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Original Research

Pregnancy and the Risk of In-Hospital Coronavirus Disease 2019 (COVID-19) Mortality

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OBJECTIVE: To evaluate whether pregnancy is an independent risk factor for in-hospital mortality among patients of reproductive age hospitalized with coronavirus disease 2019 (COVID-19) viral pneumonia.

METHODS: We conducted a retrospective cohort study (April 2020–May 2021) of 23,574 female inpatients aged 15–45 years with an International Classification of Diseases, Tenth Revision, Clinical Modification diagnosis code for COVID-19 discharged from 749 U.S. hospitals in the Premier Healthcare Database. We used a viral pneumonia diagnosis to select for patients with symptomatic COVID-19. The associations between pregnancy and in-hospital mortality, intensive care unit (ICU) admission, and mechanical ventilation were analyzed using propensity score–matched conditional logistic regression. Models were matched for age, marital status, race and ethnicity, Elixhauser comorbidity score, payer, hospital number of beds, season of discharge, hospital region, obesity, hypertension, diabetes mellitus, chronic pulmonary disease, deficiency anemias, depression, hypothyroidism, and liver disease.

RESULTS: In-hospital mortality occurred in 1.1% of pregnant patients and 3.5% of nonpregnant patients hospitalized with COVID-19 and viral pneumonia (propensity score–matched odds ratio [OR] 0.39, 95% CI 0.25–0.63). The frequency of ICU admission for pregnant and nonpregnant patients was 22.0% and 17.7%, respectively (OR 1.34, 95% CI 1.15–1.55). Mechanical ventilation was used in 8.7% of both pregnant and nonpregnant patients (OR 1.05, 95% CI 0.86–1.29). Among patients who were admitted to an ICU, mortality was lower for pregnant compared with nonpregnant patients (OR 0.33, 95% CI 0.20–0.57), though mechanical ventilation rates were similar (35.7% vs 38.3%, OR 0.90, 95% CI 0.70–1.16). Among patients with mechanical ventilation, pregnant patients had a reduced risk of in-hospital mortality compared with nonpregnant patients (0.26, 95% CI 0.15–0.46).

CONCLUSION: Despite a higher frequency of ICU admission, in-hospital mortality was lower among pregnant patients compared with nonpregnant patients with COVID-19 viral pneumonia, and these findings persisted after propensity score matching.

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Several studies have shown that symptomatic coronavirus disease 2019 (COVID-19) in pregnancy is associated with increased risk of adverse maternal and perinatal outcomes compared with patients without COVID-19.[1,2] Whether pregnancy itself is a risk factor for COVID-19 morbidity and mortality is less clear.

We previously demonstrated that the probability of in-hospital mortality in pregnant patients with COVID-19 viral pneumonia is lower than in nonpregnant patients.[3] However, the literature is conflicting.[4–7] The Centers for Disease Control and Prevention (CDC) reported that among inpatients and outpatients with symptomatic COVID-19, pregnant patients were 1.7 times more likely to die than nonpregnant patients (95% CI 1.2–2.4).[4] Multiple policies, professional society guidelines and editorials have been based on these data and other reports showing increased morbidity and mortality in pregnant compared with nonpregnant patients.[8–13] However, these data are based on registries that are limited by a significant proportion of missing data and likely suffer from selection bias.[4,6]

In observational research on COVID-19, selection bias has been found to be a major problem in estimating disease risk and severity.[14] When diseases have a spectrum of clinical presentations, severe ("noteworthy") cases are more likely than mild or asymptomatic cases to be reported to surveillance and registry-based databases by health care professionals.[15] This selection bias can falsely elevate the case-fatality rate.[14] Missing data also contribute to biased estimates.[16]

Studies with more complete ascertainment of COVID-19 in pregnancy are needed to provide the foundation for evidence-based health care policies. Large health care databases are less susceptible to case-ascertainment bias compared with registries because cases are captured along with the entire cohort without voluntary selection. Previously, we used an electronic health care database to describe the rates of in-hospital mortality, intensive care unit (ICU) admission, and mechanical ventilation in pregnant and nonpregnant patients of reproductive age with COVID-19 admitted from April through November 2020, which was a shorter time period than the current study and did not adjust for confounders owing to small numbers.[3] In this extension of that work, the primary objective of this study was to evaluate whether pregnancy is an independent risk factor for in-hospital mortality among patients of reproductive age hospitalized with COVID-19 viral pneumonia. Secondary outcomes were ICU admission and mechanical ventilation.

METHODS

We conducted a retrospective observational cohort study of patients who were discharged from hospitals in the Premier Healthcare Database, an all-payer repository of claims and clinical data from more than 120 million U.S. inpatient admissions.[17]

Premier Healthcare Database hospitals cover geographically diverse areas across the United States and capture approximately 20% of U.S. hospital discharges. Premier internally validates all data before their release into the Premier Healthcare Database. For most data elements, less than 1% of patient records have missing information, and for key elements, such as demographics and diagnostic information, less than 0.01% of data are missing.[17] COVID-19 has been previously studied using the Premier Healthcare Database by several groups, including ours.[3,18,19] This study did not include personally identifiable information and was exempt from institutional review board review. We followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.[20]

Patients of reproductive age with COVID-19 were defined as females aged 15–45 years admitted to U.S. acute care hospitals with an International Classification of Diseases, Tenth revision, Clinical Modification (ICD-10-CM) diagnosis code for COVID-19 (U07.1).[21] This code was internally validated in the Premier Healthcare Database against laboratory data and found to have a specificity of 98% and a sensitivity of 99% for laboratory-confirmed infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[22] All admissions with discharge dates from April 2020 to May 2021 and present in the Premier Healthcare Database as of the data extract date of May 26, 2021, were included in the study.[17]

For most of the pandemic, pregnant patients have been screened for SARS-CoV-2 on admission, and many of these patients, though asymptomatic, test positive.[23] Because we anticipated that our cohort includes asymptomatic pregnant patients admitted for delivery, we used a viral pneumonia diagnosis to select for patients with symptomatic COVID-19 (ICD-10-CM codes J12.8 and J12.9, Appendix 1, available online at http://links.lww.com/AOG/C669). Viral pneumonia was the most frequent diagnosis in the cohort after COVID-19 and captured 92% of in-hospital mortality among pregnant patients and 86% among nonpregnant patients (Appendices 1 and 2, available online at http://links.lww.com/AOG/C669). Patients with diagnoses of COVID-19 and viral pneumonia were used for the primary analysis.

A patient was defined as *pregnant* if the encounter included any pregnancy-related diagnosis (an ICD-10-CM diagnosis code beginning with O).[2] A gestational age was assigned using the Z3A ICD-10-CM code.[24] If no Z3A code and no delivery procedure were coded, the patient was recategorized as nonpregnant. The remainder of patients were categorized as nonpregnant.

The primary outcome was in-hospital mortality, identified from discharge disposition. Both mortality on the index encounter and mortality on any readmission in the data set were included in the primary outcome for both groups to ensure that deaths on readmissions postpartum were captured in the pregnancy group. Secondary outcomes were mechanical ventilation and ICU admission during the index encounter. In addition, delivery of the neonate during the index encounter was described for pregnant patients. Invasive mechanical ventilation use status was assessed using ICD-10 procedure codes (ie, 5A1935Z, 5A1945Z, and 5A1955Z).[25] *Intensive care unit admission* was defined as patients who had any ICU service charge during the index hospitalization.[18] Delivery of the neonate was assessed using ICD-10-PCS procedure codes (ie, 10D00Z0, 10D00Z1, 10D00Z2, 10D07Z3, 10D07Z4, 10D07Z5, 10D07Z6, 10D07Z7, 10D07Z8, 10E0XZZ). Appendix 1 (http://links.lww.com/AOG/C669) lists all codes used.

The unit of analysis was defined as a *unique patient*. The first chronological hospital encounter in which the patient had a diagnosis of COVID-19 was defined as the *index encounter*. All subsequent encounters in the data set were analyzed as readmissions for that patient. Descriptive statistics for patient and hospital characteristics were calculated using median (interquartile range) or frequency count (percentage). We used χ^2 and Fisher exact tests to test for statistical differences between groups for categorical variables and the Wilcoxon rank-sum test for continuous variables.

Unadjusted comparisons between pregnant and nonpregnant patients were made using χ^2 tests and odds ratios (ORs) estimated by logistic regression. Propensity score matching was used to reduce confounding of the association between pregnancy and in-hospital mortality. Propensity scores were calculated using the PSMATCH procedure in SAS 9.4 with optimal fixed ratio 1:1 matching between pregnant and nonpregnant patients. The covariates related to pregnancy were selected a priori through literature review and expert clinical consensus. Propensity score models were performed separately for each subgroup using the same covariates. Balance among covariates was checked by using standardized mean difference with a threshold of 0.25. Conditional logistic regression models were used to estimate the association between pregnancy and in-hospital mortality.

All models matched for age, race and ethnicity, marital status, payer, hospital number of beds, hospital region, discharge season, and Elixhauser comorbidity score (Elixhauser ICD-10-CM, Clinical Modification classification system).[26] Race and ethnicity were included because they are associated with both pregnancy and COVID-19 mortality.[27,28] In addition, matching was performed for the most common chronic comorbidities: obesity, hypertension (pregestational or gestational), diabetes mellitus (pregestational or gestational), chronic pulmonary disease, deficiency anemias, depression, hypothyroidism, and liver disease. We mapped present-on-admission diagnosis codes to Elixhauser comorbidities (eg, hypertension, obesity) using standardized Agency for Healthcare Research and Quality methodology and software (Elixhauser Comorbidity Software for ICD-10-CM 2020.1 [beta version], https://www.hcup-us.ahrq.gov/toolssoftware/comorbidityicd10/comorbidity_icd10.jsp#download, accessed August 26, 2020). Using present-on-admission Elixhauser comorbidities, we calculated unweighted (summed) Elixhauser comorbidity scores.[29,30]

All tests were two-tailed, and $P \leq .05$ was used for statistical significance testing. Analyses were performed using SAS 9.4.

To further examine the association between pregnancy and in-hospital mortality, we created two subgroups: 1) ICU admission and 2) mechanical ventilation. The models described above were repeated using these subgroups.

The Premier Healthcare Database includes weights derived from the American Hospital Association's 2019 Annual Survey to produce nationally representative inpatient discharges.[31] Using these weights, projected numbers of national in-hospital mortalities for pregnant and nonpregnant patients were estimated.

The Elixhauser comorbidity index was developed for prediction of in-hospital mortality but has not been used to predict pregnancy-associated mortality.[26] To validate the Elixhauser comorbidity score for the prediction of in-hospital mortality in the pregnant population, we generated receiver operating characteristic curves that we compared with both published data and the nonpregnant population in our study. For all pregnant patients, the area under the receiver operating characteristic curve was 0.77. In pregnant and nonpregnant patients with COVID-19, the area under the receiver operating characteristic curve was 0.78 and 0.75, respectively, similar to previous research using the index.[29]

RESULTS

Among 18,067 pregnant and 30,322 nonpregnant reproductive-age females hospitalized with COVID-19 during the study period, 2,251 pregnant (12.5%)

and 21,503 nonpregnant (70.9%) patients had diagnoses of viral pneumonia and were included in the analysis. Pregnant patients were younger, more likely to be married, have public insurance, and to be Hispanic compared with nonpregnant patients (Table 1).

The differences in characteristics of the primary analysis group and subgroups are presented in Table 2. Age and Elixhauser comorbidity score were lower in pregnant patients among all groups ($P<.01$). Median (interquartile range) length of stay was 5 days in both pregnant (3–7 days) and nonpregnant (3–7 days) patients with a viral pneumonia diagnosis ($P=.05$). Pregnant patients were less likely than nonpregnant patients to have most Elixhauser comorbidities, including hypertension, chronic pulmonary disease, diabetes, and obesity ($P<.001$, Table 1).

In-hospital mortality occurred in 1.1% (n=24) of pregnant and 3.5% (n=748) of nonpregnant patients ($P<.001$, Table 3). Median (interquartile range) time from admission to death was 16 days (6–23 days) for pregnant patients and 11 days (4–22 days) for nonpregnant patients ($P=.422$). Mortality occurred on readmission in 37 (4.9% of mortalities) nonpregnant compared with 0 pregnant patients, with a median (interquartile range) of 4 days (2–9 days) between the index discharge and readmission. Among pregnant patients, the median (interquartile range) gestational age was 31 weeks among those who died and those who survived to discharge (24–37 weeks vs 26–35 weeks, $P=.782$). Appendix 3, available online at http://links.lww.com/AOG/C669, describes the characteristics of pregnant patients who died.

The balance of covariates included in the propensity score models before and after matching are shown in Appendix 4, available online at http://links.lww.com/AOG/C669. After matching, covariate imbalance between the exposed and unexposed groups was substantially reduced for all covariates in each subgroup, indicating that matching produced groups with a highly similar distribution of risk factors. There was sufficient overlap in the distribution of propensity scores between groups, as shown in Appendix 5, available online at http://links.lww.com/AOG/C669. Characteristics of patients, after matching, are shown in Table 1. In the propensity score–matched analysis, pregnant patients had a reduced risk of in-hospital mortality compared with nonpregnant patients (OR 0.39, 95% CI 0.25–0.63, Table 3).

Intensive care unit admission for pregnant and nonpregnant patients occurred in 22.0% and 17.7%, respectively (propensity score–matched OR 1.34, 95% CI 1.15–1.55, Table 3). Mechanical ventilation was used in 8.7% and 8.7% of pregnant and nonpregnant patients, respectively (propensity score–matched OR 1.05, 95% CI 0.86–1.29, Table 3).

Among the subgroup of patients who were admitted to an ICU, in-hospital mortality was 4.6% in pregnant patients and 16.7% in nonpregnant patients (propensity score–matched OR 0.33, 95% CI 0.20–0.57, Table 3). In the ICU subgroup, the rate of mechanical ventilation was similar in pregnant patients (35.7%) compared with nonpregnant patients (45.4%, propensity score–matched OR 0.90, 95% CI 0.70–1.16, Table 3).

Among the subgroup of patients who received mechanical ventilation, in-hospital mortality occurred in 12.2% of pregnant and 34.7% of nonpregnant patients (propensity score–matched OR 0.26, 95% CI 0.15–0.46, Table 3).

Using weighted tabulations, in-hospital mortality was expected for 157 (0.2%) pregnant and 4,251 (3.1%) nonpregnant patients aged 15–45 years hospitalized with COVID-19 in the United States through the study period. Restricting to data to April through October 2020 to compare with previously published CDC data (see Discussion), in-hospital mortality was expected in 68 (0.2%) pregnant and 2,174 (3.2%) nonpregnant patients.

DISCUSSION

This study demonstrates that pregnant patients hospitalized with COVID-19 viral pneumonia are at significantly lower risk of in-hospital mortality compared with nonpregnant patients. The results contrast with prior reports of increased mortality in pregnant compared with nonpregnant patients of reproductive age. The largest study, from the CDC, showed that pregnant patients were more likely than nonpregnant patients to be admitted to the ICU, receive mechanical ventilation, and die.[4] That study was based on patients aged 15–44 years with SARS-CoV-2 infection from a voluntary reporting registry. They excluded 64% of patients owing to unavailability of pregnancy and symptom status. Additionally, based on our national projection restricted to data through October 2020, the CDC study reported approximately 50% of the expected deaths of pregnant patients and 21% of the expected deaths of nonpregnant patients. Missing data and the preferential inclusion of fatal pregnant cases contribute to the potential for serious selection bias. We propose that selection bias is the main cause of the difference between the CDC findings and our study.[16] The authors of the CDC report acknowledge the limitations of the CDC data and the potential for

Table 1. Baseline Characteristics in the Unmatched and Propensity Score–Matched Pregnant and Nonpregnant Patients With Coronavirus Disease 2019 (COVID-19) and Viral Pneumonia

	Unmatched			Matched		
Characteristic	Pregnant (n=2,251)	Nonpregnant (n=21,503)	*P*	Pregnant (n=2,250)	Nonpregnant (n=2,250)	*P*
Age (y)	30 (26–35)	38 (32–42)	<.001	30 (26–35)	30 (24–36)	.149
Race and ethnicity						
Hispanic	834 (37.1)	6,015 (28.0)	<.001	834 (37.1)	816 (36.3)	.723
Non-Hispanic White	649 (28.8)	7,528 (35.0)		648 (28.8)	688 (30.6)	
Non-Hispanic Black	418 (18.6)	5,242 (24.4)		418 (18.6)	402 (17.9)	
Non-Hispanic Asian	94 (4.2)	555 (2.6)		94 (4.2)	86 (3.8)	
None of the above or unknown	256 (11.4)	2,163 (10.1)		256 (11.4)	258 (11.5)	
Marital status						
Married	951 (42.2)	7,187 (33.4)	<.001	951 (42.3)	923 (41.0)	.678
Single	1,007 (44.7)	11,597 (53.9)		1,007 (44.8)	1,034 (46.0)	
None of the above or unknown	293 (13.0)	2,719 (12.6)		292 (13.0)	293 (13.0)	
Payer						
Public	1,230 (54.6)	8,453 (39.3)	<.001	1,229 (54.6)	1,236 (54.9)	.879
Private	816 (36.3)	9,733 (45.3)		816 (36.3)	802 (35.6)	
Other	205 (9.1)	3,317 (15.4)		205 (9.1)	212 (9.4)	
Gestational age (wk)						
Less than 20	227 (10.1)	NA	NA	227 (10.1)	NA	NA
20–27	495 (22.0)	NA		495 (22.0)	NA	
28–33	699 (31.1)	NA		699 (31.1)	NA	
34–36	410 (18.2)	NA		410 (18.2)	NA	
37–42	408 (18.1)	NA		407 (18.1)	NA	
Missing	12 (0.5)	NA		12 (0.5)	NA	
Hospital no. of beds						
0–299	553 (24.6)	8,520 (39.6)	<.001	553 (24.6)	555 (24.7)	.957
300–499	675 (30.0)	6,241 (29.0)		674 (30.0)	665 (29.6)	
500 or more	1,023 (45.4)	6,742 (31.4)		1,023 (45.5)	1,030 (45.8)	
Discharge season and year*						
Spring 2020	344 (15.3)	3,116 (14.5)	.017	344 (15.3)	372 (16.5)	.388
Summer 2020	585 (26.0)	5,203 (24.2)		584 (26.0)	588 (26.1)	
Fall 2020	361 (16.0)	4,042 (18.8)		361 (16.0)	379 (16.8)	
Winter 2020–2021	740 (32.9)	7,013 (32.6)		740 (32.9)	721 (32.0)	
Spring 2021	221 (9.8)	2,129 (9.9)		221 (9.8)	190 (8.4)	
Hospital region						
Midwest	392 (17.4)	3,762 (17.5)	.001	392 (17.4)	373 (16.6)	.832
Northeast	335 (14.9)	2,730 (12.7)		335 (14.9)	351 (15.6)	
South	1,063 (47.2)	10,953 (50.9)		1,062 (47.2)	1,060 (47.1)	
West	461 (20.5)	4,058 (18.9)		461 (20.5)	466 (20.7)	
Elixhauser score	1 (1, 3)	2 (1, 3)	<.001	1 (1, 3)	1 (1, 3)	.287
Obesity	715 (31.8)	12,166 (56.6)	<.001	715 (31.8)	738 (32.8)	.463
Hypertension†	199 (8.8)	6,857 (31.9)	<.001	199 (8.8)	198 (8.8)	.958
Diabetes mellitus†	164 (7.3)	6,144 (28.6)	<.001	164 (7.3)	156 (6.9)	.643
Chronic pulmonary disease	279 (12.4)	4,813 (22.4)	<.001	279 (12.4)	286 (12.7)	.753
Deficiency anemias	467 (20.7)	3,522 (16.4)	<.001	467 (20.8)	400 (17.8)	.011
Depression	108 (4.8)	2,360 (11.0)	<.001	108 (4.8)	109 (4.8)	.945
Hypothyroidism	116 (5.2)	2,111 (9.8)	<.001	116 (5.2)	109 (4.8)	.632
Liver disease	37 (1.6)	1,277 (5.9)	<.001	37 (1.6)	35 (1.6)	.812

NA, not applicable.
Data are median (interquartile range) or n (%) unless otherwise specified.
* Spring: March, April, May; summer: June, July, August; fall: September, October, November; winter: December, January, February.
† Pregestational or gestational.

Table 2. Key Characteristics by Subgroup and Pregnancy Status (Unmatched)

Characteristic	Viral Pneumonia		Viral Pneumonia and ICU Admission		Viral Pneumonia and Mechanical Ventilation	
	Pregnant (n=2,251)	Nonpregnant (n=21,503)	Pregnant (n=496)	Nonpregnant (n=3,800)	Pregnant (n=196)	Nonpregnant (n=1,872)
Age (y)	**30 (26–35)**	**38 (32–42)**	**31 (27–35)**	**38 (31–42)**	**32 (28–37)**	**38 (32–42)**
Elixhauser comorbidity score	**1 (1–3)**	**2 (1–3)**	**2 (1–3)**	**3 (2–4)**	**2 (1–4)**	**3 (2–4)**
Length of stay (d)	**5 (3–7)**	**5 (3–7)**	**9 (5–14)**	**10 (5–19)**	**14 (8–22)**	**17 (9–28)**
Delivery of neonate	749 (33.3)	NA	251 (50.6)	NA	143 (73.0)	NA
Gestational age at delivery (wk)*	37 (34–38)	NA	34 (31–37)	NA	33 (30–36)	NA
Gestational age at discharge if undelivered (wk)	28 (24–32)	NA	27 (23–31)	NA	24 (20–27)	NA

ICU, intensive care unit; NA, not applicable.
Data are median (interquartile range) or n (%).
Bold indicates $P<.05$ for the difference between pregnant and nonpregnant patients within each subgroup (Wilcoxon test).
* Includes only patients who delivered during the hospitalization for coronavirus disease 2019 (COVID-19) pneumonia.

bias.[4] Other national registries, such as the Canadian Surveillance of COVID-19 in Pregnancy, have separate reporting systems for pregnant and nonpregnant persons and are also likely subject to selection bias.[32]

Another study that showed an increased risk of mortality in pregnant patients found a mortality rate ratio of 13.6 for pregnant compared with nonpregnant patients using a registry of COVID-19 in pregnancy compared with publicly available data on patients aged 20–39 years in the state of Washington.[6] As the authors note, "potential for selection bias and use of imperfect denominators for comparison due to limitations in publicly available data" may have led to biased estimates.

Our findings are consistent with other recent studies with rigorous methods. A U.K. study included all symptomatic patients with COVID-19 aged 20–39 years hospitalized throughout the United Kingdom and found a mortality frequency of 0.8% (n=5) in pregnant and 3.1% (n=175) in nonpregnant persons.[7] This is similar to the mortality rates we report here among patients with COVID-19 and viral pneumonia diagnoses (1.1% in pregnant and 3.5% in nonpregnant patients). Importantly, the surveillance system used includes all 194 obstetric units in the country and study authors verified complete COVID-19 case ascertainment by communicating directly with

Table 3. Sensitivity Analyses by Subgroup for the Association of Pregnancy With In-Hospital Mortality, Intensive Care Unit Admission, and Mechanical Ventilation

	Unmatched			Matched		
	Pregnant (n=2,251)	Nonpregnant (n=21,503)	OR (95% CI)	Pregnant (n=2,250)	Nonpregnant (n=2,250)	OR (95% CI)
Viral pneumonia						
Death	**24 (1.1)**	**748 (3.5)**	**0.30 (0.20–0.45)**	**24 (1.1)**	**61 (2.7)**	**0.39 (0.25–0.63)**
ICU admission	**496 (22.0)**	**3,800 (17.7)**	**1.32 (1.19–1.46)**	**496 (22.0)**	**392 (17.4)**	**1.34 (1.15–1.55)**
Mechanical ventilation	196 (8.7)	1,872 (8.7)	1.00 (0.86–1.17)	196 (8.7)	187 (8.3)	1.05 (0.86–1.29)
Viral pneumonia and ICU admission						
Death	**23 (4.6)**	**636 (16.7)**	**0.24 (0.16–0.37)**	**23 (4.6)**	**59 (11.9)**	**0.33 (0.20–0.57)**
Mechanical ventilation	**177 (35.7)**	**1,725 (45.4)**	**0.67 (0.55–0.81)**	177 (35.7)	190 (38.3)	0.90 (0.70–1.16)
Viral pneumonia and mechanical ventilation						
Death	**24 (12.2)**	**650 (34.7)**	**0.26 (0.17–0.41)**	**24 (12.4)**	**69 (35.8)**	**0.26 (0.15–0.46)**
ICU admission	177 (90.3)	1,725 (92.1)	0.79 (0.48–1.31)	175 (90.7)	175 (90.7)	1.00 (0.50–2.00)

OR, odds ratio; ICU, intensive care unit.
Bold indicates a statistically significant difference between pregnant and nonpregnant patients.

reporting hospitals, thus minimizing the potential for bias. A report from the ISARIC (International Severe Acute Respiratory and emerging Infection Consortium) COVID-19 cohort including more than 400,000 hospitalized individuals found that pregnancy was associated with a reduced risk of death after adjusting for age and country (hazard ratio 0.44, 95% CI 0.38,0.50).[33] Sociodemographic variables associated with mortality from COVID-19, including Hispanic ethnicity and public insurance, were similar to previous reports.[34,35]

The widespread clinical and public health message has been that pregnancy is a risk factor for COVID-19–related mortality.[9,36] An international survey found that during the pandemic, pregnant or postpartum people were more likely to experience posttraumatic stress disorder, anxiety and depression symptoms than pregnant and postpartum people before the pandemic and the general population during the pandemic.[37] The effect of research results on pregnant patients' mental health requires investigation. However, we speculate that less alarming results such as this study, which supports a more balanced narrative regarding the contribution of pregnancy to COVID-19–related mortality, might provide some reassurance to pregnant patients. We caution that our results do not minimize the risk of COVID-19 in pregnancy, which is clearly associated with worse maternal and perinatal outcomes than no infection in pregnancy.[1,2]

Differential immune responses may help explain the difference in in-hospital mortality between pregnant and nonpregnant patients with COVID-19 viral pneumonia. The "cytokine storm" is hypothesized to play a large part in the pathogenesis of severe COVID-19.[38] Pregnancy profoundly alters the immune response, with the body tolerating the semi-allogenic fetus.[39] One of the adaptations to pregnancy is a shift in the predominant CD4 T cell population from the T helper 1 to T helper 2 phenotype. Several expert reviews have hypothesized that differential cytokine responses between pregnant and nonpregnant patients affect severity of disease,[40–42] and two studies of peripheral blood cytokines support this theory.[43,44] Whether immune adaptation to pregnancy influences COVID-19 pathogenicity, and how any potential effects may change across the gestational period, requires further study.

The difference in mortality between hospitalized pregnant and nonpregnant patients with COVID-19 viral pneumonia are likely explained in part by differences in medical care. Pregnant patients have a higher oxygen saturation goal (95% or higher vs 92% or higher for nonpregnant patients) owing to concern for adequate oxygenation of the fetus.[45] Pregnant individuals may be hospitalized more frequently and at a lower illness severity than nonpregnant patients.[7] In our study, pregnant patients with COVID-19 viral pneumonia were more likely to be admitted to the ICU than nonpregnant patients. Though pregnant and nonpregnant patients with pneumonia had identical mechanical ventilation rates, among only patients admitted to the ICU, mechanical ventilation was less common in pregnant patients before propensity score-matching and similar after propensity score-matching. This suggests that the higher frequency of ICU admission in pregnant patients is due to a lower threshold of intensive treatment rather than a greater severity of disease.

A strength of this study is the use of a national claims-based data set with very few missing cases (negative predictive value for the COVID-19 test 99.79%[22]) and a clearly defined population.[17] Several sensitivity analyses were performed to test for selection bias due to hospitalization, and the consistency of the results strengthens the findings.[46] Pregnancy status was reliably captured through diagnosis codes in our cohort, with similarities to nationally-representative publications in the frequency of delivery, gestational age and length of stay.[47,48]

Unlike the CDC and Canadian registries and the data from the state of Washington, which included inpatients and outpatients,[4,6,32] these results cannot be extrapolated to patients who are not hospitalized. In addition, differences between pregnant and nonpregnant females with respect to propensity for hospitalization might be responsible for some of the differences observed. Another limitation includes possible misclassification of patient clinical conditions when using diagnostic codes. The group of patients with viral pneumonia diagnoses does not perfectly represent the group of symptomatic patients, limiting comparisons with other studies. Residual confounding is likely to be present given the large imbalances in characteristics and comorbidities between pregnant and nonpregnant patients, but major confounders were matched for and given the large effect size, confounding is unlikely to change its direction. A caveat is that the data were collected before the onset of the Delta and Omicron variants, which may be associated with different outcomes.[49–52]

In summary, our data suggest that pregnancy is not an independent risk factor for in-hospital mortality in patients with COVID-19. Combining the evidence with other studies, a lower risk of in-hospital mortality in pregnant than nonpregnant

patients appears to be nearer to the true relative risk, and future studies should focus on the mechanisms of differential response to COVID-19 in pregnant and nonpregnant persons.

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