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Primary cardiac hospitalizations in pulmonary arterial hypertension: Trends and outcomes from 2001 to 2014

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ABSTRACT

Background: Hospitalizations in pulmonary arterial hypertension (PAH) are common and are often for cardiac conditions. Using the National (Nationwide) Inpatient Sample (NIS), we examined characteristics and mortality of primary cardiac hospitalizations in PAH from 2001 to 2014.
Methods: Adult hospitalizations with any diagnosis code for PAH were identified. Primary cardiac disease was defined as a primary discharge diagnosis of congestive heart failure (CHF), pulmonary heart disease, coronary atherosclerosis, acute myocardial infarction, dysrhythmia, conduction disorder, cardiomyopathy or carditis, heart valve disorder, or cardiac arrest. Temporal trends, characteristics, and in-hospital mortality were analyzed.
Results: From 2001 to 2014, there were 207,095 hospitalizations in PAH, of which 100,509 (48.5%) carried a primary cardiac diagnosis. Most primary cardiac hospitalizations in PAH were for CHF, and pneumonia was the most common primary non-cardiac diagnosis. Over the study period, primary cardiac hospitalizations in PAH fell from 52.9% to 41.4% ($p < 0.001$). CHF was the most frequent primary cardiac diagnosis associated with death, with sepsis representing the most common primary non-cardiac disease (1,226; 25.0%). Overall, the mortality in primary cardiac hospitalizations in PAH was 5.3% (vs. in primary non-cardiac, 6.9%, $p < 0.001$). On multivariable analysis, a primary cardiac discharge diagnosis remained associated with a decreased risk of death (odds ratio 0.85, $p = 0.010$).
Conclusion: Primary cardiac hospitalizations in PAH are common and are associated with decreased mortality compared to admissions for primary non-cardiac diagnoses.

1. Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease characterized by increased pulmonary vascular resistance and pathologic remodeling, leading to right heart failure. Right heart dysfunction correlates with morbidity and mortality, but the pathophysiology of PAH may also promote arrhythmias and negatively impact left ventricular diastolic function [1–10]. PAH has also been associated with an increased risk of coronary artery disease [11,12].

Moreover, hospitalizations in PAH are common and are frequently for cardiac conditions. Within the Registry to Evaluate Early And Long-term PAH Disease Management (REVEAL), over half of newly-diagnosed PAH patients required admission in the subsequent three years, with CHF and arrhythmias alone responsible for almost 40% of these stays [8]. Despite this high admission prevalence, data on inpatient PAH outcomes is limited.

The major objectives of this analysis were therefore 1) to characterize hospitalizations for primary cardiac diagnoses in PAH and 2) to study differences between the inpatient mortality of primary cardiac and primary non-cardiac hospitalizations in PAH within a large national database.

2. Materials and methods

2.1. Data source

This was a retrospective cross-sectional analysis of hospital discharges from the 2001 to 2014 NIS, a subset of the Healthcare Cost and Utilization Project (HCUP) which is sponsored by the Agency for Healthcare Research and Quality (AHRQ) [13,14]. The NIS is the largest public database of all-payer inpatient care in the United States (U.S.). Prior to 2012, it contained all discharges from a 20% stratified sample of

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HCUP-participating U.S. hospitals; in 2012, it was redesigned to capture a random 20% sample of discharges from all 100% of the reporting hospitals [15].

2.2. Study population

The 2001 to 2014 NIS was queried to identify all adult hospitalizations (age ≥18 years) with a primary or secondary discharge diagnosis of PAH (i.e. in discharge diagnosis fields 1 to 15). In the NIS, the primary diagnosis represents the major indication for hospitalization; the secondary fields may include pre-existing comorbidities, additional hospital diagnoses, or inpatient complications. To capture the entire PAH population, both primary and secondary diagnosis fields were used. PAH was defined by the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) code 416.0 for "primary pulmonary hypertension". Analysis was restricted to data collected in 2001 and later [16].

Records with any primary or secondary diagnosis of a World Health Organization (WHO) group 3–5 pulmonary hypertension (PH) etiology (based on the 2013 5th World Symposium on Pulmonary Hypertension) were excluded to further improve the accurate identification of the WHO group 1 PAH population (Supplemental Table 1) [17]. Given the potential for both chronic kidney disease and PAH to develop in certain conditions (i.e. systemic lupus erythematous, scleroderma, etc.), codes for end-stage renal disease were not removed [18,19]. To allow for evaluation of co-existing PAH and cardiac disease, diagnostic codes for WHO Group 2 PH were also not removed.

Records were stratified based on the presence of a primary diagnosis code for a cardiac condition of interest. These were defined as: acute myocardial infarction; coronary atherosclerosis and other heart disease; pulmonary heart disease; conduction disorders; CHF (non-hypertensive), dysrhythmias, cardiac arrest/ventricular fibrillation; heart valve disorders; and cardiomyopathy or peri-, endo-, myocarditis. They were selected with Clinical Classifications Software (CCS) codes, which are ICD-9-CM groupings that identify conditions of interest [20]. As secondary diagnosis codes are not specific to inpatient diagnoses or events, this study focused on primary cardiac diagnoses only [21].

2.3. Variables and outcomes

The principal outcome measure was in-hospital mortality. The variable of primary cardiac admission status was defined as above in 'Study Population'. Demographics included age, gender, race (white, black, or other), expected primary payer (private or public insurance), and admission type (emergent or other). Hospital characteristics included geographic region and type (urban/rural location with teaching status). The presence of pre-existing comorbidities was defined with the Elixhauser Comorbidity index, a validated system that assigns a dichotomous variable (present or not) using ICD-9-CM codes to each of 29 conditions [22]. As the NIS is de-identified, the unit of analysis was hospital-level discharge.

2.4. Statistical analysis

Annual rates were calculated as the number of hospitalizations (or deaths) of interest in PAH divided by the total related number in PAH, per year. Statistical significance of temporal trends was evaluated with the Cochran-Armitage test.

Categorical variables were analyzed with the Rao-Scott chi-square test, and continuous variables were studied with univariable linear regression. Multivariable logistic regression models were created to evaluate in-hospital mortality and were adjusted for factors significant on univariable analysis, as well as a-priori identified factors that may influence outcomes, regardless of univariable significance. To assess whether results were affected by the retention of certain diagnoses including end-stage renal disease and certain heart failure subtypes, sensitivity analyses were performed.

Survey procedures were used to account for the complex design of the NIS (including weighting, clustering, stratification). AHRQ-recommended modified trend weights were used to account for the 2012 NIS redesign. Unless otherwise specified, all absolute numbers shown are weighted. A two-sided p-value of <0.05 was considered significant. Statistical analysis was performed with SAS 9.3 (SAS Institute, Cary, North Carolina).

This study was granted exemption from Yale University Institutional Review Board approval and conforms to the HCUP data use agreement.

3. Results

3.1. Characteristics of primary cardiac hospitalizations in PAH

After selection (Fig. 1), there were 207,095 hospitalizations with PAH in the NIS from 2001 to 2014. Within this cohort, 48.5% of PAH hospitalizations had a primary cardiac diagnosis, and the remaining 51.5% were admitted with a primary non-cardiac diagnosis.

The mean age of the primary cardiac hospitalization cohort was 67.4 years, and most occurred in non-Hispanic whites (68.6%). These admissions were most common at urban teaching centers (58.2%). Notably, the primary cardiac hospitalization cohort had fewer comorbid conditions and a mean shorter length of stay. Table 1 displays the baseline characteristics of primary cardiac hospitalizations in PAH from 2001 to 2014. Sensitivity analyses with the removal of acute on chronic diastolic heart failure, rheumatic heart failure, or end-stage renal disease showed a similar distribution of characteristics.

3.2. Causes of primary cardiac hospitalizations in PAH

Among the 207,095 hospitalizations in PAH, CHF was the most common primary cardiac diagnosis (19.7% of all admissions in PAH), followed by pulmonary heart disease (9.4%) and dysrhythmias (5.2%). The frequencies of the additional primary cardiac diagnoses in PAH hospitalizations are shown in Table 2.

3.3. Characteristics of individual primary cardiac diagnosis hospitalizations

Hospitalization characteristics for the three most common individual primary cardiac diagnoses—CHF, pulmonary heart disease, and dysrhythmias—were further examined. Hospitalizations in PAH for primary CHF were largely emergent, whereas those with a primary diagnosis of pulmonary heart disease were more frequently elective. Admissions with a primary diagnosis of pulmonary heart disease predominated in urban teaching centers (70.9%). Additional characteristics of hospitalizations for individual primary cardiac diagnoses are shown in Supplemental Table 2.

The specific subtypes of the most common primary cardiac conditions were also further defined. Most CHF diagnoses were unspecified (74.3%), with an additional 6.3% due to rheumatic heart disease and 4.9% from acute on chronic diastolic heart failure. PAH was the primary diagnosis in the vast majority (94.5%) of pulmonary heart disease admissions. Finally, cardiac dysrhythmias were most commonly atrial fibrillation (56.5%), followed by sinoatrial node dysfunction (10.7%). Atrial flutter accounted for 7.8% of dysrhythmias, and paroxysmal ventricular tachycardia was the most common ventricular dysrhythmia (7.8%).

3.4. Temporal trends in primary cardiac hospitalizations in PAH

From 2001 to 2014, there was a significant and progressive decline in the percentage of PAH hospitalizations with primary cardiac diagnoses from 52.9% to 41.4% (from 21,622 to 2,405; $p < 0.001$; Fig. 2a), representing a relative decrease of 88.9%. This occurred in the setting of a

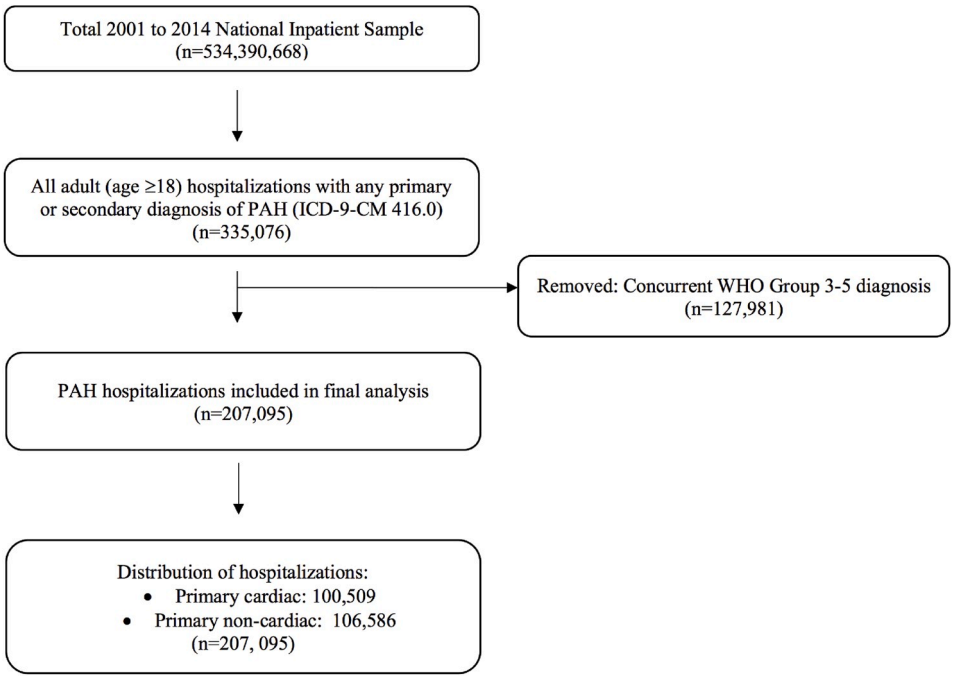

Fig. 1. Selection process for hospitalizations in pulmonary arterial hypertension (PAH) from the 2001 to 2014 National Inpatient Sample Database.

smaller but similar relative decrease in overall all-cause PAH hospitalizations of 85.8%.

The trends in hospitalizations for the three most common primary cardiac diagnoses are also shown in Fig. 2b. Among all PAH admissions, the fraction of primary CHF diagnoses declined from 20.9% to 13.8% ($p < 0.001$) over the study period, and there was a similar trend in primary dysrhythmia admissions (5.7%–4.0%; $p < 0.001$). Notably, there was a rise in the fraction of admitted with a primary diagnosis of pulmonary heart disease (5.7%–15.6%, $p < 0.001$).

3.5. Mortality in primary cardiac hospitalizations in PAH

There were 12,685 deaths among all PAH hospitalizations from 2001 to 2014 (overall all-cause mortality of 6.1%). Within the primary cardiac hospitalization cohort, there were 5,307 deaths, corresponding to an overall mortality of 5.3%. The annual mortality rates within the primary cardiac PAH hospitalizations remained relatively constant over the study period (5.6%–6.4%, $p = 0.959$), although the absolute number of deaths declined.

3.6. Characteristics of primary cardiac hospitalizations ending in death

In-hospital death in primary cardiac hospitalizations in PAH was associated with older age. It also occurred more frequently in urban teaching centers and in emergent admissions. Certain pre-existing comorbidities were also more common in primary cardiac PAH patients who died, including fluid-electrolyte disturbances and renal failure. Additional univariable predictors of inpatient death in primary cardiac hospitalizations in PAH are shown in Table 3.

3.7. Causes of death in primary cardiac hospitalizations in PAH

Among the primary cardiac PAH hospitalizations that ended in death, the most common admitting diagnosis was CHF, followed by pulmonary heart disease. Between the individual cardiac diagnoses, there was significant variation in mortality, as shown in Table 4. Only 4.6% of primary CHF hospitalizations ended in death, for example, compared to a mortality of 45.6% in admissions for cardiac arrest/ventricular fibrillation.

3.8. Mortality in primary cardiac vs. primary non-cardiac hospitalizations in PAH

On univariable analysis, the inpatient mortality in primary cardiac hospitalizations was significantly lower than that in primary non-cardiac diagnoses (5.3% vs. 6.9%, $p < 0.001$). After adjusting for key factors in multivariable analysis, a primary cardiac diagnosis remained significantly associated with a decreased risk of death (odds ratio 0.85, 95% confidence interval 0.75–0.96, $p = 0.010$) in PAH hospitalization. Sensitivity analyses with the separate removal of acute on chronic diastolic heart failure, rheumatic heart failure, and end-stage renal disease also demonstrated lower inpatient mortality in the primary cardiac hospitalization cohort.

The five most common primary non-cardiac diagnoses in inpatient PAH deaths are listed in Table 5, along with the mortality within each individual diagnosis. Among primary non-cardiac hospitalizations in PAH that ended in death, the most common diagnoses were sepsis, pneumonia, and respiratory failure. Notably, the overall mortalities within the sepsis and respiratory failure diagnoses were 24.9% and 21.4%, respectively.

4. Discussion

In a large national database of U.S. hospital discharges, cardiac conditions were the most common primary diagnoses in PAH hospitalizations from 2001 to 2014, accounting for almost half of all admissions. Over this period, the annual rates of cardiac hospitalizations in PAH declined steeply. Notably, CHF was the most common primary diagnosis in inpatient PAH deaths, followed by pulmonary heart disease itself and sepsis. While cardiac diseases contributed significantly to mortality in absolute numbers, only small fractions of these hospitalizations ended in death, and a primary cardiac diagnosis was associated with a significantly decreased risk of mortality. In contrast, PAH cohorts with certain non-cardiac conditions including sepsis were at significantly higher risk of inpatient death.

Hospitalizations in PAH are common, with 57% of REVEAL patients requiring admission within three years of diagnosis [8,23]. Despite the correlation between admission in PAH and worse long-term survival, little is known about these hospitalizations [24]. Data on admission

Table 1
Baseline characteristics of hospitalizations for primary cardiac diagnoses in pulmonary arterial hypertension from 2001 to 2014. All numbers displayed as percentages unless otherwise noted.

Variable	All PAH (n = 207,095)	Primary cardiac (n = 100,509)	Primary non-cardiac (n = 106,586)	P-value
Age, mean ± SE (years)	67.5 ± 0.3	67.4 ± 0.4	67.5 ± 0.3	0.937
Male	33.3	36.4	30.5	<0.001
Race				0.143
White	68.3	68.6	68.1	
Black	17.2	16.6	17.6	
Other	14.5	14.8	14.3	
Hospital type				<0.001
Rural	10.5	9.8	11.1	
Urban non-teaching	33.2	32.0	34.2	
Urban teaching	56.3	58.2	54.6	
Hospital region				0.020
Northeast	28.6	29.2	28.1	
Midwest	19.6	19.0	20.2	
South	34.1	35.0	33.2	
West	17.8	16.9	18.6	
Private payer[a]	22.8	24.2	21.5	<0.001
Emergent admission[b]	82.2	80.8	83.7	<0.001
Elixhauser comorbidity				
Congestive heart failure	28.9	18.3	38.8	<0.001
Valvular disease	20.2	11.2	28.7	<0.001
Fluid, electrolyte disorders	25.3	21.3	29.0	<0.001
Renal failure	14.8	14.4	15.2	0.074
Hypothyroidism	11.5	11.4	11.6	0.621
Collagen vascular disease	3.8	3.4	4.3	<0.001
Liver disease	4.3	3.3	5.2	<0.001
Comorbidity total, mean ± SE (#)	3.1 ± 0.03	2.5 ± 0.04	3.7 ± 0.03	<0.001
Length of stay, mean ± SE (days)	7.5 ± 0.1	7.2 ± 0.1	7.9 ± 0.1	<0.001
Total cost, mean ± SE (U.S. $)	46,661 ± 1329	49,357 ± 1604	44,195 ± 1257	<0.001

Abbreviations: PAH = pulmonary arterial hypertension, SE = standard error.
[a] Private includes private and self-pay; public includes Medicare, Medicaid, no charge, and other.
[b] Emergent includes emergency and urgent; other includes elective, newborn, trauma, and other.

Table 2
Primary cardiac diagnoses in pulmonary arterial hypertension hospitalizations from 2001 to 2014.

	Hospitalizations (#)	All hospitalizations in PAH (%)
Congestive heart failure (non-hypertensive)	40,705	19.7
Pulmonary heart disease	19,390	9.4
Cardiac dysrhythmias	10,730	5.2
Coronary atherosclerosis and other heart diseases	9,535	4.6
Acute myocardial infarction	8,865	4.3
Heart valve disorders	7,611	3.7
Cardiomyopathy and carditis	2,451	1.2
Conduction disorders	963	0.5
Cardiac arrest, ventricular fibrillation	259	0.1
Total	100,509	48.7

indications, for example, originates mainly from small series and registry studies and suggests that they are often cardiac in nature. Furthermore, there is even less information on inpatient outcomes—while trends in admissions with a primary diagnosis of PAH in

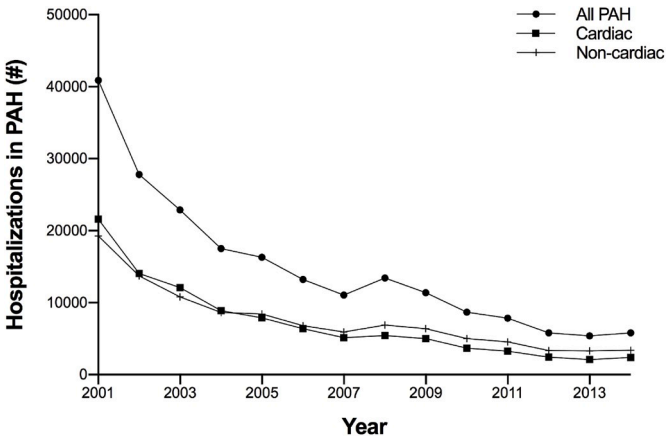

Fig. 2a. Absolute trends in all-cause and primary cardiac hospitalizations in pulmonary arterial hypertension (PAH) from 2001 to 2014.

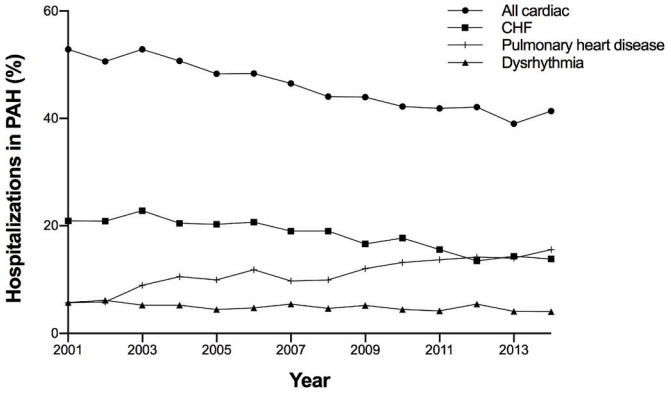

Fig. 2b. Trends in rates of hospitalization for most common primary cardiac diagnoses in pulmonary arterial hypertension (PAH) from 2001 to 2014.

the NIS were previously studied, these account for only a small fraction of the total PAH cohort [25]. This report is the one of the first analyses to study the characteristics and mortality of primary cardiac PAH hospitalizations in a large national database [8,26].

In the NIS, primary cardiac diagnoses including PAH were the most frequent cause of hospitalization in PAH from 2001 to 2014. CHF was the most common primary cardiac, as well as all-cause, hospitalization indication in PAH, comprising almost 20% of all admissions. Pulmonary heart disease and dysrhythmias, specifically atrial fibrillation, represented other common primary cardiac admission diagnoses in PAH. Notably, the rates of primary CHF and dysrhythmias in the NIS were similar to those seen in small series [8,26–29]. The observation that primary cardiac diagnoses are the most common admission indication in PAH likely reflects the pathophysiology of this disease— right sided remodeling not only causes right heart failure but also has broader detrimental implications for cardiac function with links to left ventricular diastolic dysfunction, arrhythmias, and coronary artery disease [1,3,9,11,12,30–32].

Notably, PAH hospitalizations for primary cardiac diagnoses tended to occur urban teaching centers, in line with the advanced care that is required for PAH therapy initiation and management. The average age among all PAH admissions was 67.5 years, which likely reflects an increasing recognition of this disease in the elderly as well as a predisposition for hospitalization to occur amongst older individuals [33,34].

From 2001 to 2014, primary cardiac, as well as all-cause, hospitalizations in PAH decreased in the U.S. This decline was likely driven by the advent of multiple PAH-specific therapies. While only intravenous epoprostenol was available at the beginning of 2001, 13 additional

Table 3
Univariable predictors of inpatient mortality in primary cardiac hospitalizations in pulmonary arterial hypertension from 2001 to 2014. All numbers displayed as percentages unless otherwise noted.

Variable	Alive	Died	P-value
Age, mean ± SE (years)	67.4 ± 0.4	68.5 ± 0.7	0.054
Male	36.5	34.1	0.097
Race			0.290
White	68.4	70.9	
Black	16.7	14.8	
Other	14.8	14.4	
Hospital type			0.101
Rural	9.9	8.3	
Urban non-teaching	32.1	30.8	
Urban teaching	58.0	61.0	
Hospital region			0.424
Northeast	29.2	27.9	
Midwest	19.0	18.3	
South	35.0	35.1	
West	16.8	18.7	
Private payer[a]	24.3	22.2	0.153
Emergent admission[b]	80.4	86.6	<0.001
Elixhauser comorbidity			
Congestive heart failure	17.8	26.6	<0.001
Valvular disease	11.2	11.4	0.837
Fluid, electrolyte disorders	20.2	41.7	<0.001
Renal failure	13.9	22.4	<0.001
Hypothyroidism	11.6	8.5	0.003
Collagen vascular disease	3.4	4.0	0.247
Liver disease	3.2	4.9	0.002
Comorbidity total, mean ± SE (#)	2.5 ± 0.04	2.7 ± 0.07	0.002
Length of stay, mean ± SE (days)	6.9 ± 0.1	12.0 ± 0.7	<0.001
Total cost, mean ± SE (U.S. $)	46,543 ±1515	99,596 ± 5831	<0.001

Abbreviations: PAH=pulmonary arterial hypertension, SE=standard error.
[a] Private includes private and self-pay; public includes Medicare, Medicaid, no charge, and other.
[b] Emergent includes emergency and urgent; other includes elective, newborn, trauma, and other.

Table 4
Inpatient mortality within individual primary cardiac diagnoses in pulmonary arterial hypertension hospitalizations from 2001 to 2014.

Primary cardiac diagnosis	Deaths (#)	Mortality within individual diagnosis (%)
Congestive heart failure	1,865	4.6
Pulmonary heart disease	1,392	7.2
Acute myocardial infarction	920	10.5
Heart valve disorder	398	5.2
Coronary atherosclerosis	228	2.4
Dysrhythmias	208	1.9
Cardiomyopathy and carditis	168	6.9
Cardiac arrest, ventricular fibrillation	118	45.6
Conduction disorders[a]	–	1.0

[a] Number not shown to comply with HCUP data use restrictions.

Table 5
Inpatient mortality within individual primary non-cardiac diagnoses in pulmonary arterial hypertension hospitalizations from 2001 to 2014.

Primary non-cardiac diagnosis	Deaths (#)	Mortality within individual diagnosis (%)
Sepsis	1,226	24.9
Pneumonia	766	9.4
Respiratory failure, insufficiency, arrest	696	21.4
Acute cerebrovascular disease	410	11.5
Acute and unspecified renal failure	392	11.8
Complication of device, implant, or graft	334	5.3

medications were subsequently approved in the U.S.—most during our period of study—and these therapeutics are associated with improved outcomes [35–38]. The rising use of combination therapy during our study period may have further contributed to our results [36,39,40].

While death in PAH is usually attributed to right ventricular failure, there is limited data on in-hospital causes of mortality [4,16,41]. Within the primary cardiac hospitalizations in PAH in the NIS in this analysis, the overall mortality was 5.3%, which is very similar to the 5.4% reported in first-time REVEAL PAH-related admissions [8]. Interestingly, the decline in frequency of cardiac hospitalizations over this time period did not translate to a similar change in the associated inpatient mortality—rather, while there was a fall in the absolute number of deaths, the annual mortality rate actually was largely unchanged from 2001 to 2014 in the NIS. Despite improvements in management, PAH is progressive, and therapy is only temporizing, not curative.

Moreover, there was significant variation in the mortalities of different primary cardiac diagnoses—while the rates were low in the primary CHF and dysrhythmia cohorts, mortality was higher in the group admitted with a primary diagnosis of pulmonary heart disease. It is possible that CHF and dysrhythmia hospitalizations may reflect the diagnosis of PAH, first cardiac complication, or initial worsening of PAH before deterioration. In contrast, the higher mortality in admissions for a primary diagnosis of pulmonary heart disease may indicate that these represent more advanced disease requiring inpatient management or therapy upgrade.

Furthermore, the results of this analysis emphasize the importance of non-cardiac conditions in PAH mortality. In fact, primary non-cardiac conditions were major drivers of inpatient deaths in PAH in the U.S: although they were responsible for 51.4% of all PAH hospitalizations, primary non-cardiac diagnoses accounted for a disproportionate 58.2% of inpatient deaths. While primary cardiac diseases contributed significantly to mortality in terms of absolute numbers, only small fractions of most of these hospitalizations ended in death such that overall, a primary cardiac diagnosis was associated with a significantly lower mortality risk in the NIS.

Notably, our results suggest that certain primary non-cardiac conditions pose the greatest risk of death in PAH hospitalizations. Sepsis and respiratory failure were the third and sixth most common primary causes of inpatient death with corresponding overall mortalities of 25.0% and 21.4%, respectively. These are markedly higher than the 5.3% mortality in all primary cardiac PAH hospitalizations and even than the 7.2% mortality in PAH hospitalizations with a primary diagnosis of pulmonary heart disease. It is possible that many primary cardiac hospitalizations in PAH represent the beginning of decline in this progressive disease. PAH also likely augments the high mortality risk of these diseases through right ventricular dysfunction and increased management complexity. Our results emphasize that the danger of certain non-cardiac conditions in PAH hospitalizations should not be underestimated in the risk of inpatient PAH death.

Finally, these results identified a cardiac subgroup at high risk of death—those who are older with certain comorbidities including renal disease and fluid and electrolyte disorders. This is consistent with prior analyses showing increased mortality risk in PAH patients who were older or who had renal dysfunction and fluid-electrolyte disturbances [26,42,43].

4.1. Limitations

Our study has a number of limitations. This is a retrospective analysis of the NIS database. As such, it is not possible to obtain information not contained within the NIS, such as the severity and treatment of PAH. Similarly, the method by which the diagnosis of PAH was made is also unavailable within this database. Furthermore, while the NIS is useful in the study of rare diseases like PAH, it is de-identified and so may contain more than one hospitalization per patient.

The reliance of the NIS on ICD-9-CM and CCS codes and the

retrospective nature of this study further limits analysis of specific conditions. These codes preclude the distillation of general diagnoses into specific ones: right and left heart failure in 'unspecified CHF' cannot be separated, for example, nor is it possible to determine if PAH admissions were for diagnosis, therapy initiation, or decompensation, among other causes.

Furthermore, the NIS is subject to the issues of miscoding and non-coding that are inherent to these large datasets. While these codes should be specific and while we eliminated additional WHO PH groups to further increase accuracy of the PAH code, it is possible that non-PAH PH patients were retained. Similarly, it is also possible that PAH hospitalizations that would have been appropriate for analysis were mistakenly coded under ICD-9-CM diagnoses for WHO Group 2–5 PH, which may have further limited this cohort. Furthermore, it is possible that improvements in coding over this study period contributed to the observed decline in primary cardiac and all-cause PAH hospitalizations.

5. Conclusions

In conclusion, primary cardiac diagnoses were the most common hospitalization indications in PAH from 2001 to 2014 in a large national database, representing almost 50% of the entire PAH hospitalization cohort. Over this time, primary cardiac admissions in PAH declined significantly. The overall mortality of primary cardiac PAH hospitalizations was 5.3%. While these cardiac diseases significantly contributed to death in absolute numbers, they were associated with a decreased risk of inpatient mortality in PAH. Given the negative long-term impact of admission in PAH, hospitalizations for primary cardiac are likely important in portending future decline; however, PAH cohorts with certain primary non-cardiac conditions, such as sepsis, may be at higher risk of death. Further study of the hospitalized PAH cohort is needed to determine risk stratification and optimal management of both primary cardiac and non-cardiac groups.

Author agreement

This manuscript was presented in part as an oral presentation at the 2018 American College of Chest Physicians conference (CHEST) in San Antonio, Texas in October 2018. It has not been published elsewhere, nor is it under consideration for publication elsewhere. All authors are in agreement with the content of this manuscript.

Author contributions

E.M.H. contributed to the study design, data analysis, interpretation, and manuscript writing. A.M.S. assisted with study design, statistical analysis, and interpretation. W.H.F. contributed to the study design, data analysis, interpretation, and manuscript writing.

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Informed consent

This study was granted exemption from Yale University Institutional Review Board approval and conforms to the HCUP data use agreement.

Author contributions

Eileen Harder: Conceptualization, Methodology, Formal analysis, Data curation, Writing (original draft), Writing (review and editing), Visualization, Aeron Small: Conceptualization, Methodology, Formal analysis, Data curation, Writing (review and editing), Visualization, Wassim Fares: Conceptualization, Methodology, Formal analysis, Writing (original draft), Writing (review and editing), Visualization, Supervision.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Wassim Fares is an employee of Actelion Clinical Research, Actelion, a Janssen Pharmaceutical Company of Johnson & Johnson. The other authors (E.M.H., A.M.S.) have no conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://doi.org/10.1016/j.rmed.2019.105850.

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