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# Impact of the COVID-19 pandemic on chronic disease management and patient reported outcomes in patients with pulmonary hypertension: The Pulmonary Hypertension Association Registry

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## Abstract

To better understand the impact of the COVID-19 pandemic on the care of patients with pulmonary hypertension, we conducted a retrospective cohort study evaluating health insurance status, healthcare access, disease severity, and patient reported outcomes in this population. Using the Pulmonary

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Hypertension Association Registry (PHAR), we defined and extracted a longitudinal cohort of pulmonary arterial hypertension (PAH) patients from the PHAR's inception in 2015 until March 2022. We used generalized estimating equations to model the impact of the COVID-19 pandemic on patient outcomes, adjusting for demographic confounders. We assessed whether insurance status modified these effects via covariate interactions. PAH patients were more likely to be on publicly-sponsored insurance during the COVID-19 pandemic compared with prior, and did not experience statistically significant delays in access to medications, increased emergency room visits or nights in the hospital, or worsening of mental health metrics. Patients on publicly-sponsored insurance had higher healthcare utilization and worse objective measures of disease severity compared with privately insured individuals irrespective of the COVID-19 pandemic. The relatively small impact of the COVID-19 pandemic on pulmonary hypertension-related outcomes was unexpected but may be due to pre-established access to high quality care at pulmonary hypertension comprehensive care centers. Irrespective of the COVID-19 pandemic, patients who were on publicly-sponsored insurance seemed to do worse, consistent with prior studies highlighting outcomes in this population. We speculate that previously established care relationships may lessen the impact of an acute event, such as a pandemic, on patients with chronic illness.

**KEYWORDS**

COVID-19, insurance, PHAR, pulmonary hypertension

**INTRODUCTION**

Pulmonary hypertension (PH) is a serious chronic illness defined by a mean pulmonary artery pressure greater than 20 mmHg.<sup>1</sup> Pulmonary arterial hypertension (PAH) is a subset of PH where high pressures exist in the precapillary pulmonary arterial vasculature, along with a pulmonary arterial wedge pressure less than or equal to 15 mmHg and a pulmonary vascular resistance greater than or equal to 3 Wood units.<sup>1</sup> PAH is a challenging disease associated with significant functional limitations and serious complications if left untreated, with an estimated 3-year mortality as high as 55% among high-risk PAH patients.<sup>2</sup> Studies have shown that PH patients of lower socioeconomic status have more serious disease,<sup>3</sup> with insurance status and insurance type predicting disease prognosis more so than race.<sup>4</sup> One study found that social determinants of health, such as public insurance, lower level of education, lower household income, and others, increased the risk of poor outcomes and hospitalizations.<sup>5</sup> Another study found that Hispanic PAH patients were more likely to be unemployed, have a lower annual income, have

Medicaid or be uninsured, and have higher incidence of emergency department (ED) visits and hospitalizations despite similar disease severity compared with non-Hispanic White patients.<sup>6</sup> These further emphasize that social determinants of health play an important role in healthcare utilization that is not fully understood.

The COVID-19 pandemic brought unforeseen social issues for many individuals, including changes in employment and insurance status,<sup>7</sup> which potentially limited access to care. These issues were suspected to have disproportionately impacted marginalized populations who already faced significant health disparities.<sup>8,9</sup> Mental health was also impacted by the COVID-19 pandemic. Some estimates suggest prevalence of anxiety and depression in the United States rose by nearly 20% in 2020.<sup>10</sup> This was especially concerning as patients with PAH already experience a higher burden of anxiety and depression.<sup>11</sup> During the early months of the pandemic, there was a national decrease in the number of outpatient visits<sup>12</sup> as well as disengagement or avoidance of the medical system due to fear of COVID-19.<sup>13</sup> Innovative ways to deliver routine outpatient care, such as telemedicine for PH patients, increased to reduce the

exposure risk of COVID-19.<sup>14</sup> Remote healthcare proved challenging as it is not equitably accessed by all<sup>15</sup> and many patients of low socioeconomic status did not have access to necessary technology,<sup>16</sup> potentially causing delays in diagnosis and treatment.

The Pulmonary Hypertension Association Registry (PHAR) is a multicenter, prospective registry that has enrolled over 2000 patients from over 60 centers across the US to date. There are 32 states represented in the PHAR from all parts of the United States, and some states with multiple centers. Its purpose is to measure health outcomes, determine risk factors and identify practice patterns for patients diagnosed with PAH and chronic thromboembolic pulmonary hypertension (CTEPH).<sup>17</sup> Here we report a secondary data analysis using the PHAR data set. This study seeks to better understand how PAH patients in the United States were impacted by the COVID-19 pandemic with regard to employment status, insurance status, medication adherence, healthcare utilization, and clinical and patient reported outcomes. We hypothesized that the time period of the COVID pandemic, compared to the prepandemic period, would be associated with more patients on publicly sponsored insurance, more patients unemployed, and more patients off medications. We also hypothesized there would be higher disease severity, more frequent ED visits, longer hospital stays, and higher mortality.

## METHODS

### Data

Data are longitudinal in nature, collected at approximately 6-month intervals, starting in September 2015 and continuing throughout the COVID-19 pandemic (March 2022). We calculated descriptive statistics aggregated before and after the onset of the pandemic. For each patient, we used visit index as well as whether the visit occurred before or after the onset of the pandemic (March 13, 2020). We re-indexed visits based on their proximity to the pandemic (March 13, 2020) such that negative visit indices refer to visits occurring before the pandemic ( $-1$  is the last visit before the pandemic), and positive indices (1, 2, and 3) refer to during-pandemic visits.

We excluded patients from the PHAR registry who were under 18-year-old, diagnosed with CTEPH or persistent pulmonary hypertension of the newborn, as well as patients who had incomplete information for death date. The exact dates of patient visits, which were withheld for anonymity and data security, were not available. Since the analysis of mortality was based on

the certainty of the date of death in relation to the pandemic cutoff date, for those who died during the study, we approximated death dates to within 6 months based on each patient's initiation year in the study and the time in days until the patient's death, both of which were available in the data set for deceased patients. In patients who died before the pandemic, we shifted visits indices backwards in time if the date of their death was more than 6 months before March 13, 2020. Certain variables which were asked in relation to the time since a patient's previous visit were normalized (ED visits, PAH clinic visits) to the rate of visits per 6-month period.

Since combinations of two or more reported insurance types were common in the registry, we grouped insurance types based on whether a patient was on a private insurance plan, a publicly-sponsored program, or uninsured. If a patient reported private insurance, their insurance type was determined to be "Private" for that visit. If a patient reported any publicly-sponsored insurance types in the absence of private insurance, their insurance type was determined to be "Publicly-Sponsored" for that visit. If a patient reported they were uninsured, their insurance category was "Uninsured" for that visit. Lastly, an "Other" category was kept for remaining categories (Indian Health Service and Military Care).

Some subjects were missing data on either outcomes or covariates. When possible, we used last observation carried forward (LOCF) to impute missing values of covariates. Otherwise, while all available data were used on each subject in GEEs, we exclude data points for which a covariate was still missing after LOCF.

### Models

We used generalized estimating equations (GEEs) to model each desired outcome as a function of the pandemic phase indicator (Historical/Pre-COVID-19/ During-COVID-19) which served as our primary explanatory variable. Pre-COVID-19 was the reference category for this indicator. We specified an exchangeable working correlation structure among observations from the same patient. Robust standard errors and Wald tests were used for inference. The binomial link function was used for binary outcomes such as employment, while the default (Gaussian) link function was used for continuous outcomes. When drawing conclusions from models with binary outcomes, we report adjusted odds ratios (OR) and corresponding confidence intervals (CIs). For models with continuous outcomes, we report coefficient estimates and CIs representing the slope between each covariate and the outcome, holding all other covariates

constant. Outcomes of interest include: public insurance status, employment status, off-medication status, ED visit rate, nights in hospital, mortality, 6-min walk distance (6MWD), BNP, NT-proBNP, creatinine, NEMC physical health, and NEMC mental health. The NEMC scores are two composite metrics used to measure physical and mental health based on the SF-12 form, which is a validated self-administered questionnaire used to assess components of physical and mental wellbeing.<sup>18,19</sup> Higher scores correlate with better health-related quality of life.<sup>18,19</sup>

In all models, we report both adjusted and unadjusted estimates, where adjusted models include age, sex, race, ethnicity, and education as prespecified covariates. Age was converted to a decade-scale to assist with interpretability. We evaluated potential effect modification with insurance status using Wald tests on the interaction terms between the phase indicator and insurance status.

## RESULTS

After excluding 316 subjects based on our exclusion criteria, our sample consisted of 1679 unique subjects with a combined total of 6137 visits. Of these, 3255 visits occurred before March 13, 2020 and were considered “pre-pandemic” visits. The study sample was predominantly female (75%), white (79%) and non-Hispanic (89%), and the mean age at the time of the first visit was 55.2 years (Table 1). The majority had either idiopathic PAH or connected tissue disease-associated PAH and were classified under the WHO Functional Classification (FC) as either FC III (49%) or FC II (36%). Descriptive summary statistics for our outcomes of interest, stratified by visit index (the number of visits before or after the onset of the pandemic), are presented in Supporting Information: Tables S1–S4.

### Insurance and employment status

We found evidence of an association between insurance and the pandemic phase ( $p = 0.041$ ); patients were significantly more likely to be on publicly-sponsored insurance during the pandemic compared to prepandemic, controlling for demographics (Adjusted OR: 1.103, 95% CI: 1.004–1.212) (Table 2). Although there was evidence of an unadjusted association between employment and the COVID-19 pandemic (OR: 0.897, 95% CI: 0.816–0.984), this effect did not remain significant when adjusting for demographics ( $p = 0.194$ ) (Table 2).

**TABLE 1** Patient characteristics ( $N = 1679$ ).

Variable	N (%) / mean (SD)
Age	55.2 (16.0)
Unknown	12
Female sex	1247 (75%)
Unknown	26
<i>Race</i>	
White	1233 (79%)
Black	207 (13%)
Asian	81 (5.2%)
Other	48 (3.1%)
Unknown	110
<i>Ethnicity</i>	
Hispanic or Latino	172 (11%)
Non-Hispanic or Latino	1403 (89%)
Unknown	104
<i>Education</i>	
High school or equivalent	526 (32%)
Less than high school	124 (7.6%)
Business/trade/vocational school	103 (6.3%)
Some college	298 (18%)
College graduate	417 (26%)
Beyond college graduate	164 (10%)
Unknown	47
<i>PAH classification</i>	
Idiopathic PAH	691 (42%)
Heritable PAH	46 (2.8%)
Drug/toxin induced PAH	191 (11%)
Connective tissue disease (CTD) PAH	507 (31%)
HIV-related PAH	25 (1.5%)
Portopulmonary hypertension	103 (6.2%)
Congenital heart disease (CHD) PAH	88 (5.3%)
Pulmonary veno-occlusive disease	9 (0.5%)
Other	2 (0.1%)
Unknown	17
<i>WHO functional classification</i>	
I	127 (8.0%)
II	572 (36%)
III	783 (49%)
IV	100 (6.3%)
Unknown	97

Abbreviation: PAH, pulmonary arterial hypertension.

**TABLE 2** Adjusted effects of the pandemic on outcomes of interest.

Outcome	Pandemic effect estimate ( <i>p</i> Value) <sup>a</sup>	Pandemic effect	Important** additional factors
On public insurance/uninsured	1.103 (0.041)	↑↑**	Age, sex, ethnicity, education
Employed	0.928 (0.194)	↓↓	Age, education
Off medications	1.136 (0.379)	↑↑	Age, education
ED visit rate	-0.002 (0.618)	↓↓	Age, race
PAH MD visit rate	0.006 (0.434)	↑↑	Age, sex
Nights in hospital	-0.552 (0.075)	↓↓*	Insurance status, age, race, education
Mortality	1.384 (0.051)	↑↑*	Age, sex, education
6MWD	6.960 (0.020)	↑↑**	Insurance status, age, sex, race, education
BNP	-26.842 (0.178)	↓↓	Age, education
NT-proBNP	-345.031 (0.009)	↓↓***	Age, education
Creatinine	0.013 (0.299)	↑↑	Age, sex, race, education
NEMC physical health T-score	0.543 (0.047)	↑↑**	Age, education
NEMC mental health T-score	1.005 (0.002)	↑↑**	Age, race, education

Abbreviation: PAH, pulmonary arterial hypertension.

<sup>a</sup>Models are adjusted for all listed confounders, but only those predictive of the outcome ( $p < 0.05$ ) are presented here.

\* $p < 0.1$ ; \*\* $p < 0.05$ ; \*\*\* $p < 0.01$ .

## Healthcare utilization

We did not find evidence that the utilization of medical services (ED visits, PH doctor visits, and nights in the hospital) changed from pre- to postpandemic after controlling for confounders. We found evidence of an association between being on public insurance or no insurance and a greater number of ED visits ( $p < 0.001$ ), although this association was small in magnitude; controlling for confounders, subjects on public insurance experienced an average of 0.032 more ED visits over a 6-month period than subjects with private insurance (95% CI: 0.019–0.046). We also found evidence of an association between being on public insurance or no insurance and a greater number of nights in the hospital ( $p = 0.027$ ); controlling for confounders, subjects on public insurance experienced 0.723 more nights in the hospital over a 6-month period, on average, than subjects with private insurance (95% CI: 0.084–1.361). We did not find evidence that either effect was modified by the pandemic (Table 2).

## Mortality

We found evidence of an increase in the odds of death during the COVID-19 pandemic before confounder adjustment (OR: 1.429, 95% CI: 1.055–1.935). However,

this effect was slightly attenuated after adjustment for confounders (Adjusted OR: 1.384, 95% CI: 0.999–1.919) (Table 2). A Cox regression model with approximated pandemic phase as a time varying covariate produced results that are consistent with this finding. Pandemic dates had to be estimated because we did not have exact dates relative to study entry.

## Clinical and patient reported outcomes

We found evidence that 6-min walk distances (6MWD) improved significantly during the COVID-19 pandemic, with subjects walking an average of 6.960 m further during the pandemic compared to prepandemic, controlling for demographics and insurance (95% CI: 1.112–12.809) (Table 2). For insurance, we found that while patients on public insurance or no insurance had significantly lower covariate-adjusted 6MWD (15.106 m, 95% CI: -24.366 to -5.847) compared to patients on private insurance, this effect was not significantly modified by the pandemic ( $p = 0.65$ ). Similarly, the effect of insurance on all other outcomes was not found to be significantly modified by the pandemic. On average, patients had a significantly lower N-terminal-pro-brain natriuretic peptide (NT-proBNP) value during the pandemic compared to prepandemic, controlling for



demographics and insurance (adjusted difference:  $-345$  units, 95% CI:  $-603.592$  to  $-86.469$ ) (Table 2).

Similarly, we found evidence that composite physical health scores improved during the pandemic (an adjusted improvement of  $0.543$  points on average, 95% CI:  $0.007$ – $1.080$ ) (Table 2). We also found evidence that composite mental health scores improved during the pandemic (an adjusted improvement of  $1.005$  points on average, 95% CI:  $0.360$ – $1.651$ ) (Table 2). We found similar significant improvements in the following subjective evaluations of health improving during the COVID-19 pandemic: better general subjective health evaluation, more time recalled as calm and peaceful, more energy, less time spent downhearted/depressed, less reported condition-related interference in social activities, less frustration by breathlessness, and less time spent feeling like a burden.

## DISCUSSION

The COVID-19 pandemic had a significant impact on patients with chronic medical conditions. The purpose of this study was to determine whether the COVID-19 pandemic had an effect on employment status, health insurance status, healthcare utilization, disease severity, and patient-reported and clinical outcomes in PAH patients.

We found that patients were more likely to report being on a publicly-sponsored health insurance program during the COVID-19 pandemic compared with before. This change in insurance may or may not have caused lapses in healthcare coverage, delays in care due to changes in providers, or other unmeasured effects. There was also evidence that more patients reported being unemployed during the COVID-19 pandemic compared with prior. However, this effect was not statistically significant after adjusting for age, race, ethnicity, sex assigned at birth, and education.

Although a study from China reported interruptions in medical therapies for certain individuals living with pulmonary hypertension,<sup>20</sup> our study did not find evidence of a significant change in the odds of being off medications during the COVID-19 pandemic, after controlling for age. This is consistent with a retrospective analysis looking at prescription drug claims from May 2019 to August 2020 which found that medications typically prescribed through structured programs (e.g., opioid addiction therapy), were less likely to be discontinued.<sup>21</sup> Additionally, our study found no significant difference in hospitalized nights in PAH patients before or during the pandemic. However, when stratified by insurance, patients with public insurance or those uninsured did have more visits to the ED and increased length of hospital stay irrespective of the COVID-19 pandemic.

Another study comparing outcomes between idiopathic pulmonary hypertension (IPAH) and portopulmonary hypertension (POPH) patients, using PHAR data, demonstrated that patients with lower education level had higher emergency room visits even after controlling for POPH diagnosis.<sup>22</sup> Education level and insurance status may impact access to routine care. There may be additional social factors contributing to patient outcomes that are unmeasured by our data. One qualitative study of pulmonary hypertension providers highlights this issue- despite providers' understanding that social determinants of health are large contributors to poor access to diagnostic and therapeutic care for PH patients, these are under-captured metrics in current screening tools at intake or follow-up visits for PH patients.<sup>23</sup>

Although an early and small case report showed favorable outcomes among four pulmonary hypertension patients receiving heterogenous pulmonary hypertension therapies,<sup>24</sup> we postulated that PAH patients might have an increased risk of death from COVID-19, similar to those with other chronic medical comorbidities. In April 2020, an initial Pulmonary Hypertension Association query showed only 13 cases of COVID-19 among pulmonary hypertension patients, with one death, and postulated pathobiological mechanisms to explain the low incidence of cases and deaths.<sup>25</sup> However, this study was later critiqued for its small sample size.<sup>26</sup> Interestingly, it was suggested that behavioral mitigation strategies likely contributed to the low incidence of cases rather than inherent features of the disease process or pharmacologics.<sup>26</sup> In August 2020, Ryan et al.<sup>27</sup> found that among the 77 PH centers participating in the PHAR registry, there was a mortality rate of 12%. We found that PHAR patients had a higher probability of death during the pandemic, before adjusting for demographics. However, when adjusting for demographics, this effect was attenuated and was not found to be statistically significant.

Unexpectedly, we found that some objective measures of pulmonary hypertension disease severity actually improved during the COVID-19 pandemic. This included longer 6-minute walk distances, lower NT-proBNP values and improved mental health scores. While we do not know exactly why these improvements occurred, one possibility is patients may have had more time to focus on their health, especially if not working. In addition, we postulate that participants who dropped-out of the study or missed follow-up visits may have been somehow different, more ill, or had perhaps died. Irrespective of the COVID-19 pandemic, those on public insurance or with no insurance were not able to walk as far during the 6-min walk test. Despite our findings of statistically significant improvements in composite scores of mental and physical health, our estimates for these changes are close to or under the minimum clinically



important difference (MCID) thresholds used in other works.<sup>28–30</sup>

Despite the pandemic, PAH patients reported feeling more calm and peaceful, having more energy, and fewer feelings of downheartedness and depression. This was consistent with one German study which found that the COVID-19 pandemic had little impact on anxiety and depression among PAH patients from May to August 2020.<sup>31</sup> Patients participating in the PHAR may have had easier access to care compared to other patients with chronic disease, resulting in more health-related satisfaction. For example, an early survey of the pulmonary hypertension care centers reported prioritizing in-person visits for patients who had previously reported worsening.<sup>14</sup> This prioritization of sicker patients may have helped patients feel better cared for during a time of uncertainty. In addition, access to vaccines during the pandemic may have eased fears of COVID albeit initially. Clinics also quickly implemented telehealth,<sup>14</sup> and while this may not have been equitably available for all patients,<sup>15,16</sup> this modification may have allowed more frequent check-ins with the healthcare system that would not have otherwise been available.

There are important limitations of this analysis. PHAR enrollment is not consecutive and there may be referral bias. Given the retrospective nature of this study, associations noted between follow-up data and time course related to the COVID-19 pandemic are purely associative and cannot be deemed causative. Data were only able to be collected at follow-up visits and were thus subject to recall bias. In addition, a reduction of in-person collection of 6MWD during COVID, to avoid mask nonadherence that may have occurred during the test, may have led to selection bias. Most of the PHAR centers reside in states with Medicaid expansion, which may contribute to lack of generalizability of this patient population to the general population given variable rates of uninsured persons.<sup>32,33</sup> Due to approximately half of PH centers modifying their protocols as a response to the pandemic<sup>14</sup> and prioritizing sicker patients, this may have led to sampling bias. There may have been other life stressors (e.g., lack of transportation, personal illness, or illness of a family member) contributing to lack of study follow-up and increased patient dropout during the pandemic; sicker patients may have been observed less during this period. This could have resulted in underestimation of several outcomes in this study, such as total ED visits or access to medications. We did not find evidence that subjective evaluations of health worsened during the COVID-19 pandemic, controlling for demographic covariates. As mentioned, this may be due to the consequences of death and dropout during the pandemic. Likewise, for those patients who died, we were not able

to correlate any objective data from visits and therefore cannot make inferences about disease severity and death. As exact dates were unavailable for analysis, the timing of observed changes in outcomes relative to the onset of pandemic could not be assessed with granularity. Finally, although our GEE models were able to use all available data and were versatile when modeling population-level effects with both normal and non-normal outcomes, we assumed that missing data were missing completely at random] (MCAR). If the data were truly missing at random (MAR) rather than MCAR, this assumption may have yielded biased results. However, if the data were truly missing not at random (MNAR), evidence suggests our approach would be less biased than multiple imputation.<sup>34</sup> In future work, we plan to investigate the extent to which this assumption may have impacted our results in statistical methodological research (as we have done previously).<sup>35</sup>

## CONCLUSION

PAH patients enrolled in the PHAR visited the emergency department less, spent fewer nights in the hospital, and demonstrated improvement in objective health outcomes during the COVID-19 pandemic compared with prior. Irrespective of the COVID-19 pandemic, patients who were on publicly-sponsored insurance seemed to do worse, consistent with a previous study demonstrating the impact of social determinants of health.<sup>5</sup> We speculate that established care relationships in PH comprehensive care centers may have lessened the impact of the COVID-19 pandemic on pulmonary hypertension patients.

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

## ETHICS STATEMENT

The PHAR is IRB approved and all subjects were consented before enrollment. All subject data used in the PHAR are deidentified. The University of Pennsylvania IRB has approved and primarily oversees the ethical conduct of this study under protocol #822830.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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