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RESEARCH ARTICLE

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Prediction of patient outcomes through social determinants of health: The Pulmonary Hypertension Association Registry (PHAR) evaluation

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Abstract

Outcomes of patients with pulmonary arterial hypertension (PAH) may be associated with social determinants of health (SDOH) and other baseline patient characteristics. At present, there is no prognostic model to predict important patient outcomes in PAH based on SDOH. Utilizing information from the Pulmonary Hypertension Association Registry (PHAR), we derive a model (PHAR Evaluation or PHARE) to predict an important composite patient outcomes based on SDOH and other patient characteristics. Baseline data regarding SDOH from adult patients with PAH enrolled in the PHAR

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between 2015 and March 23, 2020, were included for analysis. We performed repeated measures logistic regression modeling with dichotomous outcome data (0 for no events, 1 for one or more events) to derive the PHARE. Here, 1275 consecutive adult patients enrolled in the PHAR from 47 participating centers were included. Variables included in our model are race, gender, ethnicity, household income, level of education, age, body mass index, drug use, alcohol use, marital status, and type of health insurance. Interaction effect between variables was analyzed and several interactions were also included in the PHARE. The PHARE shows a *c*-statistic of 0.608 ($p < 0.0001$) with 95% confidence intervals (0.583, 0.632). Using SDOH and baseline characteristics from the PHAR, the PHARE correlates with our composite patient outcome. Further work evaluating the role of SDOH in prognostic modeling of PAH is indicated.

KEYWORDS
clinical registry, pulmonary arterial hypertension, social determinants of health

INTRODUCTION

Despite advances in therapy, pulmonary arterial hypertension (PAH) remains an often fatal disease with high morbidity.[1] Morbidity often includes reduced quality of life,[2] impaired exercise performance,[3] and need for hospitalization.[4] As the excessive right ventricular afterload created by PAH manifests as right ventricular failure, existing prognostic models have focused on the ability of hemodynamic and exercise data to predict patient outcomes.[5,6] Some have also included patient baseline demographic characteristics in their model. For example, in REVEAL 2.0, age was predictive of patient outcomes and was used as a variable in the model.[5] However, to this time, there has not been a focus on social determinants of health (SDOH) in prognostic modeling in PAH.

Although there are many treatments available for PAH that have improved patient outcomes, there can be many potential barriers to receiving optimal therapy. The therapies are often complex and time intensive,[6] very expensive,[7] and can have significant side effects.[8] In addition, the high symptom burden of PAH and the need for routine surveillance monitoring requires frequent contact with providers. The nature of PAH therapy and care suggests that SDOH may impact patient outcomes.[9] By SDOH, we mean the conditions into which people are born and then live. These conditions are shaped by the distribution of money, resources, and power. To date, there is no prognostic model for PAH that focuses on SDOH. Such a model would be essential to better understand if patients with a certain social disadvantage or group of disadvantages have worse outcomes, and whether interventions could change the expected outcomes.

The Pulmonary Hypertension Association Registry (PHAR) is largest active longitudinal registry in the United States. From its inception in 2015 to the time of this analysis in 2020, it has grown to include 47 accredited Pulmonary Hypertension Care Centers (PHCC) and over 1200 patients. The PHAR not only captures important patient outcomes but also has many common data elements related to SDOH that have previously correlated with patient outcomes in either PAH or other disease states. For example, all participants are asked to enter data about their level of education,[10] type of health insurance,[11] marital status,[12] household income,[13] number in household,[14] race,[15] ethnicity,[16] gender,[17] age,[18] and previous drug use.[19]

In the PHAR Evaluation (PHARE), we seek to determine whether information from subjects pertaining to SDOH can predict an important composite patient outcome. To focus on SDOH, we have purposefully excluded key hemodynamic variables that are known to have prognostic value in PAH, such as brain natriuretic peptide, right atrial pressure, and pulmonary vascular resistance.

METHODS

Participating centers

At the time of analysis, the PHAR had enrolled patients from 47 accredited PHCC. This included 40 PHCC best

categorized as academic medical centers and 7 PHCC best categorized as private practices; all PHCC must care for Medicare/Medicaid patients in addition to privately insured patients. The distribution of centers grossly reflects the United States population density and includes those in Eastern (19), Central (17), Mountain (4), and Pacific (7) times zones. Although enrollment varies between centers, no PHCC contributes more than 10% of the total PHAR population.

Patient selection

The University of Pennsylvania Institutional Review Board approved the PHAR protocols and study-related activities (Federalwide Assurance number FWA00 004028). Informed consent was obtained from each patient before enrollment. Consecutive patients included in the PHAR between 2015 and March 23, 2020, are included. All PHAR participants have been diagnosed with either "Group I" or "Group IV" pulmonary hypertension by a PHCC and established care at that PHCC within 6 months of enrollment. We excluded PHAR participants under age 18 years or with Group IV pulmonary hypertension. In this way, patients were included only if they are adults with a "real world" diagnosis of PAH from a PHCC.

Data collection

Although it is encouraged that patients enrolled in the PHAR have data collected at baseline and subsequent 6-month intervals for data entry, the timing of appointments in a "real world setting" varies and data collection occurs at the closest visit to the 6-month interval. Baseline data related to SDOH were captured for potential inclusion in the PHARE. Variables evaluated for inclusion were race, ethnicity, gender, body mass index (BMI), marital status, highest level of education achieved, household income, number of people in household, age, alcohol use, type of health insurance, and previous drug use.

Combining of subcategories for some independent variables

Some of the independent variables reported in the PHAR contain many subcategories. For the purpose of deriving the PHARE, these subcategories were consolidated into larger categories as shown in Table 1. This prevented our analysis from including subcategories with no participants or very few participants. As noted in Table 1, the result is an improved distribution of participants in each subcategory.

TABLE 1 Consolidation of independent variables with multiple subcategories

Variable	Initial categories from PHAR	Consolidated categories in PHARE (% of participants)
Race	American Indian, Asian Indian, Chinese Filipino, Japanese, Korean, Vietnamese, Other Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Unknown	White (80%) Black/African American (13%) Other (7%)
Type of insurance	Private health insurance, Medicare, Medi-gap Medicaid, Military Health Care, Indian Health Service, State sponsored health plan, other Government program, single service plan (e.g., Dental, vision), no coverage, don't know	Public (38%) Private (53%) Government (5%) No coverage (2%) Unknown (2%)
Marital status	Married, Widowed, Divorced, Separated, Never Married, Living with Partner, Don't Know	Married (49%) Widowed/Divorced/Separated (26%) Never married, Living w/Partner (25%)

Abbreviations: PHAR, Pulmonary Hypertension Association Registry; PHARE, PHAR evaluation.

Composite outcome

The dependent variable was the presence or absence of an event. An event is defined as the occurrence of any of the following: Death, all-cause hospitalization, or clinical worsening. Clinical worsening is defined as a decline in reported functional class (FC) and a decline in 6 min walk distance (6MWD) of 10% or more. A subject with multiple hospitalizations over time may therefore have more than one event.

Statistical analysis

The repeated measures logistic regression model was implemented for modeling the dichotomous outcome data (0 for no events, 1 for one or more events) available approximately every 6 months. We assessed for interaction effects between race and income, education and drug use, education and gender, income and marital status, income and gender, and marital status and gender. We assessed for association between 6MWD with alcohol use (Wilcoxon rank-sum test), race (Kruskal–Wallis test), and age (Spearman's rank correlation coefficient). Association between FC and alcohol use, race, and age was assessed using χ^2 test and Spearman's rank correlation coefficient. To assess the overall prognostic performance of the PHARE model to predict an event or not during the 6-month interval, the *c*-statistic and its 95% confidence interval were estimated based on the internal 10-fold cross-validation. A $p \leq 0.05$ was used to declare statistical significance. Statistical analyses were performed using the SAS 9.4 (SAS Institute Inc.).

RESULTS

The PHARE includes data from 1275 individual patients enrolled in the PHAR from its inception in 2015 through March 23, 2020. This includes 3785 patient encounters. There are 76 (6%) patients "lost to follow-up," 76 (6%) patients transferred care, and 12 (1%) patients underwent lung transplantation.

The baseline characteristics of the patients included in the analysis are shown in Table 2. We found that the general demographics, disease characteristics, and hemodynamic data of patients used in deriving the PHARE is similar to the baseline characteristics of patients in other registries and large clinical trials in PAH.[20,21] We show the distribution of outcomes within our composite outcome in Table 3. Of note, hospitalization comprises of 90.4% of total outcomes, whereas death (8.4%) and clinical worsening (2.6%) are less represented.

Table 4 shows the individual variables from the PHAR analyzed for inclusion in the PHARE. Significantly decreased incidence of events was present in those with reported alcohol use (odds ratio [OR] = 0.67,

TABLE 3 Distribution of outcomes within the composite outcome

Outcome	Number of events per total encounters	Contribution to composite outcome
Death	109/3785 (2.88%)	8.5%
Hospitalization	1165/3785 (30.78%)	90.4%
Clinical worsening	31/3785 (0.82%)	2.4%

Note: Total 1289/3785 (34.06%) 100%. It is noteworthy that the same subject can have hospitalization and clinical worsening during the same 6-month interval.

TABLE 2 Baseline characteristics of patients used in derivation of PHARE

A. Patient demographics		B. Disease characteristics at baseline		C. Baseline hemodynamics	
Age	55 ± 17	Type of PAH		mPAP, mmHg	49
Female, *n* (%)	699 (72)	Idiopathic	505 (39%)	PCWP, mmHg	11 ± 6
Race		Drugs/toxins	115 (9%)	CO, L/min	4.38 ± 1.5
Non-Hispanic White	616 (63%)	CTD	390 (31%)	CI L/min	2.33 ± 0.8
Hispanic	104 (11%)	HIV 14 (1%)	Familial 51 (4%)	PVR, WU	9.8 ± 5
Non-Hispanic Black	117 (12%)	CHD 102 (8%)	PoPH 98 (8%)	NT-proBNP, pg/ml	1194 ± 211
		FC I (13%), II (46%), III (32%), IV (3%)			
		Six minute walk distance, *m* 348 ± 124			

Abbreviations: BNP, brain natriuretic peptide; CHD, congenital heart disease; CI, cardiac index; CO, cardiac output; CTD, connective tissue disease; FC, functional class; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PHAR, Pulmonary Hypertension Association Registry; PHARE, PHAR evaluation; PoPH, portopulmonary hypertension; PVR, pulmonary vascular resistance.

TABLE 4 Association between main effects of SDOH variables and the composite event outcome

Variable	% Patients	Estimate	95% CI	*p*	OR
Race					
Black	13%	Reference			
White	80%	−1.4966	−2.7554, −0.2378	0.224	0.224
Other	7%	0.1884	−1.8297, 2.2064	0.855	1.207
Insurance					
Public	38%	Reference			
Government	5%	0.0567	−0.4976, 0.6110	0.841	1.058
Private	53%	−0.0189	−0.2681, 0.2302	0.882	0.981
Marital status					
Widowed/Divorced/Separated	Reference				
Never/partner		0.0697	−0.6804, 0.8199	0.855	1.072
Married		0.1012	−0.5564, 0.7588	0.763	1.106
Gender					
Female	72%	Reference			
Male	28%	0.6376	−0.2483, 1.5235	0.158	1.892
Drug use					
No	Reference				
Yes		0.1308	−0.2048, 0.4664	0.445	1.140
Prefer to not answer		0.1679	−1.9292, 2.2651	0.875	1.183
BMI		0.0086	−0.0065, 0.0237	0.264	1.008
Education		−0.1166	−0.2782, 0.0450	0.157	0.890
Income		−0.0604	−0.1353, 0.0126	0.104	0.940
Number in household		0.0690	−0.0145, 0.1526	0.105	1.071
Alcohol		−0.3997	−0.6006, −0.1988	<0.001	0.671
Age		0.0081	0.0004, 0.0158	0.038	1.008

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio; SDOH, social determinants of health.

$p < 0.001$), White versus Black (OR = 0.22, $p = 0.020$), or younger age (OR = 1.01, $p = 0.038$). Other variables showed trends toward either reduced events (marital status-married, health insurance-private, higher level of education, higher income) or increase in events (higher number in household, higher BMI, male gender, drug use), albeit not statistically significant at the level of 0.05. Table 5 shows the interaction effect between several SDOH variables, none of which reached statistical significance, yet shown here as they strengthened our model when included.

For the above variables that were significantly associated with outcomes (alcohol use, race, age), we found significant association between alcohol use and baseline 6MWD (median 360 m with alcohol use, 332 m without, $p = 0.0012$), baseline 6MWD and race (median 343 m for White, 305 m for Black, 381 m for other, $p < 0.0001$), and a negative association with age (Spearman's coefficient −0.43, $p < 0.0001$). We additionally found an association between FC and race ($p = 0.0230$, Class III dominant in White and Class II/III evenly distributed in Black and others), no difference between FC and alcohol use ($p = 0.0713$), and a significant association between FC and age (Spearman coefficient 0.17 with $p < 0.00001$).

In compiling variables for the PHARE, we found that the estimated *c*-statistic to predict an event during the 6-month interval was the greatest when including the variables shown in Tables 3 and 4. This yielded a *c*-statistic of 0.608 with the 95% confidence interval (0.583, 0.632), which was significant ($p < 0.001$) compared

TABLE 5 Association between interaction effects of SDOH variables and the composite event outcome

Variable	Estimate	95% CI	*p*
Income × Race			
Black	Reference		
White	0.0316	−0.0494, 0.1125	0.445
Other	0.0301	−0.0992, 0.1594	0.648
Education × Race			
Black	Reference		
White	0.1381	−0.0318, 0.3080	0.111
Other	0.1280	−0.1438, 0.3998	0.356
Income × Gender			
Female	Reference		
Male	0.0169	−0.0492, 0.0831	0.615
Education × Gender			
Female	Reference		
Male	−0.0153	−0.1341, 0.1036	0.801
Race × Marital status			
Black × Never/partner		Reference	
White × Never/partner	0.2905	−0.5260, 1.1070	0.486
Other × Never/partner	−1.0652	−2.8054, 0.6750	0.230
Black × Married	Married	Reference	
White × Married	0.2033	−0.5091, 0.9158	0.576
Other × Married	−1.7308	−3.4437, −0.0179	0.048
Gender × Marital status			
Female × Never/partner	Reference		
Male × Never/partner	−0.7704	−1.5038, −0.0370	0.040
Female × Married	Reference		
Male × Married	−0.6043	−1.2692, 0.0605	0.075

Abbreviations: CI, confidence interval; SDOH, social determinants of health.

with a random-chance model (Figure 1). Our data suggests that even without including key hemodynamic variables, our model can predict if patients with PAH may have an event or not in a 6-month time interval.

DISCUSSION

We have derived the PHARE to optimize its ability to use SDOH and patient characteristics to predict an important composite outcome (death, all cause hospitalization, or change in clinical worsening). We incorporated data from consecutive adult patients with clinical diagnosis of PAH enrolled in the PHAR. Variables were included in this model if they either had a significant independent association with the composite outcome, or if the predictive nature of the PHARE in terms of *c*-statistic was significantly strengthened with their inclusion. The variables with a significant independent association with the composite outcome (race, alcohol use, age) also correlated significantly with 6MWD and FC (except for alcohol use and FC, which trended but was not significant). This suggests that some of the association between these SDOH and our composite outcome is likely related to their association with 6MWD and FC, as these parameters are well established in prognostic models of PAH.

Individual baseline variables involving SDOH generally correlated with our composite outcome as expected. Although it may seem counterintuitive that consumption

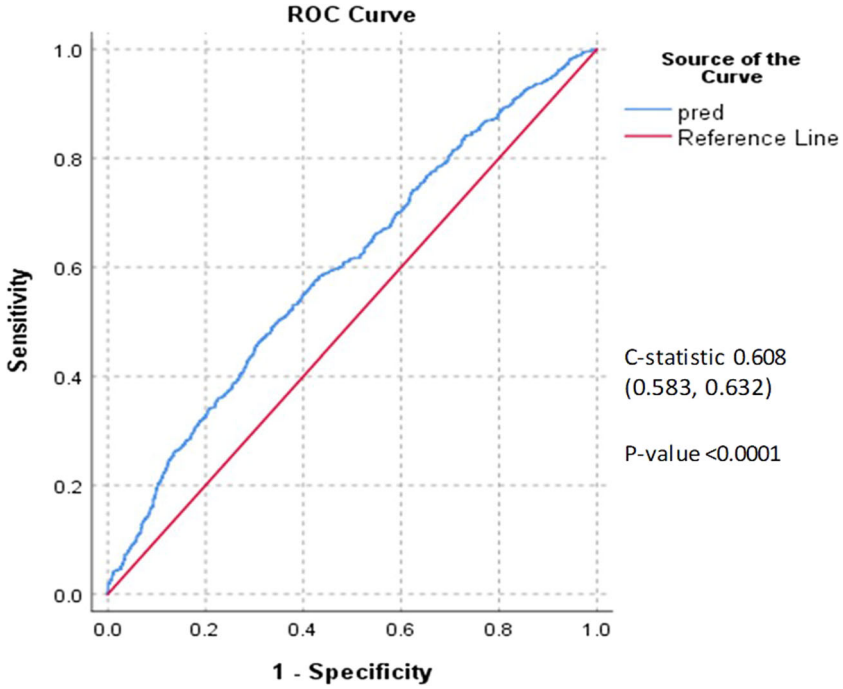

FIGURE 1 Receiver operator curve (ROC) for the composite outcome of the Pulmonary Hypertension Association Registry evaluation (PHARE), *c*-statistic = 0.608 (95% confidence interval [CI]: 0.583, 0.632), $p < 0.0001$.

of alcohol would be significantly associated with a decreased risk of an event, and we did not account for multiple comparisons in denoting significance, the cardiovascular protective effect of one to two alcoholic beverages has been well documented[22,23] and the PHAR does not distinguish the amount of alcohol consumption. Thus, it is possible that alcohol consumption reflects a large proportion of "mild to moderate" alcohol use. The association between baseline 6MWD and alcohol use suggests that those with alcohol use may have less risk of poor outcome at baseline, although there may be other unknown reasons that this population has a higher baseline 6MWD. Other variables mentioned correlate as anticipated. For example, the following all correlated with increased risk of having an event (although not reaching significance): Black race, public insurance, lower level of education, low household income, higher number of people in household, high BMI, previous drug use, age, and male gender. Variables associated with decreased events included "married" marital status and reported alcohol consumption. Several variables showed an interaction effect that correlated with increased risk of an event: for example, the interaction of "level of education" with "race" found that for Black patients, an increasing level of education is associated with an improving event incidence rate, as comparing to White patients with the same increase in level of education. A similar outcome is noted with the interaction of "income" with "race." Other variables with important interaction effects included in the PHARE were "income" and "sex," "education," and "sex," "race," and "marital status," as well as "sex" and "marital status."

In deriving this model, we found that incorporating SDOH-related variables and their interactions yielded a model with statistical significance. Our *c*-statistic of 0.608 shows a model with modest ability to predict an important composite outcome. Previous predictive models used to predict outcomes in PAH have focused on hemodynamic variables, whereas our model is intentional in leaving these variables out of the analysis. By focusing on SDOH, we can assess the impact of these variables on an important outcome in PAH patients. Although previous prognostic models have used mortality as the outcome, the PHAR does not yet have the sufficient longitudinal data to assess mortality alone as a primary outcome. Therefore, we used a composite outcome similar to that used in several major clinical trials.[24,25] The initial strength of this model can likely be improved upon as the PHAR expands.

A limitation of our derivation is that "all cause hospitalization" occurred out of proportion to other components of the composite outcomes and is thus the main "driver" of our outcome. Our cohort had 1165 hospitalizations, as compared with 109 deaths and 31 instances of clinical worsening. The relatively low incidence of clinical worsening events may be driven by the method of data collection (every 6 months) as well as potential missingness (e.g., a participant with missing 6MWD could not have clinical worsening by our definition). As the PHAR does not differentiate the cause of hospitalization, we do not know whether our model is driven by non-PAH-related hospitalizations. However, we would maintain that hospitalization (regardless of cause) is a significant event

and often associated with poor clinical outcomes in PAH patients.[26] Therefore, any event (whether hospitalization or clinical worsening or death) is likely to have a major impact on PAH patients.

Our present investigation is also limited by our statistical approach. As mentioned above, several SDOH variables that are significantly associated with our composite outcome are also associated with 6MWD and FC—indicating that some of the impact on our outcome may be connected to their association with 6MWD and FC. We recognize that this could impact our calculated odds ratios and impact the strength of our composite outcome. In future analysis, further assessment of an interaction with baseline hemodynamics and other established prognostic parameters will be important.

The derivation of a model utilizing SDOH and their interactions to predict an important patient outcome is novel and important. We anticipate that this initial work can be improved upon as the PHAR expands and with improved modeling. The ability to predict PAH outcomes based on SDOH is essential to identifying and helping those at greater risk. Prognostic models assessing hemodynamics and other related variables in PAH have been widely adopted into clinical practice to aid in clinical decision making and impact patient outcomes. We hope this investigation shows the potential of using SDOH to identify PAH patients at greater risk of poor outcomes and will motivate others to further improve risk prognostication in PAH, either through incorporation of SDOH into established prognostication models, or through the development of new models focusing on SDOH.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS STATEMENT

All authors have contributed to the development of the manuscript. No authors have received related funding. Dr. Grinnan is the guarantor for the publication and accepts all responsibility and ensures the research was performed without breach of ethics.

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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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