID controls. **B)** shows non-patients hospitalised with COVID-19 and their matched non-COVID controls. Shaded areas represent 95% confidence intervals.

Among hospitalised patients, those with at least one unmet social need were associated with a 53% increased risk of exacerbation (adjusted HR 1.53 [95% CI, 1.21–1.94]; $p < 0.001$, cluster-robust Wald Test). In contrast, among non-hospitalised patients, insurance type was the dominant socioeconomic predictor: Medicaid and Medicare beneficiaries experienced more than twice the risk of exacerbation compared to those with private insurance (Medicaid: adjusted HR 2.01 [95% CI, 1.36–2.96]; Medicare: adjusted HR 2.06 [95% CI, 1.42–2.99]; both $p < 0.001$), while unmet social needs were not significant ($p = 0.07$, cluster-robust Wald Test).

Sensitivity analyses across multiple specifications confirmed the robustness of the primary findings (Supplementary Tables S4–S8). The association between hospitalised COVID-19 and increased recurrent COPD exacerbation was consistent across all models, with adjusted hazard ratios ranging from 1.43 to 2.03. The E-value for the primary association was 2.77, indicating that an unmeasured confounder would need to be associated with both COVID-19 hospitalisation and risk of recurrent COPD exacerbation by a risk ratio of at least 2.77 to fully account for the observed association.

Discussion

In this retrospective cohort study of patients with pre-existing COPD, we found that hospitalisation for COVID-19 was associated with an increased risk of recurrent COPD exacerbations that persisted for several years after infection compared with COVID-negative controls. While the adjusted hazard ratio of 1.69 represents a relative increase in risk, patients with COVID-19 who were hospitalised also experienced a higher absolute exacerbation burden, with incidence rates of 35.7 per 100 person-years compared with 15.9 per 100 person-years among their matched patients without COVID-19, indicating a clinically meaningful absolute increase in exacerbations. In contrast, patients with COVID-19 who were not hospitalised did not have a significantly increased risk of recurrent COPD exacerbations compared with their matched patients without COVID-19. In time-stratified analyses, the elevated risk among hospitalised patients persisted across early and late follow-up periods, suggesting that the long-term impact of COVID-19 hospitalisation extends well beyond the acute recovery phase. The association between hospitalised COVID-19 and future risk of COPD exacerbations remained robust across multiple sensitivity analyses, including inverse probability weighting and shared frailty models. In secondary analyses, social and economic factors, including insurance type and unmet social needs, were also associated with risk of COPD exacerbations, highlighting the importance of socioeconomic context in post-COVID outcomes.

Although mechanistic pathways were not directly assessed in this study, prior literature describing the pathophysiology of SARS-CoV-2 infection offers a plausible biological context for the observed associations, particularly in patients with severe diseases. The pathophysiological changes associated with severe COVID-19, such as alveolar epithelial injury, endothelial dysfunction, and interstitial fibrosis,[25,26] likely predispose COPD patients to sustained airway instability, impaired mucociliary clearance, and reduced pulmonary reserve, all of which are well-established contributors to COPD exacerbations. Histopathological studies of lung tissue from patients recovering from severe COVID-19 reveal chronic inflammation, perivascular fibrosis, and microvascular damage that can persist for months after initial infection.[27] In addition, SARS-CoV-2 infection could induce lasting immune dysregulation, characterised by elevated cytokines, altered lymphocyte profiles, and monocyte/macrophage activation, even beyond the acute phase of illness.[28,29] This persistent systemic inflammation may further exacerbate the inflammatory milieu of COPD, leading to more frequent or severe exacerbations. Furthermore, COVID-19-associated endothelial injury and thromboembolic

events could impair gas exchange and vascular function, compounding the burden of disease in those with compromised pulmonary vasculature.[30]

Non-hospitalised patients did not demonstrate an increased risk of recurrent COPD exacerbations compared with non-COVID controls, consistent with prior work showing that non-severe COVID-19 is not associated with elevated risk of COPD exacerbation.[31] It is possible that this cohort likely may be a healthier subset of infected patients and that outpatient-managed exacerbations may be under-ascertained in electronic health record–based analyses, both of which could contribute to the observed null findings. The absence of an association between COVID-19 and recurrent COPD exacerbations among non-hospitalised patients argues against unmeasured confounding or systematic bias as the primary explanation for the increased risk observed in hospitalised patients. If nonspecific confounding related to healthcare utilisation, coding practices, or baseline disease severity were driving the observed association, a similar elevation in risk would be expected across all COVID-19 positive patients, regardless of hospitalisation status. The increased risk observed exclusively in patients hospitalised with COVID-19 therefore supports the interpretation that factors related to severe acute illness and hospitalisation, rather than generalised confounding, are key contributors to the observed exacerbation risk.

Only a few studies reported the risk of COPD exacerbation during or after COVID-19 recovery, but none, to our knowledge, examined recurrent COPD exacerbation over longer periods of follow-up. Kim et al. reported that individuals with COPD who experienced severe COVID-19 were at increased risk of acute exacerbations within the first 30 days.[31] Hyams et al. found that episodes of COPD exacerbations during COVID-19 hospitalisation were more clinically severe than those triggered by other viral or non-viral causes.[32] Neither study evaluated the risk of repeated exacerbations or longer-term burden following recovery. Our findings complement and extend a recent report by Lee et al., who found that SARS-CoV-2 reinfection was associated with a higher risk of COPD exacerbations in a cohort from South Korea.[33] Lee et al. addressed the relationship between reinfection dose–response and adverse outcomes, whereas our study addressed distinct and complementary questions by stratifying patients according to hospitalisation status at the index infection rather than cumulative infection burden. We also addressed reinfection contribution through exclusion to preserve focus on the consequences of the index event. A key finding of our study is that the long-term risk of recurrent COPD exacerbations was significantly elevated only among patients who required hospitalisation for COVID-19, whereas non-hospitalised patients showed no significant increase compared with matched controls. This distinction has important clinical implications, suggesting that COVID-19 severity at initial presentation, rather than re-infection alone, may identify a vulnerable COPD subpopulation warranting intensified long-term monitoring. Additionally, our study is the first to incorporate social determinants of health into the analysis of post-COVID COPD outcomes, which underscores that clinical severity and social vulnerability may operate through distinct but overlapping pathways to influence post-COVID outcomes in COPD. Finally, our cohort was drawn from a racially and ethnically diverse, underserved urban population in the United States, providing data directly relevant to health equity concerns that may not be fully captured in national administrative databases from other healthcare systems. Together, these studies reinforce the need for proactive, long-term pulmonary follow-up after severe COVID-19.

By applying recurrent-event survival models and cumulative hazard estimation, and by using frailty-based sensitivity analyses to account for within-person heterogeneity and the dependence between recurrent exacerbations and mortality (treating death as a competing terminal event), while adjusting for baseline confounders, our study provided a more comprehensive understanding of long-term COPD exacerbation risk and strengthened the robustness of the risk estimate. Our findings are not surprising, as viral infections, such as influenza and other coronaviruses, are well-established triggers of COPD exacerbations[34,35] The sheer number of patients affected by COVID-19 could spark public health concerns of COPD exacerbations.

Another novelty is that we also incorporated social determinants of health into the analysis of post-COVID COPD exacerbation burden. COVID-19 has disproportionately affected marginalised communities, with sociodemographic and socioeconomic factors contributing substantially to disease burden.[36,37] Limited access to healthcare, higher prevalence of underlying health conditions, overcrowded living environments, and employment in essential but higher-risk occupations have all contributed to the heightened impact of COVID-19 on vulnerable populations.[38,39] Racial and socioeconomic disparities in COPD outcomes have also been well-documented, with certain subgroups experiencing higher exacerbation rates due to differences in healthcare access, environmental exposures, and baseline disease severity.[40,41] The observed association between Medicaid or Medicare insurance and a higher risk of recurrent COPD exacerbations, as well as the elevated risk among patients with at least one unmet social need, aligns with prior studies demonstrating that individuals with lower socioeconomic status experience greater barriers to comprehensive COPD management.[42]

The varying strength of the differential socioeconomic associations observed by index hospitalisation status suggests that the risk of COPD exacerbations

may be driven by distinct constraints across clinical contexts. Among patients hospitalised at the index COVID-19 encounter, unmet social needs showed a strong association with recurrent exacerbations. One potential explanation is that hospitalisation marks a period of heightened vulnerability, during which recovery and COPD self-management depend heavily on practical resources such as stable housing, transportation, medication access, and caregiver support. In this setting, social barriers may represent immediate, rate-limiting obstacles to adhering to treatment plans and attending follow-up, even when insurance coverage is present. In contrast, among patients not hospitalised at the index COVID-19 encounter, insurance type emerged as the stronger predictor of recurrent exacerbations. This pattern may reflect the cumulative influence of insurance-mediated access to outpatient services, medication affordability, and continuity of chronic disease management, which can shape exacerbation risk over time. Together, these patterns highlight the importance of context-specific interventions, such as enhanced post-discharge social support for hospitalised patients and improved access to longitudinal outpatient care for non-hospitalised patients and may help clinicians and policymakers tailor strategies to reduce the risk of COPD exacerbation in vulnerable COPD populations. Examining the interplay between SDOH and COVID-19 may help identify challenges faced by high-risk populations and guide strategies to address the long-term respiratory consequences of SARS-CoV-2 infection.[43]

Finally, the consistency of these findings across a wide range of sensitivity models, along with the robustness indicated by the E-value, supports that there is an association between COVID-19 hospitalisation and subsequent COPD exacerbations rather than one driven by residual confounding. These results extend the current understanding of post-COVID respiratory morbidity[44–46] and underscore the need for longitudinal care strategies tailored to patients with pre-existing lung disease. Although the study population was drawn from a single urban health system, the cohort's racial, ethnic, and socioeconomic diversity may support the generalisability of findings to other underserved populations affected by COPD and COVID-19.

Limitations

The strengths of our study include a large, diverse cohort with multi-year follow-up and the use of recurrent event modelling to assess cumulative exacerbation burden. This addresses a clinically important issue and a public health concern. We incorporated COVID-19 vaccine data and healthcare utilisation and conducted multiple sensitivity analyses. By adjusting for care-era factors, our analysis provides a comprehensive assessment of post-COVID risk in patients with COPD.

Restricting the cohort to patients engaged with the Montefiore Health System, a predominant healthcare provider in the Bronx and surrounding areas, may introduce selection bias. Although our cohort was diverse and included large proportions of underserved minority populations, our findings may not be generalisable to less diverse populations. Additionally, this restriction may favour individuals with more consistent healthcare utilisation and access, limiting generalisability to COPD patients with intermittent engagement or those receiving care outside large urban academic health systems. While this approach was necessary to ensure reliable longitudinal capture of diagnoses, hospitalisations, and exacerbation events essential for accurate outcome ascertainment in a retrospective study, patients with intermittent engagement may have had unrecorded COVID-19 severity or COPD exacerbations. This under-ascertainment of events could bias risk estimates toward the null. As a result, our findings are most applicable to COPD populations with regular healthcare contact, and extrapolation to other settings should be made with caution. Future multi-system or claims-based studies will be important to validate these findings in broader and less continuously monitored populations.

We also relied on electronic health record data, which may be subject to misclassification. For example, COVID-19 status could have been misclassified if testing occurred outside the system and was not documented. Although vaccination data were drawn from multiple sources, including state immunisation records and patient-reported entries, some under-capture may be possible, particularly for federal vaccinations.

Certain clinically relevant confounders, including baseline inhaler therapy, objective COPD severity measures (e.g., forced expiratory volume in 1 s (FEV_1) or Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage), and home oxygen use, were unavailable or not well documented and may contribute to residual confounding. Spirometry data were not uniformly available across the cohort, precluding stratification by GOLD stage. Data on home oxygen use and medication adherence, including baseline inhaler therapy, could not be reliably ascertained. Although we adjusted for available proxies of disease severity, including prior exacerbation history and comorbidity burden, residual confounding may persist. Importantly, these unmeasured factors are unlikely to differ systematically by COVID-19 hospitalisation status and would therefore be expected to bias effect estimates toward the null.

Moreover, defining COPD exacerbations using ICD-10 codes with pharmacologic confirmation may be subject to residual misclassification, particularly for outpatient-managed events where clinical documentation and coding are less consistent. Although we excluded encounters simultaneously coded for both

asthma and COPD exacerbations to reduce diagnostic overlap, any remaining misclassification is likely to be non-differential with respect to COVID-19 hospitalisation status, which would be expected to bias effect estimates toward the null rather than create spurious associations. As such, the observed associations, particularly among hospitalised patients, are unlikely to be fully explained by residual outcome misclassification.

Our definition of "hospitalised COVID-19" included any admission with laboratory-confirmed SARS-CoV-2 infection, which may have captured patients hospitalised for other primary reasons in whom COVID-19 was an incidental finding; such patients would be expected to experience less direct COVID-related pulmonary injury, and this misclassification would likely attenuate, rather than exaggerate, the observed associations. Notwithstanding, a potential comparator for patients hospitalised with COVID-19 would be COPD patients hospitalised for other indications. However, this approach introduces additional selection biases, as hospitalisations may occur for reasons such as terminal illness or severe trauma. In this study, hospitalisation was treated as a marker of severe COVID-19 exposure rather than a generic care-setting variable. We mitigated setting-related differences by incorporating comorbidities and proxies of COPD severity associated with hospitalisation risk into the propensity score matching framework and by adjusting for prior healthcare utilisation.

Because SDOH data were available only for a subset of patients, analyses incorporating these variables may be subject to selection bias. Patients who were screened for social needs may differ from those without available SDOH data, which could limit generalisability. Finally, because the study period spans both pre- and post–COVID-19 vaccine eras, residual confounding related to temporal changes in vaccine availability and uptake cannot be fully excluded, although baseline vaccination status was included as a covariate in all models.

Although we used inverse probability weighting, shared frailty models, and multiple sensitivity analyses to adjust for confounding, unmeasured or residual confounding remains possible. Future research should further explore the mechanisms underlying these exacerbations and assess interventions tailored to high-risk COPD populations to improve long-term outcomes.

Conclusions

Hospitalisation for COVID-19 was associated with a sustained increase in the risk of recurrent COPD exacerbations, persisting for years beyond the acute COVID-19 illness. This elevated risk was not explained by markers of critical illness and remained consistent across variant periods and analytic approaches. These findings suggest that hospitalisation for COVID-19 may identify a vulnerable COPD subpopulation warranting more diligent long-term monitoring and management. Proactive care strategies are needed to reduce the burden of exacerbation in this high-risk group.

Contributors

All authors read and approved the final version of the manuscript.

SSH: conceptualised, performed literature analysis, extracted data, performed analysis, performed statistical analysis, wrote paper, edited paper, accessed and verified data.

KED: conceptualised, performed literature analysis, extracted data, performed analysis, performed statistical analysis, wrote paper, edited paper, accessed and verified data.

TQD: conceptualised, supervised, edited paper.

Data sharing statement

The data underlying this study are not publicly available due to institutional and IRB restrictions involving patient privacy and confidentiality. De-identified summary data and analysis code are available from the corresponding author upon reasonable request and contingent upon institutional approval and execution of a data use agreement. Please contact Tim Q. Duong at tim.duong@einsteinmed.edu. Sample codes used to perform analysis in this study are available at 10.5281/zenodo.18462411.

Declaration of interests

All authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ebiom.2026.106212.

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