ORIGINAL RESEARCH

Clinical Outcomes Associated with Hypoxia in Hospitalized Patients with COVID-19

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ABSTRACT

Introduction: The coronavirus disease 2019 (COVID-19) has majorly impacted millions of people worldwide. The clinical course and outcomes of infection with COVID-19 have been studied, but there remain knowledge gaps. This study aims to investigate the impact of hypoxia necessitating inpatient and post-discharge supplemental oxygen in COVID-19 patients on in-hospital mortality, clinical outcomes, and return rates.

Materials and Methods: Patients discharged from University Hospital in Columbia, Missouri between March 22, 2020 and March 21, 2022 with a primary diagnosis of COVID-19 were evaluated. Patients with inpatient or post-discharge oxygen orders were compared to those without. The primary outcome was in-hospital mortality. Secondary outcomes included length of stay, admission to the ICU, and likelihood of 30-day and 6-month return to clinic visits, the Emergency Department, and readmission to inpatient and observation units.

Results: Two thousand eleven (2011) patients were included in the study. Hypoxia requiring inpatient supplemental oxygen due to COVID-19 infection was not associated with greater in-hospital mortality ($p = 0.494$) but was associated with length of hospitalization, admission to the ICU, return and readmission rates. Hypoxia upon hospital discharge requiring supplemental oxygen was not associated with worse clinical outcomes but was associated with return and readmission rates.

Conclusions: In a cohort of patients with COVID-19, hypoxia was not associated with in-hospital mortality. Inpatient hypoxia was associated with worse clinical outcomes, and both inpatient and post-discharge hypoxia were associated with higher likelihood of short-term follow-up and readmission rates. These results may inform the management of COVID-19 patients.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) has had a major impact on millions worldwide. As of mid-2022, COVID-19 has infected nearly 94 million people and caused over one million total deaths in the United

States alone [1]. The virus has been the primary cause for approximately 380,000 hospitalizations across the country [2]. The number of patients with COVID-19 treated at one time in the intensive care unit (ICU) peaked at 28,727 in January 2021 and has risen above 25,000 twice since then [3]. In addition to health impacts, the worldwide pandemic has had far-reaching socioeconomic impacts [4-6], affecting the delivery of [7-12] and access to healthcare [13-15] for many.

The clinical course and outcomes of infection with the COVID-19 virus have been studied extensively [16, 17]. One of the most common and critical symptoms reported is hypoxia. While other symptoms such as fever, cough, and fatigue, are typically concurrently present in hospitalized patients, the primary indication for hospitalization in many cases is hypoxia requiring supplemental oxygen using both non-invasive and invasive mechanical ventilation. A phenomenon termed "happy hypoxia" or "silent hypoxia" has been described extensively, as well [18-26], although at least one study has proven no difference in mortality between those experiencing asymptomatic hypoxia and dyspnea [27]. Hypoxemia is strongly associated with worse clinical outcomes [28, 29]. Hypoxia early in the clinical course of COVID-19 infection is an early determinant of progression to a critical, severe stage of the disease [30]. Long-term outcomes have been both hypothesized [31] and described [32-34], although relatively little is known at this time given the novelty of the virus.

Information about COVID-19 has grown exponentially since its emergence. However, there remain large gaps in knowledge and there is still much to investigate. No study to date has examined the impact of increased in-hospital and post-discharge oxygen requirements in COVID-19 patients on in-hospital mortality. In one small study (n = 140), hypoxemia was independently associated with in-hospital mortality [29]. However, the study was conducted in a small subset of patients and throughout a relatively short time frame; more data would be helpful in informing the results. This study aims to investigate the effect of supplemental oxygen requirements while in-hospital and upon discharge on clinical outcomes. We aim to investigate the impact of in-hospital and post-hospitalization hypoxia due to COVID-19 infection on mortality, clinical outcomes, and return rates.

MATERIALS AND METHODS

A retrospective analysis was performed using data from a single-center hospital system (University of Missouri System) in Columbia, Missouri. Patients discharged from the hospital between March 22, 2020 and March 21, 2022 with a primary diagnosis of COVID-19 (ICD-10 code: U07.1) and an in-hospital oxygen order were included in the study. Data was curated by querying MU Health Care's registration system (IDX) and the electronic medical record (EMR). The primary outcome measured was in-patient mortality. Secondary outcomes included length of stay, admission to the ICU during hospitalization, return to clinic post-discharge, return to the Emergency Department (ED) post-discharge, readmission to an inpatient unit post-discharge, and readmission to an observation unit post-discharge. Secondary outcomes involving return visits and readmissions were analyzed at 30 days and 6 months post-discharge. Only return visits and readmissions within the University Health System, as documented in the EMR, were included. Data was then analyzed using Python library SciPy, with a p-value of 0.05 determined to be statistically significant. This study was reviewed and approved as exempt by the University of Missouri Institutional

Review Board (IRB). The requirement to obtain informed consent was waived.

RESULTS

Two thousand eleven (2011) patients were discharged with a primary diagnosis of COVID-19 during the specified two-year time period. Socio-demographic data describing the included patient population is provided in Table 1. Over 95% of patients (1920 out of 2011) required supplemental oxygen during hospitalization, and 26.4% of patients (530 out of 2011) were discharged with a prescription for supplemental oxygen.

Hypoxia requiring supplemental oxygen during hospitalization due to infection with COVID-19 was not associated with greater in-hospital mortality ($p = 0.494$) in our patient population. A supplemental oxygen requirement was, however, significantly associated with longer length of hospital stay ($p < 0.001$) and admission to the ICU for at least one day during hospitalization ($p < 0.001$). Patients that required oxygen during hospitalization were more likely to return for a clinic visit within 30 days ($p = 0.001$) and within 6 months ($p < 0.001$) post-discharge. An inpatient supplemental oxygen requirement was also associated with 30-day ($p < 0.001$) and 6-month ($p < 0.001$) post-discharge Emergency Department visits, 30-day ($p < 0.001$) and 6-month ($p < 0.001$) post-discharge readmission to inpatient units, and 30-day ($p < 0.001$) and 6-month ($p < 0.001$) post-discharge readmission to observation units.

Patients that required supplemental oxygen while hospitalized were more likely to require supplemental oxygen upon discharge ($p < 0.001$) than patients that did not require in-hospital supplemental oxygen. Moreover, patients who did not require oxygen while hospitalized secondary to COVID-19 infection also did not require oxygen upon discharge. A home oxygen order placed at discharge was not significantly associated with length of hospitalization ($p = 0.625$) or admission to the ICU at some point during hospitalization ($p = 0.194$). A discharge oxygen order was, however, significantly associated with a longer length of stay in the ICU if admitted ($p < 0.001$). Patients with COVID-19 that required oxygen upon discharge from the hospital were more likely to return for a clinic visit within 30 days ($p < 0.001$) and within 6 months ($p < 0.001$) post-discharge. Similar to an inpatient oxygen order, a supplemental oxygen requirement upon discharge was associated with 30-day ($p = 0.033$) and 6-month ($p = 0.009$) post-discharge Emergency Department visits, 30-day ($p = 0.031$) and 6-month ($p = 0.001$) post-discharge readmission to inpatient units, and 30-day ($p = 0.013$) and 6-month ($p < 0.001$) post-discharge readmission to observation units. These findings are summarized in Tables 2 and 3.

Table 1: Socio-demographic makeup of 2,011 patients included in study

Demographic		**N *(%)***
Age (years)	≥ 60	1054 *(53)*
	40-59	607 *(30)*
	18-39	350 *(17)*
Sex	Female	975 *(48)*
	Male	1036 *(52)*
Race	Black or AA	225 *(11)*
	White	1628 *(81)*
	Asian	22 *(1)*
	Other	136 *(7)*
Ethnicity	Hispanic	3 *(0.2)*
	Non-Hispanic	2008 *(99.8)*

AA = African American

Table 2: Primary and secondary outcomes assessed for patients hospitalized with COVID-19 with and without supplemental oxygen requirements

Outcome	In-hospital oxygen requirement		p-value	Oxygen requirement at hospital discharge		p-value
	Yes	No		Yes	No	
In-hospital mortality N *(%)*	166 *(8.7)*	6 *(6.7)*	0.494			
Average length of stay (days)	7.98	2.23	**< 0.001**	7.55	7.78	0.625
ICU admission* N *(%)*	652 *(34)*	8 *(8)*	**< 0.001**	186 *(35)*	474 *(32)*	0.194

*Patient was admitted to the ICU for at least one day during hospitalization

Table 3: Outcomes assessed for patients hospitalized with COVID-19 with and without supplemental oxygen requirements

Outcome		In-hospital oxygen requirement		p-value	Oxygen requirement at hospital discharge		p-value
		Yes	No		Yes	No	
Post-discharge clinic visit N *(%)*	30 days	549 *(29)*	14 *(15)*	**0.001**	223 *(42)*	340 *(23)*	**< 0.001**
	6 months	907 *(47)*	26 *(29)*	**< 0.001**	314 *(59)*	619 *(42)*	**< 0.001**
Post-discharge ED visit N *(%)*	30 days	128 *(6.7)*	13 *(14)*	**< 0.001**	27 *(5.1)*	114 *(7.7)*	**0.033**
	6 months	300 *(16)*	32 *(35)*	**< 0.001**	68 *(13)*	264 *(18)*	**0.009**
Post-discharge readmission to inpatient unit N *(%)*	30 days	163 *(8.5)*	24 *(26)*	**< 0.001**	38 *(7.2)*	149 *(10)*	**0.031**
	6 months	281 *(15)*	31 *(34)*	**< 0.001**	59 *(11)*	253 *(17)*	**0.001**
Post-discharge readmission to observation unit N *(%)*	30 days	38 *(2)*	13 *(14)*	**< 0.001**	6 *(1)*	45 *(3)*	**0.013**
	6 months	91 *(5)*	19 *(21)*	**< 0.001**	12 *(2)*	98 *(7)*	**< 0.001**

DISCUSSION

Dyspnea is both a common and serious symptom associated with COVID-19 infection. Hypoxia requiring supplemental oxygen is a common indication for hospitalization and one of the primary drivers for worsening clinical status in both hospitalized and non-hospitalized patients. Hypoxia in hospitalized patients with COVID-19 has been associated with worse clinical outcomes and, in one small study, mortality [28, 29]. However, to date, no strong association has been established between hypoxia and mortality in hospitalized patients with COVID-19 and no study has examined the effect of hypoxia on

clinical outcomes in our patient population at University Hospital.

Inpatient hypoxia requiring supplemental oxygen secondary to COVID-19 infection was not associated with an increase in mortality. However, inpatient hypoxia was associated with a statistically significant difference in all secondary outcomes measured, including average length of hospitalization, admission to the ICU, and return rates both to clinic visits and to the Emergency Department, inpatient, and observation units. These findings confirm that hypoxia secondary to COVID-19 infection in hospitalized patients is associated with worse clinical outcomes but conflict with prior research suggesting worse mortality rates in hypoxic COVID-19 patients. Patients experiencing hypoxia may require closer monitoring in higher-acuity units and may benefit from more aggressive management strategies earlier in their clinical course to prevent negative outcomes.

Interestingly, hypoxia requiring supplemental oxygen at discharge was not associated with worse clinical outcomes such as length of stay or admission to the ICU. However, patients discharged with supplemental oxygen secondary to COVID-19 infection were more likely to return for clinic visits and ED visits and were more likely to be readmitted to inpatient and observation units. These findings suggest that the patients discharged with the need for additional oxygen experienced a more severe clinical course of infection with COVID-19 than those discharged without the need for supplemental oxygen. Perhaps a more severe clinical course necessitated closer follow-up and increased the likelihood of need for further inpatient management, or perhaps a more severe clinical course was a motivator in outpatient follow-up.

Additional contributing factors to both the development of hypoxemia and outcomes measured in this study must be considered. Patients that required in-hospital supplemental oxygen were older (mean: 60 years) than those who did not require additional oxygen while hospitalized (mean: 40 years; $p < 0.001$). Older age and related factors, including increased number and severity of chronic diseases, altered lung structure and function, impaired ventilatory response to hypoxia, and declining pulmonary immunologic function, could have impacted the results [35]. Furthermore, the medical management of patients hospitalized with COVID-19 infection varied over the course of the observed time period. Patients treated shortly after the onset of the COVID-19 outbreak were treated with medications such as hydroxychloroquine, which was initially thought to reduce viral load [36]. However, after its efficacy was questioned and investigated further [37, 38], this medication was ultimately proven not to be efficacious [39-41], and routine use was discontinued. Later on, hospitalized COVID-19 patients were more frequently treated with steroids, such as dexamethasone, and other agents including remdesivir, baricitinib, and tocilizumab [42-45]. Approaches to management also changed throughout the course of the pandemic, as knowledge regarding the novel virus and clinical outcomes grew. For example, placing patients in a prone position became an increasingly widespread practice as the benefits were clinically proven [46, 47].

In interpreting these results, it is important to consider the limitations of the study. Hypoxia was defined by the need for supplemental oxygen, determined by the placement of an oxygen order, either during hospitalization or upon discharge. Using this method, we were unable to distinguish between patients who truly required additional oxygen and those who remained at their baseline oxygen status but still had an oxygen order placed. The same is true for discharge oxygen orders; the method used to

determine unresolved hypoxia upon discharge cannot distinguish patients who returned to baseline oxygen status from those who truly required additional oxygen. Patients that required supplemental oxygen upon discharge may have also had a baseline oxygen requirement upon admission. These patients may not have truly required additional oxygen due to COVID-19 infection. These patients would be expected, then, to have similar inpatient clinical outcomes as patients who did not require supplemental oxygen upon hospital discharge, which may explain the findings of the study. The study was also limited in that all post-discharge encounters (clinic visits, emergency room visits, readmission to inpatient and observation units) within the defined time frame were included, regardless of reason for the visit. Patients that required supplemental oxygen upon discharge may have also required closer follow-up in clinic and may be at increased risk of requiring care through ED visits and hospitalization as a result of chronic conditions other than COVID-19 infection. Further determination of baseline oxygen status, quantification of both in-hospital and discharge oxygen requirement, and differentiation of reason for return visits would be helpful in informing these results.

This study has additional limitations. The study was performed at a single-center institution with a limited sample size. A larger sample in a multi-center study might better detect existing differences in the primary and secondary outcomes and validate the findings. Data regarding mortality could be obtained only if the patient expired during hospitalization. Mortality rates post-discharge may further inform the results.

Data was collected during the hospitalization period and during the 30-day and 6-month period post-discharge. Future work should be done to observe long-term outcomes after COVID-19 infection. Future studies may include a comparison of baseline pulmonary function testing (PFTs) to PFTs one year or five years following infection with COVID-19 to assess the effect of hypoxia during COVID-19 infection on long-term pulmonary function. Future studies should also attempt to assess the severity of the oxygen requirement secondary to COVID-19 infection on mortality and other clinical outcomes.

Notes

Conflicts of Interest: None declared
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Ethics Approval: This study was reviewed and approved as exempt by the University of Missouri Institutional Review Board (IRB).
Consent to Participate: The requirement to obtain informed consent was waived.

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