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RESEARCH ARTICLE

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Socioeconomically disadvantaged veterans experience treatment delays for pulmonary arterial hypertension

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Abstract

Prompt initiation of therapy after pulmonary arterial hypertension (PAH) diagnosis is critical to improve outcomes; yet delays in PAH treatment are common. Prior research demonstrates that individuals with PAH belonging to socially disadvantaged groups experience worse clinical outcomes. Whether these poor outcomes are mediated by delays in care or other factors is incompletely understood. We sought to examine the association between race/ethnicity and socioeconomic status and time-to-PAH treatment. We conducted a retrospective cohort study of Veterans diagnosed with incident PAH between 2006 and 2019 and treated with PAH therapy. Our outcome was time-to-PAH treatment. Our primary exposures were race/ethnicity, annual household income, health insurance status, education, and housing insecurity. We calculated time-to-treatment using multivariable mixed-effects Cox proportional hazard models. Of 1827 Veterans with PAH, 27% were Black, 4% were Hispanic, 22.1% had an income < $20,000, 53.3% lacked non-VA insurance, 25.5% had <high school education, and 3.9% had housing insecurity. Median time-to-treatment was 114 days (interquartile range [IQR] 21–336). Our multivariable models demonstrated increased time-to-treatment among patients with lower household income (hazard ratio [HR] 0.74, 95% confidence interval [CI] 0.60–0.91 for < $20,000 vs. ≥ $100,000) and those without non-VA insurance (HR 0.90, 95% CI 0.82–1.00). Race/ethnicity, education, and housing insecurity were not associated with time-to-treatment.

Veterans with PAH experienced substantial and potentially harmful treatment delays, with median time-to-treatment of 16 weeks after diagnosis. Those with lower income and those without non-VA health insurance experienced even greater treatment delays. Additional research is urgently needed to develop interventions to improve timely PAH treatment and mitigate economic disparities in treatment.

KEYWORDS

pulmonary arterial hypertension; racial, ethnic, or social disparities in lung disease and treatment; research design/program evaluation/statistical models

INTRODUCTION

Pulmonary arterial hypertension (PAH), a rare subgroup of pulmonary hypertension (PH), is a progressive disease of the pulmonary vasculature that leads to premature mortality, with a median survival of 2.8 years without treatment.[1] Early detection of the disease and prompt initiation of PAH therapy such as phosphodiesterase-5-inhibitors (PDE5i), endothelin receptor antagonists, prostacyclins, or soluble guanylate stimulators are critical to improve quality of life, reduce healthcare utilization, and prolong survival in patients with PAH.[2–5] Guidelines therefore recommend that patients with PAH be initiated on at least one class of therapy as soon as PAH is diagnosed.[6] Yet, delays in initiation of PAH treatment are common.[7,8]

The drivers of treatment delays in PAH are incompletely understood. PAH frequently goes unrecognized,[9] and data from multiple registries have revealed a mean time from symptom onset to PAH diagnosis ranging from 1 to 4 years, with the majority of that delay occurring after the patient's first contact with the medical system.[10–12] Individuals with PAH belonging to socially disadvantaged groups including racial and ethnic minorities and those with lower socioeconomic status (SES) experience even greater delays in their diagnosis, often presenting with more advanced disease at time of presentation,[13] which may lead to higher mortality.[14,15] Whether these individuals experience further gaps in accessibility or quality of PH care, such as delays in the initiation of PAH therapy after diagnosis, is currently unknown.

The PAH clinician and researcher community have recently called for further investigation to uncover the extent, patterns, and drivers of disparities in PAH care delivery and outcomes.[16] Among a national cohort of Veterans with PAH who received pulmonary vasodilator therapy, we sought to examine the association between race/ethnicity and markers of SES and time from PAH diagnosis to treatment initiation. We hypothesized that racial and ethnic minorities and those with lower SES would experience treatment delays for PAH.

METHODS

Study design and data sources

We conducted a retrospective cohort study of all adult Veterans diagnosed with PAH between January 1, 2006 and December 31, 2019 and treated with pulmonary vasodilators. We linked data from the Veterans Health Administration (VA) Corporate Data Warehouse (CDW) and United States Veterans Eligibility Trends and Statistics (USVETS), a new VA data source with robust socioeconomic data integrated from more than 35 VA and federal data sources.[17] The VA Bedford Healthcare System institutional review board approved this study with a waiver of informed consent.

Study population

From Veterans who used VA services during the study period, we identified all adult (age ≥ 18 years) patients diagnosed with PH between 2006 (the first full year of data available after sildenafil, a PDE5i, was approved by the Food and Drug Administration for use in PAH) and 2019 (most recently available data). We defined PH based on the presence of at least two inpatient or outpatient visits linked to an *International Classification of Diseases* (ICD), 9th or 10th Revision diagnosis code for PH (416. xx or I27.x). To select incident PH, we excluded those with a PH diagnosis code between October 1, 1999 (the inception of the VA CDW) and December 31, 2005. We narrowed our sample to Veterans with PAH using an algorithm we previously validated, comprised of 1) ICD codes specific to PAH (ICD-9 code 416.0, ICD-10 code I27.0), 2) performance of a right heart catheterization within 12 months before or after the first PH diagnosis code (median = 13 [interquartile range [IQR] 0–94] days after the first PH diagnosis code), and 3) receipt of at least one class

of PAH therapy. This algorithm has high specificity (97.1%), sensitivity (77.6%), and positive predictive value (70.0%) for identifying PAH.[18] Finally, we excluded those who did not have records available in the USVETS database, and those who had missing data for our primary exposures of race/ethnicity and measures of SES. The derivation of our study cohort is shown in Figure 1.

Outcome

Our outcome was time from PAH diagnosis to therapy. Per our study population inclusion criteria, all Veterans in our cohort received PAH therapy, which we defined as at least one prescription for the following medication classes: prostacyclin, prostacyclin receptor agonist, endothelin receptor antagonist, PDE5i, or soluble guanylate cyclase stimulator. Prescriptions within 6 months before the first appearance of a PH ICD diagnosis code or any point after the first PH code were included. This time window was based on prior work showing that 17% of prescriptions for PAH medications predated the appearance of the first PH diagnosis code by a median of 4 months.[19] To ensure that PDE5i prescriptions were intended for treatment of PH rather than erectile dysfunction, we required prescription supply exceed 15 pills per month. We chose this definition based on 1) prior medical record validation,[19] and 2) VA policy restricting use of PDE5i for erectile dysfunction to ≤ 4 pills per month. As guidelines dictate that patients with PAH should be started on therapy at the time of diagnosis,[6] we defined our start of follow-up (index date) to be the first PH diagnosis code.

Exposures

Our primary exposures were race/ethnicity and markers of SES. As SES is a complex construct encompassing many diverse factors, examination of a single measure of SES can obscure important relationships with other social or economic measures, and different SES measures, while potentially correlated with each other, cannot be assumed to be interchangeable.[20] We therefore examined all available SES variables, a recommended approach in health services disparities research.[21] These included annual household income, active non-VA health insurance (including both private insurance and Medicare), education, and housing insecurity. To ensure that exposures were captured at a clinically relevant timepoint, we measured each variable at the index date (i.e., first PH diagnosis code).

Covariates

We selected patient- and facility-level variables that we hypothesized would be associated with both our primary exposures and time to treatment based on clinical experience in PAH, prior literature on delays in treatment in non-PH contexts, and prior work on drivers of treatment in other subgroups of PH.[11,22–25] Patient characteristics included demographics (age and sex), general health indicators (Elixhauser comorbidity index[26] and specific comorbid conditions), PAH-associated conditions (connective tissue disease, human immunodeficiency virus infection, congenital heart disease, and portal hypertension), and markers of healthcare utilization. Facility characteristics included geographic region, volume of outpatient PH visits, and facility complexity rating, which is comprised of patient volume and risk, level of teaching and research, number of specialists, and presence of intensive care units.[27] Patients were assigned to VA facilities based on the location of the PH-associated visit on their index date. Table 1 shows the full definitions of variables.

Statistical analyses

We constructed cumulative incidence curves and determined median time to treatment among the entire cohort and strata of race/ethnicity and SES variables using the Kaplan-Meier method. We tested for differences between the curves using the log-rank test. We calculated adjusted time to our outcome using Cox proportional hazards models with normally distributed facility-specific random effects. To disentangle the complex interaction between race/ethnicity and SES, we conducted multivariable models including both race/ethnicity and SES variables within one model, and then repeated the models including only race/ethnicity variables or only SES variables in separate models. As these two approaches led to similar results, we present the model including all variables. We evaluated for the assumption of proportional hazards using Schoenfeld residuals. All analyses were performed using SAS statistical software, version 9.4 (SAS Institute Inc). All p values were two-sided with a significance level of 0.05.

Sensitivity analyses

We conducted the following sensitivity analyses to assess the stability of our results. First, we addressed the possibility of multicollinearity among SES variables by computing variance inflation factors for each predictor in

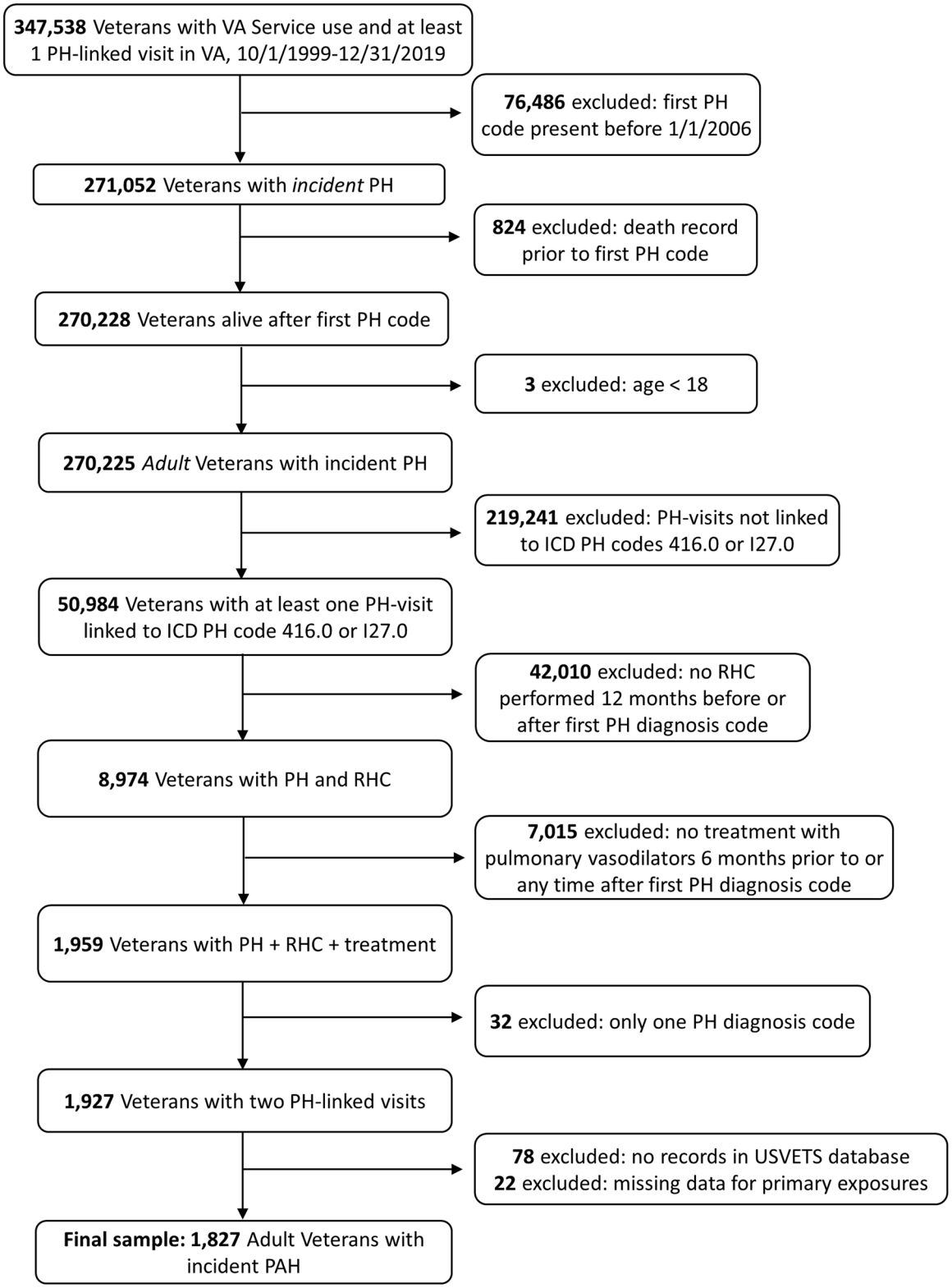

FIGURE 1 Sample derivation of adult Veterans with incident pulmonary arterial hypertension. ICD, International Classification of Diseases; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; RHC, right heart catheterization; USVETS, United States Veterans Eligibility Trends and Statistics; VA, Veterans Health Administration.

TABLE 1 Patient and facility-level variables included in multivariable analyses

Variable	Definition	Data source
Patient-level variables		
Age	Age at index date[a]	CDW
Sex	Male or female	CDW
Race/ethnicity	White, Black, Hispanic, or Other[b]	CDW
Income	Estimated household income within 2 FY of index date	USVETS
Education	Highest level achieved, within 1 FY of index date	USVETS
Active non-VA health insurance	Including both private insurance and Medicare, within 1 FY of index date	USVETS
Housing insecurity	≥2 inpatient or outpatient ICD codes within 2 years before or on the index date	CDW
Elixhauser comorbidity index	Sum of 31 comorbidity groups, determined within 2 years before or on the index date	CDW
Psychiatric illness	≥2 inpatient or outpatient ICD codes within 2 years before or on the index date	CDW
Substance use disorder	"	CDW
Connective tissue disease	≥1 outpatient or inpatient code any time before the index date or up to 1 year after the index date	CDW
Human immunodeficiency virus infection	"	CDW
Congenital heart disease	"	CDW
Portal hypertension	"	CDW
Outpatient visits	Number of outpatient visits in the year before or on index date	CDW
Hospitalizations	Number of inpatient discharges in the year before or on index date	CDW
Urgent care or emergency visits	Number of urgent care or emergency visits in the year before or on index date	CDW
Facility-level variables		
Geographic region	Categorized as North Atlantic, Southeast, Midwest, Continental, and Pacific[c]	CDW
Facility complexity rating	Comprised of patient volume and risk, level of teaching and research, number of specialists, and level of intensive care units within the facility; divided into 1a, 1b, 1c, 2, and 3[d]	CDW
Volume of PH outpatient visits	Averaged over the study period, divided into quartiles	CDW

Abbreviations: CDW, Corporate Data Warehouse; FY, fiscal year; ICD, International Classification of Diseases; PH, pulmonary hypertension; USVETS, United States Veterans Eligibility Trends and Statistics.

[a]Date of first PH diagnosis code.

[b]American Indian, Asian, Pacific Islander, Unknown.

[c]North Atlantic = Connecticut, Delaware, District of Columbia, Maine, Maryland, Massachusetts, New Hampshire, New Jersey, New York, North Carolina, Pennsylvania, Rhode Island, Vermont, Virginia, West Virginia; Southeast = Alabama, Florida, Georgia, Kentucky, Puerto Rico, South Carolina, Tennessee; Midwest = Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, Wisconsin; Continental = Arkansas, Colorado, Louisiana, Mississippi, Montana, Oklahoma, Texas, Utah, Wyoming; Pacific = Alaska, Arizona, California, Hawaii, Idaho, Nevada, New Mexico, Oregon, Washington.

[d]1a–1c: high complexity of patient volume and risk, high volume of teaching and research; 2: moderate complexity of patient volume and risk; some teaching and research; 3: low complexity of patient volume and risk, little or no teaching or research.

the model. No variables had a variance inflation factor greater than four, suggesting that multicollinearity was not problematic.[28] We thus included all SES variables in our final multivariable model. Second, we excluded those who were treated before or on their index date ($n = 170$) as these patients may have previously been initiated on PAH therapy outside the VA and thus have an inaccurate index date.

TABLE 2 Baseline characteristics of Veterans with PAH at diagnosis[a]

Patient characteristics	$n = 1827$
Demographics	
Age, year, mean (SD)	64.5 (10.3)
Female sex	130 (7.1)
Race/ethnicity	
White	1215 (66.5)
Black	493 (27.0)
Hispanic	73 (4.0)
Other[b]	46 (2.5)
Markers of socioeconomic status	
Yearly household income	
< $20,000	403 (22.1)
$20,000–$99,999	1302 (71.3)
≥$100,000	122 (6.7)
Education	
Less than high school	466 (25.5)
Completed high school	699 (38.3)
Attended vocational school	19 (1.0)
Completed college	486 (26.6)
Completed graduate school	157 (8.6)
Active non-VA health insurance[c]	853 (46.7)
Housing insecurity	71 (3.9)
Markers of general health	
Elixhauser comorbidity index, mean (SD)	9.2 (4.0)
Psychiatric illness[d]	300 (16.4)
Substance use disorder	371 (20.3)
PAH specific conditions	
Connective tissue disease	262 (14.3)
Portal hypertension	131 (7.2)
Human immunodeficiency virus infection	42 (2.3)
Congenital heart disease	101 (5.5)
Healthcare utilization[e]	
Outpatient visits, mean (SD)	29.5 (24.8)
Hospitalizations, mean (SD)	0.9 (1.4)
Urgent care or emergency visits, mean (SD)	1.5 (2.2)
Facility characteristics	$n = 1827$
Geographic region	
North Atlantic	299 (16.4)
Midwest	354 (19.4)
Southeast	399 (21.8)
Continental	361 (19.8)
Pacific	414 (22.7)
Facility complexity rating[f]	
1a	1,083 (59.3)
1b	436 (23.9)
1c	157 (8.6)
2	95 (5.2)
3	56 (3.1)
Volume of PH outpatient visits, by quartile	
Q1	239 (13.1)
Q2	605 (33.1)
Q3	549 (30.0)
Q4	434 (23.8)

Note: Data presented as No. (%) unless otherwise noted.

Abbreviations: PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; SD, standard deviation.

[a]Date of first pulmonary hypertension diagnosis code.

[b]American Indian, Asian, Pacific Islander, Unknown.

[c]Including both private insurance and Medicare.

[d]Including posttraumatic stress disorder, schizophrenia, other psychoses.

[e]In the year on or before index date.

[f]1a–1c: high complexity of patient volume and risk, high volume of teaching and research; 2: moderate complexity of patient volume and risk; some teaching and research; 3: low complexity of patient volume and risk, little or no teaching or research.

RESULTS

Study population

We identified 1,827 Veterans with incident PAH in our cohort (Figure 1). The mean age was 64.5 years; 7.1% were women; 27% were Black and 4% were Hispanic. 22.1% had a yearly income < $20,000, 53.3% did not have active non-VA health insurance, 25.5% had less than a high school education, and 3.9% had housing insecurity (Table 2). Veterans in our cohort had a high burden of comorbid disease including substance use disorder (20.3%) and psychiatric illness (16.4%), and high rates of healthcare utilization in the year before diagnosis. The most common PAH-associated condition was connective tissue disease (14.3%) followed by portal hypertension (7.2%).

Treatment patterns and time to treatment

Among our entire cohort of Veterans with PAH treated with pulmonary vasodilators, median time from PAH diagnosis to treatment was 114 days (IQR 21–336 days). The most common type of treatment was PDE5i monotherapy ($n = 1384$ [75.8%]) followed by combination therapy with more than one class of medication ($n = 388$ [21.2%]). Those treated with endothelin receptor antagonist monotherapy ($n = 34$), soluble guanylate cyclase stimulator monotherapy ($n = 15$), and prostacyclin or prostacyclin receptor agonist monotherapy ($n = 6$) represented smaller proportions of patients.

Associations with race/ethnicity and SES and time from PAH diagnosis to treatment

From our unadjusted cumulative incidence curves, annual household income and health insurance status were both associated with treatment delays. Median time to treatment among those with annual household income < $20,000 was 133 days, compared to 95 days among those with income ≥ $100,000. By contrast, there were no differences in time to treatment by race/ethnicity, education, or housing insecurity (Figure 2). Our multivariable-adjusted cox proportional models demonstrated increased time to treatment among patients with a lower household income (HR 0.74, 95% CI 0.60–0.91 for < $20,000 vs ≥ $100,000) and those without active non-VA health insurance (HR 0.90, 95% CI 0.81–1.00). Race/ethnicity, education, and housing insecurity were not associated with time to treatment (Table 3). We found similar results in our sensitivity analysis excluding those who were treated on or before their index date.

DISCUSSION

In this large national cohort study, we found that Veterans with PAH experienced delays in initiation of PAH therapy, with a median time to treatment of more than 16 weeks after diagnosis. A meta-analysis of randomized controlled trials of PAH therapies with open-label extension studies compared six-minute walk distances at 1 year among those in the trial treatment arm (initiated on treatment at study start, "early treatment") to those in the placebo arm (initiated on treatment at end of study [12–16 weeks after study start], "delayed treatment") and found that those with delayed treatment had significantly worse 6-min walk distances at 1 year.[5] Thus, a treatment delay of 16 weeks represents a substantial and potentially harmful delay.

Our results are in line with and expand upon prior research demonstrating delayed treatment for patients with advanced PAH. A prior small study assessing appropriateness of PAH therapy among patients being referred to one of three expert PH centers found that some patients with advanced PAH had not yet been initiated on appropriate therapy at time of referral.[8] Similarly, an implementation study aimed at improving guideline adherence in the management of PAH found that 45% of PAH patients who were New York Heart Association functional class IV had not yet been started on parenteral therapy at the start of the study, contrary to guideline recommendations.[7] We now show that delayed initiation of PAH therapy after diagnosis may be occurring more widely, including among patients being started on oral therapy, which carries fewer hurdles to initiation compared with parenteral therapy.

We found that those with lower annual household incomes and those without active non-VA health insurance experienced even greater delays in treatment initiation compared to their counterparts. Individuals with fewer economic means often experience multiple barriers to receiving timely, high-quality care. Prior literature has shown that those from lower economic backgrounds encounter greater transportation barriers, which may lead to missed clinic appointments and inadequate pharmacy access, in turn delaying medical care.[29] Individuals with fewer economic means may also have inadequate access to technology such as smartphones, computers, or reliable internet, which may limit their ability to engage with healthcare providers between scheduled appointments, access online patient resources, or complete online paperwork such as that required to apply for medication assistance programs or health insurance.[30] For patients with complex diseases like PAH that require frequent in-person assessments and access to specialty experts, these barriers may be even more pronounced. Indeed, prior work demonstrating higher mortality among PH patients living in rural areas compared to urban areas may reflect these access challenges.[31]

Cost of PAH therapies may represent another major hurdle to timely care, particularly for patients of lower economic means and those without health insurance. While VA substantially subsidizes all medication costs and copayments for Veterans,[32] these benefits do not extend to non-Veterans. Outside VA, the mean annual cost of PAH therapies ranges from $14,910 for the PDE5i tadalafil to $244,404 for the prostacyclin analog iloprost,[33] and these costs are rising.[34] Even among patients

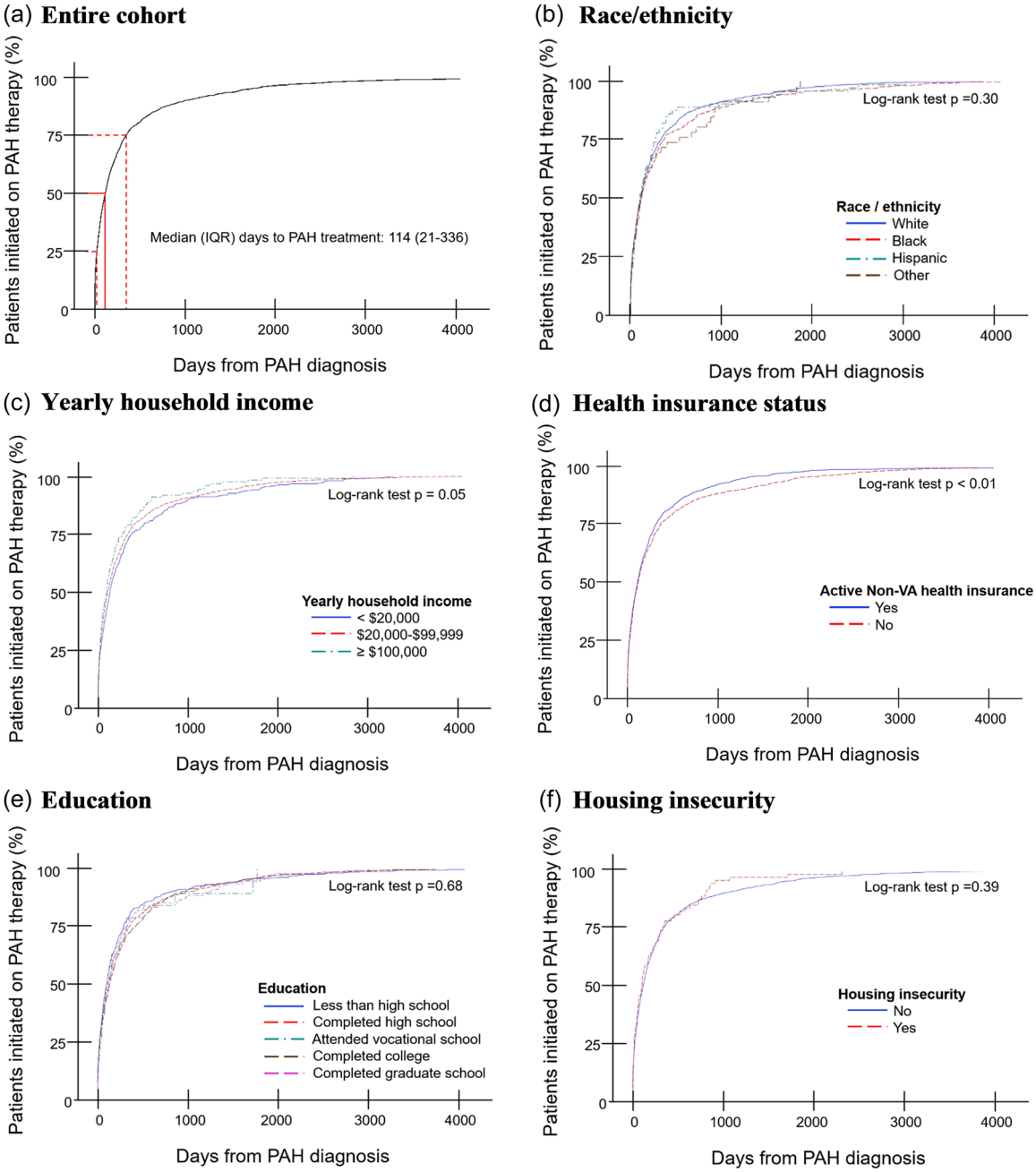

FIGURE 2 Days from pulmonary arterial hypertension (PAH) diagnosis to treatment among the entire cohort (a) and strata of race/ethnicity (b), yearly household income (c), health insurance status (d), education (e), and housing insecurity (f).

with health insurance coverage, deductibles and co-insurance can lead to substantial out-of-pocket costs for patients, exceeding $1000 per month in some cases.[35] Concerningly, even after a patient has overcome the initial barriers to start PAH treatment, ongoing financial burdens may limit adherence to therapy. A recent survey of 106 patients with PAH found that more than a quarter of patients changed their medication regimen including delaying filling prescriptions or skipping doses altogether to save money.[35] A study of pharmacy claims data similarly found that high co-payments were inversely related to adherence to PAH therapy.[36] Medication assistance programs offered through pharmaceutical companies and financial support offered through non-profit organizations provide some avenues to overcome these costs, however, not all patients qualify for these programs.[33] Clinical trials may offer an additional path for some patients to receive PAH therapy without the financial burden, though these are usually administered through expert PAH centers, and some patients may not have access to this option, may not meet the strict inclusion criteria of clinical trials, or may not be able to

TABLE 3 Association between race, ethnicity, socioeconomic status, and time to treatment in Veterans with pulmonary arterial hypertension

Variable	Hazard ratio (95% confidence interval)	*p*-value
Race/ethnicity		
Black	0.95 (0.84–1.06)	0.36
Hispanic	1.07 (0.83–1.38)	0.59
Other[a]	0.93 (0.68–1.26)	0.63
White	Ref	–
Yearly income		
< $20,000	0.74 (0.60–0.91)	<0.01
$20,000–$99,999	0.84 (0.69–1.02)	0.08
≥$100,000	Ref	–
No active non-VA health insurance	0.90 (0.81–1.00)	0.05
Education		
Less than high school	1.09 (0.91–1.32)	0.39
Completed high school	1.08 (0.90–1.29)	0.81
Attended vocational school	0.99 (0.60–1.61)	0.97
Completed college	0.98 (0.81–1.18)	0.34
Completed graduate school	Ref	–
Housing insecurity	1.12 (0.87–1.45)	0.33

[a]American Indian, Asian, Pacific Islander, Unknown.

adhere to the rigorous trial protocols due to transportation or technology barriers as previously noted.

Delays in treatment initiation among economically disadvantaged individuals may be even more pronounced in healthcare settings outside VA. Veterans who seek care within the VA are more likely to be low-income and less likely to have non-VA (i.e., private or Medicare) health insurance coverage compared to Veterans who seek care outside VA.[37] Indeed, nearly a quarter of our study cohort had an annual household income near or under the federal poverty level,[38] and fewer than half had active non-VA health insurance at the time of PAH diagnosis. Yet, the VA has created a system of eligibility for health benefits based on financial need that improves medication coverage and reduces medication non-adherence.[39–41] Unfortunately, this level of medication coverage and resulting medication adherence among low-income individuals may not extend to non-Veterans,[42] who may experience even greater delays in treatment initiation and financial challenges in treatment adherence.

We found that race/ethnicity was not associated with time from PAH diagnosis to treatment. Prior studies in other complex conditions have shown that racial/ethnic disparities in access to care or patient outcomes seen outside VA are not present within VA, suggesting that the VA system of care may provide more opportunities for equitable care and thus mitigate racial/ethnic disparities.[43–45] However, it is also important to note that we were unable to assess for differences in PAH severity or risk category at time of diagnosis between racial/ethnic groups, which could provide insight into urgency of PAH treatment.[46] Notably, prior work has shown that Black patients with PAH have more right ventricular dysfunction at diagnosis, which may warrant more rapid initiation of treatment.[47] Therefore, patients of racial/ethnic minorities may indeed experience overall longer delays in treatment that we were unable to capture given our inability to measure time from symptom onset to first PH visit. Additional studies with granular PAH severity data are needed to further investigate the association between race/ethnicity and timeliness of PAH care. It is also important to note that race and ethnicity are social constructs and not true biologic entities.[48] Thus, any disparities identified by race/ethnicity should be interpreted in that context.

As highlighted recently by the PAH community,[16] socioeconomic disparities in PAH represent a significant research gap and top priority for PAH research. Our work addresses this gap by identifying specific SES risk factors for treatment delay and potential targets for future interventions. For example, prior work has demonstrated that Medicaid expansion through the Affordable Care Act led to earlier detection of disease and an increase in timely treatment in other high-risk diseases.[49] Expansion of healthcare coverage for patients with PAH and improved coverage for PAH therapies may similarly result in improved timeliness of PH care. Indeed, recent studies conducted in Scotland, which has a publicly funded healthcare system that provides free medical treatment to its citizens, found no differences in severity of PAH disease at presentation or in mortality across strata of SES, suggesting that equal access to healthcare may help to mitigate economic disparities.[50–52] Importantly, improved healthcare coverage for PAH therapy can be achieved without increasing costs to health plans or health systems. Prior work has shown that adding the PAH medication riociguat to both non-Medicare and Medicare health plans may have minimal financial impact.[53] Additionally, starting combination therapy upfront may offer economic advantages to health systems by reducing hospital admissions and other healthcare costs.[2,54]

Our study has limitations. First, we deliberately chose a validated algorithm to select patients with PAH that required both the performance of a right heart catheterization and PAH therapy.[18] This maximized specificity and positive predictive value of our algorithm, though prevented us from identifying patients with PAH who remained untreated over the study period or who did not undergo a requisite right heart catheterization. Thus, we were able to assess for the association between race/ethnicity/SES and delays in treatment but not for associations with receipt of treatment. Additionally, our case definition likely selected Veterans who had greater access to expert care. Indeed, most individuals in our study cohort were seen at Level 1a VA facilities which have greater resources and specialist availability. Thus, the effect of low income and uninsured status on treatment delays may be even more pronounced among the general Veteran population. Second, as our study population was predominantly male in line with the Veteran population, we were unable to explore disparities in time to treatment by sex. Third, we could not capture PAH treatment that may have been received outside the VA. However, our sensitivity analysis excluding those who initiated therapy before or on their index date (and who potentially had an incorrect index date) revealed similar results. Fourth, nearly a quarter of patients experienced delays in treatment of more than a year, which may have been due to issues unrelated to socio-economic factors. For example, it is possible that some patients had minimal symptoms at diagnosis and were classified as New York Heart Association functional class I. As guidelines available during the earlier years of our study period did not advocate as strongly for early treatment as later guidelines, it is possible that these patients were not treated until their disease progressed. Finally, the granularity of our data did not permit us to adjust for some variables such as cardiopulmonary hemodynamics or functional class that might shed light on timing of treatment initiation in the context of risk stratification.

This national analysis revealed substantial delays in treatment for PAH among predominantly male Veterans, particularly for those with lower annual household income and those without active non-VA healthcare coverage. Additional research is urgently needed to demonstrate the extent of these disparities across different populations and health systems to increase awareness of this problem and ultimately develop effective interventions to improve the timely treatment of PAH and mitigate economic disparities in PAH care.

AUTHOR CONTRIBUTIONS

Study concept and design: Kari R. Gillmeyer and Renda Soylemez Wiener. Acquisition of data: Renda Soylemez Wiener and Shirley X. Qian. Analysis and interpretation of data: all authors. Drafting of the manuscript: Kari R. Gillmeyer. Critical revision of the manuscript for important intellectual content: All authors.

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CONFLICTS OF INTEREST

ESK receives research support from Bayer, Novartis, FORMA Therapeutics and United Therapeutics. She received royalties for 3 topic cards in UpToDate. She is a consultant for Bluebird Bio and CSL Behring for sickle cell disease related clinical trials (no conflict with the present work). The views expressed in this article do not necessarily represent the views of the Department of Veterans Affairs or the United States Government.

ETHICS STATEMENT

The VA Bedford Healthcare System institutional review board approved this study with a waiver of informed consent.

GUARANTOR

KRG had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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