Clinical Infectious Diseases

REVIEW ARTICLE

Clinical Presentation and Outcomes of Pregnant Women With Coronavirus Disease 2019: A Systematic Review and Meta-analysis

Reem Matar,[1] Layan Alrahmani,[2,3] Nasser Monzer,[4] Labib G. Debiane,[5] Elie Berbari,[6] Jawad Fares,[7] Fidelma Fitzpatrick,[8,9] and Mohammad H. Murad[10]

[1]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota, USA, [2]Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Mayo Clinic, Rochester, Minnesota, USA, [3]Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Loyola University Medical Center, Chicago, Illinois, USA, [4]Department of Medicine, Royal College of Surgeons in Ireland, Dublin, Ireland, [5]Division of Pulmonary and Critical Care, Department of Internal Medicine, Henry Ford, Detroit, Michigan, USA, [6]Division of Infectious Diseases, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota, USA, [7]Department of Neurological Surgery, Northwestern University, Chicago, Illinois, USA, [8]Department of Microbiology, Beaumont Hospital, Dublin, Ireland, [9]Department of Clinical Microbiology, Royal College of Surgeons in Ireland, Dublin, Ireland, and [10]Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic, Rochester, Minnesota, USA

Background. Descriptions of coronavirus disease 2019 (COVID-19) have focused on the nonpregnant adult population. This study aims to describe the clinical characteristics and perinatal outcomes of COVID-19 in pregnancy.

Methods. We searched databases from December 2019 to 30 April 2020. Eligible studies reported clinical characteristics, radiological findings, and/or laboratory testing of pregnant women during infection. Data were pooled across studies using a random-effects model.

Results. Twenty-four studies (136 women) were included. The most common symptoms were fever (62.9%) and cough (36.8%). Laboratory findings included elevated C-reactive protein (57%) and lymphocytopenia (50%). Ground-glass opacity was the most common radiological finding (81.7%). Preterm birth rate was 37.7% and cesarean delivery rate was 76%. There was 1 maternal death. There were 2 fetal COVID-19 cases.

Conclusions. The clinical picture in pregnant women with COVID-19 did not differ from the nonpregnant population; however, the rate of preterm birth and cesarean delivery are considerably higher than international averages.

Keywords. coronavirus; pregnant; neonates; transmission.

In December 2019, a virus of unknown origin was detected in Wuhan, China, and causing a cluster of pneumonia cases [1]. Shortly thereafter, the virus was classified as part of the novel enveloped RNA betacoronavirus family [2] and named the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); its associated disease is called coronavirus disease 2019 (COVID-19). The World Health Organization has recently declared COVID-19 as a pandemic [3]. As of 22 June 2020, >8 million confirmed cases had been documented globally with >400 000 deaths [4].

Many studies have reported the clinical characteristics, laboratory findings, and radiological imaging associated with COVID-19 in both the nonpregnant adult and pediatric populations. Clinical characteristics are quite similar in adults and children; the most common symptoms include fever and cough, usually dry [5–9]. Laboratory findings also appear to be similar, with lymphopenia and elevated C-reactive protein being the most common findings [5–9]. In addition, more than half of adults and children demonstrate ground-glass opacity on computed tomography (CT) of the chest [5–9].

Pregnancy poses a unique situation where the management of an affected patient is influenced by 2 patients: the mother and her fetus. Additionally, the normal pregnancy adaptations of the immune system pregnancy may theoretically cause clinical dilemmas and remains poorly understood. There is an urgent need for certain questions to be addressed: Do pregnant patients have similar clinical presentations, and are they more likely to experience adverse maternofetal or obstetrical outcomes? Understanding the clinical course of COVID-19 in the pregnant population is imperative for health providers to be able to care for the mother and her unborn fetus in a standardized way. This study aims to describe the clinical characteristics, laboratory abnormalities, radiological findings, and outcomes of pregnancy during COVID-19 to aid practitioners in managing these unique patients. To our knowledge, this is the largest systematic review and meta-analysis of its kind in pregnancy.

METHODS

Search Strategy and Data Sources

A comprehensive search of several databases from 1 December 2019 to 30 April 2020 was conducted and limited

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Correspondence: L. Alrahmani, Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (layan.md@gmail.com).

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to English-language publications. The databases included Ovid Medline and Epub Ahead of Print, In-Process and Other Non-Indexed Citations; Ovid Embase; Ovid Cochrane Central Register of Controlled Trials; and Scopus. The search strategy was conducted by a medical reference librarian. Controlled vocabulary supplemented with keywords was used to search for SARS-CoV-2 infection and pregnancy. The search strategy and terms used are available in Supplementary Item 1.

Eligibility Criteria and Quality Assessment

Eligible studies had to meet all of the following inclusion criteria: (1) participants must be women who were pregnant; (2) reverse-transcription polymerase chain reaction (RT-PCR)–confirmed COVID-19 infection through throat or nasal swabs; and (3) report of neonatal outcomes. The quality of each study was independently evaluated by 2 authors (R. M. and N. M.) using the methodological quality and synthesis of case series and case reports described by Murad et al [10]. This article followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Statistical Analysis

Means of continuous variables and rates of binary variables were pooled using the random-effects model, and the generic inverse variance method of DerSimonian and Laird [11]. Proportions underwent logit transformation prior to meta-analysis. The heterogeneity of effect size estimates across the studies was quantified using the Q statistic and the I^2 index ($P < .10$ was considered significant). A value of I^2 of 0–25% indicates minimal heterogeneity, 26%–50% moderate heterogeneity, and 51%–100% substantial heterogeneity [12]. Data analysis was performed using Open Meta analyst software (CEBM, Brown University, Providence, Rhode Island).

RESULTS

Study Selection and Characteristics

The initial search yielded 1082 potentially relevant articles from which 24 unique studies involving 136 pregnant women met eligibility criteria [13–36]. Details of the study selection process are depicted in Supplementary Item 2. The baseline characteristics of the included studies are described in Table 1. The maternal age ranged from 25 to 34 years, and the gestational age at admission ranged from 30 to 40 weeks.

Risk of Bias

Results of the quality assessment of all included studies are shown in Table 2. All of the case series were judged to have good quality. The patients appeared to represent the whole

Table 1. Baseline Characteristics of Included Studies

Author, Year	Country	Study Design	No. of Subjects	Mean Age, y	Mean Gestational Age on Admission, wk
Chen et al, 2020 [13]	China	RC	9	29.89	37.11
Chen et al, 2020 [14]	China	RC	17	29.1	NA
Liu et al, 2020 [15]	China	RC	10	29.69	33.85
Wang et al, 2020 [16]	China	Case report	1	34	40
Wang et al, 2020 [17]	China	Case report	1	28	30
Zhu et al, 2020 [18]	China	RC	9	30.89	NA
Liu et al, 2020 [19]	China	Case series	3	32.67	NA
Iqbal et al, 2020 [20]	United States	Case report	1	34	39
Chen et al, 2020 [21]	China	RC	5	28.8	NA
Chen et al, 2020 [22]	China	Case series	4	29	NA
Dong et al, 2020 [23]	China	Case report	1	29	34
Fan et al, 2020 [24]	China	Case series	2	31.5	36.5
Karami et al, 2020[a] [25]	Iran	Case report	1	27	30
Khan et al, 2020 [26]	China	Case series	3	29.33	37
Lee et al, 2020 [27]	Republic of Korea	Case report	1	28	36
Li et al, 2020 [28]	China	Case-control study	16	30.9	35.5
Liu et al, 2020 [29]	China	RC	11	32	37
Yu et al, 2020 [30]	China	RC	7	32.14	39
Peng et al, 2020 [31]	China	Case report	1	25	NA
Wu et al, 2020 [32]	China	RC	23	29	33
Xiong et al, 2020 [33]	China	Case report	1	25	33
Yang et al, 2020 [34]	China	PC	7	NA	NA
Zambrano et al, 2020 [35]	Honduras	Case report	1	41	31
Li et al, 2020 [36]	China	Case report	1	30	35

Abbreviations: NA, not available; PC, prospective cohort study; RC, retrospective cohort study.

[a]Study retracted.

Table 2. Methodological Quality Assessment Tool Results

Author, Year	Question 1	Question 2	Question 3	Question 4	Question 5
Chen et al, 2020	Yes	Yes	Yes	Yes	Yes
Chen et al, 2020	Yes	Yes	Yes	Yes	Yes
Liu et al, 2020	Yes	Yes	Yes	Yes	Yes
Wang et al, 2020	Yes	Yes	Yes	No	No
Wang et al, 2020	Yes	Yes	Yes	Yes	Yes
Zhu et al, 2020	Yes	Yes	Yes	Yes	Yes
Liu et al, 2020	Yes	Yes	Yes	Yes	Yes
Iqbal et al, 2020	Yes	Yes	Yes	Yes	No
Chen et al, 2020	Yes	Yes	Yes	Yes	Yes
Chen et al, 2020	Yes	Yes	Yes	Yes	Yes
Dong et al, 2020	Yes	Yes	Yes	Yes	Yes
Fan et al, 2020	Yes	Yes	Yes	Yes	Yes
Karami et al, 2020[a]	Yes	Yes	Yes	Yes	Yes
Khan et al, 2020	Yes	Yes	Yes	Yes	Yes
Lee et al, 2020	Yes	Yes	Yes	Yes	Yes
Li et al, 2020	Yes	Yes	Yes	Yes	Yes
Liu et al, 2020	Yes	Yes	Yes	No	No
Yu et al, 2020	Yes	Yes	Yes	Yes	Yes
Peng et al, 2020	Yes	Yes	Yes	Yes	Yes
Wu et al, 2020	Yes	Yes	Yes	Yes	Yes
Xiong et al, 2020	Yes	Yes	Yes	Yes	Yes
Yang et al, 2020	Yes	Yes	Yes	Yes	Yes
Zambrano et al, 2020	Yes	Yes	Yes	Yes	Yes
Li et al, 2020	Yes	Yes	Yes	Yes	Yes

Question 1: Does the patient(s) represent(s) the whole experience of the investigator (center)?

Question 2: Was the exposure adequately ascertained?

Question 3: Was the outcome adequately ascertained?

Question 4: Was follow-up long enough for outcomes to occur?

Question 5: Is the case(s) described with sufficient detail to allow other investigators to replicate the research or to allow practitioners make inferences related to their own practice?

[a]Study retracted.

experience of the investigator, the exposure and outcome were adequately ascertained, and the length of follow-up was adequate.

Clinical Characteristics

The demographic and clinical characteristics of the patients are described in Table 3. All patients were hospitalized during the course of delivery and treatment. Sixty-two patients were residents of Wuhan, China. Among the patients who lived in Wuhan, all had a community exposure, defined as being located within a setting with a known outbreak, and only 1 woman had direct contact with a known infected person. Fever was the most common presenting symptom, seen in 62.9% (95% confidence interval [CI], .477–.759; I^2 = 47.24%) on admission, followed by cough in 36.8% of patients (95% CI, .253–.500; I^2 = 29.31%), and sore throat in 22.6% (95% CI, .078–.502; I^2 = 27.92%). Less frequently reported symptoms included dyspnea (15.7% [95% CI, .067–.328]; I^2 = 23.46%) and diarrhea (15.6% [95% CI, .075–.295]; I^2 = 0%]) (Figure 1). Overall, 19.7% had at least 1 coexisting illness; frequently reported illnesses included hypothyroidism, hepatitis B virus infection, hypertension, gestational diabetes, autoimmune disease, and chronic obstructive pulmonary disease.

Laboratory and Radiological Findings

Table 4 describes the laboratory and radiologic findings on admission. The mean lymphocyte count was 1.233×10^9 cells/L (95% CI, .991–1.475; I^2 = 76.09%). The pooled mean leukocyte count was 10.438×10^9 cells/L (95% CI, 8.744–12.132; I^2 = 0%). Lymphocytopenia was present in 36 patients, with a pooled proportion of 50% (95% CI, .331–.669; I^2 = 39.44%), and no cases of leukopenia were identified. However, elevated neutrophil levels were reported in 67.8% of the patients (95% CI, .478–.829; I^2 = 0%). More than half of the patients had elevated levels of C-reactive protein, with a pooled proportion of 57% (95% CI, .454–.678; I^2 = 0%), which ranged from 2.975 to 32.28 mg/L; less commonly encountered were elevations in the levels of alanine aminotransferase (ALT) (22.3% [95% CI, .123–.369]; I^2 = 0%), aspartate aminotransferase (AST) (23.3% [95% CI, .128–.386]; I^2 = 0%), and a D-dimer ratio that ranged between 840 and 1710 µg/L. The mean level of ALT was 48.345 U/L (95% CI, –3.293 to 99.984; I^2 = 99.94%), while the mean

Table 3. Demographics and Clinical Characteristics of Included Patients

Author, Year	Exposure to the Environment (Unknown Contact)	Direct Contact With Infected People	Fever	Dry Cough	Sore Throat	Dyspnea	Myalgia	Diarrhea
Chen et al, 2020 [13]	Yes (4)	Yes (5)	7	4	2	1	3	1
Chen et al, 2020 [14]	NA	3	4	4	NA	1	NA	1
Liu et al, 2020 [15]	Yes (10)	6	10	1	NA	1	NA	NA
Wang et al, 2020 [16]	Yes (1)	No	1	NA	NA	NA	NA	NA
Wang et al, 2020 [17]	Yes (1)	Yes	1	NA	NA	NA	NA	NA
Zhu et al, 2020 [18]	NA	NA	8	1	NA	NA	NA	NA
Liu et al, 2020 [19]	Yes (3)	No	2	2	NA	NA	NA	NA
Iqbal et al, 2020 [20]	No	No	1	1	NA	NA	1	NA
Chen et al, 2020 [21]	NA	NA	0	2	NA	NA	NA	NA
Chen et al, 2020 [22]	NA	NA	3	2	NA	1	2	NA
Dong et al, 2020 [23]	Yes	No	1	NA	1	NA	NA	NA
Fan et al, 2020 [24]	No	Yes (2)	2	NA	NA	NA	NA	NA
Karami et al, 2020[a] [24]	NA	NA	1	1	NA	NA	1	NA
Khan et al, 2020 [26]	NA	NA	2	3	1	NA	NA	NA
Lee et al, 2020 [27]	NA	NA	1	1	0	NA	NA	NA
Li et al, 2020 [28]	NA	NA	4	0	1	0	NA	NA
Liu et al, 2020 [29]	NA	NA	9	6	NA	NA	3	3
Yu et al, 2020 [30]	Yes (7)	No	6	1	NA	1	NA	1
Peng et al, 2020 [31]	NA	NA	1	NA	NA	1	NA	NA
Wu et al, 2020 [32]	No	Yes (3)	4	6	NA	NA	NA	NA
Xiong et al, 2020 [33]	Yes (1)	No	1	1	NA	NA	NA	NA
Yang et al, 2020 [34]	Yes (7)	No	5	1	NA	NA	NA	1
Zambrano et al, 2020 [35]	No	Yes (1)	1	1	NA	NA	1	NA
Li et al, 2020 [36]	Yes	Yes (1)	0	1	NA	1	NA	NA

Abbreviation: NA, not available.
[a]Study retracted.

AST level was 34.114 U/L (95% CI, 22.972–45.256; $I^2 = 95.53\%$) (Figure 2).

Of 136 chest CT scans performed at the time of admission, 98% revealed abnormal results. The most common pattern seen on chest CT scan was ground-glass opacity (GGO) and was present in 81.7% of patients (95% CI, .701–.895; $I^2 = 0\%$). Of the 82 patients who presented with GGO, 52 patients presented with bilateral GGO and 10 patients presented with unilateral GGO. There were no specific data regarding the classification of the location of the GGO in the 20 remaining patients. The second most common pattern on chest CT was infiltrated shadows, seen in 42.5% (95% CI, .126–.791; $I^2 = 29.55\%$) (Figure 3).

Treatments Provided and Maternal Outcomes

Most patients were delivered via a cesarean delivery with a rate of 76.3% (95% CI, .658–.842; $I^2 = 10.24\%$). Fifty-nine patients received antibiotic therapy (87.7% [95% CI, .755–.943]; $I^2 = 0\%$) and 45 patients received antiviral therapy (67.5% [95% CI, .484–.821]; $I^2 = 33.44\%$). Details of antiviral therapy are provided in Table 5. Oxygen therapy, either through nasal cannula or face mask, was administered in 36 patients (73.1% [95% CI, .391–.920]; $I^2 = 57.64\%$) (Table 5). Fifteen patients received corticosteroids (50.5% [95% CI, .285–.723]; $I^2 = 30.81\%$), of which 5 patients received betamethasone. Specific indication for use of corticosteroid administration included fetal lung maturation, acute flare of autoimmune disease, prophylaxis for pneumonia, pneumonia, and to relieve inflammation. Two patients required intubation and mechanical ventilation due to multiorgan failure. One woman died due to multiorgan failure and acute respiratory distress syndrome (ARDS) (mortality, 11.1% [95% CI, .063–.187]; $I^2 = 0\%$). As shown in Table 5, premature rupture of membrane, fetal distress, and stillbirth were the most common complications during pregnancy.

Neonatal Outcomes

All neonates were all delivered in a negative-pressure isolation room, and all studies reported separation and lack of contact between the mothers and the neonates. Thirty-one of 94 neonates were delivered preterm (<37 weeks) (37.7% of neonates [95% CI, .269–.500]; $I^2 = 10.77\%$). Five newborns were delivered early preterm (<34 weeks). The birthweight of the neonates averaged 3127.639 g (95% CI, 2941.238–3314.041; $I^2 = 84.44\%$). The neonatal clinical characteristics and laboratory findings, as well as the perinatal complications, are shown in Table 6. The white blood cell count averaged 15.303 (95% CI, 12.852–17.755; $I^2 = 38.02\%$). In addition, the

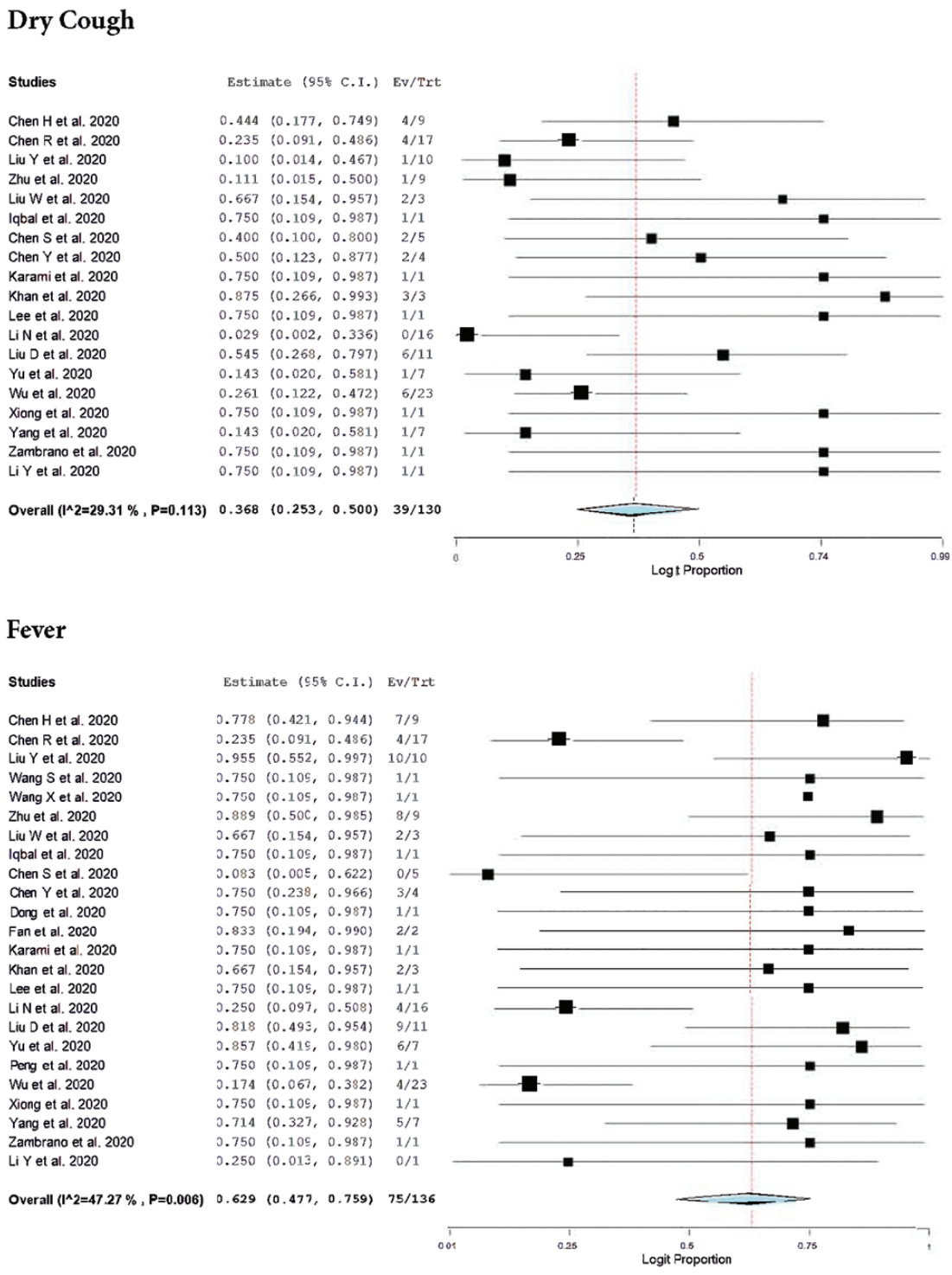

Figure 1. Forest plot of the clinical characteristics present at time of admission. Abbreviations: CI, confidence interval; Ev, xxx; Trt, xxx.

procalcitonin averaged 0.289 (95% CI, .211–.366; I^2 = 0%). The hemoglobin concentration averaged 174.109 g/L (95% CI, 163.535–184.683; I^2 = 33.82%), and the mean platelet count was 224.297 × 10^9 cells/L (95% CI, 191.729–256.866; I^2 = 68.91%). In addition, the ALT and AST averaged 11.627 U/L (95% CI, 7.322–15.933; I^2 = 67.95%) and 52.232 U/L (95% CI, 39.202–65.263; I^2 = 20.05%), respectively. Elevated levels of AST were identified in 56.1% (95% CI, .321–.776; I^2 = 0%) of patients. The lymphocyte and neutrophil counts averaged 3.278 × 10^9 cells/L (95% CI, 2.627–3.928; I^2 = 0%) and 10.416 × 10^9 cells/L (95% CI, 7.495–13.338; I^2 = 51.79%), respectively (Figure 4). Two newborns tested positive for

Table 4. Radiologic and Laboratory Findings on Admission

Author, Year	GGO, No.	Infiltrated Shadows, No.	Subpleural, No.	Lymphocytes, $\times 10^9$/L	Neutrophils, $\times 10^9$/L	Leukocytosis, $\times 10^9$/L	CRP, mg/L	ALT, U/L	AST, U/L
Chen et al, 2020 [13]	6	1	1	1.18	NA	NA	18.61	253.78	171
Chen et al, 2020 [14]	NA	NA	NA	1.22	NA	10.9	27.2	20.6	23.4
Liu et al, 2020 [15]	NA	NA	NA	NA	NA	NA	NA	NA	NA
Wang et al, 2020 [16]	1	NA	NA	0.97	9.97	NA	11.5	NA	NA
Wang et al, 2020 [17]	1	NA	NA	0.86	9.14	10.6	19.6	NA	NA
Zhu et al, 2020 [18]	NA	NA	NA	NA	NA	NA	NA	NA	NA
Liu et al, 2020 [19]	3	NA	NA	4.87	7.92	9.92	13.1	9.83	20.6
Iqbal et al, 2020 [20]	1	NA	NA	1.1	8.8	NA	25.6	23	24
Chen et al, 2020 [21]	5	NA	NA	1.24	9.54	NA	32.28	10.26	20.22
Chen et al, 2020 [22]	4	NA	NA	0.9	4.68	NA	26.75	21.75	26.5
Dong et al, 2020 [23]	1	NA	NA	1.08	6.57	NA	57	40	38
Fan et al, 2020 [24]	1	1	NA	NA	NA	NA	NA	NA	NA
Karami et al, 2020[a] [25]	1	NA	NA	0.72	NA	3	31	68	52
Khan et al, 2020 [26]	3	NA	NA	1.64	NA	NA	17.3	10.67	23.33
Lee et al, 2020 [27]	1	NA	NA	NA	NA	NA	1.5	NA	NA
Li et al, 2020 [28]	16	NA	NA	1.5	6.6	NA	4.8	11.6	16.3
Liu et al, 2020 [29]	NA	NA	NA	NA	NA	NA	NA	NA	NA
Yu et al, 2020 [30]	7	NA	NA	NA	NA	NA	31.79	NA	NA
Peng et al, 2020 [31]	1	NA	NA	NA	NA	NA	NA	NA	NA
Wu et al, 2020 [32]	23	NA	NA	NA	NA	NA	2.975	NA	NA
Xiong et al, 2020 [33]	0	1	NA	1.91	NA	NA	21.8	15	21
Yang et al, 2020 [34]	7	NA	NA	NA	NA	NA	NA	NA	NA
Zambrano et al, 2020 [35]	NA	NA	NA	NA	NA	NA	NA	NA	NA
Li et al, 2020 [36]	NA	1	NA	1.1	7.1	8.7	18.59	15	19

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; GGO, ground glass opacity; NA, not available.

[a]Study retracted.

COVID-19 (11.5% [95% CI, .067–.192]; $I^2 = 0$). Both neonates were delivered via cesarean delivery. The amniotic fluid, placenta fluid, umbilical cord, and gastric juice were all tested for COVID-19 and tested negative in all the studies. The Apgar score at 1 minute was 8.811 (95% CI, 8.382–9.240; $I^2 = 88.87\%$) and at 5 minutes was 9.516 (95% CI, 9.136–9.895; $I^2 = 82.91\%$). In addition, no severe neonatal asphyxia occurred in any of the neonates across the studies. Three fetal deaths were reported; their respective gestational ages were 34 weeks, 31 weeks, and 30 weeks. Neonatal intensive care unit admission occurred in 63.7% (95% CI, .378–.835; $I^2 = 29.38\%$) of patients. The fetal death rate was 11.7% (95% CI, .068–.192; $I^2 = 0\%$) (Figure 5). Two neonatal deaths were due to multiple organ failure and disseminated intravascular coagulation. The third neonatal death occurred immediately after delivery. The neonate was cyanotic and had an Apgar score of 0 at 1 and 5 minutes, respectively.

DISCUSSION

SARS-CoV-2 is a highly infective virus causing the greatest pandemic of the century. As of now, we are in the midst of it, seeking to determine treatments and novel ways to manage this deadly disease. In this contemporary meta-analysis, we have concluded the following: (1) Pregnant patients with COVID-19 most commonly present with fever, dry cough, and sore throat; (2) the most common radiological finding in this group of patients was the presence of GGO on CT; and (3) the perinatal risk is great, as the risk of prematurity and cesarean delivery are high. To our knowledge, this is the largest meta-analysis of its kind to describe the effects of COVID-19 on pregnancy. We believe that this study provides insight for developing the backbone for counseling and management of pregnant patients at risk for acquiring the disease.

The immunosuppressed state of pregnancy confers high risk for the development of severe complications of infectious diseases, such as influenza and severe acute respiratory syndrome (SARS) [37]. During the SARS pandemic of 2003, 40% of affected pregnant women required mechanical ventilation and had a case-fatality rate of 30%, compared to 13% and 11%, respectively, of a nonpregnant cohort [38]. Interestingly, our study did not demonstrate significantly worsened outcomes in COVID-19–affected pregnant patients when compared to nonpregnant patients reported in the literature. Our population has similar clinical presentations, laboratory abnormalities, and radiological findings compared with infected nonpregnant cohorts in the current literature [39]. Additionally, the maternal complication rate seems to be comparable to nonpregnant adults [39]. One theory is that the immunologic adaptations of pregnancy that help mothers from rejecting the fetus, a foreign

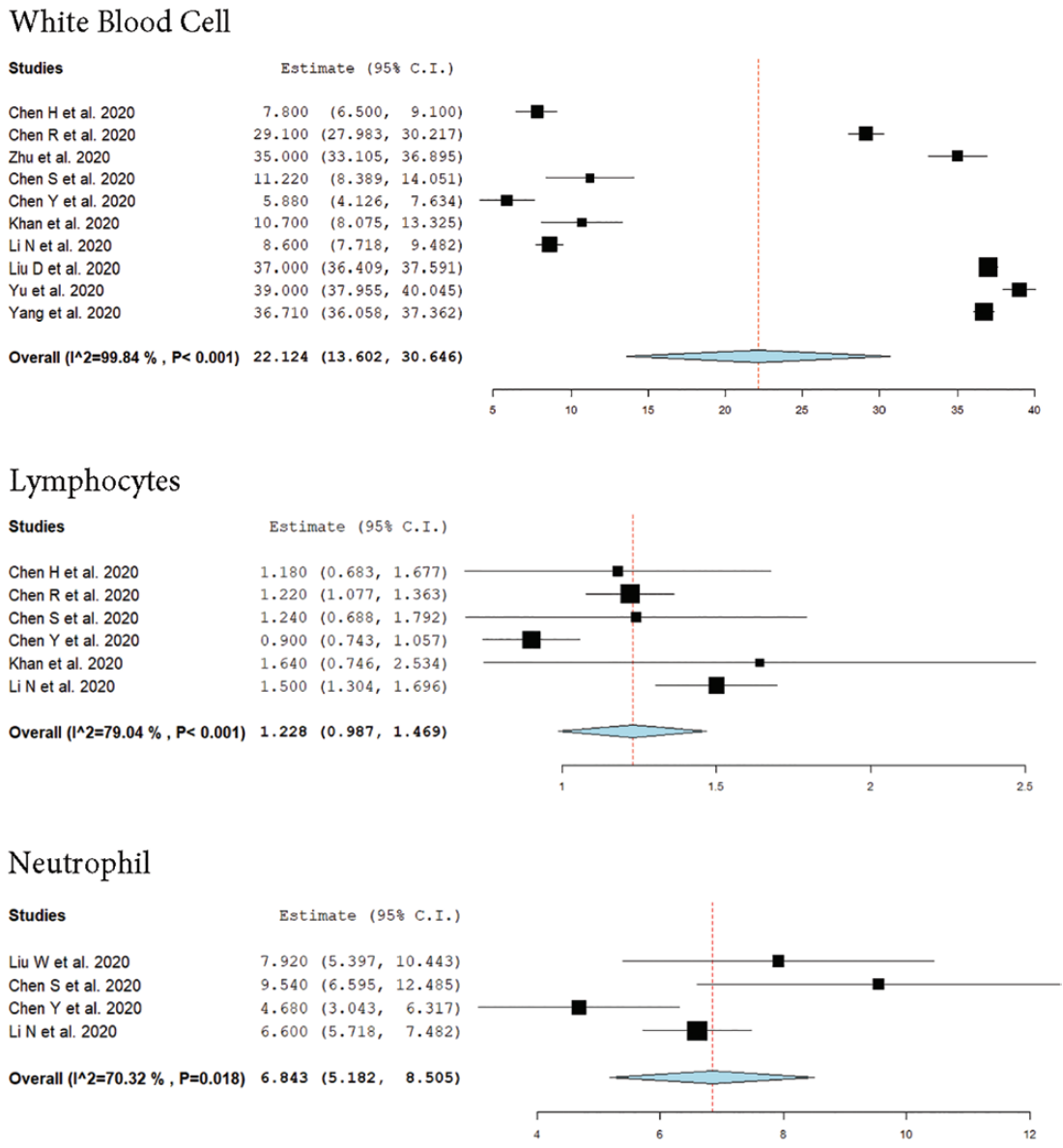

Figure 2. Forest plot of the laboratory findings present at time of admission. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval.

entity containing paternal antigens, may also aid in mounting a less robust immune response to the virus, consequently leading to less destructive effects on the body [40]. Another is that pregnancy-related organ adaptive changes may result in protection against the virus and its effects [40].

Within our subset of 136 SARS-CoV-2–infected pregnant women, a single case of maternal death secondary to ARDS and multiorgan failure was reported, resulting in a considerably lower mortality rate in comparison to previous pandemics. Moreover, with 2 patients requiring intubation and mechanical ventilation, morbidity appeared to be lower than anticipated. Although a proportion of women had comorbidities present, some of which were obstetrical in etiology, they still did not experience life-threatening manifestations of COVID-19. A recently published case series described 2 cases of COVID-19–related cardiomyopathy in pregnant women [41]. However, both of these patients possessed multiple risk factors for cardiac disease, and it remained unclear as to whether cardiomyopathy occurred as a direct complication of COVID-19, or secondary to multiorgan dysfunction. Another interesting observation was the high rate of preterm birth in this group of patients, much higher than the general pregnant population (12% in the United States and lower in other developed countries). A direct causal link between infection and premature labor has been well established in the literature [42], and it is estimated that at least 40% of premature births are

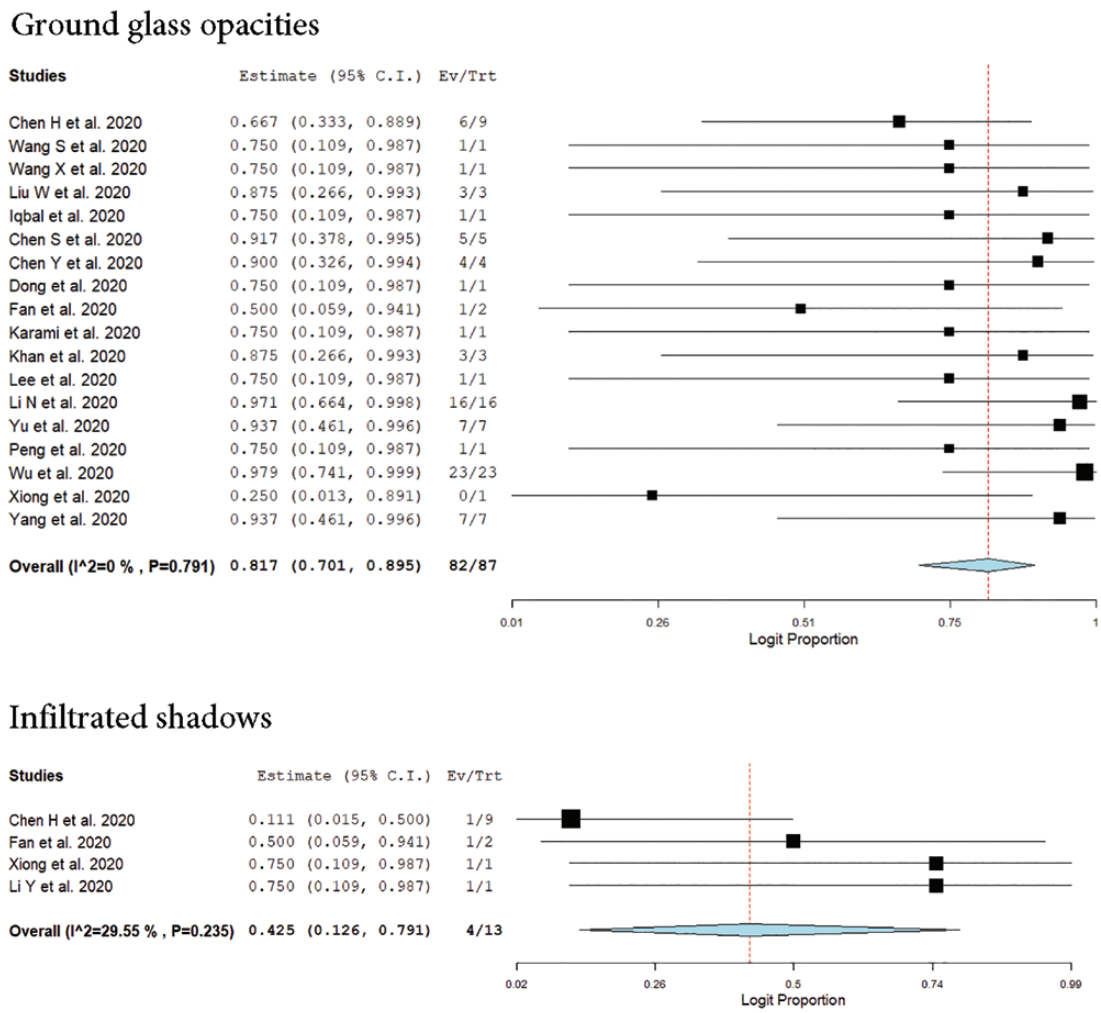

Figure 3. Forest plot of the radiological findings present at time of admission. Abbreviations: CI, confidence interval; Ev, xxx; Trt, xxx.

associated with intrauterine infection or inflammation [43]. Additionally, the high rate of cesarean delivery should not go unnoticed. Three-quarters of infected patients underwent a cesarean delivery, more than double that of the general pregnant population. Cesarean delivery, while a commonly procedure worldwide, is still a major surgery with significantly higher morbidity than a vaginal delivery, both in the short term, such as infections and bleeding, and in the long term, such as the risk of development of placenta accreta spectrum disorder in future pregnancy.

It is difficult to make conclusions on the risk of having a pregnancy affected by COVID-19 or pregnancy that is not, owing to the heterogeneity of the studies included in this meta-analysis. Although in the reported cases most neonates fared well, with the exception of 3 of them, the most worrying aspect of our finding is the high rate of preterm birth. Prematurity in and of itself is the most common cause of morbidity and mortality in neonates worldwide, both short-term and long-term. Since the immunological immaturity of neonates renders them susceptible to infections, vertical transmission is a particularly concerning complication of viral infections that occur during pregnancy [44]. In all cases, the amniotic fluid, placenta, and umbilical cord samples all tested negative for SARS-CoV-2, while 2 neonates had RT-PCR–confirmed SARS-CoV-2 infection. Based on these findings, it is impossible to conclude that these neonates acquired the infection during fetal life. Three neonatal deaths with gestational ages of 34 weeks, 31 weeks, and 30 weeks were reported in our analysis. Two fetal deaths occurred due to multiple organ failure and disseminated intravascular coagulation, and the third was a perinatal death occurring within 24 hours of birth. This is an alarming finding as neonates born at this gestational age typically have low death rates; however, due to insufficient information in the respective reports, we could not conclusively contribute these deaths to COVID-19–related complications. Previous studies on other coronavirus infections, such as Middle East respiratory syndrome and SARS coronaviruses, have demonstrated a lack of vertical

Table 5. Treatments and Pregnancy-related Complications

Author, Year	Cesarean Delivery, No.	Antiviral Therapy, No.	Specific Antiviral Medications	Antibiotic Therapy, No.	Oxygen Therapy, No.	Mechanical Ventilation, No.	Premature Membrane Rupture, No.	Fetal Distress, No.	Stillbirth, No.
Chen et al, 2020 [13]	9	6	NA	9	9	0	2	2	0
Chen et al, 2020 [14]	17	NA	NA	NA	NA	0	NA	NA	NA
Liu et al, 2020 [15]	10	NA	NA	NA	NA	1	1	3	1
Wang et al, 2020 [16]	1	1	Recombinant human IFN	NA	NA	0	0	0	0
Wang et al, 2020 [17]	1	1	Lopinavir and ritonavir	NA	NA	0	0	0	1
Zhu et al, 2020 [18]	7	5	Oral oseltamivir	NA	NA	0	3	0	0
Liu et al, 2020 [19]	2	3	Arbidol (n = 2) Atomized inhalation of IFN (n = 1)	2	3	0	0	0	0
Iqbal et al, 2020 [20]	0	NA	NA	NA	NA	0	0	0	0
Chen et al, 2020 [21]	2	0	NA	5	0	0	0	0	0
Chen et al, 2020 [22]	3	NA	NA	NA	NA	0	NA	NA	NA
Dong et al, 2020 [23]	1	1	NA	1	1	0	0	0	0
Fan et al, 2020 [24]	2	2	Oral oseltamivir	2	NA	0	0	0	0
Karami et al, 2020[a] [25]	0	1	Oseltamivir, lopinavir/ritonavir, hydroxychloroquine	1	1	1	0	0	0
Khan et al, 2020 [26]	0	3	NA	3	3	0	0	0	0
Lee et al, 2020 [27]	1	NA	NA	NA	NA	0	0	0	0
Li et al, 2020 [28]	14	1	NA	16	0	0	1	0	0
Liu et al, 2020 [29]	10	11	NA	11	11	0	NA	NA	NA
Yu et al, 2020 [30]	7	7	NA	7	7	0	0	0	0
Peng et al, 2020 [31]	1	1	IFN nebulization, oral lopinavir	1	1	0	NA	NA	NA
Wu et al, 2020 [32]	18	NA	NA	NA	NA	0	NA	NA	NA
Xiong et al, 2020 [33]	0	1	NA	1	NA	0	1	0	0
Yang et al, 2020 [34]	7	NA	NA	NA	NA	0	NA	NA	NA
Zambrano et al, 2020 [35]	0	NA	NA	NA	NA	0	NA	NA	NA
Li et al, 2020 [36]	1	1	Lopinavir, ritonavir	NA	NA	0	NA	NA	NA

Abbreviations: IFN, interferon; NA, not available.

[a]Study retracted.

transmission in pregnant women [45, 46]. Although the occurrence of vertical transmission at present seems rather unlikely, the significant implication in potentially leading to preterm birth and neonatal infection warrants continued investigation. Additionally, given the uncertainty of long-term neonatal outcomes in COVID-19, neonates should be monitored for any possible congenital defects.

Vaginal delivery and the interventions that may occur during the process, such as rupture of membranes, episiotomy, and placement of internal fetal monitors, play an important role in vertical transmission via the transplacental route of certain maternal infections to the fetus, namely blood-borne infections such as human immunodeficiency virus and hepatitis B and C [47]. In our study, both fetal COVID-19–confirmed cases were delivered via cesarean delivery. However, due to the small sample size for patients who delivered vaginally (n = 18), it is difficult to make any conclusions in that regard. Further studies should attempt to delineate these 2 groups for clarification. This

Table 6. Clinical Characteristics and Laboratory Findings of Neonates Born to Clinically Symptomatic Mothers

Author, Year	Mean Gestational Age at Birth, wk	Mean Weight at Birth, g	Hb, g/L	Platelets, $\times 10^9$/L	ALT, U/L	AST, U/L	Apgar Score at 1 Min	Apgar Score at 5 Min	Preterm labor (<37 wk), No.	COVID-19 Testing of Respiratory Tract	NICU Care, No.
Chen et al, 2020 [13]	37.11	3011	NA	NA	NA	NA	9	10	4	Negative	NA
Chen et al, 2020 [14]	NA	3030	NA	NA	NA	NA	9	10	3	Negative	17
Liu et al, 2020 [15]	NA	NA	NA	NA	NA	NA	9	NA	6	Negative	NA
Wang et al, 2020 [16]	40	NA	NA	NA	NA	143	8	9	NA	Positive	NA
Wang et al, 2020 [17]	30	1830	NA	NA	NA	NA	9	10	1	Negative	NA
Zhu et al, 2020 [18]	35	2423	166.3	218.5	7.98	45.05	9	9	6	Negative	NA
Liu et al, 2020 [19]	38	3390	171	187.67	17.67	107	8	9	NA	Negative	NA
Iqbal et al, 2020 [20]	NA	NA	NA	NA	NA	NA	8	9	0	Negative	1
Chen et al, 2020 [21]	39	3691	NA	NA	NA	NA	10	10	NA	Negative	NA
Chen et al, 2020 [22]	37.75	3400	181.7	253.33	14.67	60	8	9	NA	Negative	2
Dong et al, 2020 [23]	NA	3120	NA	NA	11	65	9	10	NA	Negative	1
Fan et al, 2020 [24]	NA	3145	NA	NA	NA	NA	9	10	NA	Negative	NA
Karami et al, 2020[a] [25]	NA	NA	NA	NA	NA	NA	0	0	NA	Negative	NA
Khan et al, 2020 [26]	NA	3373	NA	NA	NA	NA	8.67	9.67	1	Negative	NA
Lee et al, 2020 [27]	NA	3130	NA	NA	NA	NA	9	10	1	Negative	1
Li et al, 2020 [28]	38	3078	NA	NA	NA	NA	9.6	10	4	Negative	NA
Liu et al, 2020 [29]	NA	NA	NA	NA	NA	NA	NA	9	NA	Negative	NA
Yu et al, 2020 [30]	NA	3264	NA	NA	NA	NA	8–9	9–10	0	Positive	0
Peng et al, 2020 [31]	35	2600	NA	NA	NA	NA	9	10	1	Negative	1
Wu et al, 2020 [32]	NA	NA	NA	NA	NA	NA	NA	9–10	NA	Negative	NA
Xiong et al, 2020 [33]	38	3070	NA	NA	9	53	9	10	0	Negative	0
Yang et al, 2020 [34]	36.71	2096	NA	NA	11.2	59	8.29	9.29	2	Negative	5
Zambrano et al, 2020 [35]	32	1500	NA	NA	NA	NA	NA	NA	1	Negative	NA
Li et al, 2020 [36]	35	NA	NA	NA	NA	NA	NA	NA	1	Negative	NA

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; Hb, hemoglobin; NA, not available; NICU, neonatal intensive care unit.
[a]Study retracted.

is an important issue that obstetricians should take into account when considering the course of treatment for any patient with a confirmed viral infection.

Recently published reviews on this topic have reported similar findings [48–50]. However, unlike the present review, no categorization was made regarding the specific CT findings. The strengths of our study are as follows: (1) This is the largest study of its kind to date to explore pregnancy and perinatal outcomes of SARS-CoV-2 infections; (2) the patients and their neonates who were included had confirmed positive or negative RT-PCR SARS-CoV-2, preventing any uncertainty regarding the group of patients who had a clinical presentation but were not representative of the entire cohort; (3) to our knowledge, this is the first meta-analysis to look at the pooled effect of COVID-19 across all eligible studies; and (4) our study reports medication use for treatment of COVID-19 that includes antiviral therapy and corticosteroid use in more depth than existing studies.

Our systematic review and meta-analysis has some limitations. The main limitation is primarily the lack of high-quality data in the included studies. Due to the urgent timeline for data extraction and the complications requiring preterm labor, some cases had incomplete documentation of the epidemiological history, laboratory testing, and outcomes. In addition, our meta-analysis had a limited number of studies, most of which were either case series or case reports. This makes it difficult to draw any conclusions regarding clinical presentation and outcomes of patients. Additionally, patients who were asymptomatic or had mild cases and who did not require hospitalization were not accounted for due to publication bias. Last, due to the nature of the virus and the urgent need for more studies, our meta-analysis might have missed studies that were recently published in the literature, particularly in languages other than English.

As this global pandemic continues to spread, there will be a need for additional information on the effects of COVID-19 on pregnant women and their infants. Sufficiently understanding the clinical presentations and outcomes of SARS-CoV-2 infection among pregnant women and their neonates, along with pathological and molecular characterization of the virus, is valuable in determining the disease trajectory within this subset of patients. Currently, the American College of Obstetricians and Gynecologists has developed an algorithm to aid practitioners in evaluating

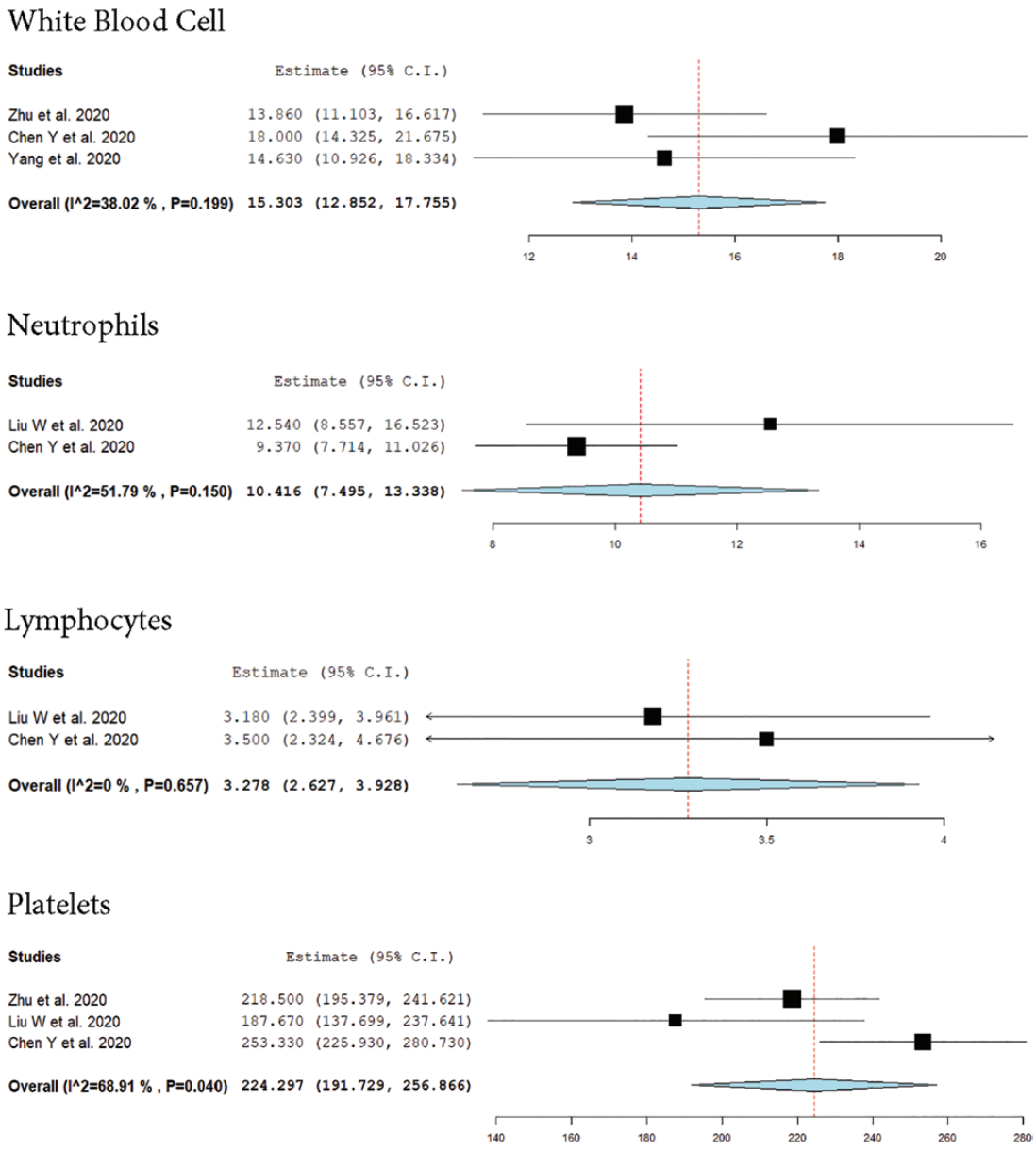

Figure 4. Forest plot of neonatal laboratory findings present after birth. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval.

and treating pregnant women with known exposure or symptoms consistent with COVID-19 infection [51]. The algorithm includes assessing patients' symptoms such as fever and cough; conducting an illness severity assessment; and, based on degree of severity, assessing clinical and social risks [51]. With the disease burden increasing every day, the probability of a second wave of COVID-19 infection this upcoming winter, and the ongoing debate regarding whether pregnant front-line healthcare workers should continue working, are important matters that will hopefully be answered as more studies emerge. This review aims to provide physicians with an understanding of the clinical presentation and outcomes of pregnant women with confirmed COVID-19 and their neonates, to help them make better decisions when devising a counseling and treatment plan for their patients.

In summary, this meta-analysis demonstrates that pregnant women with COVID-19 have similar clinical characteristics and outcomes as the nonpregnant population and there appears to be little evidence of vertical transmission. However, when compared to the general pregnant population, infected women are at significantly higher risk for cesarean delivery and preterm birth. We urge obstetricians to continue reporting their data, especially that of asymptomatic patients or those with mild disease, so we are better able to understand this novel virus and hopefully improve outcomes.

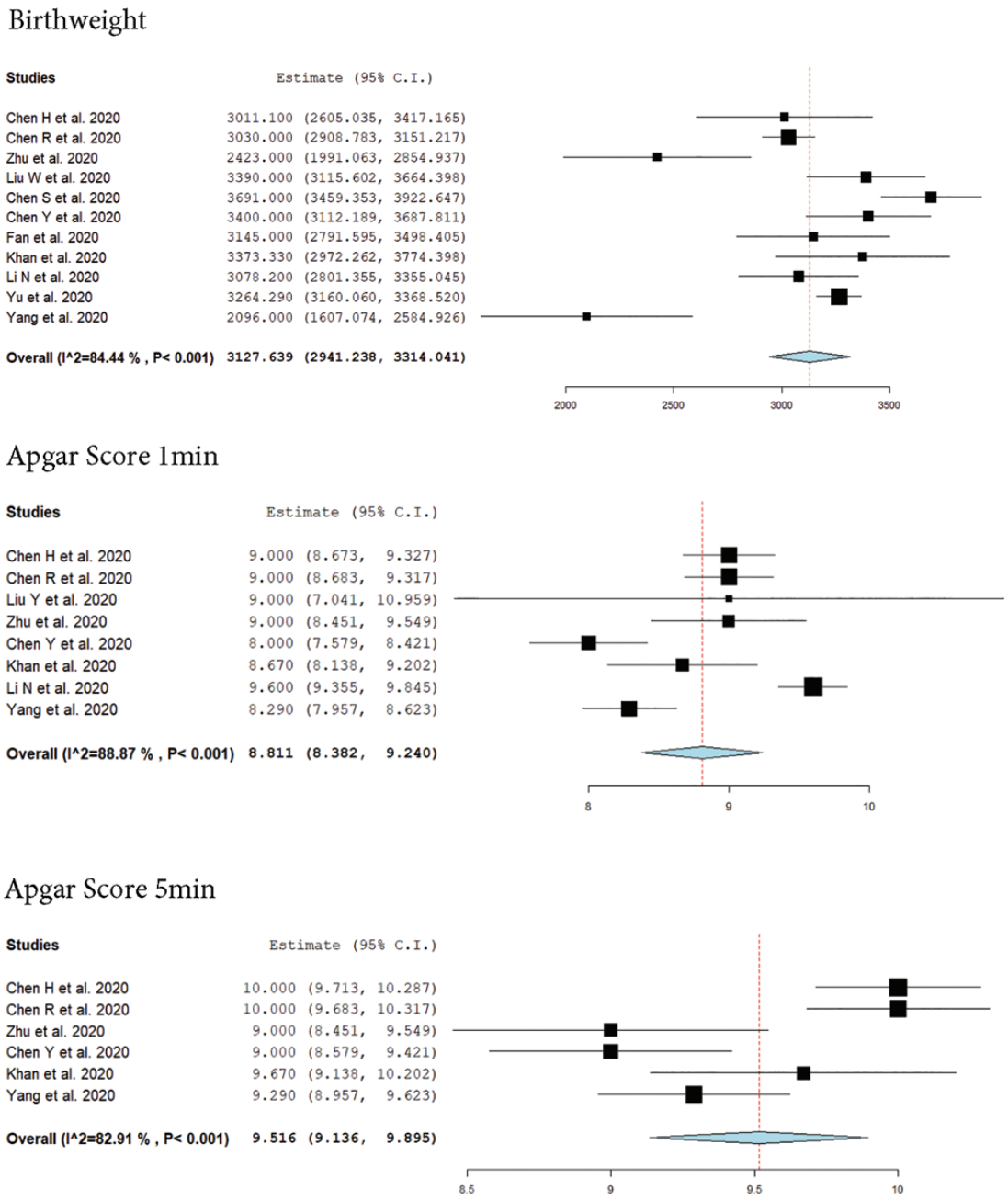

Figure 5. Forest plot of neonatal outcomes after birth. Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; NICU, neonatal intensive care unit.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. R. M. and N. M. conceived the study, searched the literature, extracted the data, assessed the quality of the studies, and drafted the manuscript. D. G. searched the literature. R. M. and M. H. M. performed the statistical analysis and drafted the manuscript. L. A., L. D., E. B., J. F., and F. F. drafted the manuscript. All authors read and approved the final manuscript.

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