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Original Research Article

Trends and factors affecting in-hospital mortality of patients with pulmonary arterial hypertension

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ABSTRACT

Background: Pulmonary arterial hypertension (PAH) can be fatal without prompt treatment, but targeted therapies have greatly improved life expectancy in the 21st century. Despite these advances, PAH still involves high morbidity and mortality. Over the past decade, new drugs have been approved for PAH, yet research remains limited, and optimal management guidelines are lacking.
Methods: This retrospective study used the NIS database from 2016 to 2020 to examine PAH patients. Univariate and multivariate analyses were conducted, adjusting for confounders and Elixhauser comorbidity index was used to assess baseline comorbidity impact. Primary outcomes included mortality trends and factors influencing mortality. Secondary outcomes focused on length of stay and hospitalization charges.
Results: PAH admissions increased from 3.8% in 2016 to 30.36% in 2020s. A mortality rate of 6.4% was observed. Despite advancements in therapies, no significant difference in mortality rates was observed during these years. However, total hospitalization charges increased from 2016 to 2020. Age and race significantly influenced mortality. Female gender was associated with lower mortality, while the northeastern and western US had the highest mortality rates compared to the Midwest and South. Uninsured status was linked to higher mortality odds, while obesity had a protective effect. No significant difference in length of stay was noted.
Conclusions: This study summarized PAH trends and outcomes from 2016 to 2020, identifying predictive factors for inpatient mortality, length of hospital stays, and treatment costs.

Keywords: Endothelin receptor, Heart failure, Pulmonary arterial hypertension, Pulmonary hypertension, Pulmonary vascular disease

INTRODUCTION

Pulmonary hypertension is a chronic lung disease characterized by remodelling of the pulmonary vessels leading to increased pulmonary vascular resistance and elevated pulmonary arterial pressure and eventually causing right heart failure.[1] The diagnosis is made when mean pulmonary arterial pressure is more than 20 mmHg on right heart catheterization.[2-4] The 2022 guidelines from the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) characterize pulmonary hypertension (PH) as a mean pulmonary arterial pressure (mPAP) exceeding 20 mm Hg at rest. Additionally, pre-capillary pulmonary hypertension in group 1 pulmonary arterial hypertension (PAH) is identified by both a pulmonary vascular resistance (PVR) above 3 Wood units (WU) and a pulmonary artery wedge pressure (PAWP) under 15 mmHg.[5]

Pulmonary hypertension stands as a substantial health concern on a global scale, affecting approximately 1% of the world's population. While it can impact individuals of all age groups, there has been a substantial rise in its occurrence among those aged 65 and above. The primary

contributor to pulmonary hypertension worldwide is left heart disease, particularly heart failure with preserved ejection fraction. Schistosomiasis, rheumatic heart disease, and sickle cell disease are among the other causative factors in regions where these diseases are endemic.[4]

Pulmonary hypertension is categorized into five subgroups according to its underlying etiology, and this article primarily concentrates on the first subgroup, known as pulmonary arterial hypertension (PAH).[3]

METHODS

We conducted a retrospective study including all patients with a primary or secondary diagnosis of pulmonary arterial hypertension, using the National Inpatient Sample (NIS) database. Our analysis covered a five-year period from 2016 to 2020. The NIS is the largest publicly available database under the healthcare cost and utilization project (HCUP), encompassing over 97% of all US hospitals. It represents 20% of randomly stratified inpatient hospitalizations, with discharge weights applied to each hospital encounter to estimate the overall inpatient population in the United States. Since the NIS data is publicly available and de-identified, studies using this data are exempt from institutional review board (IRB) approval.

Patients with group 1 pulmonary hypertension were identified using International Classification of Diseases, 10th revision, clinical modification (ICD-10 CM) codes. Those undergoing procedures such as non-invasive or mechanical ventilation were identified using ICD-10 procedural codes (ICD-10 PCS). Univariate logistic and linear regression analyses were performed to identify potential confounders, and multivariate logistic and linear regression analyses were used for adjustments. The Elixhauser comorbidity index (ECI), a widely used tool in medical research encompassing 31 broad categories of comorbidities, was used to assess baseline comorbidity and its impact on in-hospital mortality and the risk of 30-day readmission. ECI again uses ICD-10 CM codes to identify the co-morbidities. Higher comorbidity scores indicate higher in-hospital mortality and increased risk of 30-day readmission. Each hospitalization was adjusted based on their Elixhauser comorbidity index. Alpha risk was set at 5% to determine statistically significant result.

The primary outcome was to assess mortality trends and factors influencing mortality. The secondary outcomes included analyzing trends in the length of stay and hospitalization charges, along with the factors affecting them.

RESULTS

A total of 1.8 million patients with a primary or secondary diagnosis of PAH were identified. The cohort had an average age of 71.71 years and was predominantly female (57.55%). Racial composition was 68.17% White, 19.32% Black, 7.47% Hispanic, 2.26% Asian, 0.55% Native American, and 2.23% other races. Most patients (92.25%) lived in urban areas, with 7.75% in rural areas. A majority (73.23%) were treated at teaching hospitals, while 26.77% were at non-teaching facilities.

Table 1: Baseline characteristics of the patients with pulmonary arterial hypertension.

Characteristics	%
Females	57.55
Age, years	71.71
Race	
White	68.17
Blacks	19.32
Hispanics	7.47
Asians	2.26
Native Americans	0.55
Others	2.23
Location	
Rural	7.75
Urban	92.25
Teaching facility	
Nonteaching	26.77
Teaching	73.23
Region	
Northeast	18.27
Midwest	25.96
South	37.02
West	18.75
Insurance	
Medicare	77.66
Medicare	9.36

Continued.

Characteristics	%
Private	11.37
Selfpay	1.62
Hospital bed size	
Small	20.96
Medium	29.4
Large	49.63
Elixhauser's comorbidities	
Congestive heart failure	74.37
Cardiac arrhythmias	58.99
Valvular heart disease	37.24
Peripheral vascular disorder	15.88
Uncomplicated hypertension	13.58
Paralysis	1.95
Other neurological disorders	16.93
Chronic pulmonary disease	46.18
Uncomplicated diabetes	9.95
Complicated diabetes	35.27
Hypothyroidism	20.52
Renal failure	47.28
Liver disease	9.19
Peptic ulcer disease excluding bleeding	0.89
AIDS/HIV	0.38
Lymphoma	1.47
Metastatic cancer	2.61
Solid tumor without metastasis	5.13
Rheumatoid arthritis/collagen vascular disease	5.96
Coagulopathy	13.65
Obesity	26.12
Weight loss	11.83
Fluid and electrolyte disorders	51.49
Blood loss anemia	1.57
Deficiency anemia	9.32
Alcohol abuse	4.34
Drug abuse	4.71
Psychosis	1.42
Depression	15.39
Year	
2016	0.38
2017	6.94
2018	30.21
2019	32.11
2020	30.36

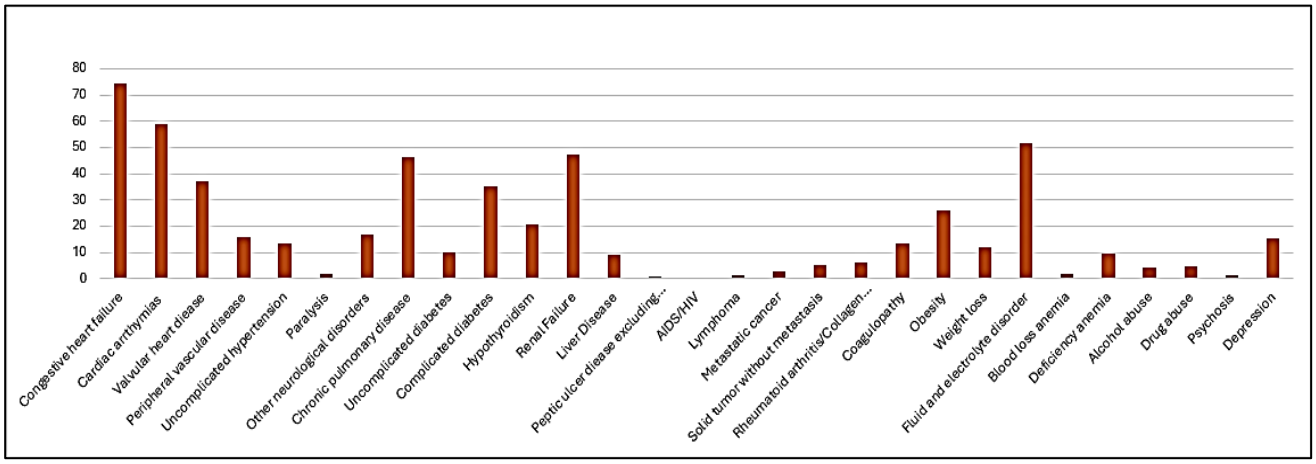

Figure 1: Co-morbidity distribution of patients with pulmonary arterial hypertension.

Geographically, 18.27% were in the Northeast, 25.96% in the Midwest, 37.02% in the South, and 18.75% in the West. Regarding insurance, 77.66% were covered by Medicare, 9.36% by Medicaid, 11.37% by private insurance, and 1.62% were self-pay. Hospital admissions were distributed as 20.96% in small hospitals, 29.4% in medium-sized hospitals, and 49.63% in large hospitals. The proportion of hospitalized patients with a PAH diagnosis increased significantly from 0.38% in 2016 to 30.21% in 2018, then stabilized (Table 1). The distribution of co-morbidities is shown in Figure 1.

Among these 1.8 million patients, 121,170 (6.4%) died. Mortality increased by 2.7% with each additional year of age [adjusted odds ratio (aOR) 1.02, 95% CI 1.025-1.029, p value 0.000)]. Females had 12% lower odds of mortality compared to males (aOR 0.88, 95% CI 0.86-0.91, p value 0.000). Blacks had 13.05% lower odds of mortality compared to Whites (aOR 0.86, 95% CI 0.83-0.9, p value 0.000). No statistical difference was found between Hispanic and white (aOR 0.97, 95% CI 0.91-1.03, p value 0.377). The Northeast had the worst outcomes, with the Midwest and South having 25.75% (aOR 0.74, 95% CI 0.7-0.78, p value 0.000) and 20.39% (aOR 0.79, 95% CI 0.75-0.83, p value 0.000) lower odds of mortality, respectively. No statistically significant difference was seen between the West and Northeast regions (aOR 0.96, 95% CI 0.91-1.02, p value 0.25). Teaching hospitals had 16.68% (aOR 1.16, 95% CI 1.11-1.22, p value 0.000) higher odds of mortality than non-teaching hospitals, possibly due to higher patient severity and numbers. Mortality rates were 8.1%, 12.01%, and 10.4% lower in 2017, 2018, and 2019 compared to 2016, though not statistically significant (p value 0.56, 0.37, and 0.48 respectively). In 2020, mortality odds were 9.8% higher, but this was also not statistically significant (p value 0.51) (Figure 2).

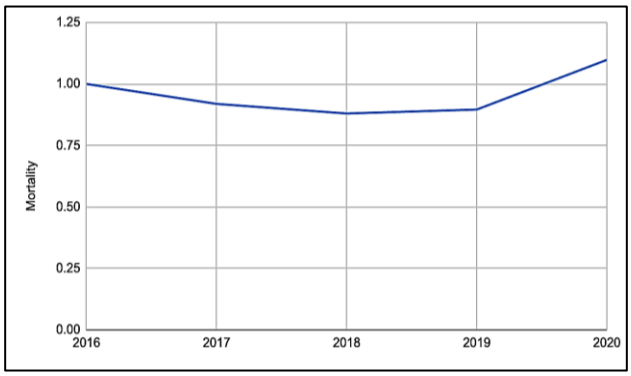

Figure 2: Mortality trends from 2016-2020.

Patients with private and self-pay insurance had 24.66% (aOR 1.24, 95% CI 1.18-1.31, p value 0.000) and 18.39% (aOR 1.18, 95% CI 1.03-1.35, p value 0.017) higher odds of mortality compared to those with Medicare (Figure 3a). Cardiac arrest patients had 4.2 times higher odds of mortality (aOR 4.28, 95% CI 3.83-4.77, p value 0.000), and those with sepsis, non-invasive ventilation (NIV), and mechanical ventilation had 4.18 times (aOR 4.18, 95% CI 3.95, p value 0.000), 2 times (aOR 2.0, 95% CI 1.9-2.1, p value 0.000), and 11.52 times (aOR 11.52, 95% CI 11.09-11.97, p value 0.000) higher odds of mortality, respectively (Figure 3b).

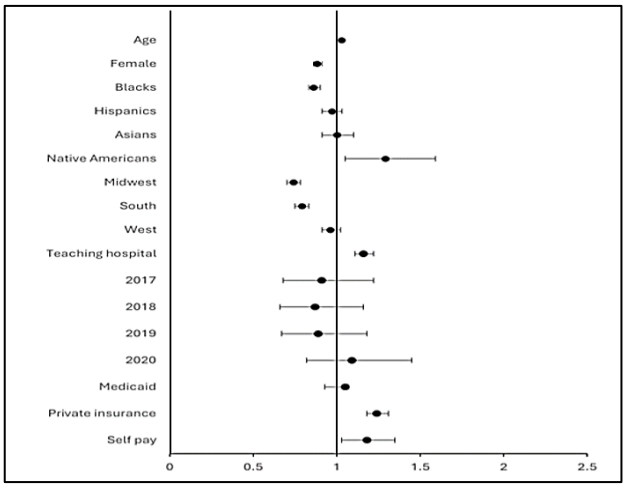

Figure 3a: Forest plot showing demographic factors affecting mortality in patients with pulmonary arterial hypertension.

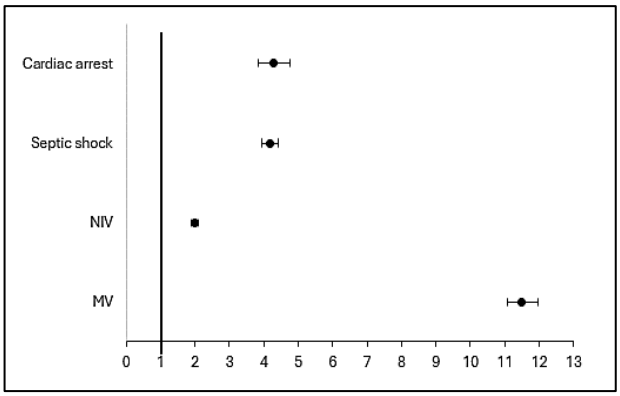

Figure 3b: Conditions/procedures during the hospital stay affecting in-hospital mortality.

The mean length of stay (LOS) was 7.19 days (p: 0.000, 95% CI 7.14-7.24). Each additional year of age decreased LOS by 0.02 days, and females had a 0.19-day shorter LOS than males. Blacks, Hispanics, and Asians had 0.2, 0.19, and 0.54-day longer LOS compared to Whites, respectively, though clinically insignificant. No yearly differences in LOS were observed. Patients with cardiac arrest had a 0.8-day longer LOS, and those with septic shock, NIV, and mechanical ventilation had 2.3, 0.84, and 5.2 days longer LOS, respectively.

The median total hospitalization charges (TOTCHG) were $413,799. Each additional year of age reduced TOTCHG by $800 (p: 0.000, 95% CI $868-$736).

Females had $8,187 lower TOTCHG (p: 0.000, 95% CI $9301-$7400). Blacks had $3,038 lower TOTCHG, while Hispanics had $21,247 higher TOTCHG. The Midwest had $32,019.8 lower and the South had $14,665 lower TOTCHG compared to the Northeast, while the West had $14,090 higher TOTCHG compared to the Northeast. Private insurance resulted in $13,695 higher TOTCHG compared to Medicare. No significant TOTCHG differences were found between Medicaid, Medicare, and self-pay patients. Patients with cardiac arrest, septic shock, and those on mechanical ventilation had higher TOTCHG.

DISCUSSION

Pulmonary hypertension encompasses five main categories based on the underlying pathophysiological processes: group 1, which involves pulmonary arterial hypertension; group 2, associated with pulmonary hypertension due to left heart diseases; group 3, which pertains to pulmonary hypertension due to chronic lung diseases; group 4, linked with pulmonary hypertension due to chronic thromboembolic disease; and group 5, involving pulmonary hypertension arising from unclear or multifactorial mechanisms.[6]

Pulmonary arterial hypertension

PAH can be subdivided into different categories based on its underlying causes, as outlined in Table 2. Nevertheless, despite the various etiologies, the management approach remains the same.[7] Idiopathic, heritable, and anorexigen-induced forms collectively represent approximately half of all PAH cases.[8,9]

Table 2: Etiological classification of PAH.

Classification of PAH
1. Idiopathic
2. Heritable
3. Drug and toxin induced (amphetamines, appetite suppressants, dasatinib, leflunomide etc.)
4. Associated with other conditions **a. Connective tissue disease** **b. HIV infection** **c. Portal hypertension** **d. Congenital heart disease** **e. Schistosomiasis**
5. PAH long-term responders to calcium channel blockers
6. PAH due to pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis (PVOD/PCH)
7. Persistent pulmonary hypertension of newborn

Pathogenesis

The development of PAH is influenced by a multitude of genetic and environmental factors, culminating in endothelial injury, often considered the initial trigger. This leads to dysfunction in endothelial cells and impedes vascular regeneration. Consequently, abnormal vasculogenesis occurs, initiating the remodelling of small pulmonary arterioles.[10] Endothelial cells undergoing apoptosis release a range of cytokines and growth factors, fostering an environment that promotes vessel constriction and the development of highly proliferative and apoptosis-resistant pulmonary arterial vascular cells. These cells include pulmonary arterial smooth muscle cells, adventitial fibroblasts, and even endothelial cells themselves. These changes contribute to a progressive narrowing of the vascular lumen, potentially leading to complete occlusion.[11] This process elevates pulmonary vascular resistance (PVR) and mean pulmonary arterial pressure (mPAP). The ensuing rise in pressure imposes strain on the right ventricle, resulting in right ventricular dysfunction and eventual reduction in cardiac output, leading to heart failure.[12]

Moreover, PAH involves an imbalance between vasodilation and vasoconstriction, favoring vasoconstriction. This imbalance includes increased levels of vasoconstrictors like thromboxane, endothelin, and serotonin, and decreased levels of vasodilators such as prostacyclin, nitric oxide (NO), and vasoactive intestinal polypeptide. Understanding PAH's pathophysiology has led to treatments targeting the NO, prostacyclin, and endothelin pathways.[13]

Given the similarities in phenotype between advanced-stage PAH cells and cancer cells, insights from oncology may offer valuable perspectives on PAH pathogenesis suggesting potential for repurposing cancer drugs to address PAH. While inflammation and genetic abnormalities are recognized as key factors in PAH pathogenesis, investigating the roles of DNA damage response, metabolic reprogramming, endothelial-mesenchymal transition, and epigenetics has become a primary focus in PAH research.[14]

Genetics

It's now widely accepted that a vast majority of familial PAH cases (around 70-80%) and a significant portion of idiopathic PAH cases (10-20%) are linked to mutations in BMPR2 (bone morphogenetic protein receptor type 2), a member of the transforming growth factor-β (TGF-β) superfamily.[15] BMPR2 is prominently expressed on pulmonary vascular endothelial cells, forming complexes with type I receptors like ALK1 or ALK2. These complexes respond to circulating BMP ligands, particularly BMP9 and BMP10, with ENG acting as a coreceptor.[16] BMP9 functions as a circulating vascular quiescence factor, preserving endothelial cell integrity and inhibiting excessive proliferation and vascular permeability. Loss of BMPR2 disrupts this balance, promoting endothelial dysfunction and endothelial-to-mesenchymal transition.[17] Mutations involving the above

receptors and co-receptors have also been implicated in the pathogenesis.

Additionally, mutations in Smad8 (encoded by SMAD9) impair BMP signalling, suggesting a potential role for microRNAs regulated by this pathway in PAH development.[18] Other mutations implicated in the development of PAH involve BMPR2 ligands like GDF2 (which encodes BMP9), the type I receptor ACVRL1, EIF2AK4 (also known as general control non-derepressible 2 (GCN2), among others. Mutations of caveolin-1 (CAV1) a key protein in caveolae (plasma membrane invaginations) and highly expressed in endothelial cells have also been identified. Loss of CAV1 reduces BMPR2 membrane localization and signaling.[19] Interestingly, some carriers may never experience symptoms since PAH mutations often exhibit an autosomal dominant pattern with low penetrance. Mitochondrial metabolism impairments have also been associated with PAH development possibly explaining the higher prevalence of females in PAH cases. The variability in BMPR2 mutation penetrance, with only 14% of men and 42% of women affected, suggests a potential association between sex hormones like estrogen, their metabolism, and PAH pathogenesis.[20]

Presenting features and physical examination

The most common presenting symptom of pulmonary hypertension (PH) often manifests as exertional dyspnea or a decline in exercise capacity. Given the nonspecific nature of these symptoms, it's essential to thoroughly assess each patient and rule out other potential causes of dyspnea. Symptoms like orthopnea and lower extremity edema typically indicate advanced disease, suggesting right ventricular dysfunction, which is a known late complication of PH. Concerning symptoms such as exertional dizziness, light headedness, or syncope are considered high-risk features in patients with right ventricular failure and should prompt an immediate diagnostic evaluation.[21]

During physical examination, distinct signs include a loud pulmonic component of the second heart sound (P2), the presence of a tricuspid regurgitation murmur, and palpable right ventricular heave. As right ventricular function deteriorates, there may be an increase in jugular venous pulsation, presence of hepatojugular reflex, and development of peripheral edema. It's essential to conduct a thorough examination to identify any signs of associated conditions or related diagnoses.

Diagnostic evaluation

It is recommended to perform a screening transthoracic echocardiogram in patients with suspected clinical signs and symptoms of pulmonary arterial hypertension. It is a non-invasive method of estimating the right ventricular systolic pressure (RVSP), thus providing insight into pulmonary artery systolic pressure (PASP). RVSP or PASP exceeding 40 mmHg Is a cause for concern. Additional echocardiographic findings such as right ventricular enlargement, flattening of the interventricular septum indicative of RV volume or pressure overload, and specific Doppler patterns in the right ventricular outflow tract can also suggest PH.[22]

If the echocardiographic likelihood of PH is deemed high or intermediate, further assessment is recommended, including evaluation for underlying heart or lung conditions and performing a right heart catheterization which is the gold standard for confirming the diagnosis of PH. PH is defined as mean PAP equal to or greater than 20 mmHg at rest. PAH is characterized by precapillary PH with mean PAP equal to or greater than 20 mmHg, pulmonary artery wedge pressure (PAWP) less than or equal to 15 mmHg, and pulmonary vascular resistance (PVR) greater than 3 Wood units. Once PH is confirmed via RHC and PAH is suspected based on cardiac and pulmonary evaluations, other potential causes such as connective tissue disease, HIV, liver disease, and illicit drug use should be ruled out. Additionally, a ventilation/perfusion (V/Q) scan is crucial for screening chronic thromboembolic disease.[23]

Treatment strategies

Numerous drugs are currently available in the market but the widely used ones target three common signaling pathways, namely cyclic guanosine monophosphate (cGMP), endothelin, and prostacyclin. Patients with PAH often exhibit reduced synthesis of prostacyclin and nitric oxide (NO), the latter being crucial for activating soluble guanylyl cyclase (sGC) and promoting pulmonary vascular cGMP synthesis.[24]

In PAH, there's an increase in the expression of phosphodiesterase type-5 (PDE5), the enzyme responsible for cGMP degradation, as well as elevated pulmonary endothelin synthesis, which leads to pulmonary vasoconstriction. Medications such as phosphodiesterase type 5 inhibitors (PDE5i) like sildenafil, tadalafil, and the recently approved udenafil, and sGC stimulators (sGCS) such as riociguat, work by boosting cGMP levels, thereby inducing vasodilation. Endothelin receptor antagonists (ERA), like bosentan, macitentan, and ambrisentan counteract the vasoconstrictive effects of endothelin. Additionally, prostacyclins and their analogs (e.g., epoprostenol, treprostinil) act as potent vasodilators and inhibit platelet aggregation. Combining these medications can yield additive effects, enhancing clinical outcomes.[25] The AMBITION study revealed that initiating treatment with a combination of the phosphodiesterase type 5 inhibitor (PDE5i) tadalafil and the endothelin receptor antagonist (ERA) ambrisentan was superior in enhancing the six-minute walk distance (6MWD) and prolonging the time to clinical worsening compared to either medication used individually.[26] Supplemental oxygen and diuretic therapy are usually required for symptom alleviation.

Trends observed in PAH

The following conclusions can be drawn from the above study, which includes data from the National Inpatient Sample, through the years 2016 to 2020.

The average age of patients diagnosed with PAH was found to be 71.71 years, consistent with evidence indicating a substantial increase in PAH incidence among those aged 65 years and above.[4] It should be noted that mortality steadily increases with advancing age. Females are primarily affected, aligning with existing literature. The REVEAL registry study, conducted between 2006 and 2007, estimated that approximately 79.5% of patients were females.[27] However, data from our study period indicate that 57.55% were males, raising concerns about a potential increase in incidence among males. Another intriguing aspect of the sex difference in mortality could be attributed to the interplay of estrogen and other sex hormones. Despite being less likely to be affected, males tend to have a poorer prognosis and worse clinical outcomes compared to females and therefore have increased total hospitalization charges (TOTCHG).[8]

The prevalence of pulmonary arterial hypertension is higher in teaching hospitals, where patients have 16.68% increased odds of mortality compared to non-teaching hospitals. This may stem from the fact that the hospitals are primarily located in densely populated areas and an increased number of patients being transferred for a higher level of care. Whites constitute approximately 68.7% of the overall patient population impacted by PAH, followed by blacks and then Hispanics. This notable prevalence among whites may be linked to their larger population size. While earlier studies often reported increased mortality rates among blacks, this study revealed higher mortality rates among whites than compared to African americans.[28] No statistically significant difference was found between whites and Hispanics. Regarding hospitalization charges, Hispanics incurred higher charges, while blacks had the lowest.

The majority of patients (77.6%) were Medicaid recipients, yet significantly higher odds of mortality were noted among those covered by self-pay and private insurance, likely due to the elevated costs linked with these insurance models. Although the length of hospital stays did not show clinical significance across different insurance types, patients with private insurance experienced higher total charges (TOTCHG) compared to others.

Congestive heart failure (CHF) emerged as the predominant comorbidity seen in about 74.37% of patients with PAH. Longer hospital stays, higher TOTCHG, and increased odds of mortality were observed in patients who suffered cardiac arrest and those with septic shock, Non-invasive ventilation, and mechanical ventilation.

This study has several limitations. Firstly, since it was a retrospective study, a cause-and-effect relationship cannot be established. Secondly, there's a risk of misclassification bias due to the use of ICD-10 coding. The study relies on data from the National Inpatient Sample (NIS), which is susceptible to issues such as miscoding and non-coding inherent in large datasets. This ambiguity could lead to inaccuracies in identifying PAH cases. Thirdly, there's the presence of unadjusted confounders, which could potentially skew the results. These factors collectively underscore the need for a cautious interpretation of the study findings and highlight areas for potential refinement in future research endeavours.

CONCLUSION

After assessing mortality and other in-hospital outcomes, we have identified potential factors that warrant further investigation. Recognizing these disparities in pulmonary arterial hypertension (PAH) is crucial as it marks the initial step toward addressing them effectively. Our findings underscore the necessity for devising strategies that can identify and mitigate these disparities and enhance the overall care and outcomes for individuals with PAH across diverse demographic groups. Despite the vast array of medical treatments that have been developed, pulmonary arterial hypertension (PAH) continues to present a formidable challenge, marked by increased mortality rates. Consequently, research efforts are indispensable in bridging the gap in treatment efficacy and reducing the existing disparities. It is imperative to explore novel strategies to address PAH comprehensively and improve patient outcomes significantly.

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