Review / Derleme

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A meta-analysis for the risk and prevalence of preeclampsia among pregnant women with COVID-19

COVID-19'lu gebe kadınlarda preeklampsi riski ve prevalansı: Bir meta-analiz

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Abstract

Preeclampsia and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection are both life-threatening disorders when they occur during pregnancy. They are similarly characterized by systemic immune activation and have a deleterious effect on maternal endothelial cells. During the coronavirus disease-2019 (COVID-19) pandemic, there were reports of preeclampsia or a preeclampsia-like syndrome occurring in pregnant women with SARS-CoV-2 infection. We performed a meta-analysis to estimate the risk and prevalence of preeclampsia and SARS-CoV-2 infection in pregnant women. A comprehensive literature search was conducted in PubMed, Web of Science, Scopus, and China National Knowledge Infrastructure to identify all relevant studies published up to February 29, 2020. All studies that reported the prevalence of preeclampsia in pregnant women with SARS-CoV-2 infection were selected. A total of 10 case-control studies and 15 case series met our inclusion criteria. Pooled data revealed no significant difference between infected pregnant women and uninfected pregnant women for the risk of preeclampsia [odds ratio (OR)=1.676, 95% confidence interval (CI) 0.679-4.139, p=0.236]. The stratified analysis revealed significant risk in the infected Asian pregnant women (OR=2.637, 95% CI 1.030-6.747, p=0.043), but not Caucasian. The prevalence of preeclampsia was 8.2% (95% CI 0.057-0.117) in infected pregnant women with COVID-19 in the overall population. Its prevalence was highest in North America (10.7%), followed by Asian (7.9%), Caucasian (6.7%), European (4.9%), and West Asian (2.6%) infected pregnant women. Our pooled data showed that the prevalence of preeclampsia in pregnant women with SARS-CoV-2 infection was 8.2%. However, there was no increased risk of occurrence of preeclampsia among pregnant women with SARS-CoV-2 infection.
Keywords: SARS-CoV-2, COVID-19, preeclampsia, pregnancy, hypertensive disease of pregnancy, meta-analysis

Öz

Preeklampsi ve şiddetli akut solunum yolu sendromu koronavirüsü-2 (SARS-CoV-2) enfeksiyonu, gebelikte ortaya çıktıklarında hayatı tehdit eden bozukluklardır. İkisi de benzer şekilde sistemik immün aktivasyon ile karakterizedir ve maternal endotel hücreleri üzerinde zararlı bir etkiye sahiptir. Koronavirüs hastalığı-2019 (COVID-19) pandemisi sırasında, SARS-CoV-2 enfeksiyonu olan hamile kadınlarda preeklampsi veya preeklampsi benzeri bir sendrom oluştuğuna dair raporlar mevcuttur. Burada, hamile kadınlarda preeklampsi ve SARS-CoV-2 enfeksiyonu riskini ve prevalansını tahmin etmek için bir meta-analiz gerçekleştirdik. 30 Şubat 2020'ye kadar yayınlanan tüm ilgili çalışmaları belirlemek için PubMed, Web of Sciences, Scopus ve Çin Ulusal Bilgi Altyapısı'nda kapsamlı bir literatür taraması yapıldı. SARS-CoV-2 enfeksiyonlu hamile kadınlarda preeklampsi prevalansıyla ilgili tüm çalışmalar seçildi. Toplam 10 olgu kontrol çalışması ve 15 olgu serisi dahil etme kriterlerimizi karşıladı. Toplanan veriler, enfekte hamile kadınlar ile enfekte olmayan hamile kadınlar arasında preeklampsi riski açısından anlamlı bir fark olmadığını ortaya koydu [risk oranı (RO=1,676, %95 güven aralığı (GA) 0,679-4,139, p=0,236]. Tabakalı analiz, enfekte Asyalı hamile kadınlarda (RO=2,637, %95 GA 1,030-6,747, p=0,043) anlamlı risk ortaya çıkardı, ancak Kafkasyalılarda

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bulunmadı. Genel popülasyonda COVID-19 ile enfekte hamile kadınlarda preeklampsi prevalansı %8,2 (%95 GA 0,057-0,117) idi. Prevalans en yüksek Kuzey Amerika'da (%10,7) olup, bunu Asya (%7,9), Kafkasya (%6,7), Avrupa (%4,9) ve Batı Asya (%2,6) izlemekteydi. Birleştirilmiş verilerimiz, SARS-CoV-2 enfeksiyonlu gebe kadınlarda preeklampsi prevalansının %8,2 olduğunu gösterdi. Bununla birlikte, SARS-CoV-2 enfeksiyonu olan hamile kadınlar arasında preeklampsi oluşma riskinde artış görülmemiştir.
Anahtar Kelimeler: SARS-CoV-2, COVID-19, preeklampsi, gebelik, gebeliğin hipertansif hastalığı, meta-analiz

Introduction

Hypertensive disorders of pregnancy are common complications that put mothers and their fetuses at heightened risk for perinatal morbidity and mortality in addition to life-long sequelae and long-term risk of cardiovascular disease[1]. Preeclampsia is the most frequent hypertensive complication of pregnancy, occurring in approximately five to seven percent of pregnancies globally, with a higher incidence in some indigenous women and those from low- and middle-income countries, such as those in sub-Saharan Africa[2,3]. In addition to its being an obstetrical management challenge, preeclampsia is also a major global maternal health and public health problem as it is responsible every year for over 70,000 maternal deaths and 500,000 fetal deaths worldwide. In the United States, preeclampsia is a leading cause of maternal death, severe maternal morbidity, maternal intensive care admissions, cesarean sections, low birth weight and fetal growth restriction, preterm rupture of membranes, and prematurity[2,4]. It also accounts for up to 18% of maternal deaths in the United States annually[5]. As a multisystem disease, preeclampsia has many known risk factors, including obesity, primiparity, renal disease, chronic hypertension, advanced maternal age, multiple- or molar pregnancy, and pre-gestational- or gestational diabetes mellitus. However, these factors alone do not account for the disease onset. Preeclampsia is considered to have its origin in pathological factors related to placental development, implantation, and defective remodeling of the spiral arteries. These result in uteroplacental and maternal vascular malperfusion accompanied by altered immunoregulation and inflammatory response[6-8].

Coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has been the most critical public health crisis to occur in this century. The effects of this global pandemic will persist for many years[9-11]. As is often the case with an emerging viral disease, pregnant women and their infants have been of great concern, especially since pregnant women with SARS-CoV-2 infection and their infants are at higher risk for poor outcomes than are those who are not pregnant[12].

Several clinical studies reported that COVID-19 is associated with an increased risk of preeclampsia and a preeclampsia-like syndrome in infected pregnant women[13-15], but their results remain controversial[16,17]. COVID-19 is also associated with immune activation that results in elevated levels of pro-inflammatory cytokines, including interleukin (IL)-2, IL-6, IL-7, and tumor necrosis factor-α[18]. Although it is considered a respiratory disease primarily, SARS-CoV-2 infection also affects endothelial cells, and during pregnancy, it can lead to endotheliitis, microthrombi deposition, and microvascular dysfunction[19]. As of January 22, 2020, there were over 47,096 confirmed COVID-19 cases during pregnancy, with 58 related deaths in the United States[20]. Some studies have suggested that preeclampsia may be more common in pregnant women with COVID-19 than other adverse outcomes[19]. Thus, we performed a meta-analysis to estimate the risk and prevalence of preeclampsia and SARS-COV-2 infection in pregnant women.

Materials and Methods

Publication Search

Ethical approval or patient consent was not needed because this is a meta-analysis, and all data were extracted from published literature. We performed a comprehensive literature search in PubMed, Web of Knowledge, Web of Science, Embase, Scientific Information Database, WanFang, VIP, Chinese Biomedical Database, Scientific Electronic Library Online, and the China National Knowledge Infrastructure database to collect all relevant studies published up to February 29, 2020. Combinations of the following keywords were used in the search: ("COVID-19 virus disease" OR "severe acute respiratory syndrome coronavirus 2" OR "SARS-CoV-2" OR "2019 novel coronavirus infection" OR "2019-nCoV infection" OR "coronavirus disease" OR "coronavirus disease-19" OR "2019-nCoV disease" OR "COVID-19 virus infection") AND ("preeclampsia" OR "Preeclampsia toxemia" OR "toxemia" OR "hypertrophic decidual vasculopathy" OR "gestational hypertension" OR "pregnancy-associated hypertension") AND ("Risk" OR "Prevalence" OR "Incidence" OR "Frequency" OR "Prevalence"). Moreover, the reference list of the retrieved studies and reviews were manually checked to identify more potentially eligible studies. The search was conducted in English, Chinese, and Persian. When overlapping data on the same cases were included in more than one publication, only the one with the larger sample size was selected.

Selection Criteria

The inclusion criteria for these studies included: 1) case-control and case series studies; 2) studies reporting the prevalence of preeclampsia in pregnant women with SARS-CoV-2 infection; 3) studies published in English and Chinese; 4) detailed data for estimating the odds ratio (OR) and 95% confidence interval (CI), and available allele genotype frequencies for cases and controls. The exclusion criteria were as follows: 1) studies not describing the incidence of preeclampsia in pregnant women with SARS-CoV-2 infection; 2) Studies not providing usable or sufficient data for pooling; 3) studies focusing on animals or ***in***

vitro; 4) abstracts, comments, conference abstracts, editorials, reviews, meta-analysis; and 7) duplicated studies or data.

Data Extraction

Two authors extracted the data from included studies and verified the accuracy of the data, and a third author resolved discrepancies. The following data were extracted from each article: first author name, year of publication, ethnicity (Asian, Caucasian, African, and mixed populations), country of origin, diagnostic methods, number of pregnant women with SARS-CoV-2 infection and healthy women, and number of preeclampsia in infected women. If selected articles did not report the necessary data, the corresponding authors were contacted by email to request the missing data.

Statistical Analysis

All statistical calculations were performed using Comprehensive Meta-Analysis software version 2.0 (Biostat, USA). Two-sided p-values <0.05 were considered statistically significant. The ORs and 95% CIs were used to assess the risk and prevalence of preeclampsia in pregnant women with COVID-19. The significance of the pooled OR was determined by the Z-test, and a value of $p<0.05$ was regarded as statistically significant. The between-study heterogeneity was identified with the Q-test and I^2 index (range, 0% to 100%), where $p\leq0.10$ indicated significant heterogeneity. I^2 values of >50% indicated heterogeneity among studies. The random-effects model (DerSimonian-Laird method) was applied to calculate the pooled OR and 95% CI if there was obvious heterogeneity among the studies. Otherwise, we used a fixed-effect model (Mantel-Haenszel method) for the meta-analysis. Stratified analyses were performed according to ethnicity, genotyping methods, and sources of controls. A sensitivity analysis was performed to assess the effects of individual studies on pooled results and the stability of the results. We used Egger's and Begg's tests to evaluate publication bias, with $p>0.05$ as evidence for no potential publication bias. The trim and fill method was also applied to detect publication bias. All tests were two-sided, and $p<0.05$ was considered statistically significant.

Results

Characteristics of Selected Studies

As shown in Figure 1, our initial search yielded 620 studies, with duplicate studies removed, resulting in 252 studies remaining. Among them, 121 studies were excluded based on titles and abstracts. The selection criteria excluded 106 studies. Finally, 25 publications, including 10 case-control studies[21-30] and 15 case series[31-45], were selected. Their basic information and preeclampsia distributions for case-control studies and case series are presents in Tables 1 and 2. These studies included 2039 pregnant women with SARS-CoV-2 infection (with 121 preeclampsia) and 15,834 healthy women (with 1126 preeclampsia) in case-control studies, and 2021 pregnant women with SARS-CoV-2 infection with 98 preeclampsia) in the case series. The publication year of all selected studies was 2020. The majority of study patients came from the Mainland China (n=10), followed by United States (n=4), Spain (n=2), Sweden (n=1), France (n=1), Canada (n=1), Turkey (n=1), Iran (n=1), Peru (n=1), Kuwait (n=1), and India (n=1). The individual study sample sizes ranged from 5 to 1285 (Table 1). Of the 23 studies, 21 studies used real-time polymerase chain reaction (qRT-PCR) to diagnose SARS-CoV-2 infection, one study used a combination of PCR and chest CT. One study used only a serum antibody test.

Quantitative Data Synthesis

Risk

The summaries of risk for preeclampsia in pregnant women with SARS-CoV-2 infection are shown in Table 3. The pooled data revealed that SARS-CoV-2-infected pregnant women had no significant risk in the occurrence of preeclampsia (OR=1.676, 95% CI 0.679-4.139, p=0.236, Figure 2A) compared with non-infected pregnant women. However, the stratified analysis showed a significant risk among infected Asian pregnant women (OR=2.637, 95% CI 1.030-6.747, p=0.043, Figure 2B), but not among Caucasian (OR=1.335, 95% CI 0.436-4.089, p=0.613, Figure 2B), Chinese (OR=2.437, 95% CI 0.628-9.459, p=0.198), North America (OR=1.296, 95% CI 0.279-6.030, p=0.741), and European (OR=1.771, 95% CI 0.908-3.454, p=0.094) pregnant women with SARS-CoV-2 infection.

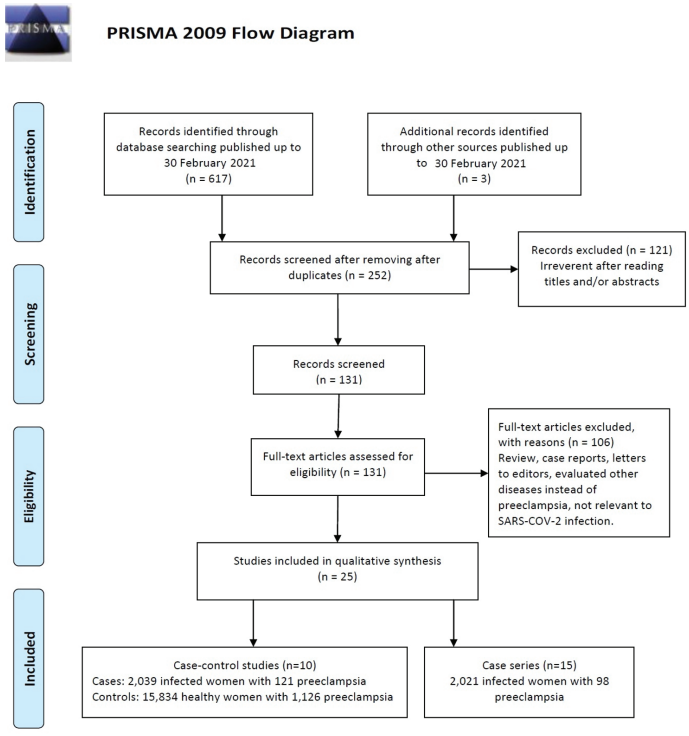

Figure 1. The study selection and inclusion process

Table 1. Details of included studies in the current meta-analysis

First author	City (country)	Ethnicity	Study design	Diagnostic method	Clinical presentation at admission	Confirmed cases	Sever or critical	Preeclampsia	Age group or mean
Adhikari	Texas (US)	Caucasian	Case/ Control	qRT-PCR	Symptomatic and asymptotic	245	13	26	27.0±6.6
Wang	Boston (US)	Caucasian	Case/ Control	PCR	Symptomatic and asymptotic	53	8	10	29.8±5.9
Patberg	New York (US)	Caucasian	Case/ Control	PCR	Symptomatic and asymptotic	77	NA	5	29.9±6.2
Brandt	New Brunswick (Canada)	Caucasian	Case/ Control	qRT-PCR	Symptomatic and asymptotic	61	7	6	30.3±6.4
Ahlberg	Karolinska (Sweden)	Caucasian	Case/ Control	qRT-PCR	Symptomatic and asymptotic	155	NA	12	32.1±4.9
Egerup	Copenhagen (Denmark)	Caucasian	Case/ Control	qRT-PCR	Symptomatic and asymptotic	1285	NA	53	28.6-34.7
Pirjani	Babol (Iran)	West Asian	Case/ Control	qRT-PCR	Symptomatic and asymptotic	66	NA	6	30.97±6.38
Yang	Hubei (China)	East Asian	Case/ Control	qRT-PCR and CT	Symptomatic and asymptotic	65	NA	1	NA
Li	Hubei (China)	East Asian	Case/ Control	qRT-PCR	Symptomatic and asymptotic	16	0	1	26-37
Zhang	Hubei (China)	East Asian	Case/ Control	qRT-PCR	Symptomatic and asymptotic	16	1	1	NA
London	New York (US)	Caucasian	Case Series	qRT-PCR	Symptomatic and asymptotic	55	0	3	24-38
Sahin	Ankara (Turkey)	Caucasian	Case Series	qRT-PCR	Symptomatic and asymptotic	533	7	5	28.04±5.84
Sentilhes	Strasbourg (France)	Caucasian	Case Series	qRT-PCR	Symptomatic and asymptotic	54	17	3	30.6±6.2
Mendoza	Barcelona (Spain)	Caucasian	Case Series	qRT-PCR	Symptomatic	42	6	6	26-37
Perez	Spain	Caucasian	Case Series	qRT-PCR	Symptomatic and asymptotic	82	4	4	19-48
Arroyo	Trujillo (Peru)	Mixed	Case Series	Serologically	Symptomatic and asymptotic	20	4	12	21-45
Chen	Wuhan (China)	East Asian	Case Series	qRT-PCR	Symptomatic	9	0	2	26-40
Chen	Hubei (China)	East Asian	Case Series	qRT-PCR	Symptomatic	5	0	1	25-31
Hu	Wuhan (China)	East Asian	Case Series	qRT-PCR	Symptomatic	6	0	2	26-36
Yang	Wuhan (China)	East Asian	Case Series	qRT-PCR	Symptomatic	7	0	1	NA
Yan	Wuhan (China)	East Asian	Case Series	qRT-PCR	Symptomatic	116	NA	4	24-41
Zhang	Wuhan (China)	East Asian	Case Series	qRT-PCR	Symptomatic	18	1	1	24-34
Cao	Hube i(China)	East Asian	Case Series	qRT-PCR	Symptomatic and asymptotic	10	0	3	30-31
Ayed	Al-Jahra (Kuwait)	West Asian	Case Series	qRT-PCR	Symptomatic	185	22	1	27-34
Mahajan	Mumbai (India)	South Asia	Case Series	qRT-PCR	Symptomatic	879	2	50	24-36

RT-PCR: Real-time polymerase chain reaction, NA: Not available

Prevalence

The summaries of the prevalence of preeclampsia in pregnant women with SARS-CoV-2 infection are shown in Table 3. The prevalence of preeclampsia was 8.2% (95% CI 0.057–0.117, Figure 3A) in infected pregnant women overall. The stratified analysis by ethnicity and region showed that the prevalence of preeclampsia infected pregnant women was the highest in North America (10.7%; 95% CI 0.082-0.139), followed by Asian (7.9%; 95% CI 0.046-0.132, Figure 3B), Caucasian (6.7%; 95% CI 0.043-0.104, Figure 3C), European (4.9%; CI 0.026-0.088), and West Asian (2.6%; CI 0.002-0.315) women. Moreover, the stratified analysis by country of origin revealed that the prevalence of preeclampsia among US-American- and Chinese-infected women were 10.8% (CI 0.081-0.143) and 10.4% (CI 0.050-0.201), respectively.

Table 2. Details of selected case-control studies

First Author	Pregnant women with COVID-19		Uninfected pregnant women	
	Total	Preeclampsia	Total	Preeclampsia
Adhikari	245	26	3035	939
Wang	53	10	760	59
Patberg	77	5	56	0
Brandt	61	6	122	10
Ahlberg	155	12	604	26
Egerup	1285	53	28	1
Pirjani	66	6	133	4
Yang	65	1	10930	83
Li	16	1	121	0
Zhang	16	1	45	4

COVID-19: Coronavirus disease-2019

Heterogeneity Test

In this meta-analysis, there was a significant difference between-study heterogeneity for risk (I^2=84.05; P_H≤0.001) and prevalence (I^2=81.54; P_H≤0.001) in the overall population. Therefore, we performed stratified analyses by ethnicity to explain the potential source of heterogeneity. Results showed that the heterogeneity disappeared in the subgroup analysis among Asian, Chinese, and European women for preeclampsia risk and among North American women for prevalence, indicating that ethnicity might be the major source of heterogeneity in this study (Table 3).

Table 3. Summary for the risk and prevalence of preeclampsia in pregnant women with COVID-19

Subgroup	Type of model	Heterogeneity		Odds Ratio				Publication bias	
		I^2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
Risk									
Overall	Random	84.04	≤0.001	1.676	0.679-4.139	1.120	0.236	0.858	0.049
Caucasian	Random	89.11	≤0.001	1.335	0.436-4.089	0.506	0.613	1.000	0.181
Asian	Fixed	8.059	0.353	2.637	1.030-6.747	2.022	0.043	1.000	0.719
North American	Random	91.64	≤0.001	1.296	0.279-6.030	0.331	0.741	0.734	0.276
European	Fixed	0.00	0.664	1.771	0.908-3.454	1.677	0.094	NA	NA
Chinese	Fixed	19.34	0.289	2.437	0.628-9.459	1.287	0.198	1.000	0.364
US	Random	93.99	≤0.001	1.405	0.180-10.950	0.325	0.745	1.000	0.504
Prevalence									
Overall	Random	81.54	≤0.001	0.082	0.057-0.117	-12.101	≤0.001	0.779	0.263
Caucasian	Random	82.01	≤0.001	0.067	0.043-0.104	-10.828	≤0.001	0.350	0.615
Asian	Random	58.99	0.004	0.079	0.046-0.132	-8.427	≤0.001	0.541	0.416
North American	Fixed	38.68	0.163	0.107	0.082-0.139	-14.113	≤0.001	0.089	0.122
European	Random	80.17	0.010	0.049	0.026-0.088	-9.146	≤0.001	0.734	0.234
West Asian	Random	85.98	0.008	0.026	0.002-0.315	-2.496	0.013	NA	NA
Chinese	Random	51.37	0.030	0.104	0.050-0.201	-5.434	≤0.001	0.788	0.630
US	Fixed	53.62	0.091	0.108	0.081-0.143	-13.140	≤0.001	0.308	0.627

NA: Not applicable, OR: Odds ratio, CI: Confidence interval

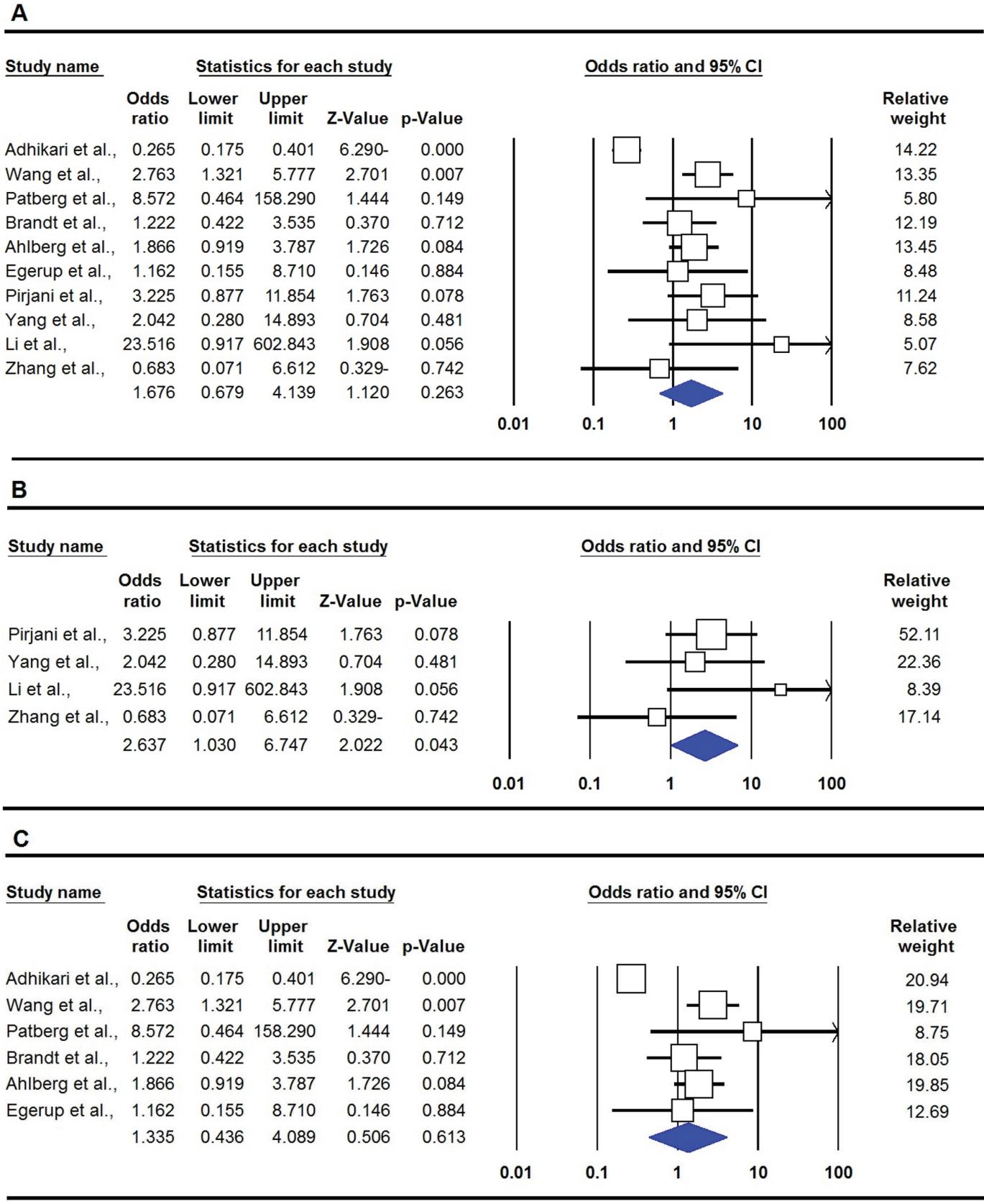

Figure 2. Forest plots for the risk of preeclampsia in pregnant women with SARS-CoV-2 infection. A: overall population; B: Caucasians; and C: Asians

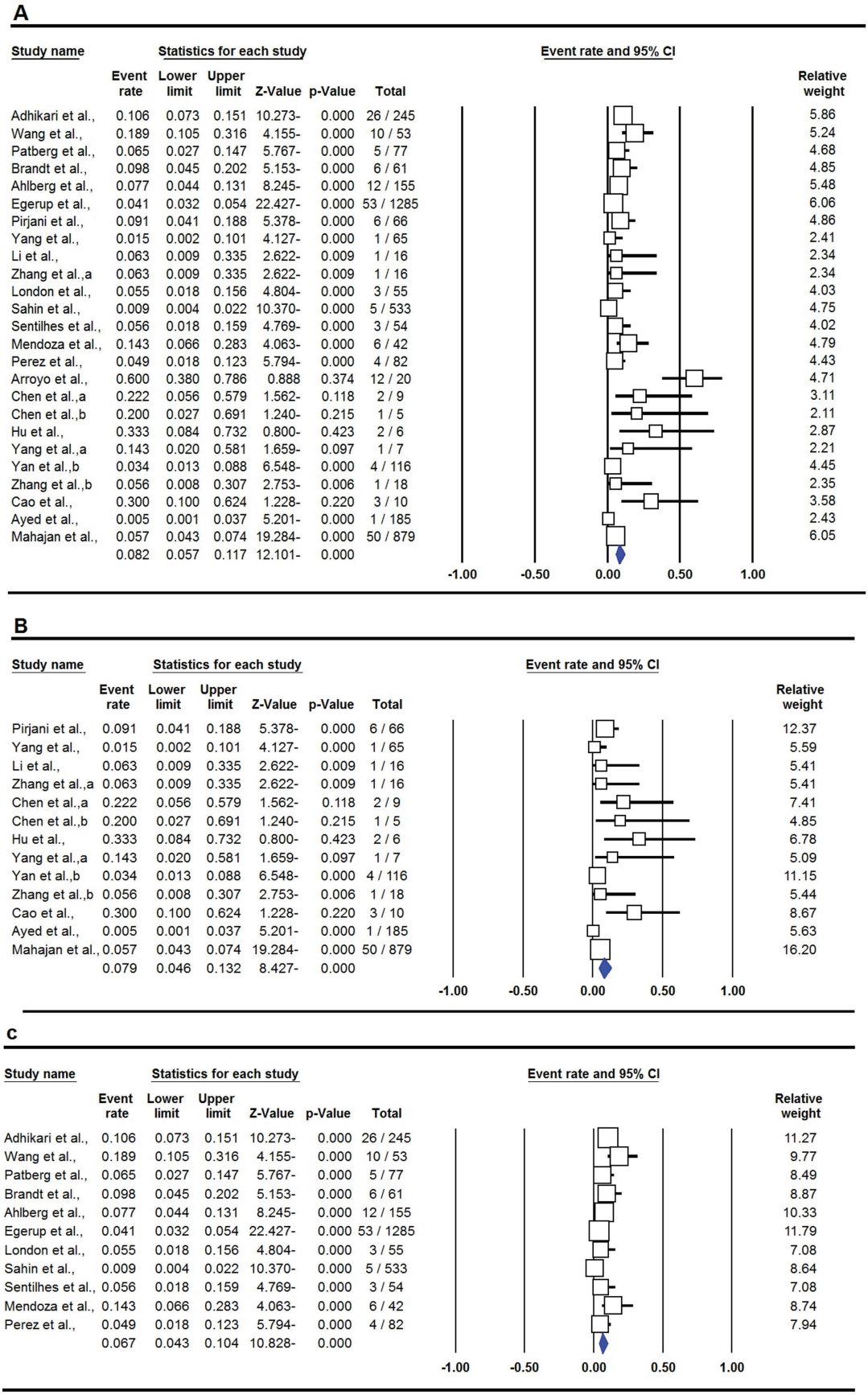

Figure 3. Forest plots for the prevalence of preeclampsia in pregnant women with SARS-CoV-2 infection. A: overall population; B: Caucasians; and C: Asians

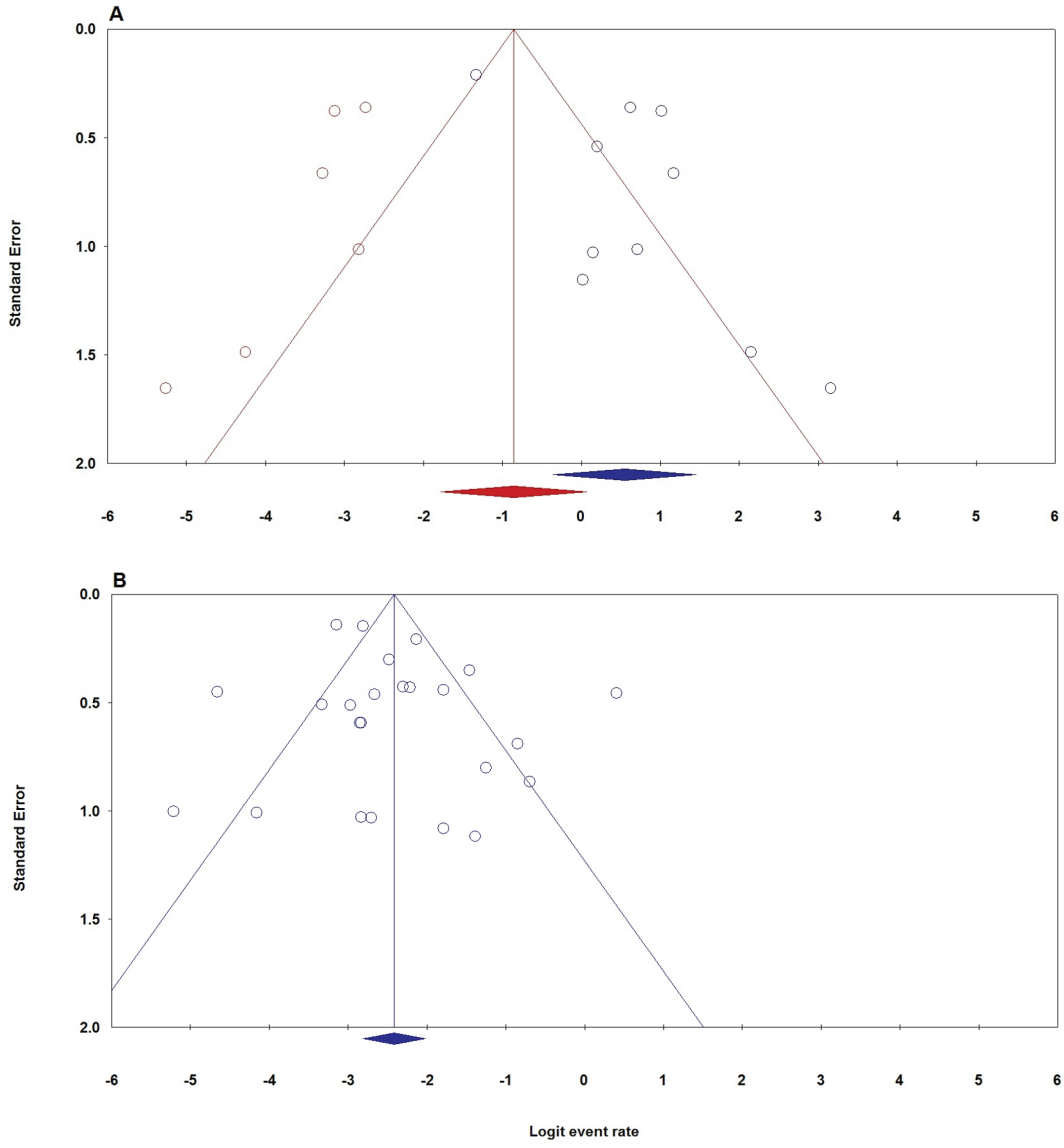

Figure 4. Begg's funnel plot for publication bias test for the risk and prevalence of preeclampsia in pregnant women with SARS-CoV-2. A: Risk; B: Prevalence

Sensitivity Analysis and Publication Bias

We conducted a leave-one-out sensitivity analysis to identify the impact of individual research on the pooled data. The significance of the pooled ORs was not influenced by excluding those studies, indicating that our pooled data were statistically robust. This sensitivity analysis showed that our findings were not dependent on a single study. We also checked for publication bias, and a funnel plot showed symmetrical distribution. Egger's regression test p-value for risk was (P_{Beggs}=0.858; P_{Eggers}=0.049, Figure 4A) and the prevalence (P_{Beggs}=0.779; P_{Eggers}=0.263, Figure 4B) of preeclampsia in pregnant women with COVID-19 (Table 3). Moreover, Begg's funnel plot showed evidence of publication bias for risk of preeclampsia in pregnant women with SARS-CoV-2 infection. Thus, we used the Duval and Tweedie "trim and fill" method to adjust for possible publication bias in the literature for preeclampsia risk. Figure 3 shows the Duval and Tweedie non-parametric "trim and fill" method funnel plot. The results did not change for preeclampsia risk in women with SARS-CoV-2 infection, indicating that our pooled ORs are reliable.

Discussion

The pathogenesis of SARS-CoV-2 infection occurring during pregnancy and its relationship to co-morbid conditions is not well understood[46]. Recently, some studies reported SARS-CoV-2 infection was not associated with a heightened risk of preeclampsia in infected pregnant women[13,31]. Moreover, some of them explained that preeclampsia-like features could be present in some pregnancies with a severe course of COVID-19[13]. Joudi et al.[47] provided the first description of treatment for preeclampsia in a woman with severe manifestations and concurrent COVID-19 disease.

To the best of our knowledge, this is the first meta-analysis examining the risk of preeclampsia in pregnant women with SARS-CoV-2 infection. Our pooled data showed no significant difference in the occurrence of preeclampsia between SARS-CoV-2-infected and uninfected pregnant women. Angiotensin-converting enzyme 2 (ACE2) is implicated in pregnancy complications, such as miscarriage, ectopic pregnancy, and preeclampsia[48]. Bloise et al.[49] reported that the expression of ACE2 or transmembrane protease serine 2 (TMPRSS2) at the decidual interface (placenta and decidua) did not change in pregnancies complicated by preeclampsia. Thus, their results did not show that pregnancies complicated by preeclampsia are at increased risk of placental SARS-CoV-2 infection and vertical transmission. Based on the consecutive case series, the rates of gestational diabetes, hypertensive disorders of pregnancy, and preeclampsia were not higher in pregnant women with COVID-19 than in non-infected pregnant women[50]. In a retrospective analysis of 2682 pregnant women who delivered at a single hospital in Sweden between March 25 and July 24, 2020, Ahlberg et al.[25] reported that 156 women (5.8%) were positive for SARS-CoV-2. They found that pregnant women with SARS-CoV-2 infection had a higher prevalence of preeclampsia than uninfected pregnant women (7.7% vs 4.3%; OR=1.84; 95% CI 1.004-3.36). Moreover, their data demonstrated that SARS-CoV-2 test positivity in women in active labor was associated with a higher prevalence of preeclampsia and a lower prevalence of labor induction. They suggested that COVID-19 is a complex respiratory infection with systemic effects that may resemble preeclampsia.

Our study revealed that the pooled prevalence of preeclampsia was 8.2% (95% CI 0.057-0.117) among pregnant women with SARS-CoV-2 infection. Its prevalence based on ethnicity and region was highest in North American (10.7%), followed by Asian (7.9%), Caucasian (6.7%), European (4.9%), and West Asian (2.6%) infected pregnant women. Moreover, stratified analysis by country of origin revealed that the prevalence of preeclampsia among US-American and infected Chinese women was 10.8% and 10.4%, respectively. The two other medically significant coronavirus pathogens are severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV)[51,52]. Both SARS-CoV and MERS-CoV are associated with increased complications, such as preeclampsia[15,53]. Di Mascio et al.[14], in a meta-analysis based on 19 studies, including 79 hospitalized women (41 pregnancies affected by COVID-19, 12 by MERS, and 26 by SARS), described the outcomes of the combined coronavirus spectrum (SARS, MERS, and SARS-CoV-2) in pregnant women. Their results showed that the prevalence of preeclampsia in pregnant women was 16.2% (2/19; 95% CI 4.2-34.1). However, the prevalence could not be reliably attributed to the virus infections alone. It is plausible that such manifestations result from widespread inflammation and endothelial damage, in a process called the "cytokine storm," responsible for many symptoms of coronavirus-related organ injury. Chi et al.[54] performed a meta-analysis on outcomes of pregnant women with COVID-19 showing that four (12.90%) of confirmed COVID-19 patients had preeclampsia. Diriba et al.[55] revealed that preeclampsia was observed among 5.7% of pregnant women infected with COVID-19 and MERS-CoV. Bellos et al.[56] performed a meta-analysis examining maternal and perinatal outcomes in pregnant women with COVID-19, finding that 5.4% (8/148) of infected women had preeclampsia. Mahajan et al.[45], in a study of 879 infected pregnant women with COVID-19 (859 singleton pregnancies and 20 multiple gestation pregnancies), described a higher risk of preeclampsia among women with multiple gestation pregnancies and COVID-19[43].

Mendoza et al.[34] conducted an observational study describing a preeclampsia-like syndrome in 14.3% (6/42) or 6 of 8 (62.5%) pregnant women with severe COVID-19 (at >20 weeks of gestation) who were admitted to the intensive care unit. However, there were no symptoms of preeclampsia among the 34 pregnant women with non-severe forms of COVID-19. Five of these subjects did not have evidence of pre-eclampsia before the diagnosis of severe COVID-19 pneumonia. They explained that pregnant women with severe COVID-19 could develop a preeclampsia-like syndrome, which might be distinguished from actual preeclampsia by sFlt-1/PlGF, LDH, and UtAPI assessment[31]. However, their report should be interpreted with caution because of the observational nature of the study, the small number of pregnant women with severe infection, and the possible role of confounding factors[16]. ACE2 receptors in the placenta might be associated with an increased risk of mother to neonate transmission of the virus[57-59]. It is speculated that the placenta possesses ACE2 receptors on villous cytotrophoblasts and syncytiotrophoblasts. Their high expression at the maternal-fetal interface is dysregulated by SARS-CoV-2 and Poly (U) Specific (ENDOU, placental protein 11 or PP11) might be involved in the high rates of preeclampsia associated with severe COVID-19[60,61]. Bloise et al.[49] reported that pregnancies complicated by preeclampsia are not associated with changes in the expression of ACE2 and TMPRSS2.

Although the current meta-analysis was designed systematically to include all the eligible studies, some limitations need to be mentioned. Most of the included studies were conducted in Caucasian and East Asian pregnant women with SARS-CoV-2 infection, and so the findings may not apply to other racial/ethnic groups. Further studies with larger sample sizes across different racial/ethnic groups are necessary. Second, since our meta-analysis was confined to certain variables, we could not perform any sub-analyses by age, the severity of COVID-19 and preeclampsia, and history of preeclampsia because of the lack of data in primary studies. In addition, due to the small numbers of cases and reporting, we could not specifically address the relationship between SARS-CoV-2 infection and

other hypertensive complications of pregnancy, including eclampsia and HELLP syndrome.

Conclusion

In summary, this study revealed that the prevalence of preeclampsia in pregnant women with SARS-CoV-2 infection was 8.2%. Its occurrence among SARS-CoV-2-infected pregnant Asian women was higher than among women of other ethnicities. However, infected pregnant European women had a lower prevalence than seen in other ethnic groups. In contrast, SARS-CoV-2 infection was not significantly associated with an increased risk of preeclampsia in infected pregnant women compared with non-infected pregnant women. Identifying the prevalence of preeclampsia in pregnant women with SARS-CoV-2 infection is essential to provide proper obstetrical management and deliver the necessary critical interventions for pregnant women during the COVID-19 pandemic.

Ethics

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.K.Z., S.A.D., A.J., R.S.T., F.F., F.A., Concept: M.K.Z., S.A.D., D.A.S., R.B., Design: D.A.S., R.B., Data Collection or Processing: M.K.Z., D.A.S., R.B., S.A.D., A.J., R.S.T., F.F., F.A., H.N., Analysis or Interpretation: M.K.Z., D.A.S., R.B., S.A.D., A.J., R.S.T., F.F., F.A., H.N., Literature Search: M.K.Z., D.A.S., R.B., S.A.D., A.J., R.S.T., F.F., F.A., H.N., Writing: M.K.Z., S.A.D., R.S.T., H.N.

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