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COVID-19 and pregnancy: a comprehensive study of comorbidities and outcomes

Shang-Ming Zhou[1*], Hossein Ahmadi[1], Lin Huo[2], Lisa M. Lix[3], Kate Maslin[4], Jos M. Latour[4] and Jill Shawe[4]

Abstract

Objectives This study aimed to investigate the impact of pregnancy and pre-existing comorbidities on COVID-19 infections and associated complications of hospitalisation and mortality in women of reproductive age (WRA). The study also compared the risk of severe COVID-19 complications between pregnant women (PW) and non-pregnant women (NPW) with and without pre-existing comorbidities. Special focus was placed on some understudied comorbidities of immunosuppression, chronic renal disease and chronic obstructive pulmonary disease (COPD).

Methods The study utilized anonymized patient-related information for a population of 7,342,869 WRA from the Mexican Ministry of Health data repository on COVID-19. Descriptive variables were characterized using frequencies, percentages, means, and standard deviations. Adjusted odds ratios (aORs) were used to assess the associations between risk factors and outcomes of hospitalisation and mortality. The study covered the entire COVID-19 pandemic period from January 30, 2020, to May 5, 2023.

Results The findings revealed that PW were not more likely to get COVID-19 infections than NPW. PW with COVID-19 infections were more likely to require hospital admission, intubation treatments, and ICU admission compared to NPW with COVID-19. PW with immunosuppression had an increased odds ratio (aOR) of getting COVID-19 infections compared to NPW (PW: aOR = 1.0396; NPW: aOR = 0.8373). NPW with immunosuppression had higher risk of mortality (all-cause death: aOR = 1.7084; COVID-19-associated death: aOR = 1.4079) and hospitalisation (all-cause hospitalisation: aOR = 4.1328; COVID-19-associated hospitalisation: aOR = 3.0451) than NPW without immunosuppression. Renal disease was identified as a concerning pre-existing condition that increased the risks of COVID-19 associated mortality/hospitalizations and all-cause mortality/hospitalizations for both PW and NPW. NPW with renal disease had much higher odds ratio (aOR) of either COVID-19-associated-hospitalisations (NPW: aOR = 8.639; PW: aOR = 1.7603) or all-cause hospitalisations (NPW: aOR = 8.8594; PW: aOR = 1.786) than PW with renal disease.

Conclusions This study provides valuable insights into the impact of pregnancy and pre-existing comorbidities on COVID-19 outcomes in WRA. The findings underscore the importance of considering demographic factors and pre-existing comorbidities in the management of PW with COVID-19. The study also highlights the need for further research to understand the unique impacts of different comorbidities, particularly immunosuppression and renal disease, on COVID-19 outcomes in WRA.

Keywords COVID-19, Pregnancy, Comorbidities, Hospitalisation, Mortality, Immunosuppression, Renal disease, Diabetes, Obesity, Pneumonia

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Introduction

The novel coronavirus disease COVID-19 can be fatal for susceptible populations such as the elderly, patients with comorbidities, and pregnant women (PW) [1]. This is particularly true for PW with comorbidities.

Evidence has shown that COVID-19 disease or other viral infections, are more likely to affect PW as being a high risk group [2–4]. Severe COVID-19 illness has been linked to underlying medical conditions. Although the precise mechanisms by which pre-existing conditions affect COVID-19 susceptibility and severity are unknown, strong evidence now indicates the increased risks of COVID-19 infections for individuals with medical conditions, such as diabetes, lung and liver diseases [5]. This varies across medical conditions. For example, people with psychological disorders are at the highest risk of COVID-19 infection, whereas those with CVD are at a lower risk [6]. According to a report on women of 15–44 years age (reproductive age) with COVID-19, 88.7% of women of reproductive age had symptoms related to COVID-19, of which 5.7% were pregnant [7]. However, pregnancy in women with COVID-19 can have more severe clinical consequences in increased hospitalization and maternal mortality [7]. A study in Brazil showed that the mortality rate of women with COVID-19 during pregnancy and the postpartum period reached 12.7% [8]. A UK national cohort study showed that severe perinatal outcomes were more common in women with moderate to severe COVID-19, during the delta dominant period and among unvaccinated women [9]. The INTERCOVID multinational cohort study indicated a consistent association between pregnant individuals with COVID-19 and higher rates of adverse outcomes, including maternal mortality, preeclampsia, and preterm birth compared with pregnant individuals without COVID-19 [10].

The immunosuppressed state of pregnancy may have a paradoxical protective effect against severe COVID-19 in some cases: Some studies suggest that immunosuppression during pregnancy could protect against cytokine release syndrome associated with severe COVID-19 [11]. However, immunocompromise from other causes was associated with increased mortality risk, indicating the relationship between immunosuppression and COVID-19 outcomes is complex [11].

Future health system planning requires a better understanding of the relationship between comorbidities and adverse outcomes of mortality and hospitalisation in PW. Studies showed that PW with COVID-19 who have comorbidities are at increased risk of complications [12–15], such as ICU admission, intubation. However, some common comorbidities such as immunosuppression, COPD and chronic renal disease are still missing in existing studies, in terms of their impact on hospitalisation and/or mortality in PW. On the other hand, the majority of studies on COVID-19 infections in PW to date have been constrained by associative studies with small sample numbers or have been centred on particular pregnancy outcomes, such as type of delivery, miscarriage, or neonatal health [16–19]. Little research has examined the hospitalisation, morbidity and clinical complications for PW with pre-existing comorbidities, such as immunosuppression, COPD and chronic renal disease during the entire COVID-19 pandemic.

WRA who are immunosuppressed, or who have COPD or chronic renal disease, would have a reduced ability to fight infections including COVID-19. A particular concern is the vulnerability of PW who have been pharmacologically immunosuppressed during the pandemic. Although the evidence from the SARS (severe acute respiratory syndrome) and MERS (Middle East respiratory syndrome) outbreak indicate that immunosuppression was largely safe in these pandemics [20, 21], how immunosuppression in PW has impacted on mortality and hospitalisation during the COVID-19 pandemic is unknown. Such evidence on COPD and chronic renal disease in PW is also missing.

Our aim was to conduct extensive investigation of the impact of a range of pre-existing comorbidities (particularly, immunosuppression, COPD, chronic renal disease) and lifestyle factors in PW on COVID-19 infections, COVID-19-associated and all-cause hospitalisation and mortality, and compare with NPW. Such analysis is essential for policy makers to make evidence-based recommendations for the management of PW with COVID-19, allowing consideration of a variety of social, economic, and health implications of protective interventions to fight future pandemics or other seasonal periods of infectious diseases.

Methods

Study population and data description

We extracted the anonymised patient-related information for a population of 7,342,869 WRA from the Mexican Ministry of Health (MMH) data repository on COVID-19 through the "Dirección General de Epidemiología" website [22]. This study covered the entire COVID-19 pandemic period from 30 January 2020 to 5 May 2023 as declared by the WHO [23, 24]. Figure 1 shows the process of extracting e-health data for WRA aged between 15 and 49 [25].

These WRA include people suspected of having COVID-19, those who tested negative, and those who tested positive. The MMH defines a suspected case as someone who has experienced at least two out of three symptoms (cough, fever, or headache) within the past 7 days, along with at least one of these additional symptoms: trouble breathing, joint pain, muscle aches, sore

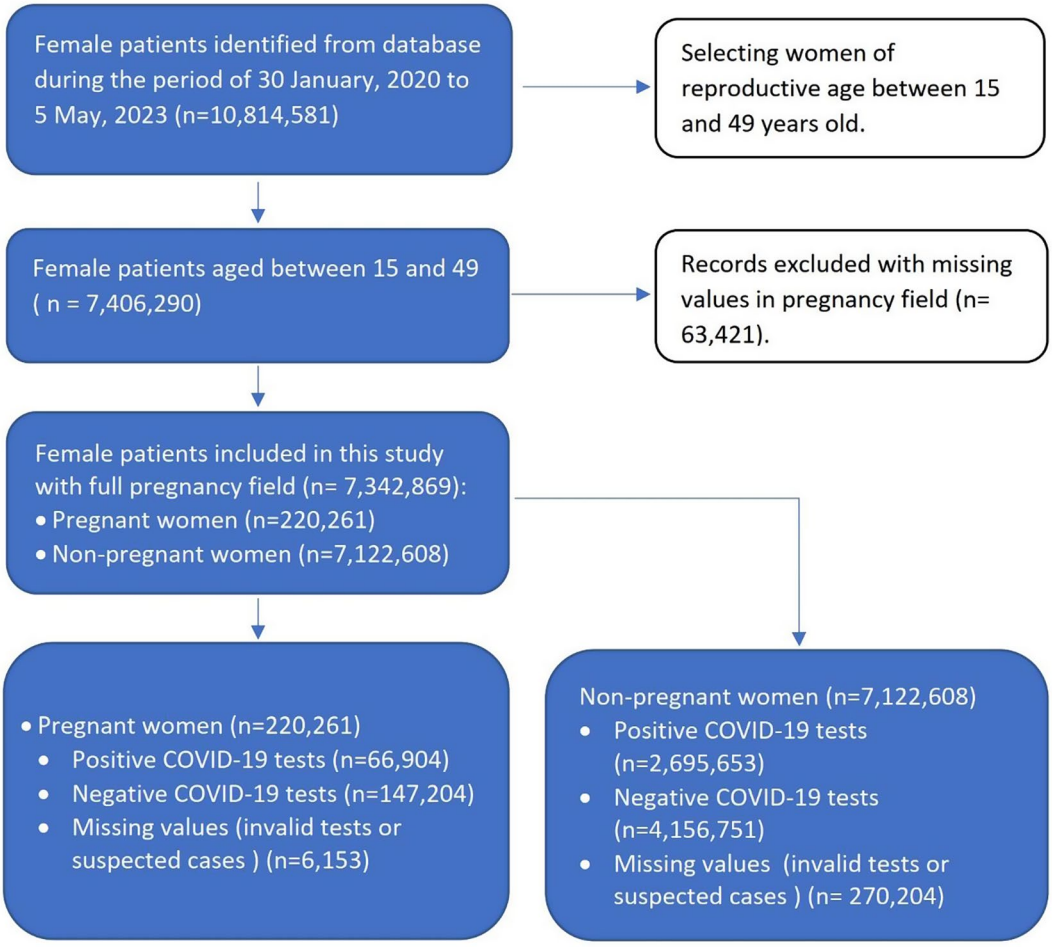

Fig. 1 Flowchart of data extraction

throat, runny nose, pink eye, or chest pain. Doctors confirmed or ruled out COVID-19 with a specific laboratory test called RT-PCR.

Before testing, patients were asked about underlying health conditions that could increase their risk of complications from COVID-19. These pre-existing conditions included diabetes, obesity, hypertension, lung diseases (COPD and asthma), smoking, immunodeficiency, cardiovascular diseases, chronic kidney problems, and pregnancy.

The presence of pneumonia was also documented, but in this study was considered as a symptom of COVID-19 rather than a separate pre-existing condition. Clinical manifestations for each patient were collected about whether the patient received outpatient care or required hospitalization, the time elapsed from symptom onset to hospitalization and presence or absence of specific signs. In this study, COVID-19 cases were defined as those with a positive test for a RT-PCR assay.

In this way, our dataset contains 4 main categories of information about patients including demographic characteristics, pre-existing medical conditions, COVID-19 testing results and presence of complications. The demographic characteristics include age, pregnancy, smoking status, symptoms and death. The complications include diagnosis of pneumonia, hospitalisation, ICU and intubation requests, and mortality.

Study outcomes included hospital admission and mortality. Data fields for mortality modelling included Age, Smoker, Pneumonia, Diabetes, COPD, Asthma, Immunosuppression, Hypertension, CVD, Obesity, Renal Disease, Other Disease, Intubation, ICU, and COVID-19. However, due to insufficient data coverage by COPD in PW, mortality analysis for PW did not involve COPD. Hospitalisation modelling used the data fields of Age, Smoker, Pneumonia, Diabetes, COPD, Asthma, Immunosuppression, Hypertension, CVD, Obesity, Renal Disease, Other Disease, and COVID19.

The women with missing data were excluded from the analysis.

Epidemiological analysis

Descriptive variables were characterized by frequencies, percentages, or means, and standard deviations,

as appropriate. Differences between the PW and NPW were tested using the χ^2 test for dichotomous variables of of health events. Adjusted odds ratios (aORs), 95% confidence intervals (CIs) and p-values were generated by multivariable logistic regression models to assess the associations between risk factors and outcomes while controlling for the effects of other predictor variables. Risk ratios (RRs) were used to compare the risk of a health event among PW with that among NPW. All p-values were generated from 2-sided tests.

All analyses were performed using R 3.6.3 and the relevant packages – *rstatix*, *jtools*.

Results

Characteristics of the studied cohorts

From the total population of 10,814,581 women during the study period, 7,342, 869 WRA between 15 and 49 years old were extracted with a single COVID-19 test for each individual, and there were 2,762,557 confirmed COVID-19 cases (37.6%) (see Fig. 1). Of the total 220,261 PW, there were 66,904 COVID-19-confirmed cases (30.4%).

Table 1 depicts the clinical characteristics of WRA during the pandemic. PW did not experience a higher rate of getting COVID-19 infections than NPW (RR=0.803), but PW were more likely to have pneumonia infection, hospital admission, intubation treatments and ICU admission than NPW. On the other hand, PW had lower rates of pre-existing immunosuppression, COPD, renal disease than NPW. The same patterns were evident in PW with diabetes, asthma, hypertension, CVD, obesity, and smoking.

The clinical characteristics of COVID-19-infected PW and NPW are shown in Table S1 (Supplementary Materials). The PW with COVID-19 infections had a higher rate of immunosuppression (RR=1.05) than NPW. Not surprisingly, hospital admission (RR=4.39), intubation treatments (RR=2.17), and ICU admission (RR=4.5) are more likely in PW with COVID-19.

Getting COVID-19 infections in PW vs. NPW

Table 2 shows the associations of COVID-19 infections in PW (left) and NPW (right) with comorbidities. Immunosuppression (PW: aOR=1.0396, 95% CI=[0.892, 1.2116]; NPW: aOR=0.8373, 95% CI=[0.8164, 0.8586]) and renal disease (PW: aOR=1.0215, 95% CI= [0.8138, 1.2823]; NPW: aOR=0.7858, 95% CI=[0.7668, 0.8052]) demonstrated an increasing risk factor for getting COVID-19 infections in PW rather than in NPW.

Both PW and NPW with diabetes (PW: aOR=1.1451, 95% CI = [1.0748, 1.22]; NPW: aOR=1.0156, 95% CI =[1.0066, 1.0247]), or obesity (PW: aOR=1.0759, 95% CI =[1.0296, 1.1242]; NPW: aOR=1.1376, 95% CI =[1.1312, 1.1441]) had an increased odds of getting COVID-19 infections. Increasing age is also a factor in PW and NPW for getting COVID-19 infected (PW: aOR=1.0337, 95% CI =[1.0322, 1.0352];; NPW: aOR=1.0099, 95% CI =[1.0097, 1.0101]).

COVID-19 associated death and all-cause death of PW vs. NPW

Our χ^2 test revealed that COVID-19 infection had a significant association with mortality amongst WRA ($p<0.001$). Specifically, the rate of death in PW with COVID-19 infection was 6.5491 times higher than those PW without COVID-19 ($p<0.001$), and the rate of death in NPW with COVID-19 infection was 4.676 times higher than those NPW without COVID-19 ($p<0.001$). When considering the whole population, the rate of death in WRA with COVID-19 infection was 4.7226 times higher than those WRA without COVID-19 ($p<0.001$).

As shown in Table 3, COVID-19-infected PW with renal disease significantly increased the risk of death (aOR=4.6677, 95% CI=[1.6414, 13.2733]). Also diabetes (aOR=2.166, 95% CI=[1.3922, 3.3698]), intubation treatment (aOR=19.4037, 95% CI=[13.6688, 27.5446]), and increasing age (aOR=1.0313, 95% CI=[1.0126, 1.0504]) emerged as risk factors for death in COVID-19-infected PW.

Among the general PW population, renal disease (aOR=2.8369, 95% CI=[1.0802, 7.4509]) and COVID-19 infections (aOR=3.1129, 95% CI=[2.442, 3.9681]) significantly increased the risk of death compared with the PW without renal disease and COVID-19 infections, respectively. Other risk factors in the general PW include diabetes (aOR=1.8446, 95% CI=[1.2551, 2.7109]), obesity (aOR=1.6837, 95% CI=[1.2284, 2.3078]), and intubation treatment (aOR=18.4491, 95% CI=[13.6295, 24.9729]) for increasing the risk of death compared with the PW without such conditions and treatment.

Comparatively, in COVID-19-infected NPW (see Table 3), age (aOR=1.0427, 95% CI=[1.0401, 1.0452]), COPD (aOR=1.2569, 95% CI=[1.0464, 1.5097]), immunosuppression (aOR=1.4079, 95% CI=[1.2665, 1.5652]), renal disease (aOR=2.499, 95% CI=[2.3164, 2.6961]), and intubation (aOR=11.41, 95% CI=[10.6558, 12.2175]) emerged as important factors for increasing the risk of death. These factors presented similar positive associations with mortality in the general NPW population.

COVID-19-Associated hospitalisations and all-cause hospitalisations of PW vs. NPW

PW had higher rates of hospitalisation than NPW (11.2% vs. 2.6%, RR=4.378) (see Table 1). COVID-19-infected PW had a higher rate of hospitalisation at 13.37% (see Table S1 in Supplementary Materials). The RR of hospital admissions in COVID-19-infected PW compared

Table 1 Clinical characteristics of women of reproductive age by pregnancy status

	Pregnant women *n* (%)	Non pregnant women *n* (%)	Risk ratio (Pregnant women vs. Nonpregnant women)	*p* value (χ^2 test)
Total	220,261 (100)	7,122,608 (100)		
Pneumonia			1.454	< 0.001
Yes	5,207(2.4)	115,815(1.6)		
No	208,378(94.6)	6,931,635(97.3)		
Missing	6,676(3)	75,158(1.1)		
Diabetes			0.649	< 0.001
Yes	4,831(2.2)	240,701(3.4)		
No	215,212(97.7)	6,868,734(96.4)		
Missing	218(0.1)	13,173(0.2)		
COPD			0.653	< 0.001
Yes	228(0.1)	11,297(0.2)		
No	219,833(0.998)	7,098,780(99.7)		
Missing	200(0.1)	12,531(0.2)		
Asthma			0.661	< 0.001
Yes	3,614(1.6)	176,859(2.5)		
No	216,461(98.3)	6,933,254(97.3)		
Missing	186(0.1)	12,495(0.2)		
Immunosuppression			0.923	0.0212
Yes	819(0.004)	28,706(0.4)		
No	219,250(99.5)	7,081,335(99.4)		
Missing	192(0.1)	12,567(0.2)		
Hypertension			0.49	< 0.001
Yes	5,011(2.3)	330,759(4.6)		
No	215,048(97.6)	6,779,275(95.2)		
Missing	202(0.1)	12,574(0.2)		
CVD			0.651	< 0.001
Yes	562(0.3)	27,934(0.4)		
No	219,514(99.7)	7082,117(99.4)		
Missing	185(0.1)	12,557(0.2)		
Obesity			0.561	< 0.001
Yes	10,319(4.7)	595,015(8.4)		
No	209,765(95.2)	6,515,544(91.5)		
Missing	177(0.1)	12,049(0.2)		
Chronic Renal Disease			0.414	< 0.001
Yes	400(0.2)	31,241(0.4)		
No	219,667(99.7)	7,078,869(99.4)		
Missing	194(0.1)	12,498(0.2)		
Smoking			0.316	< 0.001
Yes	3,200(1.5)	3,27,474(4.6)		
No	216,855(98.5)	6,782,228(95.2)		
Missing	206(0.1)	12,906(0.2)		
Other Disease			1.646	< 0.001
Yes	4,370(2)	85,875(1.2)		
No	208,658(94.7)	6,942,498(97.5)		
Missing	7,233(3.3)	94,235(1.3)		
COVID-19 Infection			0.803	< 0.001
Yes	66,904(30.4)	2,695,653(37.8)		
No	147,204(66.8)	4,156,751(58.4)		
Missing	6,153(2.8)	270,204(3.8)		
Hospital Admission			4.378	< 0.001
Yes	24,621(11.2)	181,875(2.6)		
No	195,640(88.8)	6,940,733(97.4)		

Table 1 (continued)

	Pregnant women *n* (%)	Non pregnant women *n* (%)	Risk ratio (Pregnant women vs. Nonpregnant women)	*p* value (χ^2 test)
Missing	0(0)	0(0)		
Intubation			1.807	< 0.001
Yes	552(0.3)	9,881(0.1)		
No	23,898(10.8)	168,938(2.4)		
Missing	195,811(88.9)	6,943,789(97.5)		
ICU Admission			3.695	< 0.001
Yes	1,024(0.5)	8,962(0.1)		
No	23,426(10.6)	169,851(2.4)		
Missing	195,811(88.9)	6,943,795(97.5)		
Died			0.64	< 0.001
Yes	518(0.2)	26,170(0.4)		
No	219,743(99.8)	7,096,438(99.6)		
Missing	0(0)	0(0)		

Table 2 Odds ratios for COVID-19 infections by pregnancy status

Pregnant women (size of data: 207,355)					Nonpregnant women (size of data: 6,765,099)			
aOR	**95% CI**		***p* value**	**Variable**	**aOR**	**95% CI**		***p* value**
1.0337	1.0322	1.0352	< 0.001	Age	1.0099	1.0097	1.0101	< 0.001
0.8830	0.8157	0.9558	0.0021	Smoker	0.7872	0.7813	0.7932	< 0.001
3.1632	2.9849	3.3522	< 0.001	Pneumonia	2.3839	2.3545	2.4137	< 0.001
1.1451	1.0748	1.2200	< 0.001	Diabetes	1.0156	1.0066	1.0247	< 0.001
0.9119	0.6676	1.2454	0.5618	COPD	0.9264	0.8901	0.9642	< 0.001
0.9677	0.8987	1.0419	0.3832	Asthma	0.8768	0.8680	0.8857	< 0.001
1.0396	0.8920	1.2116	0.6189	Inmsupr*	0.8373	0.8164	0.8586	< 0.001
0.8606	0.8068	0.9179	< 0.001	Hypertension	0.9941	0.9864	1.0019	0.1373
0.9681	0.7984	1.1739	0.7419	CVD	0.8744	0.8525	0.8969	< 0.001
1.0759	1.0296	1.1242	0.0011	Obesity	1.1376	1.1312	1.1441	< 0.001
1.0215	0.8138	1.2823	0.8544	Renal Disease	0.7858	0.7668	0.8052	< 0.001
1.1774	1.1042	1.2554	< 0.001	Other Disease	1.1847	1.1682	1.2014	< 0.001

* Immunosuppression

with COVID-19-infected NPW reached 4.39 (13.37% vs. 3.05%) (see Table S1 in Supplementary Materials).

Table 4 depicts the relationship between hospitalisations (COVID-19-associated and all-cause hospitalisations) and the factors of age, pre-existing medical conditions in PW and NPW. COVID-19-infected PW with pre-existing renal disease significantly increased the risk of hospitalisation (aOR = 1.7603, 95% CI=[1.0811, 2.866]). Other factors included diabetes (aOR = 2.4543, 95% CI=[2.1684, 2.7779]), hypertension (aOR = 1.6876, 95% CI=[1.4656, 1.9434]), and obesity (aOR = 1.2245, 95% CI=[1.1026, 1.3599]).

In all PW, immunosuppression (aOR = 1.4659, 95% CI=[1.1989, 1.7924]), renal disease (aOR = 1.786, 95% CI=[1.3603, 2.3449]), and COVID-19 (aOR = 1.1194, 95% CI=[1.0855, 1.1543]), diabetes (aOR = 2.1765, 95% CI=[2.0119, 2.3545]), hypertension (aOR = 1.8514, 95% CI=[1.7093, 2.0052]), CVD (aOR = 2.0348, 95% CI=[1.624, 2.5495]), obesity (aOR = 1.2508, 95% CI=[1.1751, 1.3314]), emerged as important factors of increasing the odds of hospitalisation.

In COVID-19-infected NPW, the pred-existing conditions of immunosuppression (aOR = 3.0451, 95% CI=[2.8289, 3.2778]) and renal disease (aOR = 8.639, 95% CI=[8.1493, 9.1582]), significantly increased the risk of hospitalisation. Increasing age (aOR = 1.0283, 95% CI=[1.0272, 1.0293]), diabetes (aOR = 2.8624, 95% CI=[2.7805, 2.9468]), hypertension (aOR = 1.5921, 95% CI=[1.5462, 1.6393]), CVD (aOR = 1.2632, 95% CI=[1.151, 1.3863]), obesity (aOR = 1.7052, 95% CI=[1.6657, 1.7458]) also emerged as important factors for hospitalisation.

The same factors were also found to contribute to hospitalisations in NPW.

Discussion

This study assessed the impact of pregnancy on risk of getting COVID-19 infections and its complications in WRA, with and without pre-existing comorbidities, by using the data of the entire COVID-19 pandemic period

Table 3 Odds ratios for COVID-19-associated death (right) and all-cause death (left) by pregnancy status

All pregnant women (size of data: 23,432)					**COVID-19 Infected pregnant women (size of data: 8,783)**			
aOR	**95% CI**		***p* value**	**Variable**		**95% CI**		***p* value**
1.0308	1.0147	1.0471	< 0.001	Age	1.0313	1.0126	1.0504	0.001
0.5626	0.2292	1.3811	0.2094	Smoker	0.7200	0.2646	1.9595	0.5202
4.5353	3.6012	5.7116	< 0.001	Pneumonia	4.8428	3.6984	6.3414	< 0.001
1.8446	1.2551	2.7109	0.0018	Diabetes	2.1660	1.3922	3.3698	< 0.001
0.8522	0.4305	1.6870	0.6463	Asthma	0.9858	0.4299	2.2604	0.9731
0.9429	0.3740	2.3771	0.9009	Inmsupr*	0.5802	0.1749	1.9244	0.3735
0.7304	0.4630	1.1525	0.1770	Hypertension	0.8290	0.4929	1.3944	0.4797
1.0166	0.2781	3.7164	0.9802	CVD	1.0621	0.1970	5.7270	0.9441
1.6837	1.2284	2.3078	0.0012	Obesity	1.4312	0.9854	2.0788	0.0598
2.8369	1.0802	7.4509	0.0343	Renal Disease	4.6677	1.6414	13.2733	0.0039
1.8951	1.2964	2.7701	0.001	Other Disease	1.6308	1.0268	2.5903	0.0383
18.4491	13.6295	24.9729	< 0.001	Intubation	19.4037	13.6688	27.5446	< 0.001
1.0698	0.7741	1.4784	0.6827	ICU	0.8765	0.6025	1.2750	0.4905
3.1129	2.4420	3.9681	< 0.001	COVID19				
All nonpregnant women (size of data: 167,040)					**COVID-19 Infected nonpregnant women (size of data: 79,939)**			
1.0424	1.0404	1.0445	< 0.001	Age	1.0427	1.0401	1.0452	< 0.001
0.7518	0.6906	0.8185	< 0.001	Smoker	0.7056	0.6361	0.7826	< 0.001
2.2778	2.2042	2.3538	< 0.001	Pneumonia	2.0719	1.9920	2.1549	< 0.001
1.4157	1.3609	1.4727	< 0.001	Diabetes	1.4418	1.3764	1.5102	< 0.001
1.2737	1.1015	1.4730	0.0011	COPD	1.2569	1.0464	1.5097	0.0145
0.7769	0.7099	0.8501	< 0.001	Asthma	0.8057	0.7241	0.8965	< 0.001
1.7084	1.5828	1.8439	< 0.001	Inmsupr*	1.4079	1.2665	1.5652	< 0.001
1.3251	1.2710	1.3815	< 0.001	Hypertension	1.3822	1.3165	1.4512	< 0.001
1.0712	0.9666	1.1871	0.1898	CVD	1.1335	0.9889	1.2993	0.0719
1.2020	1.1573	1.2484	< 0.001	Obesity	1.2775	1.2235	1.3340	< 0.001
2.1057	1.9859	2.2326	< 0.001	Renal Disease	2.4990	2.3164	2.6961	< 0.001
1.7685	1.6621	1.8816	< 0.001	Other Disease	1.5838	1.4623	1.7153	< 0.001
11.0197	10.4252	11.6482	< 0.001	Intubation	11.4100	10.6558	12.2175	< 0.001
0.8325	0.7796	0.8890	< 0.001	ICU	0.8073	0.7463	0.8733	< 0.001
2.8893	2.7887	2.9936	< 0.001	COVID19				

* Immunosuppression

as declared by the WHO (30 January 2020 to 5 May 2023). Special focus was put on some understudied comorbidities – immunosuppression, renal disease and COPD. The major health outcomes of COVID-19 infections, COVID-19 associated and all-cause hospital admission, and death during the pandemic were considered.

Comparison with existing evidence

Our study revealed that using data from the entire pandemic period, PW were not more likely to get COVID-19 infections than NPW (see Table S1 in Supplementary Materials), which is consistent with one existing study [26]. It is noteworthy, however, that COVID-19 infection was a threat to both PW and NPW (see Table S1 in Supplementary Materials).

Both PW and NPW with increasing age and comorbidities of diabetes and obesity were more likely to get COVID-19 infections compared with those with younger age or without these conditions. Our study supports the claim that increased maternal age is associated with COVID-19 [27]. PW with pre-existing immunosuppression and renal disease had increasing risk of getting COVID-19 infections, but these two conditions were not found to be risk factors in NPW getting COVID-19 infections.

Our study revealed a lower mortality rate in PW than in NPW. However the impact of COVID-19 on maternal mortality remains a subject of debate. Research findings have been inconsistent, with some studies suggesting a higher risk and others indicating a lower threat. For instance, one small-scale investigation reported an alarming fatality rate, with 7 out of 9 pregnant women with COVID-19 succumbing to the disease [28]. However, this stands in contrast to other research that has documented significantly lower mortality rates among expectant mothers infected with the virus [29, 30]. Such

Table 4 Odds ratios of COVID-19-associated hospitalisation (right) and all-cause hospitalisation (left) by pregnancy status

All pregnant women (size of data: 207,355)					**COVID-19 Infected pregnant women (size of data: 66,194)**			
aOR	**95% CI**		***p* value**	**Variable**	**aOR**	**95% CI**		***p* value**
0.9823	0.9800	0.9846	< 0.001	Age	0.9897	0.9856	0.9937	< 0.001
1.0677	0.9517	1.1979	0.2644	Smoker	1.0257	0.8314	1.2656	0.8127
29.7619	27.7860	31.8782	< 0.001	Pneumonia	42.1756	38.177	46.5930	< 0.001
2.1765	2.0119	2.3545	< 0.001	Diabetes	2.4543	2.1684	2.7779	< 0.001
0.6956	0.4340	1.1147	0.1314	COPD	0.1185	0.0369	0.3806	< 0.001
1.0653	0.9559	1.1873	0.2524	Asthma	1.0794	0.8923	1.3057	0.4316
1.4659	1.1989	1.7924	< 0.001	Inmsupr*	1.0782	0.7453	1.5597	0.6895
1.8514	1.7093	2.0052	< 0.001	Hypertension	1.6876	1.4656	1.9434	< 0.001
2.0348	1.6240	2.5495	< 0.001	CVD	1.4018	0.8977	2.1889	0.1375
1.2508	1.1751	1.3314	< 0.001	Obesity	1.2245	1.1026	1.3599	< 0.001
1.7860	1.3603	2.3449	< 0.001	Renal Disease	1.7603	1.0811	2.8660	0.023
1.7340	1.5932	1.8871	< 0.001	Other Disease	1.8858	1.6483	2.1575	< 0.001
1.1194	1.0855	1.1543	< 0.001	COVID19				
All nonpregnant women (size of data: 6,765,099)					**COVID-19 Infected nonpregnant women (size of data: 2,674,422)**			
1.0071	1.0064	1.0077	< 0.001	Age	1.0283	1.0272	1.0293	< 0.001
0.6777	0.6582	0.6977	< 0.001	Smoker	0.7125	0.6803	0.7463	< 0.001
72.5244	71.4969	73.5668	< 0.001	Pneumonia	94.9293	93.097	96.7976	< 0.001
2.8315	2.7765	2.8877	< 0.001	Diabetes	2.8624	2.7805	2.9468	< 0.001
0.9608	0.8772	1.0524	0.3894	COPD	0.8793	0.7664	1.0089	0.0668
0.9980	0.9661	1.0309	0.9028	Asthma	1.0200	0.9688	1.0740	0.4506
4.1328	3.9633	4.3095	< 0.001	Inmsupr*	3.0451	2.8289	3.2778	< 0.001
1.6097	1.5782	1.6419	< 0.001	Hypertension	1.5921	1.5462	1.6393	< 0.001
1.8601	1.7638	1.9617	< 0.001	CVD	1.2632	1.1510	1.3863	< 0.001
1.3701	1.3477	1.3929	< 0.001	Obesity	1.7052	1.6657	1.7458	< 0.001
8.8594	8.5650	9.1639	< 0.001	Renal Disease	8.6390	8.1493	9.1582	< 0.001
2.7710	2.6881	2.8565	< 0.001	Other Disease	2.4189	2.3056	2.5377	< 0.001
1.0073	0.9960	1.0188	0.2052	COVID19				

*Immunosuppression

inconsistent evidence highlights the need for further research to clarify the true risk to PW.

Although PW were not found to have a higher rate of mortality than NPW in this study, PW had a higher risk of developing complications if they contracted COVID-19. For example, intubation was the biggest mortality threat to both PW and NPW, but comparatively, PW were much more vulnerable when facing intubation treatments than NPW in our study. This is different from existing studies [13, 31, 32] showing no significant differences in rates of invasive ventilation or death.

COPD and hypertension were demonstrated to be important risk comorbidities in NPW for either all-cause death or COVID-19-associated death, but these comorbidities were not found to be important risk factors for mortality in PW. However, PW with these comorbidities and COVID-19 may experience more severe respiratory complications. Patients with these comorbidities are advised to seek immediate medical attention if they show symptoms of COVID-19, as early treatment can significantly improve outcomes. It is therefore essential for PW with COPD and hypertension to follow guidelines for managing COVID-19 during pregnancy [33].

Our findings showed that PW were more likely to be admitted to hospital than NPW during the whole pandemic, which is consistent with some existing studies [13, 27].

Our study revealed that renal disease turned out to be a concerning pre-existing condition for increasing the risk of either COVID-19-associated hospitalisations or all-cause hospitalisations during the pandemic for every population of WRA including PW, NPW, with or without COVID-19 infections. Studies have shown that PW with COVID-19 and renal disease are more likely to experience severe illness requiring hospitalization compared to NPW [34, 35]. In contrast, our study revealed that NPW with pre-existing renal disease had much higher risk of either COVID-19-associated hospitalisations or all-cause hospitalisations. Such great disparity of impact by renal disease merits further research. As a vulnerable population, WRA with COVID-19 and renal disease are at

high risk and require care from a multidisciplinary team, including nephrologists.

Currently, studies on outcomes of PW with immunosuppression compared to NPW are scarce. In our study, immunosuppression showed great disparity of impact on hospitalisations between PW and NPW, with or without COVID-19 infections. For example, immunosuppression significantly increased risk of either COVID-19-associated hospitalisation or all-cause hospitalisations in NPW compared to those without immunosuppression. However, immunosuppression only remained an increasing risk of all-cause hospitalisations in PW.

Highlighted conditions

Well-studied conditions

Using the data of the entire pandemic period, our study confirmed that the three conditions – pneumonia, diabetes and obesity adversely affect PW and NPW in different ways, in agreement with existing studies [5, 12–15]. Pre-existing diabetes and obesity in both PW and NPW were significantly associated with complications – COVID-19 infection, (COVID-19-associated and all-cause) hospital admissions, and (COVID-19-associated and all-cause) death. Diabetes is a more serious risk to PW than NPW in terms of COVID-19 infection and hospitalisation, however it presented a more serious threat to mortality in NPW than PW.

Immunosuppression

Our study revealed that NPW with immunosuppression may experience more adverse health outcomes of mortality and hospitalisation than PW during the pandemic, while PW with immunosuppression are more likely to get COVID-19 infections.

However, the relationship between pregnancy, immunosuppression, and COVID-19 severity presents an intriguing paradox. Some research indicates that immunosuppression during pregnancy might actually offer a degree of protection against severe COVID-19 outcomes in certain instances [11]. Specifically, studies have proposed that the pregnancy-related dampening of the immune system could potentially mitigate the risk of cytokine release syndrome, a severe complication associated with COVID-19. On the other hand, it is crucial to note that this protective effect appears to be specific to pregnancy-induced immunosuppression. In contrast, individuals who are immunocompromised due to other factors face an elevated risk of mortality from COVID-19 [11]. This disparity underscores the complex and nuanced nature of the relationship between immunosuppression and COVID-19 outcomes, suggesting that the source and nature of immune system suppression play significant roles in determining disease severity and prognosis.

Despite significant advancements in understanding immunology of pregnancy over the past decade, numerous unanswered critical questions persist, such as how immune function is modulated during gestation and what the potential consequences of these alterations for susceptibility to and severity of infectious diseases are [36]. Therefore, our study on the relationship between immunosuppression and adverse health outcomes of hospitalisation and mortality in PW vs. NPW is important to understand the impact of immunosuppression on the well-being of both mother and her fetus during the pandemic.

Renal disease

In our study, PW with renal disease were more likely to get COVID-19 infections than PW without renal disease. This could be due to the physiological changes that occur during pregnancy, which affect both the immune system and respiratory function [35].

However, our analyses highlighted that renal disease had strong associations with either COVID-19-associated death or all-cause death in every population of WRA. In particular, this study revealed great disparities of the impacts of renal disease on hospitalisation between all PW and all NPW, or between COVID-19-infected PW and COVID-19-infected NPW. The mechanism causing such a disparity merits further investigation.

COPD

Studies on PW with COPD compared to NPW during the pandemic are scarce. Our study showed that NPW had a higher rate of COPD than PW. COVID-19-infected NPW with the COPD had an increasing the risk of death than those without COPD. No further relationships between COPD and death/hospitalisation were found in all PW or COVID-19-infected PW or all NPW.

Implications for clinical guidelines

Several key disparities in risk between PW and NPW revealed by this study can inform clinical guidelines for managing COVID-19 in the population of WRA more efficiently.

Whilst PW were not more likely to get COVID-19 infections than NPW, certain pre-existing conditions increased their risk. For example, immunosuppression and renal disease increased COVID-19 infection risk in PW, but not in NPW. Both PW and NPW with diabetes, obesity, and increasing age had higher odds of COVID-19 infection. PW with COVID-19 were at higher risk for severe complications - higher rates of hospital admission, intubation treatments, and ICU admission compared to NPW. While overall mortality rates were not higher for PW, certain factors increased their risk. For example, intubation and COVID-19 infection had a greater impact

on mortality risk for PW than NPW. Renal disease significantly increased death risk in COVID-19-infected PW. Different pre-existing conditions affected PW and NPW differently. For PW, renal disease, diabetes, and obesity were significant risk factors for complications. For NPW, COPD, immunosuppression, and renal disease were important factors increasing risk of death.

These findings suggest that clinical guidelines for managing COVID-19 in PW should (1) Emphasize early and aggressive intervention for PW with COVID-19, particularly those with pre-existing conditions; (2) Implement specialized care protocols for PW with renal disease, immunosuppression, diabetes, and obesity; (3) Establish lower thresholds for hospital admission and intensive care for PW compared to NPW; (4) Develop tailored risk assessment tools that account for the unique risk profiles of PW and NPW; (5) Create condition-specific management protocols for high-risk PW to minimize complications and mortality.

By incorporating these disparities into clinical guidelines, healthcare providers can offer more targeted and effective care for PW during the COVID-19 pandemic and future similar health crises.

Strengths and limitations

Firstly, this study data covering the entire pandemic period to examine the associations of pre-existing comorbidities with risk of severe COVID-19 complications for PW. Secondly, our study addressed some unique factors that have not been well investigated, such as immunosuppression, COPD, renal disease and complications of COVID-19 in PW. In addition, this study conducted epidemiological analysis to investigate the extent to which demographic factors and pre-existing comorbidities in PW are associated with both COVID-19-associated and all-cause hospitalization and mortality outcomes of PW. This can help generate a big picture of the impact of demographic factors and pre-existing comorbidities on health outcomes and understand their unique contributions. As the understanding of COVID-19 and its impact on pregnancy continues to evolve, it is important for PW to stay informed about the latest guidance from trusted health authorities and consult with healthcare professionals for personalized advice.

However, this study has some limitations. Firstly, the quality of the data collected from real world practices was not always verifiable. For example, PW often quit smoking or report they are not smoking to health care professionals [37]. Further robust data are still needed to assess the associations between variables of demographic characteristics and comorbidities and COVID 19 related outcomes. Secondly, pregnancy status was self-reported, which could lead to underreporting cases if patients did not know they were pregnant yet. Thirdly, this study did not examine differences within the pandemic (e.g., early versus later pandemic period). The outcomes, particularly hospitalization, may have been influenced by pandemic-related policies such as lockdowns. In addition, our study was conducted using Mexican national health COVID 19 testing practices and policies, reflecting Mexican healthcare. However, the findings of this study should be generalisable to the populations with similar healthcare settings.

Conclusion and future work

PW were not found to have higher rates of COVID-19 infections or mortality than NPW. However, PW were more likely to require hospital admission, intubation treatments, and ICU admission compared to NPW during the pandemic. Intubation was the biggest mortality threat to both PW and NPW. PW with immunosuppression were more likely to get COVID-19 infections, while NPW with immunosuppression had more adverse health outcomes of mortality and hospitalisation than PW during the pandemic. Renal disease was a leading comorbidity for developing complications in both PW and NPW. Special medical care, preventive and protective measures are needed to reduce the risk of severe clinical outcomes in PW, for future pandemics or other seasonal periods for infectious diseases.

Considering significant imbalance in the cohorts of PW and NPW, future research will explore the use of propensity score matching and Synthetic Minority Oversampling Technique (SMOTE) [38] to improve the quality of generated samples.

Abbreviations

CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease
ICU	Intensive care unit
MERS	Middle East respiratory syndrome
MMH	Mexican Ministry of Health
NPW	Non-pregnant women
aOR	Adjusted odds ratio
PW	Pregnant women
RR	Risk ratio
SARS	Severe acute respiratory syndrome
WRA	Women of reproductive age

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-024-20416-w.

Supplementary Material 1

Author contributions

SMZ conceived the study and methods, conducted data analysis, wrote up and revised the paper. HA collected and extracted data. SMZ, LH, LML, KM, JL, JS interpreted the results. All authors reviewed the results and approved the final manuscript.

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Data availability
This data can be obtained from the General Directorate of Epidemiology of Mexico Government on open data [22].

Declarations

Ethical approval
This data was obtained in accordance with the Decree published in the Official Gazette of Mexico Government on Open Data, the General Directorate of Epidemiology [22]. Only anonymised patient-related information was available. No patient identifiable data were used. No ethical approval was necessary for this study because the data were publicly available.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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