NON-INTERVENTIONAL/LOW-INTERVENTIONAL STUDY TYPE 1 STUDY REPORT ABSTRACT

Title: A standing cohort to understand the characteristics of patients with COVID-19 and contextualize the COVID-19 complication and safety events of interests using US OPTUM EHR data

Date: 18 February 2026

Name and affiliation of the main author: [redacted]

Keywords: COVID-19, Paxlovid, SARS-CoV-2

Rationale and background: There is limited information about the safety and effectiveness of using Paxlovid to treat people with mild-to-moderate Coronavirus disease 2019 (COVID-19) in the real-world setting. Understanding the epidemiology and clinical manifestations of COVID-19, as well as the background rates of health outcomes of interest among COVID-19 patients who are at high and standard risk of progression to severe illness in the real-world setting can provide critical context for interpreting health outcomes and clinical manifestations from post-marketing clinical trials, with broadened patient populations.

Research question and objectives: The primary objectives were to describe the distribution of demographics, co-morbid conditions, medical history, selected biomarkers, and healthcare utilization at baseline for COVID-19 patients, to describe the time to clinical events, to estimate background incidence of COVID-19 manifestations/complications and health outcomes of interest following COVID-19 infection or Paxlovid exposure, to estimate incidence of Long COVID-19 (defined based on post-covid conditions [PCC]) and assess health effects of Long COVID, and finally to describe the health equity and demographic and clinical characteristics among patients treated with Paxlovid. The secondary objective was to estimate the incidence of oxygen supplementation among COVID-19 patients hospitalized with mechanical ventilation/extracorporeal membrane oxygenation (ECMO). In exploratory objectives, machine learning approaches were used to identify key predictors of severe COVID-19 outcomes and long COVID, while real-world effectiveness of Paxlovid in reducing COVID-19–related outcomes was assessed through rigorous cohort balancing via propensity score matching (PSM) and comparative analyses.

Study design: This was a non-interventional (NI) population-based cohort study with retrospective data collection utilizing an electronic healthcare data (EHR) database in the US. This study included adults (≥18 years of age) and pediatric patients (<18 years of age) with a COVID-19 diagnosis.

Setting: This study was conducted using the Optum® COVID-19 EHR Database during the period of January 01, 2020 to June 30, 2024.

Subjects and study size, including dropouts: The study population consisted of patients who tested positive or were diagnosed with COVID-19. Within the study population, three Source Cohorts of general population with COVID-19 were formed consisting of overall, hospitalized, and non-hospitalized patients. Within the Source Cohort, the following Trial Similar Cohorts will be formed including High Risk of progression to severe illness and Standard Risk of progression to severe illness, as well as all Paxlovid users in the real-world setting.

Variables and data sources: Covariates included baseline demographic, clinical characteristics, medications, and health utilization, as well as those needed for the study cohort inclusion and exclusion criteria. Given the urgent need to clinically understand the novel virus of COVID-19, Optum developed a low latency data pipeline that enabled minimal data lag, while preserving as much clinical data as possible. The data were sourced from Optum's longitudinal EHR repository, which was derived from dozens of healthcare provider organizations in the US, including more than 700 hospitals and 7,000 clinics.

Results:

When examining baseline characteristics, patient profiles differed by cohort and treatment status. In the Overall Source Cohort, demographic and clinical heterogeneity was exhibited with substantial chronic disease burden and high rates of acute complications occurring within one day of diagnosis. The Overall Source Cohort included the broadest population, spanning a wide age, comorbidity, and socioeconomic range, with intermediate incidence of clinical complications. Clinical severity varied across risk strata, with the High-Risk Trial Similar Cohort showing the highest incidence of hospitalization, pneumonia, multi-organ dysfunction, and other acute events. The High-Risk Trial Similar Cohort was older and more comorbid, consistently showing the highest incidence rates of complications—including hospitalization, pneumonia, organ failure, and mortality—across all periods and time windows. Meanwhile the Standard-Risk patients consistently had the lowest complication rates, as this cohort was younger and healthier, with the lowest complication and healthcare-utilization rates among the risk-stratified groups. Prior to propensity score matching (PSM), Paxlovid-treated patients were older, more comorbid, more frequently Medicare-insured, ad more often vaccinated with slightly lower pre-index healthcare utilization than untreated comparators, aligning with higher baseline risk. After propensity score matching, demographic, clinical, and healthcare utilization characteristics were well balanced, enabling rigorous assessment of treatment effects. After PSM, Paxlovid treated and untreated groups were well-aligned as all pre-treatment utilization differences dropped to ≤0.04 standardized difference, which indicated that the matching was effective in equalizing baseline demographic and clinical characteristics between Paxlovid users and non-users.

When examining clinical event timing and early outcomes, results showed that COVID-19 patients treated with Paxlovid had markedly lower short-term risks of severe outcomes. In propensity-matched analysis, the 30-day hospitalization rate in Paxlovid-treated patients was 0.90% versus 5.91% in comparable untreated patients. Similarly, 15-day hospitalization incidence was 0.64% with Paxlovid compared to 5.55% without treatment. These differences correspond to relative risk (RR) reductions on the order of 80–88% (RR ~0.17 at 30 days; ~0.12 at 15 days). This pronounced early benefit of Paxlovid was consistent across subgroups: risk ratios for 30-day hospitalization remained well below 1 for all categories (e.g., ~0.16 in patients <65 years; ~0.19 in Black patients), indicating a substantially lower likelihood of progression to severe COVID-19 in the Paxlovid treated group. In summary, Paxlovid treatment was associated with substantially lower 15- and 30-day hospitalization risk, consistent reductions across age, race, and vaccination subgroups, and lower incidence of acute complications, safety events, and long-COVID outcomes compared with matched untreated patients.

For acute COVID-19 complications and potential health outcomes, the study found that acute COVID-19 complications were common, especially in high-risk patients and during hospitalization. Within 30 days of infection, major complications (e.g. pneumonia, organ failure, sepsis) occurred frequently across cohorts, with incidence rates for leading events ranging from hundreds to over 1,000 per 1,000 person-years. For example, pneumonia occurred at roughly 1,100 per 1,000 person-

years in the Source Cohort, 1,200 in the High Risk Trial Similar Cohort, and 640 in the Standard Risk Cohort. The 30-day hospitalization rate was similarly elevated in higher-risk patients (approximately 1,800 per 1,000 in the High Risk Trial Similar Cohort vs roughly 1,675 in the Source Cohort and 998 in Standard Risk Cohort). All complications and potential Paxlovid safety endpoints (e.g. acute kidney or liver injury, severe allergic reactions) were more frequent in those who were hospitalized during acute COVID-19, and less frequent when compared to patients who did not receive Paxlovid. Despite differences in magnitude, the spectrum of common complications was similar across cohorts, with respiratory (pneumonia, respiratory failure), cardiovascular, and systemic events (sepsis, multi-organ dysfunction) dominating the early post-infection period.

Long COVID, as defined by post-COVID conditions (PCC), were infrequent but non-negligible, and patients who developed them tended to have higher baseline risk profiles. In the 31–120 days after infection, ~3.3% of patients had a newly diagnosed primary post–COVID condition (PCC, "Long COVID"), with slightly lower risk (3.1%) for those infected during the Omicron period. Newly diagnosed pulmonary and cardiovascular PCCs occurred in approximately 2–3% and 1.4–1.5% of patients, respectively, while secondary (more severe) PCC manifestations were rare (0.3–0.4%). Among patients who developed PCC, symptom onset was typically 2–3 months post-infection – for example, the median time to first PCC diagnosis was approximately 65–67 days (with interquartile range up to 90 days) across primary, cardiovascular, and pulmonary PCC outcomes. Patients who went on to experience Long COVID had notably different profiles: they were older (e.g. approximately 27% were age ≥65 vs 16% among those without PCC) and carried a higher burden of comorbidities – for instance, 35% had pre-existing hypertension vs 21% without PCC, and 16% had diabetes vs 10% without. During acute infection, they also required more intensive therapies and care, such as higher utilization of corticosteroids (10% received dexamethasone vs 5% of those without PCC) and therapeutic anticoagulation (9% vs 4%), in line with more severe initial illness.

Paxlovid uptake was concentrated in older age groups and varied by race/ethnicity, with differences in comorbid profiles suggesting potential health disparities. Nearly all Paxlovid prescriptions occurred during 2022 (after its Emergency Use Authorization), peaking in mid-2022. Treated patients skewed older (mean age 64 years, median 68 years), roughly 60% were ≥65 years old and only 2.5% were under 30. Over 70% of recipients were White, while 7% were Black, 5% Asian, 11% Hispanic (broadly reflecting the COVID patient population). Notably, there were socio-demographic disparities: Black and Hispanic individuals on Paxlovid were more likely to have lower household incomes, whereas White and Asian recipients more often had higher incomes (e.g. 62% of White vs 16% of Black patients resided in high-income households). Clinical profiles differed by race as well – for example, Black and Hispanic patients had higher rates of obesity and diabetes (e.g. 33% of Black and 32% of Hispanic Paxlovid users had diabetes vs ~20% of White users) and were less likely to be vaccinated against COVID-19 prior to treatment (vaccination in 30% of Black patients vs 49% in Asian patients). Overall, these findings highlight that Paxlovid was primarily used in older, comorbidity-burdened patients, and they underscore the need to address racial and socioeconomic gaps in COVID-19 therapy access.

When examining oxygen supplementation usage, results illustrate that the need for intensive respiratory support in COVID-19 declined over time. Among hospitalized COVID-19 patients requiring mechanical ventilation and/or ECMO, the incidence of ICU-level oxygen support was extremely high in the early (pre-vaccine) pandemic: on the order of 4,300–4,800 per 1,000 person-years in late 2020. During the post-vaccine period, these rates fell to roughly 3,600–3,960 per 1,000 in 2021, and during the Omicron wave (2022) further to about 3,050–3,900 per 1,000 (a 15–30%

relative drop compared to the pre-vaccine period). Differences across patient populations were modest: the High Risk and Source Cohorts had similar overall mechanical ventilation rates (~370–424 per 1,000), whereas the Standard Risk Cohort's rate was lower (~227 per 1,000). By contrast, non-hospitalized patients rarely required advanced oxygen support (only 6–34 per 1,000 across cohorts), underscoring that this severe outcome was concentrated in the sickest (hospitalized) segment of patients.

Discussion: In this study, among COVID-19 patients, hospitalized patients and patients in the High Risk Cohort experienced the greatest incidence of complications, interventions, safety events and Long COVID symptoms. The Paxlovid treated patients had lower incidence rates of hospitalization, complications, health outcomes and Long COVID symptoms, as compared to patients who did not receive Paxlovid. Real-world Paxlovid effectiveness against hospitalization during the Omicron period among COVID-19 patients at high risk of severe disease is consistent with previously demonstrated clinical trial efficacy, while black patients underutilized Paxlovid despite high effectiveness compared to white patients. Multiple machine learning and deep learning models identified the Charlson comorbidity score, age, and frequency of healthcare utilization, which may help predict the occurrence of new post-COVID conditions to identify Long COVID and demonstrate the utility of the models for individualized risk prediction.

Marketing Authorization Holder(s): Pfizer Limited

Names and affiliations of principal investigators:

Name, degree(s)	Affiliation
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Document Approval Record

Document Name:	C4671040 Non-Interventional-Low-Interventional Study Type 1 Study Report Abstract
Document Title:	C4671040 Non-Interventional-Low-Interventional Study Type 1 Study Report Abstract

Signed By:	Date(GMT)	Signing Capacity
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]