Maternal and Fetal Outcomes in Pulmonary Hypertension During Pregnancy: A Contemporary Nationwide Analysis

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Pulmonary hypertension (PH) disproportionately affects women, presenting challenges during pregnancy. Historically, patients with PH are advised to avoid pregnancy; however, recent reports have indicated that the incidence of adverse events in pregnant patients with PH may be lower than previously reported.

We conducted a retrospective cohort study in pregnant patients with PH using the National Readmission Database from January 1, 2016, to December 31, 2020. PH was categorized according to the World Health Organization classification. Primary end points include maternal mortality and 30-day nonelective readmission rate. Other adverse short-term maternal (cardiovascular and obstetric) and fetal outcomes were also analyzed.

Of 9,922,142 pregnant women, 3,532 (0.04%) had PH, with Group 1 PH noted in 1,833 (51.9%), Group 2 PH in 676 (19.1%), Group 3 PH in 604 (17.1%), Group 4 PH in 23 (0.7%), Group 5 PH in 98 (2.8%), and multifactorial PH in 298 (8.4%). PH patients exhibited higher rates of adverse cardiovascular events (15.7% vs 0.3% without PH, p <0.001) and mortality (0.9% vs 0.01% without PH, p <0.001). Mixed PH and Group 2 PH had the highest prevalence of adverse cardiovascular events in the World Health Organization PH groups. Patients with PH had a significantly higher nonelective 30-day readmission rate (10.4% vs 2.3%) and maternal adverse obstetric events (24.2% vs 9.1%) compared with those without PH (p <0.001) (Figure 1).

In conclusion, pregnant women with PH had significantly higher adverse event rates, including in-hospital maternal mortality (85-fold), compared with those without PH. © **2024 Published by Elsevier Inc. (Am J Cardiol 2024;221:113−119)**

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Pulmonary hypertension (PH) predominantly affects women, with ratios ranging from 1.8 to 3.06 times more likely compared with men, notably higher in a younger age group.[1−3] The physiologic challenges posed by pregnancy in PH patients are significant, with implications for both maternal and fetal well-being. Although consensus guidelines discourage pregnancy in PH, women with PH do become pregnant and often choose to proceed despite counseling on risk.[4] However, limited information exists on real-world contemporary outcomes in PH-associated pregnancies.[5]

Cardio-Obstetrics programs have emerged nationwide to improve cardiovascular care delivery, from preconception to postpartum. Cardio-Obstetrics focuses on coordinated and specialized cardiovascular care with collaboration from high-risk maternofetal medicine and aims to improve maternal and fetal outcomes in high-risk pregnancies.[6]

Recognizing the potential complexities of PH in pregnancy is pivotal for informed prenatal counseling and optimization of perinatal care.[7] Unfortunately, a shortage of current data regarding maternal outcomes in women with PH limits clinician ability to accurately ascribe risk.[4] In response to this dilemma, we sought to delineate maternal outcomes in women with PH, leveraging a large nationally representative database.

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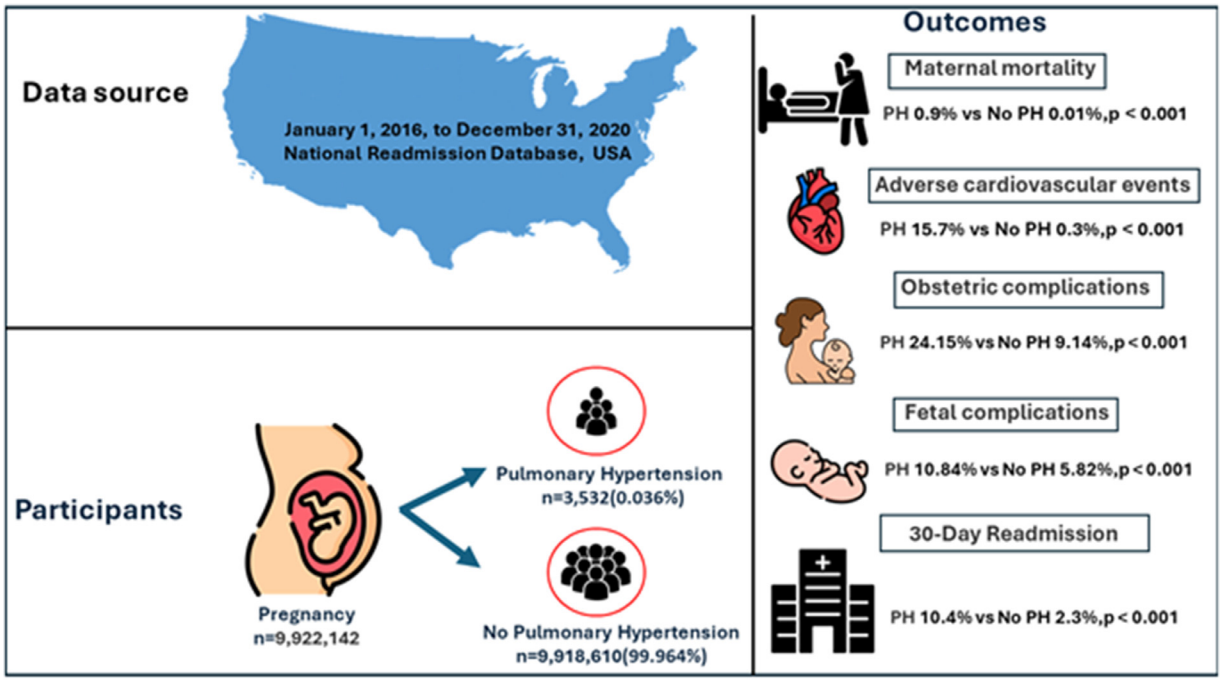

Figure 1. PH-pulmonary hypertension.

Methods

We utilized data from the Nationwide Readmissions Database (NRD) from January 1, 2016, to December 31, 2020. NRD is a publicly available database funded by the Healthcare Cost and Utilization Project under the Agency for Healthcare Research and Quality. It includes information on in-hospital stays and readmissions across 31 states, accounting for 62.2% of the total United States resident population and 60.8% of all hospitalizations in the United States.[8,9] Each patient in NRD is assigned a unique de-identified number, enabling tracking and identifying readmissions across different hospitals within the same calendar year. NRD database contains deidentified datasets, thus negating the need to obtain individual informed consent and Institutional Review Board approval.

We employed the International Classification of Diseases, Tenth Revision (ICD-10) codes to identify women older than 18 years with either a primary or secondary diagnosis related to pregnancy, that is, Z33XX, Z34XX, Z36XX, Z37XX, Z38XX, Z39XX, Z3AXX, and ICD-10 procedure code OXX. Hospitalizations during pregnancy were defined as any discharge record indicating the need for care during pregnancy, childbirth, and postpartum, as detailed in Supplementary Table 1.

Data from the NRD were gathered to investigate various factors related to patients, including age, mortality rate, hospital ownership, teaching status of urban hospitals, length of stay, total charges, primary payer, and median household income based on patient zip codes.[10] The NRD does not provide racial and ethnic categories. In addition, the Elixhauser co-morbidity variables were utilized to analyze conditions such as hypertension, diabetes, hypothyroidism, AIDS, and rheumatoid arthritis.[11] Specific ICD-10-Clinical Modification (CM) codes were applied to extract information about patients with gestational diabetes mellitus, systemic sclerosis, systemic lupus erythematosus, multiple gestations, cardiac arrest, acute myocardial infarction, arrhythmias, including atrial fibrillation, ventricular fibrillation, and ventricular tachycardia, cerebrovascular events, obstetric embolism, obstetric thromboembolism, obstetric shock, shock unspecified, cardiogenic shock, cardiac complications of anesthesia or other sedation in labor and delivery, respiratory failure, need for mechanical ventilation, and acute kidney injury. ICD-10-CM codes are listed in Supplementary Table 1.

A 2-step approach classified PH into World Health Organization (WHO) groups. Initial categorization utilized ICD-10 codes, as listed in Supplementary Table 1. The methodology of Trammell et al[12] was employed to subdivide those coded as PH, unspecified, into WHO Groups 1 to 5 multifactorial PH groups. This comprehensive approach ensures accurate stratification, providing valuable insights into understanding this complex condition according to established WHO groups.

The primary aim was to assess maternal mortality and the 30-day nonelective readmission rate in pregnant patients with PH Additionally, the cumulative incidence of adverse cardiovascular events (maternal mortality, cardiac arrest, acute myocardial infarction, various arrhythmias (e.g., atrial fibrillation, ventricular fibrillation, and ventricular tachycardia), cerebrovascular events, and cardiogenic shock), noncardiovascular adverse events (unspecified shock, respiratory failure, the need for mechanical ventilation, and acute kidney injury), maternal adverse obstetric events (eclampsia, mild to severe preeclampsia, hemolysis, elevated liver enzymes, and low platelets [HELLP] syndrome, antepartum hemorrhage, intrapartum hemorrhage,

postpartum hemorrhage, obstetric embolism, and obstetric shock), fetal adverse events (preterm labor, different types of abortions [spontaneous, incomplete elective, missed, uncomplicated elective termination, and complicated elective termination], intrauterine death, and stillbirth), and the most common causes of 30-day nonelective readmission were analyzed. Outcomes were defined using relevant ICD-10-CM codes listed in Supplementary Table 1.

Categorical variables as frequencies and percentages and continuous variables as mean ± standard deviation (SD) or median with interquartile range (IQR) were used to summarize the data. Continuous variables such as age, length of stay, and total charges were compared using the student *t* test or one-way analysis of variance), or Wilcoxon rank-sum (Mann-Whitney) test, when appropriate. In contrast, categorical variables were compared using the Mantel Haenszel or Fisher's Exact chi-square test as appropriate. For the calculation of 30-day readmission rates, patients discharged in December were excluded, along with elective readmissions. All statistical analyses were conducted with unweighted samples with Stata Corp. 2023. Stata Statistical Software: Release 18 (College Station, Texas: Stata Corp LLC.).[13]

Results

Of 9,922,142 total pregnant women in the dataset, 3,532 (0.036%) had PH, with Group 1 PH noted in 1,833 (51.90%), Group 2 PH in 676 (19.14%), Group 3 PH in 604 (17.10%), Group 4 PH in 23 (0.65%), Group 5 PH in 98 (2.77%), and multifactorial PH in 298 (8.44%) (Figure 2). Pregnant patients with PH were significantly older (31.7 ± 6.8 years) than those without PH (29.2 ± 5.7 years; p <0.001). Patients with PH had a longer length of stay 4 (IQR: 3 to 8) days compared with pregnant patients without PH 2 (IQR: 2 to 3) days; p <0.00 and a higher total inpatient charge of $43,500 (IQR: $23,310 to $86,600) vs $16,814 (IQR: $10,859 to $26,386); p <0.001.

Although systemic hypertension (21.04% in PH patients vs 0.23% in non-PH patients; p <0.001) and diabetes mellitus (9.48% in PH patients vs 1.10% in non-PH patients; p <0.001) were more prevalent in PH patients, the prevalence of gestational diabetes mellitus was similar (8.04% in PH patients vs 7.90% in non-PH patients, p = 0.752). PH patients also had higher rates of hypothyroidism, rheumatoid arthritis, systemic sclerosis, systemic lupus erythematosus, and multiple gestations (p <0.001 for all). PH patients were also less likely to seek care at nonmetropolitan hospitals (2.97% in PH patients vs 8.03% in non-PH patients). Table 1 lists baseline characteristics.

Analyses across WHO PH groups also revealed variations in age, length of stay, and total charges. For example, in Group 1 patients (n = 1,833), the average age was 30.8 years, with a median length of stay of 4 (IQR: 3 to 7) days and inpatient charges of $37,369.5 (IQR: $21,140 to $73,551). In contrast, Group 2 patients (n = 676) were much older (33.3 years), had a longer length of stay 6 (IQR: 4 to 11), and had much higher inpatient charges of $65,534.5 (IQR: $31,365 to $146,745). Detailed findings across all WHO subgroups are listed in Supplementary Table 2.

Overall crude maternal mortality was 0.85% (30 events in 3,532 women with PH), compared with 0.01% (974 events in 9,918,610 women without PH, p <0.001). The nonelective 30-day readmission rate for women with PH was 10.44%, significantly higher than the 2.30% for women without PH. Subgroup analyses showed variations within WHO PH groups, with multifactorial PH having the highest

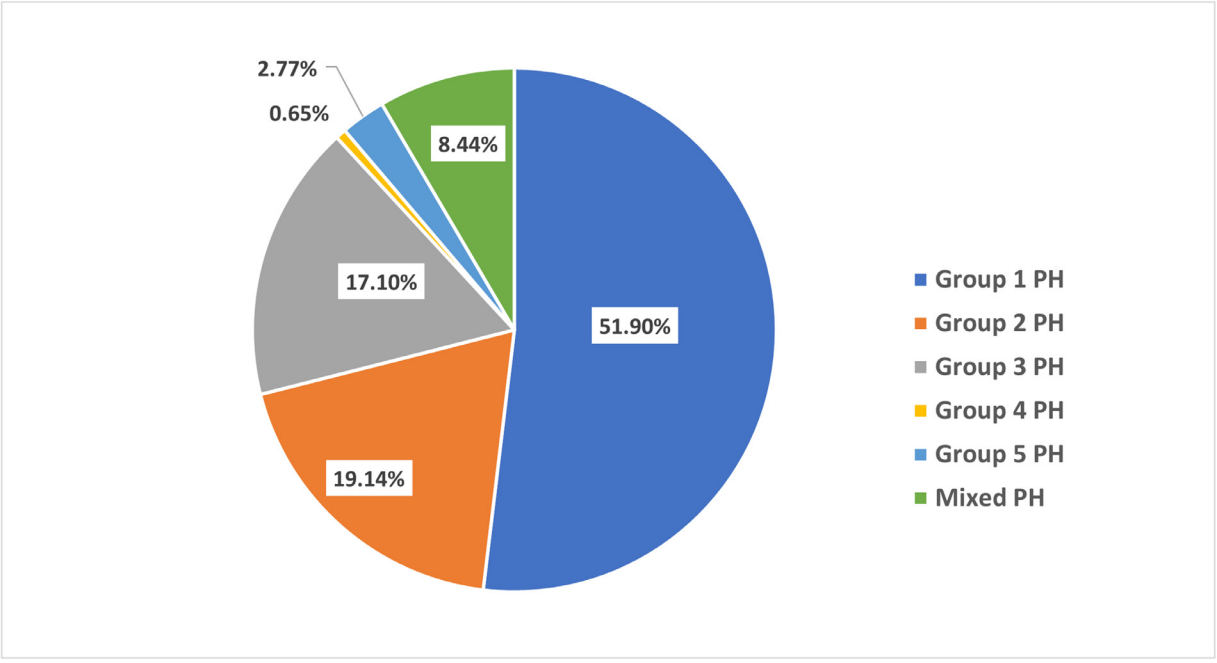

Figure 2. Distribution of WHO pulmonary hypertension groups in pregnant women.
WHO = World Health Organization.

Table 1
Characteristics of pregnant women with and without PH

	PH (n=3,532)	Without PH (n=9,918,610)	p-value
Age at admission, y, n±SD	31.7 (6.8)	29.2 (5.7)	<0.001
Hypertension, n (%)	743 (21.04%)	22,895 (0.23%)	<0.001
Diabetes mellitus, n (%)	335 (9.48%)	109,350 (1.10%)	<0.001
Gestational diabetes mellitus, n (%)	284 (8.04%)	783,322 (7.90%)	0.752
Hypothyroidism, n (%)	235 (6.65%)	372,362 (3.75%)	<0.001
AIDS/HIV, n (%)	<10	1,818 (0.02%)	<0.001
Rheumatoid Arthritis, n (%)	150 (4.25%)	38,782 (0.39%)	<0.001
Systemic sclerosis, n (%)	14 (0.40%)	766 (0.01%)	<0.001
Systemic lupus erythematosus, n (%)	96 (2.72%)	15,927 (0.16%)	<0.001
Multiple gestation, n (%)	100 (2.83%)	172,048 (1.73%)	<0.001
Teaching status of hospitals			<0.001
Metropolitan, nonteaching, n (%)	370 (10.48%)	2,091,041 (21.08%)	
Metropolitan, teaching, n (%)	3,057 (86.55%)	7,031,341 (70.89%)	
Nonmetropolitan, teaching, n (%)	105 (2.97%)	796,228 (8.03%)	
Residence by county location			<0.001
"Central" counties of metro areas of >=1 million population, n (%)	1,215 (34.59%)	3,050,961 (30.80%)	
"Fringe" counties of metro areas of >=1 million population, n (%)	916 (26.07%)	2,509,735 (25.34%)	
Counties in metro areas of 250,000-999,999 population, n (%)	708 (20.15%)	2,232,581 (22.54%)	
Counties in metro areas of 50,000-249,999 population, n (%)	288 (8.20%)	899,918 (9.08%)	
Micropolitan counties, n (%)	229 (6.52%)	708,340 (7.15%)	
Not metropolitan or micropolitan counties, n (%)	157 (4.47%)	504,396 (5.09%)	
Length of stay, d, median(IQR)	4(IQR:3-8)	2(IQR:2-3)	<0.001
Total charges, median(IQR) in dollars	$43,500(IQR:$23,310-$86,600)	$16,814 (IQR:$10,859-$&26,386)	<0.001

rate at 20.45% and Group 4 PH having the lowest at 4.55%. The most common causes of readmission in the PH cohort were diseases of the circulatory system complicating the puerperium (8.1%), hypertensive heart disease with heart failure (7.6%), and peripartum cardiomyopathy (6.8%). In contrast, the non-PH cohort had severe preeclampsia complicating the puerperium (12.9%), unspecified preeclampsia complicating the puerperium (7.4%), and endometritis after delivery (7.4%) as the most common causes of readmission.

Women with PH demonstrated a higher incidence of adverse cardiovascular events, with 533 events (15.09%) in 3,532 women compared with 22,704 events (0.23%) in 9,918,610 women without PH (p <0.001). The PH cohort had high incidences of cardiac arrest (1.42%), acute myocardial infarction (0.88%), arrhythmia (10.62%), cerebrovascular events (1.19%), and cardiogenic shock (3.96%) (p <0.001 for all).

The PH cohort had a higher incidence of unspecified shock with 35 events (0.99%) compared with 2,489 (0.03%) events in the non-PH cohort (p <0.001). The incidence of respiratory failure was also similarly higher in the PH cohort, with 617 events (17.47%), although only 15,273 (0.15%) events were noted in the non-PH cohort (p <0.001). Women with PH required mechanical ventilation more often, 15 (0.42%) events, compared with 285 (<0.001%) events in the non-PH cohort (p <0.001). PH patients exhibited a greater incidence of acute kidney injury, with 431 events (12.20%) compared with 35,895 events (0.36%) in the non-PH cohort (p <0.001) (Table 2).

Table 2
Comparison of morbidity and mortality Burden in pregnant women with and without pulmonary hypertension

	PH (n=3,532)	No PH (n=9,918,610)	p- value
CV Events, n (%)	533 (15.09)	22,704 (0.23)	0.000
Mortality (maternal), n (%)	30 (0.85)	974 (0.01)	0.000
Cardiac Arrest, n (%)	50 (1.42)	1,170 (0.01)	0.000
Acute myocardial infarction, n (%)	31 (0.88)	643 (0.01)	0.000
Arrhythmia (AF, VF, VT), n (%)	375 (10.62)	17,014 (0.17)	0.000
Cerebrovascular events, n (%)	42 (1.19)	3,817 (0.04)	0.000
Cardiogenic shock, n (%)	140 (3.96)	598 (0.01)	0.000
Non-CV Events			
Shock unspecified, n (%)	35 (0.99)	2,489 (0.03)	0.000
Respiratory failure, n (%)	617 (17.47)	15,273 (0.15)	0.000
Mechanical ventilation, n (%)	15 (0.42)	285 (0.00)	0.000
Acute Kidney Injury, n (%)	431 (12.20)	35,895 (0.36)	0.000

AF = atrial fibrillation; CV = cardiovascular; PH = pulmonary hypertension; VF = ventricular fibrillation; VT = ventricular tachycardia.

Table 3
Comparison of obstetric adverse outcomes and fetal adverse outcomes between hospitalized women with and without pulmonary hypertension

	PH	No PH	p-value
Maternal Adverse Obstetric Outcomes, n (%)	1,021 (28.91)	1,290,519 (13.01)	<0.001
Eclampsia, n (%)	25 (0.71)	7,231 (0.07)	<0.001
Mild to moderate preeclampsia, n (%)	49 (1.39)	121,883 (1.23)	0.393
Severe preeclampsia, n (%)	331 (9.37)	208,181 (2.10)	<0.001
HELLP, n (%)	46 (1.30)	26,483 (0.27)	<0.001
Antepartum hemorrhage, n (%)	128 (3.62)	202,128 (2.04)	<0.001
Intrapartum hemorrhage, n (%)	13 (0.37)	28,109 (0.28)	<0.001
Postpartum hemorrhage, n (%)	233 (6.60)	374,156 (3.77)	<0.001
Obstetric embolism (including obstetric thrombo-embolism), n (%)	181 (5.12)	5,718 (0.06)	<0.001
Obstetric thromboembolism, n (%)	104 (2.94)	3,708 (0.04)	<0.001
Obstetric Shock, n (%)	43 (1.22)	3,481 (0.04)	<0.001
Preterm labor, n (%)	286 (8.10)	470,796 (4.75)	<0.001
Fetal Adverse Outcomes	126 (3.57)	119,580 (1.21)	<0.001
Any abortion, n (%)	94 (2.66)	52,241 (0.53)	<0.001
Spontaneous abortion, n (%)	48 (1.36)	25,709 (0.26)	<0.001
Incomplete elective abortion, n (%)	<10	966 (0.01)	0.005
Missed abortion, n (%)	24 (0.68)	23,310(0.24)	<0.001
Uncomplicated elective termination of pregnancy, n (%)	19 (0.54)	2,399 (0.02)	<0.001
Complicated Elective termination of pregnancy, n (%)	<10	1,436 (0.01)	<0.001
Intrauterine death, n (%)	24 (0.68)	47,641 (0.48)	0.087
Stillbirth, n (%)	34 (0.96)	73,585 (0.74)	0.126

HELLP = hemolysis, elevated liver enzymes, and low platelets; PH = pulmonary hypertension.

In analyses across different WHO groups, adverse cardiovascular events were most prevalent in multifactorial PH (35.91%) and Group 2 PH (29.59%). Supplementary Table 3 details all CV and non-CV adverse event rates across various WHO PH groups.

Overall, in the PH cohort, 853 women (24.15%) experienced adverse obstetric events, compared with 906,122 women (9.14%) in non-PH pregnancies (p <0.001). All analyzed obstetric complications, including eclampsia, severe preeclampsia, HELLP syndrome, antepartum hemorrhage, intrapartum hemorrhage, postpartum hemorrhage, amniotic fluid embolism, obstetric thromboembolism, and obstetric shock, were more prevalent in the PH cohort. Similarly, fetal adverse events were also more common in the PH cohort (10.84%) compared with the non-PH cohort (5.82%) (p <0.001). Although preterm labor and spontaneous abortion were more prevalent in PH patients, no significant differences were observed in the occurrence of intrauterine death (p = 0.087) and stillbirth (p = 0.126, Table 3). Supplementary Table 4 details all adverse obstetric events across various WHO PH groups.

Discussion

In a contemporary national claims dataset of hospitalized pregnant women, the inpatient maternal mortality for women with PH was 0.85%, 85-fold higher than the non-PH cohort. Prevalent PH was also associated with an increased likelihood of 30-day readmission and increased incidence of adverse cardiac and obstetric events. This study, spanning 5 years (2016 to 2020) and involving over 3,500 pregnant women with PH, represents one of the largest cohorts of such patients ever reported. The incidence of adverse cardiovascular events was high (~20%), but many women with PH achieved a successful pregnancy. It is essential to recognize that pregnancy-induced hemodynamic changes may exacerbate the progression of PH, impacting variables such as volume status, pulmonary vascular resistance, venous return, and cardiac output.[14,15]

Over 95% of pregnant women with PH sought treatment in metropolitan hospitals and this reflects heightened awareness of the elevated risks associated with such pregnancies in the PH community at large or patients with PH are more likely to live in metropolitan areas.

It is not surprising that women with mixed and Group 2 PH had the highest incidence of adverse cardiovascular events in various WHO PH groups. Additionally, both WHO Group 2 PH and cardiomyopathy are deemed class III or IV in terms of pregnancy risk, signaling a significant risk of maternal morbidity and mortality or contraindication to pregnancy.[16] These distinct patterns underscore the need for targeted postpartum care approaches tailored to the unique clinical circumstances of women with PH Group 2.

In the past, pregnancies in women with PH were linked to alarming maternal mortality rates, reaching up to 56%, and neonatal mortality rates as high as 13%.[17–19] Despite advancements in PH treatment and innovative approaches to managing pregnancies and the peripartum period, maternal mortality has seen a decrease but persists at elevated levels in more recent literature data.[20–22] Consequently, traditional guidelines for diagnosing and treating PH have consistently advised patients with significant PH to avoid pregnancy.

However, the incidence of maternal mortality, although still higher than desired, is lower when compared with historical data.[17,20] This decreased incidence of maternal mortality in this dataset is likely explained by either less severe

PH in this cohort or progress in identifying and addressing PH risks during pregnancy with improved multidisciplinary Cardio-Obstetric care.

Although our findings are encouraging, the nearly 0.85% mortality rate of the PH cohort is considerably higher than the non-PH cohort (0.01%). It is critical to exercise caution and refrain from interpreting these results as an endorsement for pregnancy in individuals with PH. Notably, this dataset lacks information on PH severity, including the degree of right ventricular dysfunction and hemodynamic parameters. The cohort may underrepresent PH patients with more severe right ventricular dysfunction and hemodynamic instability because of potential advisories against pregnancy. These results merely describe contemporary outcomes in PH-associated pregnancies and inform evolving practice patterns. To gain a comprehensive understanding, prospective registries with detailed information on PH severity, including right ventricular dysfunction and hemodynamic parameters, are imperative.

Next, we observed a nonelective 30-day readmission rate of 10.44% in women with PH compared with 2.30% in women without PH, suggesting a distinct vulnerability in the PH population. Women with PH were readmitted because of diseases of the circulatory system, complicating the puerperium, hypertensive heart disease with heart failure, and peripartum cardiomyopathy. In contrast, non-PH patients were readmitted because of severe preeclampsia and endometritis after delivery. This is expected as cardiovascular adaptations of pregnancy persist in the early postpartum period,[23] potentially explaining the high readmission rates experienced in the PH cohort and underscoring the need for ongoing cardio-obstetric postpartum care. Our observed rates of obstetric complications in women with PH were similar to previously published studies.[22,24] Specifically, the incidence of preeclampsia/eclampsia, preterm delivery, fetal demise, obstetric and postpartum bleeding, and cesarean delivery was substantial in this population. These complications emphasize the intricate challenges faced by pregnant women with PH and underscore the necessity for specialized care to navigate these complexities effectively.

Our study has several limitations. Although NRD provides a valuable, representative sample for investigating PH in pregnancy across the United States, it has inherent drawbacks of using administrative ICD-10 codes which are prone to misclassification bias. NRD is also limited to inpatient data and lacks details on medication use, disease severity, mode of delivery, neonatal complications, and hemodynamic profiling. Early out-of-hospital and late maternal mortality, a significant concern, remains unaddressed in our study. Despite these limitations, our findings shed light on the current status of outcomes in PH-associated pregnancies nationwide, reinforcing existing cardiac and obstetric complications paradigms.

In conclusion, hospitalized pregnant women with PH experience significantly higher adverse event rates and readmissions than those without PH. Maternal mortality, although lower than previously reported, remains elevated in women with PH. Cardiovascular events varied in PH groups, with left heart disease-associated PH and mixed PH exhibiting the highest rates. Common complications in pregnant women with PH included preeclampsia/eclampsia, preterm delivery, fetal demise, and obstetric/postpartum bleeding, highlighting the need for early recognition, intensive up-front risk counseling, and multidisciplinary approach to pregnancy management.

Declaration of competing interest

The authors have no competing interests to declare.

CRediT authorship contribution statement

Anand Maligireddy: Writing – original draft, Software, Methodology, Formal analysis. **Ahmad Jabri:** Writing – review & editing, Validation. **Mohammad Zghouzi:** Writing – review & editing, Visualization, Validation. **Chaitanya Rojulpote:** Methodology, Investigation. **Gabriella VanAken:** Writing – review & editing. **Chaitra Janga:** Writing – review & editing, Visualization, Validation. **Ryhm Radjef:** Writing – review & editing, Writing – original draft. **Herbert Aronow:** Writing – original draft, Investigation. **Rana Awdish:** Writing – review & editing. **Bryan Kelly:** Writing – review & editing. **Gillian Grafton:** Writing – review & editing, Writing – original draft, Visualization. **Timir K. Paul:** Writing – review & editing. **Chien-Jung Lin:** Writing – review & editing. **Deana Mikhalkova:** Writing – review & editing. **Khaldoon Alaswad:** Writing – review & editing, Writing – original draft. **Domingo Franco-Palacios:** Writing – review & editing. **Pedro Villablanca:** Writing – review & editing. **Vikas Aggarwal:** Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2024.04.016.

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