

Cardiac and Obstetric Outcomes Associated With Mitral Valve Prolapse



Gianna L. Wilkie, MD^{a,1}, Waqas T. Qureshi, MD, MS^{b,1}, Kevin W. O'Day, MD^b, Gerard P. Aurigemma, MD^b, Robert J. Goldberg, PhD^{b,c}, Waseem Amjad, MD^d, Shehabaldin Alqalyoobi, MD^{e,f}, Nikolaos Kakouros, MD, PhD^b, Julianne R. Luring, MD^a, Heidi K. Leftwich, DO^a, and Colleen M. Harrington, MD^{b,*}

Mitral valve prolapse (MVP) is the most common valvular heart disease in women of reproductive age. Whether MVP increases the likelihood of adverse outcomes in pregnancy is unknown. The study objective was to examine the cardiac and obstetric outcomes associated with MVP in pregnant women. This retrospective cohort study, using the Healthcare Cost and Utilization Project National Readmission Sample database between 2010 and 2017, identified all pregnant women with MVP using the International Classification of Disease, Ninth and Tenth Revisions codes. The maternal cardiac and obstetric outcomes in pregnant women diagnosed with MVP were compared with women without MVP using multivariable logistic and Cox proportional hazard regression models adjusted for baseline demographic characteristics. There were 23,000 pregnancy admissions with MVP with an overall incidence of 16.9 cases per 10,000 pregnancy admissions. Pregnant women with MVP were more likely to die during pregnancy (adjusted hazard ratio 5.13, 95% confidence interval [CI] 1.09 to 24.16), develop cardiac arrest (adjusted odds ratio [aOR] 4.44, 95% CI 1.04 to 18.89), arrhythmia (aOR 10.96, 95% CI 9.17 to 13.12), stroke (aOR 6.90, 95% CI 1.26 to 37.58), heart failure (aOR 5.81, 95% CI 3.84 to 8.79), or suffer a coronary artery dissection (aOR 25.22, 95% CI 3.42 to 186.07) compared with women without MVP. Pregnancies with MVP were also associated with increased risks of preterm delivery (aOR 1.21, 95% CI 1.02 to 1.44) and preeclampsia/hemolysis, elevated liver enzymes, and low platelets syndrome (aOR 1.22, 95% CI 1.05 to 1.41). In conclusion, MVP in pregnancy is associated with adverse maternal cardiac outcomes and higher obstetric risks. © 2021 Elsevier Inc. All rights reserved. (Am J Cardiol 2022;162:150–155)

Cardiac conditions are responsible for greater than one-third of pregnancy-related deaths.¹ As 3 of 5 pregnancy-related deaths have been deemed preventable, significant attention has been directed at identifying pregnant women at increased risk for adverse outcomes with the goal of decreasing maternal morbidity and mortality.^{2,3} Mitral valve prolapse (MVP) is the most common valvular heart disease in women of reproductive age.² It is estimated to affect 1% to 3% of the general population, with an unknown prevalence in pregnant women.² The adverse

outcomes associated with MVP range from hemodynamically significant mitral regurgitation, heart failure, and endocarditis to malignant cardiac arrhythmias and sudden cardiac death.⁴ The association between sudden cardiac death and MVP may be greater than previously suspected, occurring with an estimated annual risk as high as 2% in the general population.^{5–7} There are few published data about the risk of adverse cardiac outcomes associated with MVP in pregnant women, and the few published reports include a few patients.⁸ One such study indicates that women of reproductive age with MVP may be at a disproportionate risk of sudden cardiac death.⁹ Accordingly, the objective of this study was to compare cardiac and obstetric outcomes in pregnant women with MVP with pregnant women without MVP, utilizing a large database of patients.

Methods

The study population consisted of a nationally representative cohort of hospital admissions that took place between January 1, 2010 and December 31, 2017. The database was obtained from the Nationwide Readmission Database (NRD), Healthcare Cost and Utilization Project (HCUP), and the Agency for Healthcare Research and Quality dataset between 2010 and 2017. The NRD is the largest publicly available all-payer inpatient care database in the United States and contains discharge-level data from state data organizations, hospital associations, and private data

^aDivision of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, University of Massachusetts Memorial Healthcare; ^bDivision of Cardiovascular Medicine, University of Massachusetts Memorial Healthcare; ^cDepartment of Population and Quantitative Health Sciences, University of Massachusetts Medical School, Worcester, Massachusetts; ^dDepartment of Internal Medicine, Albany Medical College, Albany, New York; ^eDepartment of Pulmonary and Critical Care Medicine, East Carolina University, Greenville, North Carolina; and ^fDepartment of Bioinformatics and Biostatistics, School of Public Health and Information Sciences, University of Louisville, Louisville, Kentucky. Manuscript received May 10, 2021; revised manuscript received and accepted September 10, 2021.

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¹Co-primary authors Gianna L. Wilkie and Waqas T. Qureshi contributed equally.

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*Corresponding author: Tel: 508-856-3924; fax: 774-441-7657.

E-mail address: Colleen.Harrington@umassmemorial.org (C.M. Harrington).

organizations that participate in the HCUP project. The database provides a stratified sample of approximately 20% of discharges from HCUP-participating hospitals in the United States, representing more than 95% of the national population, and deidentified patient demographic and clinical information.¹⁰ This study was exempt from our Institutional Review Board review because we used a deidentified publicly available dataset.

The NRD was used to identify pregnant women who had a diagnosis of pregnancy and delivery by the International Classification of Diseases (ICD), Ninth Revision (ICD-9) and ICD, Tenth Revision (ICD-10) diagnosis codes from 2010 to 2017. We used ICD-9 and ICD-10 codes to identify patients with MVP (ICD-9 424.0 and ICD-10 I34.1). Only pregnant women ≥ 18 years of age were included.

We obtained baseline patient demographic, clinical, cardiac, and obstetric outcome data. Patient demographic data included age, obesity (body mass index ≥ 30), smoking history, location of medical care (urban vs rural), preexisting chronic hypertension, hyperlipidemia, chronic kidney disease, peripheral vascular disease, chronic obstructive pulmonary disease/airway disease, malignancy, diabetes, and the Charlson co-morbidity index.

The primary study outcome was maternal death during the pregnancy-related admission. The secondary maternal outcomes included hospital readmission, cardiac arrest, any cardiac arrhythmia, stroke, acute congestive heart failure, myocardial infarction, coronary artery dissection, aortic dissection, thromboembolism, and endocarditis. Obstetric outcomes included Cesarean delivery, preterm delivery (before 37-week gestation), gestational hypertension, preeclampsia, hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome (a life-threatening condition of pregnancy marked by hemolysis, elevated liver enzyme levels, and low platelet levels), obstetric hemorrhage, or perinatal death. All associated ICD-9 and ICD-10 diagnosis codes are shown in [Supplementary Table 1](#) for each outcome of interest.

The baseline characteristics of the study population were expressed as weighted values based on the prevalence of characteristics at the time of hospital discharge weights provided in the database. This weighting was performed to estimate the prevalence of the characteristics in a nationally representative sample for comparison with our data. Continuous variables with normal distribution were expressed as weighted mean $\pm$ SDs and with skewed distribution as weighted median with interquartile range. Categorical variables were expressed as weighted numbers with percentages and compared between respective comparison groups with the chi-square test and analysis of variance where appropriate for patients with and without MVP. We examined differences in inpatient mortality and hospital readmission between women with and without a diagnosis of MVP in multivariable Cox regression models adjusted for age (reference is age < 35 years), elective admission, obesity, smoking status, histories of hypertension, diabetes mellitus, hyperlipidemia, chronic kidney disease, peripheral vascular disease, chronic obstructive pulmonary disease/asthma, cancer, family history of premature coronary artery disease, urban versus rural hospital location, teaching hospital status, insurance status (could include multiple insurances),

and Charlson co-morbidity index; multivariable adjusted hazard ratio with accompanying 95% confidence intervals (CIs) were calculated. For our secondary study outcomes, we computed odds ratio with 95% CI in multivariable adjusted logistic regression models adjusted for similar variables as previously mentioned. Weighted analyses were used for all statistical calculations. Statistical analysis was performed using STATA version 14.2 (StataCorp, College Station, Texas). All *p* values were 2-sided, with a significance threshold of *p* < 0.05 .

Results

In a total of 13,620,427 pregnancy admissions between 2010 and 2017, there were 23,000 patients diagnosed with MVP, yielding an overall incidence rate of 16.9 cases per 10,000 pregnancy admissions. Of these, 22,996 were discharged alive and 315 women (1.4%) were readmitted within 30 days of discharge ([Figure 1](#)).

The baseline characteristics of the study population are shown in [Table 1](#). Pregnant women with MVP were older, were less likely to be obese, have a higher co-morbidity burden, have private health insurance, and were more likely to be admitted to a teaching urban hospital.

After adjusting for several patient demographic and clinical characteristics, women with MVP were at significantly higher risk for dying during hospitalization (adjusted hazard ratio 5.13, 95% CI 1.09 to 24.16). In addition, women with MVP were significantly more likely to experience cardiac arrest, cardiac arrhythmia, stroke, congestive heart failure, and spontaneous coronary artery dissection ([Table 2](#)). Of note, only 235 women (1.0%) who had MVP had an echocardiogram during their hospitalization.

After adjusting for several patient demographic and clinical characteristics, women with MVP were at significantly increased risk for preterm delivery and preeclampsia/HELLP syndrome but not with other obstetric related end points ([Table 3](#)).

Discussion

The major findings of our study are that MVP in pregnancy is associated with several clinically important adverse cardiac and obstetric outcomes. To the best of our knowledge, this is the first report of an association between MVP and these significant adverse clinical outcomes in pregnant women. Although coding data may not provide insights into the underlying physiology of the observed relations reported, our data highlight a possible adverse association requiring further evaluation.

The most concerning findings of our study are the 11-fold increase in risk of cardiac arrhythmia and 4-fold increase in cardiac arrest associated with MVP in pregnancy. Our reported risk of death of 0.02% is in line with previous reports of sudden cardiac death because of MVP.^{6,11,12} Although we have no direct confirmation, we suspect that the heightened risk of sudden cardiac death likely relates to the functional consequences of MVP, specifically the degree of coexistent mitral regurgitation.¹³ It is unknown from our data whether pregnancy confers an additional risk to the patient with MVP, predisposing toward

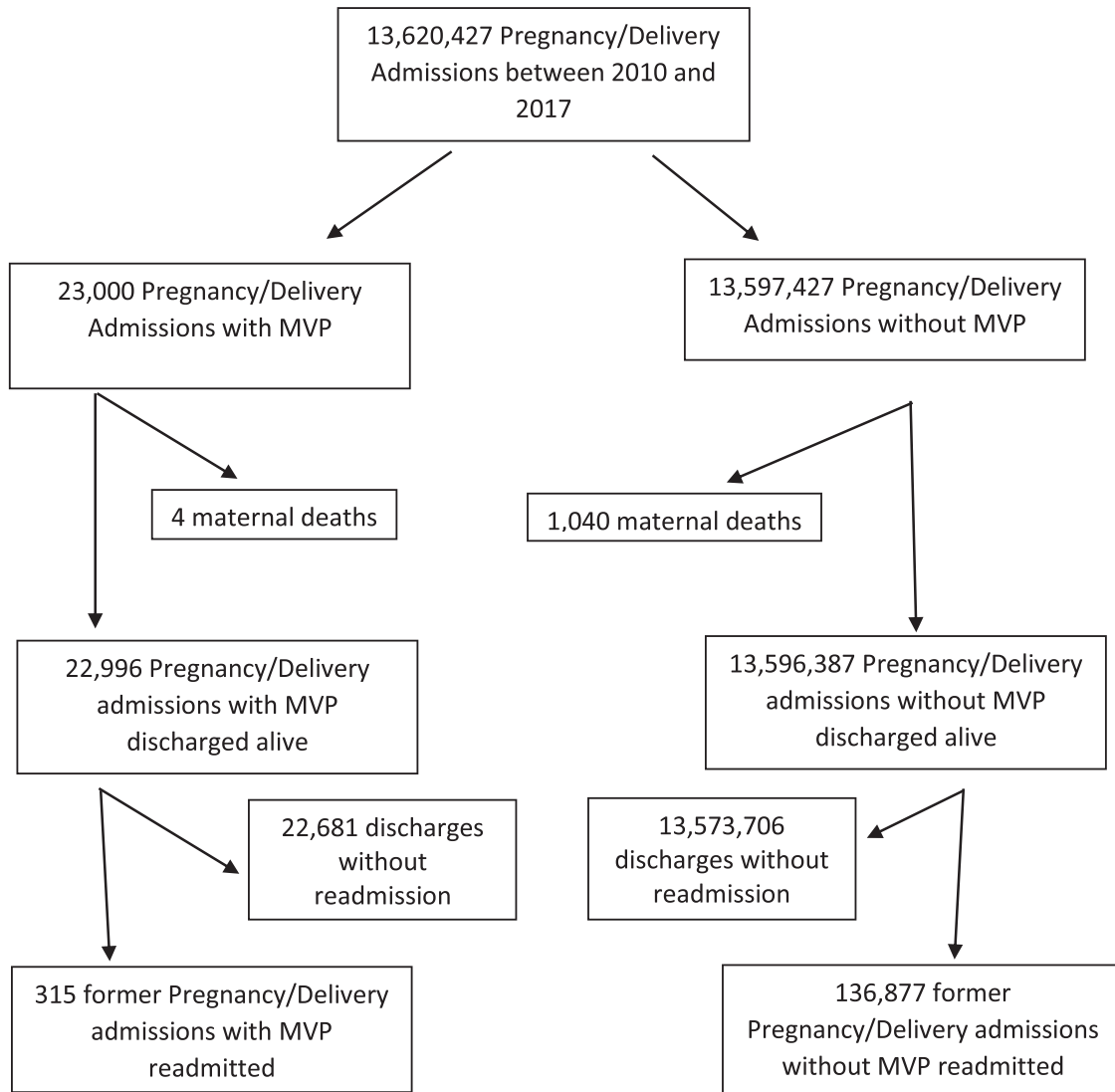


Figure 1. Study flow diagram.

arrhythmia and sudden cardiac death, or whether the risk of these adverse outcomes is elevated because of the presence of MVP. Recent studies have called attention to arrhythmic risk in MVP, especially in the phenotype characterized by mitral valve disjunction.^{13–15} Whether the degree of mitral valve regurgitation or mitral valve disjunction that are both associated with MVP are the underlying causative factors cannot be ascertained from our data.

In addition, we observed an increased risk for heart failure complicating pregnancy in patients with MVP. MVP, particularly when associated with a flail leaflet, is associated with heart failure as has been established in other cohorts.¹⁶ Mitral regurgitation usually progresses insidiously, because the heart compensates for increasing regurgitant volume by left atrial enlargement, causing left ventricular overload, dilation and dysfunction, and yields poor outcome generally when it becomes severe.¹⁷ It is therefore plausible that the increased cardiac demands seen in pregnancy may contribute to an acute overload state leading to heart failure in women with MVP.

Previous studies examining the cardiac outcomes associated with MVP in pregnancy have shown minimal increased risks with expected excellent pregnancy outcomes.^{18,19} However, our findings differ perhaps because a larger sample size is needed to address these rarer associated outcomes. The elevated risk of preterm delivery associated with patients with MVP may be a consequence of this condition's predisposition for hemodynamic compromise. When considering the burden of arrhythmia and heart failure management in a pregnant patient, obstetric providers may favor medically indicated preterm delivery for maternal benefit. Interestingly, the association between preterm delivery and MVP has previously been shown and believed to reflect iatrogenic preterm delivery for maternal cardiac indications.²⁰ The incidence of preeclampsia or HELLP syndrome in pregnant patients with MVP has not previously been noted. Although the etiology of this relation remains unclear, it conceivably may be related to the increase in heart failure seen in this population. Maternal hemodynamic status compromise (e.g., hypertension or laboratory

Table 1
Baseline demographic characteristics of the cohort

Variable	Mitral valve prolapse		p-value
	Present (n= 23,000)	Absent (n= 13,597,427)	
Age (years)	34±6	30±6	<0.001
Pre-Gravid Body Mass Index ≥30 kg/m ²	1,384 (6.0%)	1,118,108 (8.2%)	<0.001
Current smoker	1,024 (4.5%)	616,142 (4.5%)	0.74
Pre-existing Diabetes	352 (1.5%)	178,113 (1.3%)	0.12
Pre-Existing Hypertension	1,892 (8.2%)	899,914 (6.6%)	<0.001
Hyperlipidemia	181 (0.8%)	35,301 (0.3%)	<0.001
Chronic kidney disease	98 (0.4%)	19,189 (0.1%)	<0.001
Peripheral vascular disease	54 (0.2%)	5,407 (0.04%)	<0.001
COPD/airway disease	3,102 (14%)	725,556 (5%)	<0.001
Cancer	57 (0.2%)	13,192 (0.1%)	<0.001
Family history of CAD	509 (2%)	140,398 (1.0%)	<0.001
Academic Teaching hospital	16,179 (70%)	8,827,873 (65%)	<0.001
Urban hospital	17,374 (76%)	9,963,151 (73%)	0.001
Charlson Score			<0.001
0	18,811 (82%)	12,576,400 (93%)	
1	3,471 (15%)	923,384 (6.8%)	
2	501 (2.2%)	68,726 (0.5%)	
≥3	217 (0.9%)	28,917 (0.2%)	
Insurance status			<0.001
Medicare	363 (1.6%)	111,673 (0.8%)	
Medicaid	5,399 (24%)	5,417,436 (40%)	
Private	16,312 (71%)	7,412,956 (55%)	
Self-pay	236 (1.0%)	233,391 (1.7%)	

All data are reported as N (%) or mean (standard deviation).

Hyperlipidemia was noted for any patient with an ICD-9 or ICD-10 code for hyperlipidemia, leading to heterogeneity in the diagnosis as it may include hypertriglyceridemia, hypercholesterolemia, or familial hypercholesterolemia.

abnormalities, including mildly abnormal liver function tests or impaired kidney function that may be routinely attributed to preeclampsia) may instead reflect acute heart failure in this population.

Our study's strengths include the large sample size of this national database, which represents a large and diverse obstetric cohort. Previous studies regarding MVP in pregnancy have largely been based on case reports and retrospective reviews at single medical centers. To our knowledge,

this study is the largest evaluation of a cohort of pregnant women with MVP to date. We identified both adverse cardiac and obstetric outcomes associated with this condition.

The study is limited by its reliance on diagnostic billing codes to correctly identify both the patient population of interest and outcomes. Previous studies have also assessed the validity of these codes and found that they can be accurately used to identify pregnancy; however, the accuracy of identifying MVP by ICD codes in pregnancy is unknown.²¹

Table 2
Maternal cardiac outcomes

Maternal Outcomes	Mitral valve prolapse		Adjusted HR (95% CI)
	Present (n= 23,000)	Absent (n= 13,597,427)	
Readmission	315 (1.4%)	136,877 (1.0%)	1.07 (0.77- 1.50)
			Adjusted OR (95% CI)
Maternal Cardiac Arrest	12 (0.05%)	1,283 (0.01%)	4.44 (1.04-18.89)
Cardiac arrhythmia	1,055 (4.6%)	50,107 (0.37%)	10.96 (9.17-13.12)
Stroke	20 (0.09%)	472 (0.003%)	6.90 (1.26-37.58)
Heart Failure	730 (3.2%)	24,103 (0.18%)	5.81 (3.84-8.79)
Acute Myocardial Infarction	97 (0.4%)	6,298 (0.05%)	1.08 (0.24 - 4.79)
Thromboembolism in Pregnancy	32 (0.1%)	5,213 (0.04%)	0.81 (0.19-3.37)
Endocarditis	36 (0.2%)	910 (0.007%)	1.92 (0.25-14.73)
Aortic dissection	0 (0%)	96 (0.001%)	0.99 (0.93-1.05)

Data are listed as n (%) or adjusted odds ratio with 95% confidence interval. Weighted logistic regression analysis adjusted for age, insurance status, elective admission, obesity, smoking status hypertension, diabetes mellitus, hyperlipidemia, chronic kidney disease, peripheral vascular disease, COPD/asthma, cancer, family history of premature coronary artery disease, hospital teaching status, hospital location and Charlson comorbidity index.

Table 3
Obstetric outcomes

Obstetric Outcomes	Mitral valve prolapse		Adjusted OR (95% CI)
	Present (n= 23,000)	Absent (n= 13,597,427)	
Cesarean Delivery	138 (0.6%)	77,511 (0.6%)	0.60 (0.31 – 1.15)
Preterm Delivery	1,621 (7.0%)	655,808 (4.8%)	1.21 (1.02 -1.44)
Gestational Hypertension	899 (3.9%)	579,637 (4.3%)	0.95 (0.85 – 1.06)
Pre-eclampsia/HELLP syndrome	1,598 (6.9%)	634,978 (4.7%)	1.22 (1.05 – 1.41)
Obstetric Hemorrhage	749 (3.3%)	432,813 (3.2%)	1.06 (0.88- 1.28)
Perinatal Death	122 (0.5%)	89,591 (0.7%)	0.78 (0.48 – 1.28)

HELLP = hemolysis, elevated liver enzymes and low platelets.

Data are listed as N(%) or adjusted odds ratio with 95% confidence interval. Weighted logistic regression analysis adjusted for age, insurance status, elective admission, obesity, smoking status hypertension, diabetes mellitus, hyperlipidemia, chronic kidney disease, peripheral vascular disease, COPD/asthma, cancer, family history of premature coronary artery disease, hospital teaching status, hospital location and Charlson co-morbidity index.

In addition, it is important to acknowledge that ascertainment bias may contribute to the findings. Patients with underlying cardiac disease who are more at risk for arrhythmia and cardiac arrest are more likely to have had an echocardiogram and therefore be diagnosed with MVP. Our study is also limited in its ability to comment on the distinction between the inherent baseline risk associated with pregnancy and the subsequent interaction of pregnancy and MVP by gestational age as this is not reported in the NRD. It is also notable that the CIs surrounding certain reported outcomes are wide, suggesting significant dispersion within the data and a smaller sample size. Given that the outcomes of interest such as maternal cardiac arrest, stroke, and endocarditis are exceedingly rare, further study is required to validate this data.

We would argue that the signal apparent in our data suggest that we should adopt a more vigilant posture when caring for the patient with MVP disease in pregnancy, with perhaps a lower threshold for cardiac imaging. The low rate of cardiac imaging has been observed in the past where only 0.6% of the 3,582 patients with MVP underwent echocardiographic evaluation during the preceding 3 years to pregnancy.²² Currently, there are no guidelines regarding assessment of MVP before and during pregnancy. This is likely reflective of the previous assumption that MVP is a benign condition; however, our research findings challenge this notion.

In conclusion, data from the NRD show that pregnancies with MVP may be more likely to be associated with adverse cardiac and obstetric outcomes than women without this condition. Further investigations involving MVP in pregnancy are warranted.

Disclosures

The authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.amjcard.2021.09.014>.

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