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ORIGINAL RESEARCH

OUTCOMES AND QUALITY

Cardiovascular Complications Associated With COVID-19 During Delivery Hospitalizations in Pandemic Year 2020

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ABSTRACT

BACKGROUND Persons with COVID-19 infection have an increased risk of pregnancy-related complications. However, data on acute cardiovascular (CV) complications during delivery admissions remain limited.

OBJECTIVES The purpose of this study was to determine whether pregnant individuals with COVID-19 have an increased risk of acute peripartum CV complications during their delivery admission.

METHODS This population-based retrospective cohort study used the 2020 National Inpatient Sample database. The International Classification of Diseases, 10th Revision codes were used to identify delivery admissions with a diagnosis of COVID-19. A multivariable logistic regression model was performed to determine the association between COVID-19 and acute peripartum CV complications at delivery.

RESULTS A total of 3,458,691 weighted delivery admissions were identified, of which 1.3% were among persons with COVID-19 (n = 46,375). Persons with COVID-19 were younger (median 28 vs 29 years, $P < 0.01$) and had a higher prevalence of gestational diabetes mellitus, preterm births, and Cesarean delivery ($P < 0.01$). After adjustment for age, race/ethnicity, comorbidities, insurance, and income, COVID-19 remained independently associated with peripartum CV complications including preeclampsia (adjusted odds ratio [aOR]: 1.33 [95% CI, 1.29-1.37]), peripartum cardiomyopathy (aOR: 2.09 [1.54-2.84]), acute coronary syndrome (aOR: 12.94 [8.85-18.90]), and arrhythmias (aOR: 1.55 [1.45-1.67]), compared with no COVID-19. Likewise, the risks of in-hospital mortality, acute kidney injury, stroke, pulmonary edema, and venous thromboembolism were higher with COVID-19. For resource utilization, the cost of hospitalization ($5,374 vs $4,837, $P < 0.01$) was higher for deliveries among persons with COVID-19.

CONCLUSIONS In the year 2020, pregnant persons with COVID-19 had a higher risk of preeclampsia, in-hospital mortality, and other serious CV complication during delivery hospitalizations compared to pregnant individuals without COVID-19. (JACC Adv 2023;2:100386) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

AKI = acute kidney injury

aOR = adjusted odds ratio

CBSA = Core-Based Statistical Area

CV = cardiovascular

GDM = gestational diabetes mellitus

HF = heart failure

NIS = National Inpatient Sample

PCOS = polycystic ovary syndrome

PPCM = peripartum cardiomyopathy

VTE = venous thromboembolism

The novel COVID-19 is associated with a myriad of cardiovascular (CV) complications including myocardial infarction, cardiac arrhythmias, inflammation-related myocardial injury, and microvascular and macrovascular thrombosis.[1-3] According to recent data from the Centers for Disease Control and Prevention, COVID-19 is associated with adverse pregnancy outcomes including the need for intensive care admission, mechanical ventilation, and mechanical circulatory support.[4] However, there is a paucity of conclusive data to establish an association between COVID-19 and acute peripartum CV complications at the time of delivery.[5] Data supporting a link between COVID-19 infection with thrombotic complications, ventricular dysfunction, and arrhythmias during pregnancy remain limited to case reports and case series.[6,7]

Thus, we aimed to study the association of COVID-19 with acute peripartum CV complications at the time of delivery admissions using a nationally representative United States database.

METHODS

The National Inpatient Sample (NIS) data are publicly available. The specific data supporting this study's findings are available from the corresponding author upon request.

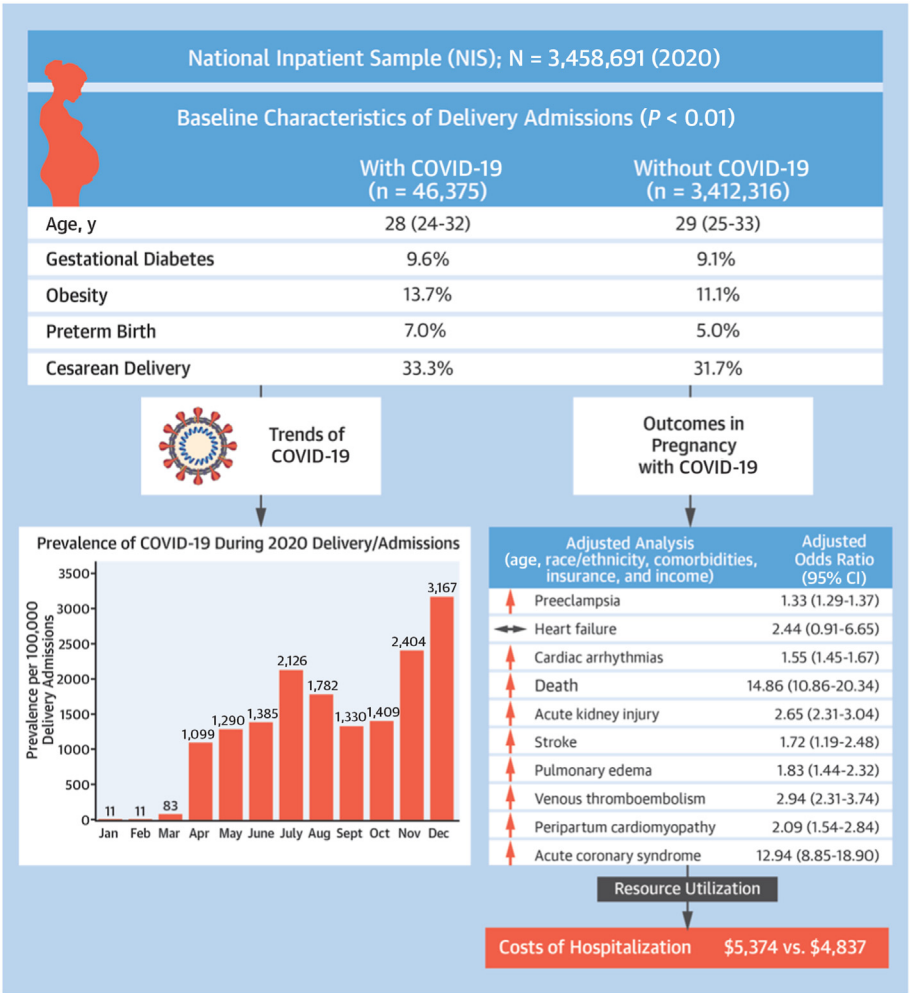
STUDY DATA. This study used data from the NIS database from January 1, 2020, to December 31, 2020, which was prior to the approval of COVID-19 vaccines. Hence, all included individuals in this study were not vaccinated against COVID-19. The NIS is managed by the Agency for Healthcare Research and Quality through a Federal-State-Industry partnership called the Healthcare Cost and Utilization Project (HCUP).[8] The NIS contains administrative claims data from more than 7 million inpatient hospitalizations annually in 47 participating states plus the District of Columbia, representing more than 97% of the US population. The NIS provides sample weights to calculate national estimates. The HCUP Comorbidity Software, which has been updated to account for the International Classification of Diseases-10th Revision-Clinical Modification (ICD-10-CM) coding system, used information from hospital records to identify 38 different pre-existing conditions that were present at the time of a patient's hospitalization. These conditions were identified based on secondary diagnoses listed in the administrative data and are considered comorbidities, meaning they exist alongside the primary condition for which the patient was hospitalized.[9] For the cost of care, charge-to-cost ratio supplied by HCUP derived from the Centers for Medicare and Medicaid Services was applied to total hospital charges. The data on race/ethnicity were collected by the HCUP participating organizations.[10] Median household annual income was categorized into 4 quartiles: 0 to 25th percentile quartile ($1-$49,999), 26th to 50th quartile ($50,000-$64,999), 51st to 75th quartile ($65,000-$85,999), and 76th to 100th quartile ($86,000+).[11] The Core-Based Statistical Area (CBSA) criteria were used to determine whether hospitals were designated as urban or rural. Hospitals situated in counties classified as metropolitan by CBSA were labeled as urban, whereas hospitals located in counties classified as micropolitan or noncore by CBSA were labeled as rural. The categorization of bed sizes in hospitals is based on the number of short-term acute care beds that are available and staffed. These categories are specific to the location and teaching status of the hospital. Information about hospital beds and their respective sizes was obtained from the American Hospital Association Annual Survey by HCUP.[12]

This study was deemed exempt from Institutional Review Board approval and informed consent because NIS data are de-identified and publicly available.

STUDY DESIGN AND DATA SELECTION. We analyzed NIS data using ICD-10-CM claims codes. We first identified delivery hospitalizations for adult patients (age >17 years) with ICD-10-CM codes (Supplemental Table 1). Among the selected cases, we used ICD-10-CM code U07.1 to identify delivery hospitalizations with COVID-19.[13] All diagnosis fields were queried to determine and categorize the study population. The study overview and detailed methods flowsheet are presented in **Central Illustration** and **Figure 1**, respectively.

STUDY ENDPOINT. The primary study endpoints were preeclampsia, peripartum cardiomyopathy (PPCM), acute coronary syndrome (ACS), and heart failure (HF). Secondary endpoints included in-hospital mortality, stroke, pulmonary edema, cardiac arrhythmias, acute kidney injury (AKI), acute venous thromboembolism (VTE), and cost of hospitalization. To ascertain the causes of left ventricular dysfunction, we also evaluated rates of myocarditis and stress cardiomyopathy. Associated procedures and complications were identified using ICD-10-CM codes. Due to the low number of eclampsia cases in the sample, they were categorized as preeclampsia

CENTRAL ILLUSTRATION **Cardiovascular Complications During Delivery Admissions Associated With COVID-19**



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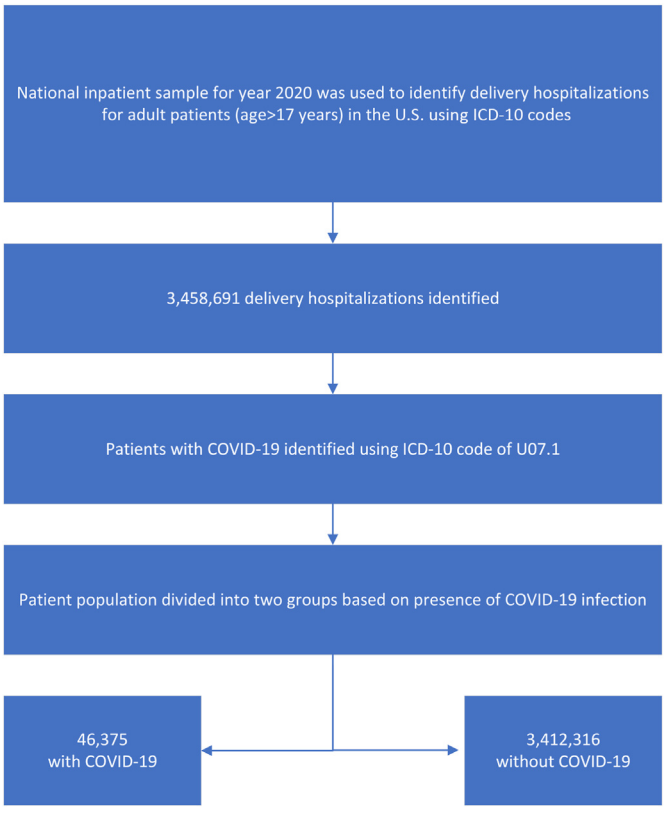
(Supplemental Table 1). We used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines to report the study findings.[14] The STROBE checklist can be found in Supplemental Table 2.

STATISTICAL ANALYSIS. Descriptive statistics were presented as frequencies (percentages) for categorical variables and as median (IQR) for continuous variables. Baseline characteristics were compared using a Pearson chi-square test or Fisher exact test as appropriate for categorical variables and the Mann-Whitney U test for continuous variables.

The Cochran-Mantel-Haenszel test was utilized to evaluate the association between COVID-19 and acute CV complications using the unadjusted odds ratio (OR). The Bonferroni correction was utilized to account for the potential impact of the family-wise error.[15] A multivariable logistic regression model was fitted to test the association of COVID-19 with in-hospital outcomes, adjusted for age, race/ethnicity, prepregnancy comorbidities (chronic hypertension, dyslipidemia, HF, chronic kidney disease, coronary artery disease, polycystic ovary syndrome [PCOS],[16] obesity, smoking, multiple gestation, gestational diabetes mellitus [GDM]),[17] Cesarean delivery,

FIGURE 1 Study Flow Diagram



median household income, and primary insurance. All variables were selected a priori based on their clinical relevance, which was determined by a comprehensive review of prior literature.[17-20] Variables such as preterm birth were not included in the logistic regression model, as it is typically considered an adverse pregnancy outcome rather than a confounder in our analysis. Given the low prevalence rate of study outcomes (<10%), the OR may be interpreted as an approximation of the relative risk.[21]

We performed several sensitivity analyses. Since preeclampsia is already known to be associated with CV complications at delivery,[18] we performed a supplementary analysis and retested the association using the aforementioned multivariable logistic regression model with additional adjustment for preeclampsia/eclampsia to see if COVID-19 was independently associated with acute CV complications after accounting for preeclampsia. As COVID-19 testing was not widely available during the initial months of the pandemic, a supplementary analysis after excluding cases from January to May 2020 was performed. Similarly, a supplementary analysis was also performed after excluding cases of PCOS, GDM, pre-existing diabetes, dyslipidemias, obesity, multiple gestations, coronary artery disease, chronic HF, and chronic kidney disease to retest the association between COVID-19 and peripartum CV complications to confirm the robustness of our findings. Since data were collected from across multiple hospitals in the United States, a supplementary analysis with additional adjustment for hospital characteristics (hospital bed size and hospital teaching status) was performed.

The missing values present in the data set are reported in Table 1. The missing values were predominantly present in the race/ethnicity (3.2%) variable, which was re-coded with the "other" category. Given the overall low number of missing data (<0.7%) in other variables, we used listwise deletion and did not include missing data in the logistic regression analysis.

All statistical analyses were performed using Statistical Package for Social Science (SPSS) version 27 (IBM Corp). Given the complex survey design of NIS, sample weights, clusters, and strata were applied to generate US national estimates.

RESULTS

HOSPITALIZATION CHARACTERISTICS OF THE STUDY POPULATION. A total of 3,458,691 weighted hospitalizations for deliveries were identified in the United States during the year 2020, out of which 1.34% (n = 46,375) had a diagnosis of COVID-19. Pregnant patients with COVID-19 had a lower median age (28 vs 29 years, $P < 0.01$) and were more likely to be of Black race (17.0% vs 14.7%) or Hispanic ethnicity (41.2% vs 20.2%), compared to pregnant patients without COVID-19. Furthermore, pregnant patients with COVID-19 more frequently had GDM (9.6% vs 9.1%), pre-existing diabetes mellitus (0.9% vs 0.7%), and obesity (13.7% vs 11.1%). The detailed baseline characteristics are mentioned in Table 1. During the study duration, the prevalence of COVID-19 increased from <11 per 100,000 deliveries in January 2020 to 3,167 per 100,000 deliveries in December 2020 (Figure 2).

CARDIOVASCULAR COMPLICATIONS ASSOCIATED WITH COVID-19 AND HOSPITAL RESOURCE USE. Patients with COVID-19 had a higher incidence of acute peripartum CV complications when compared to patients without COVID-19 during delivery hospitalizations, as described in Table 2. Notably, the mortality rate was higher among persons with COVID-19 than those without COVID-19 (130 vs <11

per 100,000 delivery hospitalizations; $P < 0.01$). Furthermore, the rates of preeclampsia (9,962 vs 7,246; $P < 0.01$), PPCM (129 vs 57; $P < 0.01$), ACS (86 vs <11; P value < 0.01), stroke (65 vs 35; $P < 0.01$), HF (86 vs 43, $P < 0.01$), cardiac arrhythmias (1,747 vs 1,092, $P < 0.01$), VTE (151 vs 54; $P < 0.01$), and AKI (485 vs 170, $P < 0.01$) per 100,000 deliveries were also greater in patients with COVID-19. There were <11 cases of myocarditis and 75 cases of stress cardiomyopathy reported in the non-COVID-19 group, whereas no cases of myocarditis or stress cardiomyopathy were reported in the COVID-19 group. Among the acute HF group, the significant difference was mainly driven by rates of acute HF with reduced ejection fraction (65 vs 26, $P < 0.01$), whereas no significant difference was observed in the HF with preserved ejection fraction group (12 vs <11, $P = 0.90$), per 100,000 deliveries. In terms of resource utilization, the cost of delivery hospitalization ($5,374 vs $4,837, $P < 0.01$) was significantly higher in individuals with COVID-19 compared to those without COVID-19. Both groups had a similar median length of stay of 2 days (IQR: 2-3 days).

ODDS RATIOS FOR IN-HOSPITAL COMPLICATIONS. After adjustment for age, race and ethnicity, comorbidities, insurance, and income, COVID-19 was found to be independently associated with higher in-hospital mortality as well as multiple acute CV complications during delivery hospitalization (Table 2 and Figure 3). The adjusted OR [aOR] for mortality at delivery admission was 15-fold higher (aOR: 14.86 [95% CI: 10.85-20.34]; P value < 0.01) with COVID-19 compared to no COVID-19. Additionally, pregnant individuals with COVID-19 had higher risk for the development of preeclampsia (aOR: 1.33 [95% CI: 1.29-1.37]; $P < 0.01$), PPCM (aOR: 2.09 [95% CI: 1.54-2.84]; $P < 0.01$), AKI (aOR: 2.65 [95% CI: 2.31-3.04]; $P < 0.01$), stroke (aOR: 1.72 [95% CI: 1.19-2.48]; $P < 0.01$), cardiac arrhythmias (aOR: 1.55 [95% CI: 1.45-1.67]; $P < 0.01$), pulmonary edema (aOR: 1.83 [95% CI: 1.44-2.32]; $P < 0.01$), and VTE (aOR: 2.94 [95% CI: 2.31-3.74]; $P < 0.01$) during delivery hospitalization, compared with pregnant persons without COVID-19. In contrast, the odds of HF during delivery among COVID-19 patients were not statistically significant compared with patients without COVID-19 on adjusted analysis (aOR: 2.44 [95% CI: 0.91-6.54]).

ODDS RATIOS FOR IN-HOSPITAL COMPLICATIONS AFTER ADDITIONAL ADJUSTMENT OF PREECLAMPSIA. A supplementary analysis after additional adjustment of preeclampsia mirrored primary analysis with few

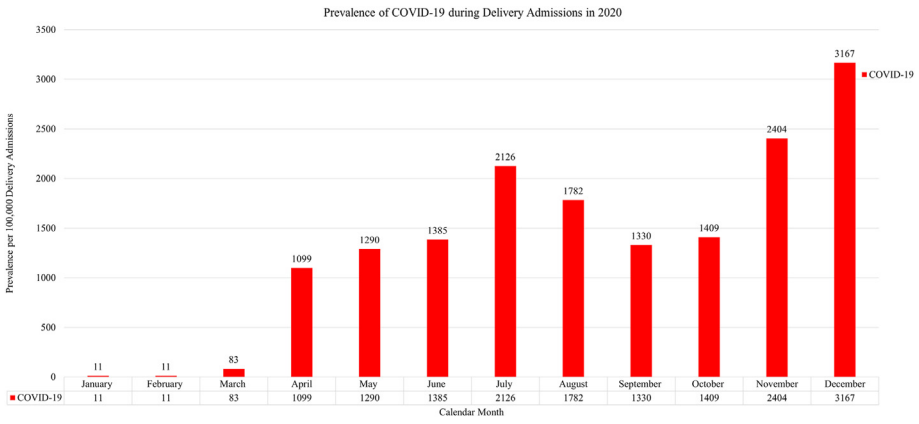
TABLE 1 Characteristics of Patients With and Without COVID-19 at Pregnancy Delivery Hospitalization

	Without COVID-19 (3,412,316)	With COVID-19 (46,375)	*P* Value
Demographics			
Age, y	29 (25-33)	28 (24-32)	<0.01
Race/Ethnicity			<0.01
White	1,739,525 (51.0)	13,215 (28.5)	
Black	502,380 (14.7)	7,895 (17.0)	
Hispanic	690,955 (20.2)	19,115 (41.2)	
Asian or Pacific Islander	200,445 (5.9)	1,660 (3.6)	
Native American	24,470 (0.7)	315 (0.7)	
Other	254,540 (7.5)	4,175 (9.0)	
Pre-existing comorbidities			
PCOS	29,075 (0.9)	305 (0.7)	<0.01
GDM	311,970 (9.1)	4,430 (9.6)	<0.01
Pre-existing diabetes	24,430 (0.7)	430 (0.9)	<0.01
Dyslipidemia	13,660 (0.4)	200 (0.4)	0.29
Chronic hypertension	42,301 (1.2)	260 (0.6)	<0.01
Heart failure	1,970 (0.1)	45 (0.1)	<0.01
Chronic kidney disease	740 (0.0)	35 (0.1)	<0.01
Coronary artery disease	875 (0.0)	<11[a] (<0.0)	<0.01
Obesity	379,760 (11.1)	6,365 (13.7)	<0.01
Smoking	153,185 (4.5)	855 (1.8)	<0.01
Obstetric characteristics			
Multiple gestation	59,005 (1.7)	810 (1.7)	0.78
Cesarean delivery	1,083,215 (31.7)	15,440 (33.3)	<0.01
Preterm birth	171,645 (5.0)	3,235 (7.0)	<0.01
Still birth	28,035 (0.8)	545 (1.2)	<0.01
Hospital characteristics			
Bed size			<0.01
Small	693,719 (20.3)	8,140 (17.6)	
Medium	989,630 (29.0)	13,375 (28.8)	
Large	1,728,966 (50.7)	24,860 (53.6)	
Teaching status			<0.01
Rural	299,821 (8.8)	2,575 (5.6)	
Urban, nonteaching	582,191 (17.1)	6,365 (13.7)	
Urban, teaching	2,530,303 (74.2)	37,435 (80.7)	
Socioeconomic characteristics			
Median household income			<0.01
0-25th percentile	924,036 (27.3)	16,140 (35.0)	
26th-50th percentile	888,665 (26.2)	12,380 (26.9)	
51st-75th percentile	816,755 (24.1)	10,835 (23.5)	
76th-100th percentile	757,930 (22.4)	6,695 (14.5)	
Missing	24,930 (0.7)	325 (0.7)	
Primary insurance			<0.01
Medicare	21,185 (0.6)	335 (0.7)	
Medicaid	1,404,580 (41.2)	27,110 (58.5)	
Private insurance	1,807,145 (53.0)	16,070 (34.7)	
Self-pay	78,150 (2.3)	1,785 (3.9)	
No charge	2,640 (0.1)	90 (0.2)	
Other	95,070 (2.8)	930 (2.0)	
Missing	3,545 (0.1)	55 (0.1)	

Values are median (IQR) or n (%). [a]Observations <11 are not reportable per HCUP guidelines.

COVID-19 = coronavirus disease-19; GDM = gestational diabetes mellitus; PCOS = polycystic ovary syndrome; SD = standard deviation.

FIGURE 2 Trends of Prevalence of COVID-19 During U.S. Delivery Admissions From January to December 2020



Observations <11 are not reported as per HCUP guidelines.

important exceptions. For instance, the association between stroke and pulmonary edema with COVID-19 did not reach statistical significance, whereas other acute peripartum CV complications including PPCM, ACS, AKI, cardiac arrhythmias, and VTE retained significant association (Supplemental Table 3).

ODDS RATIOS FOR IN-HOSPITAL COMPLICATIONS FROM SUPPLEMENTARY ANALYSIS. A supplementary analysis after excluding cases from January to May 2020 replicated the results of our primary analysis which included cases from January through December 2020 (Supplemental Table 4). A supplementary analysis after excluding cases of PCOS, GDM, pre-existing diabetes, dyslipidemias, obesity, multiple gestations, coronary artery disease, chronic HF, and chronic kidney disease reiterated the results of our primary analysis by showing a significant association between COVID-19 infection and acute peripartum CV complications at the time of delivery compared to no COVID-19 (Supplemental Tables 5 to 11). Similarly, the association of COVID-19 with acute CV complications at delivery hospitalization (compared with no COVID-19) remained significant after additional adjustments of hospital characteristics such as bed size and teaching status of the hospital (Supplemental Table 12).

TABLE 2 Complication Rates and Hospital Resource Utilization in Patients With and Without COVID-19 During Pregnancy Delivery Hospitalizations

	Without COVID-19 (n = 3,412,316)	With COVID-19 (n = 46,375)	*P* Value	*P* Value, Corrected[b]
Complication rates (per 100,000 delivery hospitalizations)				
Died	<11[a]	130	<0.01	<0.01
Preeclampsia	7,246	9,962	<0.01	<0.01
Peripartum cardiomyopathy	57	129	<0.01	<0.01
Heart failure	43	86	<0.01	<0.01
Acute coronary syndrome	<11[a]	86	<0.01	<0.01
Acute kidney injury	170	485	<0.01	<0.01
Stroke	35	65	<0.01	0.01
Pulmonary edema	76	151	<0.01	<0.01
Cardiac arrhythmias	1,092	1,747	<0.01	<0.01
Venous thromboembolism	54	151	<0.01	<0.01
Resource utilization				
Cost of hospitalization, $	4,837 (3,387-7,051)	5,374 (3,724-8,151)	<0.01	

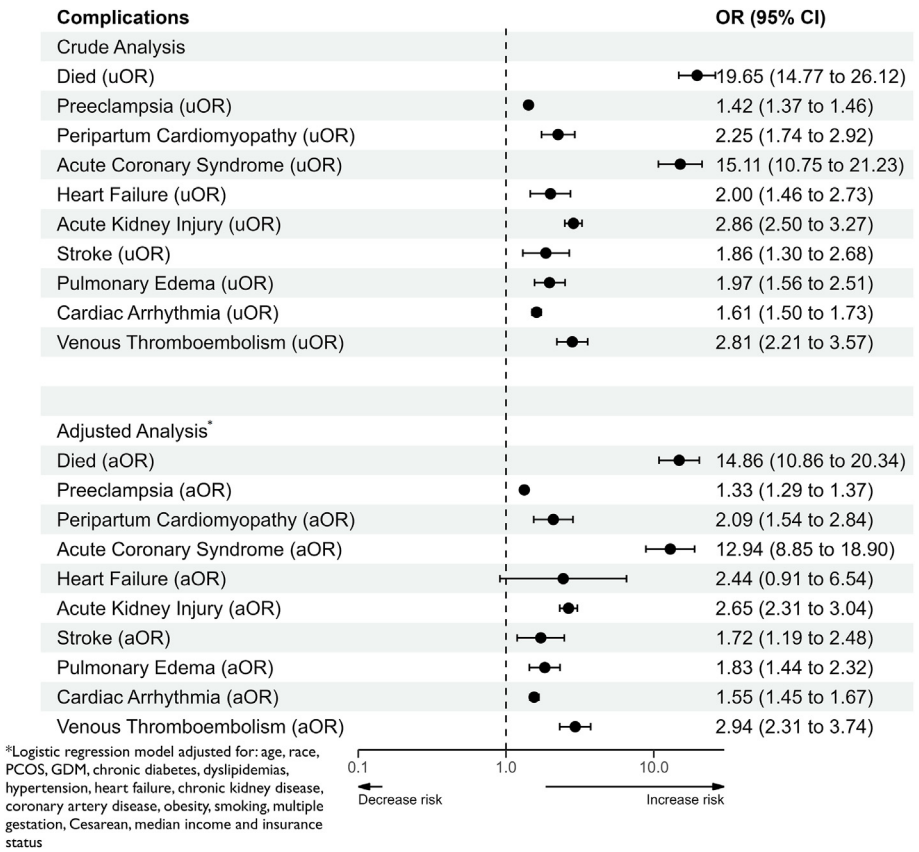
Values are median (IQR) unless other indicated. [a]Observations with cell count <11 are not reportable per HCUP guidelines. [b]*P* value after Bonferroni correction.

DISCUSSION

The results of our large-scale contemporary national database, including over 3 million hospitalizations in the United States, showed the following key findings: 1) COVID-19 in pregnant individuals was independently associated with higher in-hospital mortality; 2) COVID-19 is independently associated with increased CV complications such as preeclampsia, PPCM, ACS, stroke, cardiac arrhythmias, AKI, and VTE; and 3) deliveries among COVID-19 patients had a higher cost of hospitalization.

Cardiac complications with COVID-19 infection have been well-described, even very early in the pandemic, with a spectrum of CV manifestations

FIGURE 3 Adjusted and Unadjusted Odds Ratios for In-Hospital Complications Associated With COVID-19 Compared With Patients Without COVID-19 During Delivery Admissions



including myocardial infarction, myocarditis, stress cardiomyopathy, cardiac arrhythmia, stroke, and VTE.[22] The stress of a serious viral infection can unmask subclinical CV disease or exacerbate pre-existing CV disease. Furthermore, the viral affinity for angiotensin-converting enzyme 2 receptors (also expressed in the endothelium of blood vessels) and the inflammatory cascade that the virus triggers may directly cause endothelial damage. Pregnancy, which is a relatively immunosuppressed state, maybe a particularly vulnerable period for CV complications associated with COVID-19 infection. It was already known that COVID-19 is associated with adverse outcomes during pregnancy.[4] However, the magnitude and types of excess CV risks had not been well elucidated and we set out to examine this question in a large, nationally representative sample of pregnant persons at delivery during the pandemic year of 2020, which was before COVID-19 vaccine became available at the end of December 2020.

Preeclampsia complicates 2% to 8% of pregnancies.[23] Pregnant persons with COVID-19 infections have been noted to have increased rates of preeclampsia, which may be amplified among individuals with pre-existing hypertension or diabetes.[24] The INTERCOVID study also showed that the relative risk of preeclampsia in COVID-19 patients was 1.76 (95% CI: 1.27-2.43), independent of the confounding variables and after adjusting for the traditional preeclampsia risk factors.[25] Our study finding now further confirms this association by describing COVID-19 to be an independent risk factor for preeclampsia during the time of delivery admission in a large multiethnic national U.S. sample. The proposed mechanisms linking COVID-19 to preeclampsia have been purported to be due to inflammation, impact on the renin-angiotensin-aldosterone system, and endothelial damage.[26] However, we also found that COVID-19 was still associated with mortality, PPCM, ACS, arrhythmias, AKI, and VTE in pregnant persons

at delivery even after further adjusting for pre-eclampsia development.

Pregnancy is a hypercoagulable state.[27,28] The VTE risk in pregnant and post-partum women is known to be 7 to 10 and 15 to 25 times higher than age-matched controls, respectively.[29] COVID-19 infection can also confer a hypercoagulable state and is associated with an increased risk of VTE because of systemic inflammation, platelet activation, and endothelial dysfunction.[30] Therefore, it would be hypothesized that since pregnancy is a hypercoagulable state and a risk factor for severe COVID-19 that pregnant patients with COVID-19 would be at higher risk of VTE than pregnant patients without COVID-19. Interestingly, the pre-existing literature had not confirmed that hypothesis. Knight et al[31] demonstrated no excess VTE incidence among 427 hospitalized pregnant COVID-19 patients. Among 64 hospitalized pregnant COVID-19 patients in the United States, Pierce-Williams et al[32] reflected that 58% and 16% were anticoagulated with prophylactic and therapeutic heparin, respectively, but there were no cases of VTE. On the other hand, our nationwide study did show that COVID-19 is associated with higher VTE rates and a nearly 3-fold increased risk of VTE during delivery admission in adjusted analysis, compared to pregnant persons without COVID-19. This conflicts with the existing literature and likely is secondary to the larger sample size our study; in contrast, prior studies have only studied a smaller sample size.

ACS is typically a rare event in pregnancy and post-partum, with prior literature estimating the rate being 3 to 10 per 100,000 pregnant women, which is 3 to 4 times higher than similar aged nonpregnant women.[33] We found similar rates of ACS (<11 per 100,000 deliveries) in the group of pregnant persons without COVID-19 infection. However, a much higher rate of ACS (86 per 100,000 deliveries) was seen among pregnant persons with COVID-19, confirming that the thrombotic risk associated with pregnancy is magnified further in the setting of COVID-19 infection with a nearly 13-fold greater odds of ACS.

High cardiometabolic demands during pregnancy can either result in PPCM in patients without any prior cardiac dysfunction or cause HF exacerbation in patients with previous HF. COVID-19 has also been associated with HF and stress cardiomyopathy.[22,34] However, there is limited knowledge of the true incidence of HF associated with COVID-19, especially in the setting of pregnancy.[20,35] The pathophysiology behind COVID-19-induced cardiomyopathy entails systemic inflammation, oxygen supply-demand mismatch, and microvascular thrombosis.[36] The timing is crucial in differentiating COVID-19-induced cardiomyopathy, which will occur at the time of infection, and PPCM usually occurs toward the end of pregnancy or months following delivery. Mercedes et al,[20] in their study, showed that 9.7% of pregnant patients with COVID-19 had left ventricular dysfunction along with elevated troponin and natriuretic peptide. Additionally, in that study, left ventricular dilation was seen in 13% of cases.[20] In another case series by Juusela et al,[6] 28.5% of pregnant patients with COVID-19 were noticed to have a low left ventricular ejection fraction (40%-45%). Similarly, our study also showed higher rates of HF and PPCM in the pregnant patient cohort with COVID-19 infection who were admitted for delivery. In our nationwide analysis, we found that although COVID-19 remained an independent risk factor for PPCM, it failed to show an independent association with HF.

COVID-19 can result in cardiac arrhythmias via electrolyte changes, myocardial insult, or the infection itself.[37] The prevalence varies from 11.7% to 16.7%.[38] Both bradyarrhythmia and tachyarrhythmia have been observed. Among pregnant persons with COVID-19, Mercedes et al[20] showed the development of atrial fibrillation, Torsade de Pointes, and supraventricular arrhythmia. Similarly, our findings also demonstrated that COVID-19 was an independent risk factor for cardiac arrhythmia in pregnant patients affected with COVID-19 during admission for delivery.

COVID-19 has also been associated with stroke. The endothelial injury resulting from the inflammatory cascade can act as a nidus for thrombosis resulting in acute stroke. Similarly, COVID-19 has been associated with AKI. These described relationships have previously been limited to case reports.[39,40] Our large nationwide study shows that COVID-19 is a strong risk factor for both stroke and AKI in pregnant patients admitted for delivery.

We also showed that pregnant persons with COVID-19 were also at increased risk for mortality during their delivery hospitalization compared to pregnant persons without COVID-19, even after adjusting for sociodemographics and comorbidities including chronic hypertension and diabetes. Racial and socioeconomic disparities have been well-described for both pregnancy complications[18,41] and COVID-19 complications,[42] but we found our associations of worse CV outcomes at pregnancy delivery

even after accounting for racial differences, insurance status, and income as a marker of health inequities. Notably, more than 50% of patients in the COVID-19 group had Medicaid as their primary insurance and 61.9% of the patients had median household income below the 50% percentile. These findings suggest that the most vulnerable population groups are also exposed to the greatest risk of developing acute peripartum CV complications with COVID-19.

STRENGTHS AND LIMITATIONS. The strengths of our study include a large multiethnic sample nationally representative of the US delivery population, which allowed us to have sufficient statistical power to examine CV complications associated with deliveries among pregnant persons with and without COVID-19. Our data indicate that COVID-19 imposes a significant CV burden on pregnant patients undergoing delivery. These complications can very well stretch beyond the discharge and closer monitoring of such high-risk cohort is integral.

Despite these strengths, our findings should be considered in the context of several limitations of our study. NIS is an administrative claim-based database that uses ICD-10 codes for diagnosis, and hence, coding errors cannot be excluded. One known limitation of administrative database research is misclassification bias that can happen in ICD-10 diagnostic codes usage, which may imperfectly define the studied condition. An important misclassification bias related to the current analysis is the possibility that individuals might have been incorrectly coded or diagnosed as PPCM when in fact they had viral myocarditis or stress cardiomyopathy. It is plausible that COVID-19-related myocarditis or stress cardiomyopathy might not have been well-described at the time leading to diagnostic errors. The overall count of peripartum CV complications is low which is expected in an obstetric population. We tested multiple CV outcomes; it is also possible that 1 out of every 20 significant associations may be a false positive. However, our findings are meant to be exploratory and hypothesis generating and warrant further study in other cohorts from a similar time period. Also, differences in outcomes between the COVID-19 and non-COVID-19 groups were still statistically significant after Bonferroni correction. In addition to residual confounding, collider bias is a concern that has been documented in recent COVID-19 studies.[43,44] Though NIS provides a weighted national estimate from a random sample of a representative U.S. population, collider bias through adjustment of variables in the logistic regression model may exist.

Additionally, during the early months of the pandemic, the diagnostic tests for COVID-19 were either not available or did not have high sensitivity/specificity which could have influenced our study findings. However, our supplementary analysis after the exclusion of the early months of the pandemic did not deviate significantly from our primary analysis. An additional constraint of this study is that the NIS database is structured as an inpatient database, capturing only data during hospitalization. This feature of the database limits its ability to provide detailed information regarding the timing of outcomes during hospitalization and does not furnish data on long-term outcomes. However, the CV risk among pregnant individuals may extend beyond the delivery admission and requires closer surveillance. Furthermore, association does not mean causation, and conclusions should be drawn cautiously.

Finally, and perhaps most importantly, our analyses were conducted during the pandemic year of 2020 before COVID-19 vaccine was largely available; HCUP has not yet released the NIS data from the years 2021 or 2022 in the postvaccination era. Hence, the applicability of our study findings to the current US pregnant population which is largely vaccinated needs to be further explored. Our findings may be relevant for pregnant persons who still remain unvaccinated. COVID-19 vaccination is safe in pregnancy and associated with improved maternal and fetal outcomes,[45,46] and as such COVID-19 vaccination in pregnant persons is endorsed by the American College of Obstetrics and Gynecology.[47] Future analyses should re-examine the association of COVID-19 with maternal peripartum CV outcomes to see if some of these excess risks are mitigated by vaccination, as would be anticipated.

CONCLUSIONS

In summary, we report higher acute peripartum CV complication rates of preeclampsia, PPCM, stroke, ACS, AKI, pulmonary edema, cardiac arrhythmias, and VTE in pregnant patients with COVID-19 during delivery hospitalizations. Pregnant persons with COVID-19 need close attention to CV risk throughout the pregnancy and post-partum period, and future studies are needed to evaluate the impact of COVID-19 vaccination on reducing CV risks during pregnancy, as well as implementation of other

risk-reducing strategies in the setting of COVID-19 infection.

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Unrelated to this work, Dr Michos reports consultation for Amgen, AstraZeneca, Amarin, Bayer, Boehringer Ingelheim, Edwards Lifesciences, Esperion, Medtronic, Novartis, Novo Nordisk, and Pfizer. Dr Michos is supported by the Amato Fund for Women's Cardiovascular Health research at Johns Hopkins University and an American Heart Association grant 946222. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: COVID-19 is associated with higher acute peripartum CV complication rates of preeclampsia, PPCM, stroke, ACS, AKI, pulmonary edema, cardiac arrhythmias, and VTE during delivery hospitalizations compared to pregnant persons without COVID-19. Pregnant persons with COVID-19 need close attention to CV risk throughout the pregnancy and post-partum period.

TRANSLATIONAL OUTLOOK: Future studies are needed to evaluate the impact of COVID-19 vaccination on reducing CV risks during pregnancy, as well as implementation of other risk-reducing strategies in the setting of COVID-19 infection.

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KEY WORDS **cardiovascular disease, COVID-19, mortality, preeclampsia, pregnancy**

APPENDIX **For supplemental tables, please see the online version of this paper.**