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Comparative analysis of COVID-19 pneumonia in pregnant versus matched non-pregnant women: radiologic, laboratory, and clinical perspectives

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This study aimed to assess the severity and outcomes of COVID-19 in pregnant women, focusing on laboratory and radiological discrepancies between pregnant women and matched nonpregnant women. In this retrospective cross-sectional analysis, we matched 107 nonpregnant women with 66 pregnant women in terms of age, comorbidities, and the interval between symptom onset and hospital admission. Demographic, clinical, laboratory, and radiological data were collected, and chest CT scans were evaluated using a severity scale ranging from 0 to 5. Logistic regression and adjusted Cox regression models were used to assess the impact of various factors on pregnancy status and mortality rates. Differences in several laboratory parameters, including the neutrophil-to-lymphocyte ratio, liver aminotransferases, alkaline phosphatase, urea, triglycerides, cholesterol, HbA1c, ferritin, coagulation profiles, and blood gases, were detected. Radiologic exams revealed that nonpregnant women had sharper opacities, whereas pregnant women presented with hazy opacities and signs of crypt-organizing pneumonia. A notable difference was also observed in the pulmonary artery diameter. The mortality rate among pregnant women was 4.62%, which was comparable to the 5.61% reported in nonpregnant patients. Compared with nonpregnant patients, pregnancy did not significantly affect the severity or mortality of COVID-19. Our study revealed discernible differences in specific laboratory and imaging markers between pregnant and nonpregnant COVID-19 patients.

Keywords SARS-CoV-2, Computed tomography, Python, Comorbidities, Pregnancy, Severity

Abbreviations

ALT	Alanine transaminase
AST	Aspartate aminotransferase
ALKP	Alkaline phosphatase
BE	Bass excess
BILL	Bilirubin
BMI	Body mass index
CA	Calcium
CKMB	Creatine kinase MB

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CKD	Chronic kidney disease
CR	Creatinine
COP	Cryptogenic organizing pneumonia
COVID-19	Coronavirus disease 2019
CPK	Creatine phosphokinase
CRP	C-reactive protein
DM	Diabetes mellitus
ESR	Erythrocyte sedimentation rate
FBS	Fasting blood sugar
FDP	Fibrinogen-degradation product
Fe	Serum iron
GI diseases	Gastrointestinal diseases
GGO	Ground-glass opacity
HB	Hemoglobin
HbA1C	Hemoglobin A1c
HICs	High-income countries
HDL	High-density lipase
HR	Hazard ratio
HTN	Hypertension
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHD	Ischemic heart disease
IL-6	Interleukin-6
INR	International normalized ratio
IQR	Inter-quantile range
K	Potassium
LDH	Lactate dehydrogenase
LDL	Low-density lipase
LMICS	Low to middle-income countries
LOS	Length of stay
LPA	Left pulmonary arteries
Lymphs	Lymphocyte
MCV	Mean corpuscular volume
MG	Magnesium
MPA	Main pulmonary arteries
NA	Sodium
Neut	Neutrophil
OR	Odds ratio
P	Phosphorous
PCT	Procalcitonin
PLT	Platelets
PRO-BNP	N-Terminal pro b-type natriuretic peptide
PT	Prothrombin time
PTT	Partial thromboplastin time
RPA	Right pulmonary arteries
LLL	Left lower lobe
LUL	Left upper lobe
O_2 Sat	Oxygen saturation
RLL	Right lower lobe
RML	Right middle lobe
RUL	Right upper lobe
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
TG	Triglyceride
TIBC	Total iron-binding capacity
TSH	Thyroid stimulating hormone
T3	Triiodothyronine
T4	Thyroxine
WBC	White blood cell

The World Health Organization (WHO) announced the emergence of a new disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in December 2019[1]. The COVID-19 pandemic can affect pregnancy outcomes through both the direct effects of the disease and the indirect effects of the outbreak. A modeling study of 118 countries demonstrated that this trend could result in 1,157,000 excess child deaths and 56,700 excess maternal deaths[2].

Immunocompromised individuals, including those with malignancies and solid-organ transplant recipients, are particularly vulnerable to COVID-19 infection[3]. Pregnancy can alter the immune system and modify the response to infections. Both pregnancy and COVID-19 are characterized by decreased lymphocytes, NKG2A inhibitory receptors, and increased levels of angiotensin-converting enzyme 2 (ACE2), IL-8, IL-10, and interferon-gamma inducible protein-10 (IP-10)[4]. Furthermore, physiological changes during pregnancy,

including reduced total lung capacity, insufficient clearance of pulmonary secretions, urinary stasis, and altered blood flow, may increase disease severity during pregnancy[5]. Therefore, pregnant women may be at risk for more significant morbidity and disease severity, requiring special attention for the diagnosis and management of COVID-19. Recognizing the clinical presentation and integrating laboratory and radiological findings are crucial steps for optimal clinical management[6].

As shown in Table 1, several publications have investigated the clinical presentation of COVID-19 during pregnancy, and valuable systematic reviews and meta-analyses have been conducted on this topic[7–14]. However, only two meta-analyses included studies that compared the clinical manifestations of COVID-19 between pregnant and nonpregnant patients[7,14]. This gap in the literature is due to several factors**:** 1) a lack of high-quality studies that consider comparisons with matched groups[12], 2) studies with small sample sizes (fewer than 150 participants)[14], and 3) unavoidable selection bias in certain types of studies (case reports, case studies, and case series studies)[7]. Moreover, the majority of data have been obtained from high-income countries (HICs)[8,14], highlighting the need for studies from different regions of the world, including low- to middle-income countries (LMICs), to provide a more comprehensive understanding of the differences in clinical presentation, clinical course, and long-term outcomes of COVID-19 in pregnant and nonpregnant women.

Considering these issues, this study investigated the distinct clinical, laboratory, and radiological features of COVID-19 during pregnancy in Tehran, Iran, which is one of the LMICs and less reported regions. Since age and preexisting comorbidities are related to the severity and mortality of COVID-19 patients[15], these potential confounders were controlled for more accurate comparisons by matching the nonpregnant group, allowing us to isolate the pure influence of pregnancy[16].

Methods

Ethical consideration

The study and all experiments were performed in accordance with regulations and the Declaration of Helsinki guidelines for human studies. The institutional review board of Shahid Beheshti University of Medical Sciences approved the study (IR.SBMU.MSP.REC.1401.384). A previously collected dataset of COVID-19 patients used in this study for matching was approved for use (IR.SBMU.RIGLD.REC.004). Patient confidentiality was considered during the study, and informed consent was obtained from all participants or their legal guardians.

Study context

This study was conducted in two tertiary centers with dedicated COVID-19 wards and ICUs in Tehran, Iran. The study time window was before the vaccination of the general population, which took place in August 2021 in Iran; thus, none of the pregnant and nonpregnant cohorts were vaccinated. The first three peaks of COVID-19 were covered in our study window, including the alpha, beta, and delta variants, but not the Omicron variant[17].

Ref	Duration	Country (percentages of data)	No	Design (no. of included studies)	Study population
7	up to October 2020	China*, USA, Iran*, Italy, Japan, UK, France, Turkey*, Germany, Israel, Switzerland, Australia, Belgium, Brazil*, Dominican Republic*, Honduras*, Hong Kong, Iraqi Kurdistan*, Mexico*, Oman, Peru, Portugal, Saudi Arabia, Spain, Sweden, Taiwan, Thailand*, 22 countries	349	Retrospective (209), Retrospective Case–control (18), Prospective Case–control (1), Case–Control (1), Cross-sectional case–control (1), Case reports (57), Case Study (3), Case series (10), Cross-sectional (6), Descriptive (3), Cohort (2), Retrospective Cohort (4), Prospective (8), Observational (1),	128,176 non-pregnant/10,000 pregnant
8	March 1 to December 31, 2020	USA (24%), India* (11%), Brazil* (9%), Colombia* (9%), China* (7%), Spain (7%), Iran* (7%), France (6%), UK (5%), Mexico* (4%), other 25 countries (11%)	225	Case report (95), Case series (40), Cohort (37), Cross-sectional (27), Observational (14), Case–control (5), Case study (3), Retrospective (3), Prospective (1)	10,582 women
9	December 2019 to February 2021	Australia, Africa (Egypt*, French Guinea*, Ghana*, Nigeria*), Asia (China*, India*, Indonesia*, Iran*, Japan, Kuwait, Oman, Pakistan*, Russia*, Singapore), Europe (Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Israel, Italy, Moscow*, North Macedonia*, Portugal, Republic of Kosovo*, Romania, Serbia*, Slovenia, Spain, Sweden, Switzerland, Netherlands, Turkey*, UK), North America (Dominica Republic*, Mexico*, USA), South America (Argentina*, Brazil*, Colombia*, Peru*)	62	Prospective/retrospective Cohorts (51), Case series (11)	31,016 pregnant
10	April 2020	China* (84.89%), USA (14.29%), Iran* (0.55%), Turkey* (0.27%)	35	Case reports (17), Case series (6), Case study (4), Retrospective (3), Case–control (2), Cohorts (2), Cross-sectional (1)	364 pregnant
11	March to May 2020	China* (59.95%), EUA (27.18%), Italy (12.14%), Iran* (0.24%), Portugal (0.24%), Turkey* (0.24%)	34	Case report/Multiple case report (23), Observational (11)	412 pregnant
12	December 2019 to April 30, 2020	China* (97.06%), Honduras* (0.74%), Iran* (0.74%), Republic of Korea* (0.74%), USA (0.74%)	24	Case reports (10), Retrospective cohort (8), Case series (4), Prospective cohort (1), Case–control (1)	136 women
13	Up to April 18, 2020	China* (79.57%), USA (18.70%), Honduras* (0.43%), Iran* (0.43%), Korea* (0.43%), Turkey* (0.43%)	20	Case reports (15), Retrospective Cohort (4), Case–control (1)	230 pregnant
14	February 25, 2021	USA (69.30%), Mexico* (30.64%), China* (0.06%), Israel (<0.01%)	9	Retrospective cohort (6), Case–control (2), Prospective Cohort (1)	562,261 nonpregnant/28,797 pregnant

Table 1. Summary of systematic reviews and meta-analyses on the clinical manifestations of COVID-19 in pregnant and nonpregnant women. *Indicates low- to middle-income countries (LMICs) according to the World Bank data.

The first national guideline for COVID-19 during pregnancy was published in early 2021. Admission for pregnant patients with chest pain and admission to a tertiary center were recommended if the respiratory rate was higher than 24 or if the oxygen saturation was less than 95%. The PCR test was requested for all suspicious pregnant patients or patients who required admission due to any cause. Similar protocols were applied to the control group, with the exception of more stringent PCR testing criteria for pregnant individuals.

Pregnant cohort and data gathering

In this retrospective cross-sectional study, a purposive sampling technique was employed for the pregnant cohort, which included all pregnant COVID-19 patients admitted to Imam Hussein Hospital or Taleghani Hospital from March 20, 2020, to September 25, 2021. The inclusion criteria were as follows: (1) current pregnancy, (2) positive COVID-19 PCR results, and (3) admission to Imam Hussein Hospital, or Taleghani Hospital from March 20, 2020, to September 25, 2021. A medical team collected patients' symptoms, comorbidities, habitual history, vital signs at admission, and treatment protocol through the hospital information system and medical Patients with negative PCR were excluded. The interval between the patients' first symptoms and admission was defined as early referral (1–5 days), intermediate referral (6–10 days), or late referral (11–15 days). Laboratory values during the first and second days of admission were gathered and sorted from the hospitals' electronic laboratory records via the Python program (Python Software Foundation. Python Language Reference, version 4. Available at http://www.python.org).

Nonpregnant cohort and matching

We used a previously collected dataset with the same data collection pipeline and time window, including 2,276 women. After excluding pregnant patients, we used this dataset to match admitted COVID-19 patients to each individual in the pregnant arm of the study considering (1) being in the ± 5-year range; (2) having the same history of smoking (binary), alcohol consumption (binary), hypertension (binary), ischemic heart disease (binary), diabetes mellitus (binary), and chronic kidney disease (binary); and (3) having the same interval between disease onset and admission (early, intermediate, or late)[18]. Notably, as the pregnant cohort contained no individuals with a history of smoking or alcohol consumption, these characteristics were correspondingly absent in the matched non-pregnant cohort. While we aimed to find two matched nonpregnant patients for each pregnant patient, which was achieved for 41 cases, we found only one matched pair for 25 cases.

Radiologic examination

A qualified clinician evaluated the chest CT scans of pregnant and nonpregnant patients. The pattern, parenchymal type, and distribution of lung involvement were recorded. For the evaluation of the CT scan severity score (CT-SS), every five lobes of the lung received a score from 0–5 (0, no involvement; 1, < 5% involvement; 2, 5–25% involvement; 3, 26–49% involvement; 4, 50–75% involvement; and 5, > 75% involvement). We previously reported an association between the CT-SS score and poor outcomes, and the same approach was used for reporting radiologic exams in this study[19]. The widest short-axis diameter of the main, left, and right pulmonary arteries was calculated on the transverse section of the CT scan image at the level of the bifurcation of the pulmonary artery trunk.

Statistical analysis

Descriptive statistics are reported as the means ± standard deviations (SDs) or medians (interquartile ranges (IQRs)) for numeric variables and frequencies (percentages) for categorical factors. Variables significantly related to either the exposure (pregnancy) or outcome (time to death) were identified as confounders, according to the study by Zoller et al.[20]. To identify confounders, the relationships between potential confounders and time to event were examined via Cox regression. In this study, backward stepwise analysis was conducted to identify the best predictor variables from a more extensive set of potential predictor variables. All predictors were used in the analysis, followed by the removal of variables with the highest p values one by one until the Akaike information criterion (AIC) was calculated. In general, backward stepwise analysis is preferred because all variables are taken into account at once when starting with the full model[21].

Results

In this study, we analyzed 173 COVID-19 patients, comprising 66 pregnant and 107 nonpregnant women. The median age was 34.3 years, with pregnant patients being significantly younger (median age: 31.2 years, $p < 0.001$). All pregnant participants were in their late stages of pregnancy (median gestational age: 31 weeks). No significant differences were observed in BMI or symptom-to-admission duration between the two groups. The patients' characteristics, comorbidities, laboratory tests, and radiologic presentations are summarized in Tables 2 and 3. (More extensive tables are available in Supplementary Tables S1, S2).

The main symptoms at admission and past medical history of diseases (such as HTN, DM, asthma, pneumonia, GI disease, and cancer, as shown in Table 2) were not significantly different between the two groups. The only significant difference was in thyroid problems, which were more prevalent in pregnant patients (24.24% vs. 8.41% in nonpregnant patients, $p = 0.008$). Clinical manifestations such as cough, dyspnea, and fever were not significantly different between the groups. However, vital signs revealed higher pulse (103.5 vs. 89.2 beats/min) and respiratory rates (24.2 vs. 19.7 breaths/min) but lower systolic blood pressure (110.1 vs. 116 mmHg) in pregnant patients, all of which were statistically significant ($p < 0.001$ for pulse and respiratory rate, $p = 0.002$ for systolic blood pressure).

Variables	Total (N = 173)	Nonpregnant (N = 107)	Pregnant (N = 66)	P value
Demographics				
Age (y)	34.3 (26.6, 42.0)	36.2 (27.9, 44.5)	31.2 (25.9, 36.5)	< 0.001
Gestational age (week)	31.0 (25.0, 34.0)	0.0 (0.0, 0.0)	31.0 (25.0, 34.0)	–
BMI (kg/m^2)	27.8(21.8, 33.8)	27.4 (21.4, 33.4)	30.0 (24.3, 35.7)	0.186
Symptom to admission (days)	6.0 (3.0, 7.0)	6.0 (3.0, 7.0)	6.0 (4.0, 10.0)	0.333
Past medical history				
HTN	2 (1.16%)	0 (0.00%)	2 (3.03%)	0.281
Asthma	8 (4.62%)	8 (7.48%)	0 (0.00%)	0.057
DM	5 (2.89%)	4 (3.74%)	1 (1.52%)	0.703
Pneumonia	1 (0.58%)	1 (0.93%)	0 (0.00%)	1.000
GI disease	3 (1.73%)	3 (2.80%)	0 (0.00%)	0.440
Cancer	5 (2.89%)	5 (4.67%)	0 (0.00%)	0.189
Thyroid problem	25 (14.45%)	9 (8.41%)	16 (24.24%)	0.008
Clinical manifestations				
Cough	107 (61.85%)	63 (58.88%)	44 (66.67%)	0.388
Dyspnea	112 (64.74%)	68 (63.55%)	44 (66.67%)	0.800
Fever	87 (50.29%)	59 (55.14%)	28 (42.42%)	0.142
Presenting vital signs				
Pulse rate (beats/min)	94.8 (77.6, 112.0)	89.2 (72.7, 105.7)	103.5 (89.0, 118.0)	< 0.001
Diastolic BP (mmHg)	72.9 (64.0, 81.8)	73.9 (64.9, 82.9)	71.5 (72.9, 79.1)	0.057
Systolic BP (mmHg)	113.5 (101.2, 125.8)	116.0 (103.7, 128.3)	110.1 (98.7, 121.5)	0.002
Respiratory rate (breaths/min)	21.5 (15.6, 27.4)	19.7 (15.0, 24.4)	24.2 (17.8, 30.6)	< 0.001
Temperature (°C)	37.3 (36.5, 38.1)	37.2 (36.4, 38.0)	37.3 (36.5, 38.1)	0.403
Radiological findings				
Peripheral	123 (71.10%)	82 (76.64%)	41 (62.12%)	0.061
Perihilar	4 (2.31%)	3 (2.80%)	1 (1.52%)	0.978
Peribronchovascular	69 (39.88%)	39 (36.45%)	30 (45.45%)	0.310
Normal	5 (2.89%)	3 (2.80%)	2 (3.03%)	1.000
GGO	108 (62.43%)	64 (59.81%)	44 (66.67%)	0.458
Consolidation	67 (38.73%)	41 (38.32%)	26 (39.39%)	1.000
Crazy-paving pattern	4 (2.31%)	4 (3.74%)	0 (0.00%)	0.285
Reverse halo	10 (5.78%)	8 (7.48%)	2 (3.03%)	0.378
Sharp opacities	23 (13.29%)	21 (19.63%)	2 (3.03%)	0.004
Hazy opacities	10 (5.78%)	1 (0.93%)	9 (13.64%)	0.002
Linear	30 (17.34%)	14 (13.08%)	16 (24.24%)	0.094
COP	20 (11.56%)	5 (4.67%)	15 (22.73%)	0.001
MPA (mm)	25.0 (23.0, 27.0)	25.0 (23.0, 26.0)	26.0 (24.0, 29.5)	0.009
RPA (mm)	15.0 (13.0, 17.0)	14.0 (13.0, 16.0)	17.0 (16.0, 19.0)	< 0.001
LPA (mm)	15.0 (14.0, 17.0)	15.0 (14.0, 16.0)	17.0 (16.0, 19.0)	< 0.001
Disposition and special treatment				
COVID ward admission	34 (19.65%)	22 (20.56%)	12 (18.18%)	0.703
ICU admission	139 (80.34%)	85 (79.43%)	54 (81.81%)	
Dialysis	2 (1.16%)	2 (1.87%)	0 (0.00%)	0.700
Blood Injection	6 (3.47%)	1 (0.93%)	5 (7.58%)	0.059
Intubation	4 (2.31%)	2 (1.87%)	2 (3.03%)	1.000
Outcome				
LOS (days)	6.0 (2.0, 8.0)	6.0 (2.0, 8.5)	5.5 (4.0, 8.0)	0.567
Death	9 (5.20%)	6 (5.61%)	3 (4.55%)	1.000

Table 2. Comparison of characteristics, comorbidities, and radiologic presentations between pregnant and nonpregnant patients with COVID-19. A more comprehensive table is available in Table S1. Data are presented as the mean difference (95% confidence interval) or frequency (%).

Laboratory exam

We present the summarized laboratory findings in Table 3, and the laboratory data highlighted several significant differences (a more extensive table is accessible in Supplementary Table S2). The white blood cell count was notably greater in pregnant women (8.1 vs. 6.5 × 103/μL, $p < 0.001$), as was the neutrophil-to-lymphocyte ratio

Variables	Total (N = 173)	Nonpregnant (N = 107)	Normal range in nonpregnant	Pregnant (N = 66)	Normal range in 3rd trimester	P value
WBC ($\times 10^3/\mu L$)	7.1 (3.3, 10.9)	6.5 (2.5, 10.5)	4.4–11.2	8.1 (4.7, 11.5)	5.6–16.9	< 0.001
LYMPHS (%)	20.7 (9.7, 31.7)	23.8 (11.9, 35.7)	19–48	16.3 (8.4, 24.2)	20–40	< 0.001
LYMPHS count ($\times 10^3/\mu L$)	1.5 (1.1–1.9)	1.5 (1.0–2.0)	1–4.8	1.3 (1–1.6)	1–3.6	< 0.001
NEUT (%)	73.1 (59.7, 86.5)	69.6 (55.7, 83.5)	40–74	78.1 (67.0, 89.2)	40–74	< 0.001
NEUT count ($\times 10^3/\mu L$)	5.2 (4.7–5.8)	4.5 (4–5)	1.4–4.6	6.3 (5.9–6.7)	3.9–13.1	< 0.001
PLT ($\times 10^3/\mu L$)	198.5 (124.0, 273.0)	196.1 (122.8, 269.4)	150–450	202.0 (125.3, 278.7)	146–429	0.296
NLR	3.5 (2.3–4.7)	2.9 (1.7–4.1)	1-3[a]	4.8 (3.4–6.2)	2.3–4.7[a]	< 0.001
PLR	132.3 (98–166.6)	130.7 (99.5–161.5)	90-210[a]	155.4 (110.1–200.7)	76.1–160.1[a]	0.110
HB (g/dL)	11.6 (9.9, 13.3)	11.8 (10.1, 13.7)	12–16	11.3 (9.9, 12.7)	9.5–15	< 0.001
UREA (mg/dL)	17.5 (14.2, 24.9)	20.7 (15.9, 27.0)	7–20	15.0 (12.9, 19.2)	3–11	< 0.001
CA first (mg/dL)	8.3 (7.7, 8.9)	8.4 (7.8, 9.0)	8.5–10.5	8.2 (7.6, 8.8)	8.2–9.7	0.273
ALKP first (U/L)	177.0 (123.0, 256.0)	151.5 (114.3, 212.3)	64–306	210.0 (160.0, 283.0)	38–229	< 0.001
BILL (T) first (mg/dL)	0.6 (0.5, 0.9)	0.5 (0.4, 0.6)	0.5–1.5	0.8 (0.6, 1.1)	0.1–1.1	< 0.001
BILL (D) first (mg/dL)	0.2 (0.2, 0.4)	0.2 (0.2, 0.3)	Up to 0.5	0.3 (0.2, 0.5)	Up to 0.1	0.090
ALBUMIN first (g/dL)	3.7 (3.3, 4.1)	3.9 (3.6, 4.2)	3.5–5.5	3.3 (3.2, 3.7)	2.3–4.2	< 0.001
TG first (mg/dL)	215.0 (120.0, 241.5)	128.0 (114.0, 182.0)	< 150	278.5 (219.8, 334.3)	131–453	0.009
Cholesterol first (mg/dL)	138.5 (122.3, 145.3)	121.0 (115.0, 137.0)	< 200	155.0 (140.0, 171.0)	219–349	0.024
HDL first (mg/dL)	36.0 (30.0, 38.8)	30.0 (27.4, 37.5)	30–80	37.9 (36.0, 39.0)	48–87	0.099
LDL first (mg/dL)	85.3 (44.0, 126.8)	74.0 (69.8, 78.3)	< 100	106 (34.1, 177.9)	101–224	0.933
ESR first (mm/h)	46.0 (28.0, 65.0)	45.5 (27.0, 64.3)	Up to 20	47.0 (31.0, 68.0)	13–70	0.759
CRP (mg/L)	45.1 (17.0, 73.1)	43.9 (14.0, 73.8)	Up to 5.9	42.7 (22.3, 63.2)	0.4–8.1	0.439
IL-6 first (pg/mL)	34.0 (9.9, 58.9)	60.4 (60.4, 60.4)	Up to 5.9	30.3 (6.1, 74.6)	Up to 4.40[c]	0.500
CPK first (IU/L)	75.0 (48.5, 148.5)	72.0 (49.0, 150.0)	24–170	80.0 (47.0, 144.0)	13–101*	0.975
PCT first (ng/mL)	0.2 (0.1, 0.4)	0.3 (0.1, 0.5)	< 0.05	0.2 (0.1, 0.3)	< 0.05	0.735
Fe (µg/dL)	28.0 (16.0, 55.0)	21.0 (16.0, 42.5)	65–150	61.0 (47.5, 74.5)	30–193	0.231
Ferritin (ng/mL)	171.9 (94.9, 262.0)	228.5 (152.0, 354.3)	10–291	112.0 (60.0, 160.7)	Up to 166	< 0.001
D-Dimer first (ng/mL)	899.0 (462.5,1541.3)	534.5 (326.8,1016.0)	Up to 600	1353.0 (825.0,1914.3)	130–1700	< 0.001
FDP (µg/mL)	6.0 (3.5, 8.9)	5.4 (2.2, 8.5)	Up to 5	7.5 (5.3, 14.0)	2.39–4.96	0.131
T4 (µg/dL)	11.1 (9.5, 16.3)	9.5 (8.2, 10.1)	4.6–12.5	13.7 (10.8, 17.0)	6.3–9.7	< 0.001
T3 (ng/mL)	1.2 (0.9, 1.6)	0.9 (0.8, 1.0)	0.6–2.10	1.6 (1.1, 1.9)	1.89–2.29	< 0.001
PH first (mmHg)	7.4 (7.3, 7.5)	7.4 (7.3, 7.5)	7.38–7.42*	7.4 (7.4, 7.5)	7.39–7.45*	0.651
PH (mmHg)	7.4 (7.3, 7.5)	7.4 (7.4, 7.4)		7.4 (7.3, 7.5)		0.595
PCO_2 first (mm Hg)	39.3 (35.7, 45.1)	42.2 (38.8, 46.8)	40–52	36.5 (30.2, 38.9)	38–52	< 0.001
PCO_2 (mm Hg)	43.4 (38.3, 48.4)	44.8 (40.1, 49.6)		40.1 (37.3, 44.1)		0.001
BE first (mmol/L)	0.3 (− 2.8, 2.6)	1.7 (0.1, 4.1)	− 2 to 2	− 2.6 (− 4.5, − 0.1)	Not reported	< 0.001
BE (mmol/L)	1.5 (− 1.6, 4.0)	2.4 (− 0.4, 4.6)		0.5 (− 2.7, 2.6)		0.001
LACTATE First (mmol/L)	16.8 (13.1, 22.0)	17.4 (13.1, 21.8)	6–18	16.0 (13.3, 24.0)	6–18	0.956
VitD3 (ng/mL)	18.8 (14.5, 28.5)	18.1 (13.0, 27.8)	31–70	19.0 (17.0, 29.4)	60–119	0.193

Table 3. Comparison of laboratory data between pregnant and nonpregnant patients with COVID-19. A more comprehensive table is accessible in Supplementary Table S2. Data are presented as the mean difference (95% confidence interval) or frequency (%). Some normal values were derived from different references, which are indicated as * (UpToDate: https://www.uptodate.com/contents/normal-reference-ranges-for-laboratory-values-in-pregnancy). [a]References[65,66]. [b]Reference[67]. [c]Reference[68].

(NLR) (4.8 vs. 2.9, p < 0.001). Hemoglobin levels were lower in pregnant women (11.3 vs. 11.8 g/dL, p < 0.001). Kidney function tests revealed significantly higher urea levels in nonpregnant patients (p < 0.001). Liver function tests revealed greater alkaline phosphatase levels in pregnant women (210.0 vs. 151.5 U/L, p < 0.001) and a significant difference in total bilirubin levels (0.8 vs. 0.5 mg/dL, p < 0.001). Serum triglycerides and cholesterol were significantly greater in pregnant patients (p = 0.009 and p = 0.024, respectively).

The neutrophil-to-lymphocyte ratio (NLR) was significantly greater in pregnant patients (4.8 (3.4, 6.2) vs. 2.9 (1.7, 4.1)), whereas the platelet-to-lymphocyte ratio (PLR) was normal and did not significantly differ between the two groups. The mean albumin level was significantly lower in the pregnant group (3.3 g/dL (3.2, 3.7)) than in the nonpregnant group (3.9 g/dL (3.6, 4.2)). A significantly greater D-dimer level was detected in pregnant patients (1353 ng/mL (825, 1914.3) than in the control group (534.5 ng/mL (326.8, 1016), $p < 0.001$)).

Inflammatory markers such as the ESR and CRP level were elevated in pregnant patients but not significantly different between pregnant patients and nonpregnant patients. Interleukin-6 (IL-6) was high in all participants (30.3 (6.1, 74.6)) but was not significantly different between the two groups. The mean creatine phosphokinase

(CPK) level was normal in both groups, but some pregnant patients presented high CPK. Elevated procalcitonin (PCT) was detected (0.2 (0.1, 0.4)) in all participants, but it was not significantly different between the two groups.

Radiologic exam

As shown in Table 2 and Supplementary Table S1, the distributions of lung abnormalities across various lobes (RMLs and RLLs) were not significantly different between pregnant and nonpregnant women. Ground glass opacity (GGO) appeared in 62.43% of all patients, with a marginally greater occurrence in pregnant women (66.67% vs. 59.81% in nonpregnant patients; $p = 0.458$), although this difference was not statistically significant. The consolidation patterns, which were found in 38.73% of the cases, also did not differ significantly between the pregnant and nonpregnant groups ($p = 1.000$).

Furthermore, the study revealed minor disparities in the predominant locations of abnormalities, such as greater peripheral involvement in nonpregnant patients (62.12% vs 76.64%, $p = 0.061$) and greater peribronchovascular involvement in pregnant patients (45.45% vs 36.45%, $p = 0.31$). The specific lesion patterns, including crazy-paving, sharp opacities, and cryptogenic organizing pneumonia (COP), were similarly distributed across both patient groups. However, we noted significant differences in the diameters of the main, right, and left pulmonary arteries, which were greater in pregnant women (MPA: $p = 0.009$; RPA: $p < 0.001$; LPA: $p < 0.001$), indicating that vascular changes are associated with pregnancy. These findings highlight that while certain vascular dimensions vary among pregnant women, the overall pulmonary manifestation patterns of COVID-19 remain largely similar between pregnant and nonpregnant patients.

Outcome and disposition

Among all participants in this study, 80.34% were admitted to the special intensive care unit (ICU) for COVID-19 patients. No significant increase in ICU admission was observed between pregnant patients (N = 54, 81.81%) and matched patients (N = 85, 79.43%) ($p = 0.703$). There was no statistically significant difference between the two groups in terms of special treatments, such as dialysis, injection of blood, platelets and FFP, or intubation (Supplementary Table S1). The length of hospital stay and mortality rates were also similar between the groups. Cox regression modeling indicated that pregnancy did not increase the risk of death among COVID-19 patients (Table 4).

Prognostic factors

As shown in Supplementary Table S3, the univariate logistic regression analysis revealed that age, thyroid problems, pulse rate, systolic blood pressure, respiratory rate, and some laboratory data, such as WBC, lymphocyte and neutrophil counts, hemoglobin, urea, creatinine, NA final, K first, Ca final, ALBUMIN first, TG first, HDL first, Fe, TIBC, ferritin, PT, PTT, INR, D-dimer, FDP, T4, T3, PCO_2, and HCO_3, and BE, as well as radiological manifestations, such as sharp opacities, hazy opacities, COP, and the diameter of pulmonary arteries (main, left and right), were associated with pregnancy in COVID-19 patients. The prognostic indicators of pregnancy outcome were gestational age, loss of consciousness, O_2 saturation with supplementary O_2, WBC count, lymphocyte count, Na first and finally, K first, Albumin first, TG first, CPK first, PH, BE first, vitamin D3, and intubation in COVID-19 patients.

Table 4 shows the Cox regression model used to evaluate the risk of pregnancy at the time of death in our patients. The hazard ratio of time to death was 0.45, with a 95% CI between 0.11 and 1.90 ($p = 0.276$) in the unadjusted model. A stepwise analysis with variables including the serum ALB concentration (ALBUMIN) and CPK showed an HR of 0.26, with a 95% CI between 0.06 and 2.14 ($p = 0.348$). The risk of death was not increased in pregnant women in the fully adjusted model ($p = 0.981$, HR: 5.61, 95% CI: 0-inf).

Discussion

A tremendous body of evidence supports the idea that elderly individuals and those with comorbidities such as HTN, DM, cardiovascular disease, COPD, and obesity, as well as the interval between the onset of symptoms and admission, have a greater risk of complications and adverse outcomes of COVID-19[22–24], which is why having a matched control group facilitates any conclusion about pregnancy as an isolated risk factor for COVID-19. Figure 1 briefly summarizes differences in the incidence of COVID-19 and similarities between pregnant and nonpregnant patients. Consistent with previous meta-analyses, pregnant and nonpregnant COVID-19 patients presented similar clinical characteristics[7], and the common symptoms were dyspnea, cough, and fever[11]. They were followed by myalgia, chill, and nausea/vomiting in both groups. Owing to immunological and physiological changes during pregnancy, vital signs can be dissimilar to those of nonpregnant individuals. Unlike reports from a meta-analysis performed in 2021, where pregnant individuals demonstrated a heightened risk of severe

Model	HR (95% CI)	P value
Nonadjusted	0.45 (0.11, 1.90)	0.276
Full adjusted	5.61 (0, INF)	0.981
Stepwise	0.26 (0.06, 2.14)	0.348

Table 4. The impact of pregnancy on the time to death was evaluated via unadjusted, fully adjusted, and stepwise models. Variables, including ALBUMIN first and CPK first, were used for the stepwise model.

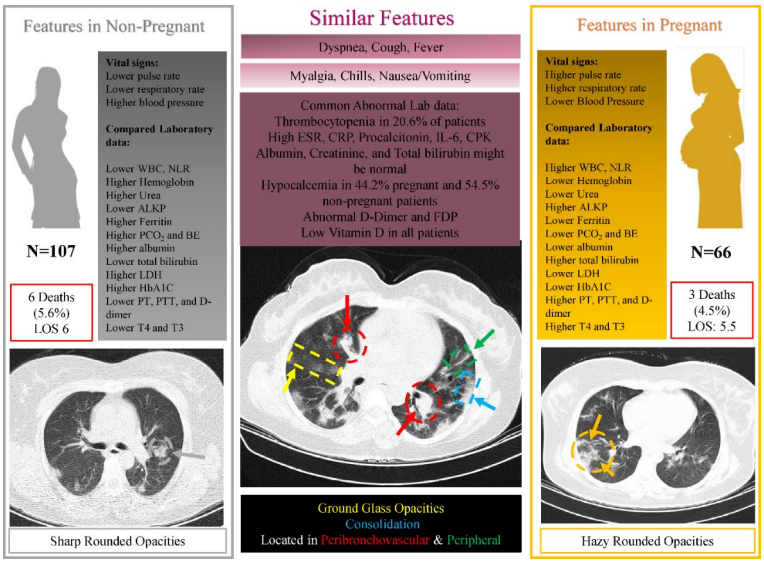

Fig. 1. Summary of findings between pregnant and nonpregnant COVID-19 patients, including laboratory and radiological examinations.

COVID-19[9], our patients were admitted with similar clinical signs and symptoms to hospitals, with no excessive severity compared with nonpregnant individuals.

Owing to the universal screening of all pregnant patients, pregnancy provides a great chance for proper estimation of asymptomatic carriers in the population. Two hundred eleven asymptomatic pregnant women were admitted to New York Hospital between March and April 2020, 29 (13.7%) of whom tested positive for SARS-CoV-2; this indicates that the prevalence of the disease is underestimated in the general nonpregnant population[25]. Greater supervision and sensitivity toward pregnant women has a significant impact on tracing and managing COVID-19 among this vulnerable group of patients, leading to early hospitalization of pregnant patients, which may explain why, despite being more susceptible to infection, these patients have the same presentations and outcomes[26].

It has been recommended that laboratory tests be performed, as well as a comprehensive past medical history and assessment of clinical symptoms and signs for the diagnosis and prognosis of COVID-19 pneumonia[11,27]. Furthermore, laboratory changes and their variations during hospitalization should be closely monitored in pregnant COVID-19 patients to assess the severity of the disease and the prognosis[28]. Lymphocytopenia is reported to be the most common laboratory abnormality found in COVID-19 patients, followed by thrombocytopenia[29]. We did not have participants with lymphocyte counts less than 1000/μL, but we detected high and significantly different NLRs in pregnant COVID-19 patients (mean 4.8) compared with nonpregnant patients. A high NLR is known to be correlated with other inflammatory markers in COVID-19 patients with poor outcomes (ICU admission and death) and should be followed by chest CT for further evaluation[29–31]. Some studies have suggested a cutoff of 3.13, and others have suggested a cutoff of 5.1 for the NLR. On the basis of our results, we assume that greater attention should be given to the NLR in pregnant COVID-19 patients. Further studies in this area could be beneficial for the treatment of pregnant patients with COVID-19.

Increased ALT, AST, ALKP, bilirubin, BUN, CR, and hypoalbuminemia are prevalent changes associated with liver and kidney function and the risk of severe disease in COVID-19 patients[32–34]. Serum ALKP elevation is not significantly greater in patients with severe COVID-19 patients. In the present study (Supplementary Table S2), we observed increased aminotransferases (increased ALT in 48.1% of pregnant patients and 28.9% of nonpregnant patients and increased AST in 53.7% of pregnant patients and 40% of nonpregnant patients with COVID-19), no albumin, total bilirubin, CR abnormalities, or significantly high ALKP levels in the pregnant group compared with the nonpregnant group. Although increasing ALKP is a physiological response during pregnancy[35], 44.1% of pregnant COVID-19 patients in this study presented abnormal increases in ALKP. While some studies have shown that high levels of ALKP are associated with intrauterine growth restriction (IUGR) and placental insufficiency[36], some case reports have shown no pathological associations[35]. Since COVID-19 infection is known to cause adverse maternal and fetal outcomes such as placental insufficiency, preeclampsia, preterm birth, and IUGR[9,37], we recommend monitoring abnormal ALKP levels in pregnant COVID-19 patients and considering the need for vasopressor drugs[33].

Elevated levels of CRP, CPK, and PCT serve as important biomarkers in COVID-19 patients, with their alterations being associated with more severe outcomes[38]. We detected high CRP and PCT levels but no significant difference between the two groups, which is consistent with the study of Mohr-Sasson et al.[39]. Similarly, other inflammatory markers (ESR, IL-6, CPK) did not significantly differ between pregnant COVID-19 patients and matched nonpregnant individuals. Increased pancreatic enzymes, especially those present in more than three patients, may exacerbate the complications of COVID-19[40]. Although the mean amylase and lipase levels were within the normal range in this study (Supplementary Table S2), the data were not sufficient to provide a conclusive

statement because of the lack of reported results in the included patients. Cardiac biomarkers (troponin, CKMB, and pro-BNP) and lipid profiles (total cholesterol, HDL, LDL) also provide valuable prognostic information for assessing the severity and mortality of COVID-19[41]. There was a normal range of cardiac biomarkers and low HDL (< 48) in pregnant COVID-19 patients (Supplementary Table S2), and no significant differences were observed among the groups. Overall, these findings may help elucidate the similar clinical courses observed between the two groups in our study.

Electrolyte imbalances such as hyponatremia, hypernatremia, and hypocalcemia are known to be associated with poor COVID-19 outcomes[42]. Although we did not observe hypo- or hypernatremia in this study, hypocalcemia was identified in 44.2% (19 out of 43) of pregnant individuals and 54.5% (36 out of 66) of nonpregnant patients (Supplementary Table S2). Notably, calcium supplementation is required during pregnancy for normal growth and skeletal development of the fetus. In the context of COVID-19 pneumonia, the virus can induce hypoparathyroidism either directly, through damage to parathyroid glands, or indirectly, by increasing the resistance of PTH receptors. This can ultimately result in hypocalcemia[43]. Additionally, vitamin D levels were abnormal across all participants. Vitamin D plays a pivotal role in facilitating the absorption of calcium from the intestine. Thus, it is important to emphasize the importance of calcium and vitamin D supplementation during COVID-19 management, with a specific focus on pregnant patients.

Lung CT plays a key role in the diagnosis and follow-up of COVID-19; therefore, we thoroughly assessed pregnant patients' imaging data and compared them with those of nonpregnant matched controls in our study. According to a 2020 published paper in Wuhan, China, 23 hospitalized pregnant patients with COVID-19 were enrolled in the study[44] and underwent lung low-dose CT scanning. Some had intralobular interstitial thickening with consolidation and fibrous stripes, whereas others manifested ground-glass opacity of symmetrical spheres and concomitant hydropericardium and/or hydrothorax, which is generally similar to the findings of nonpregnant patients with COVID-19 pneumonia, which aligns with our study. Our findings suggest that COVID-19 imaging (chest CT scan) of lung involvement patterns and severity align with epidemiological data among nonpregnant controls over time.

Most participants presented with abnormal radiological findings highlighted through GGOs and consolidation distributed in peripheral and peribronchovascular regions. Pregnant COVID-19 patients had more hazy opacities and COP than nonpregnant patients did. Hazy opacities indicate a more widespread distribution of infection than sharp-rounded opacities do. It is also associated with inflammation, edema, interstitial lung diseases, and diffuse alveolar damage. COP involves organized granulation tissue plugs in small alveoli. COP is extremely rare during pregnancy but is essential in terms of prognosis, complications, and treatment[45]. Notably, the incidence of COP was significantly higher in the pregnant cohort. In our study, patient matching by symptom-to-admission time eliminated delayed presentation as a factor in the higher COP prevalence observed in pregnant women. Pregnancy-related immunological and physiological changes may explain the differential pulmonary pathology, warranting further investigation.

The main, left, and right pulmonary artery diameters (MPA, LPA, RPA) in CT scans are valuable measurements indicating pulmonary hypertension. Pulmonary hypertension increases maternal and fetal complications during pregnancy[19]. Notably, hazy opacities, COP, and significantly greater pulmonary artery diameters can indicate a more widespread distribution of infection and pose important considerations for prognosis, complications, and treatment in the pregnant group, both during pregnancy and postpartum.

Surprisingly, our findings revealed that pregnancy did not influence disease severity. A 2021 meta-analysis consisting of 31,016 women affected by COVID-19 from 62 studies revealed that despite pregnant women being at increased risk of experiencing symptoms such as headache, fever, expectoration, myalgia, chest tightness, wheezing, diarrhea, and anosmia as primary symptoms of COVID-19, there was no difference in the severity of the disease between the two groups[14]. A review of 10,996 cases of COVID-19 and pregnancy in 15 countries revealed that maternal and neonatal outcomes are not worse or different from those of the general population[46]. Moreover, in July 2020, a letter to the New England Journal from Wuhan noted that severe disease had the same prevalence in the pregnant population (8%) as in the general population of patients presenting with COVID-19 across mainland China (15.7%). On the other hand, a report from the Centers for Disease Control and Prevention (CDC) compared 8,207 cases of COVID-19 among pregnant women with 83,205 cases among nonpregnant women[47]. Although the report revealed a greater number of hospitalizations among pregnant women (31.5 vs. 5.8%), the number of ICU admissions during pregnancy was slightly greater (1.5 vs. 0.9%), and the need for mechanical ventilation was not greater during pregnancy (0.5%) than among nonpregnant women (0.3%)[48]. There are multiple rationales justifying the variety of clinical presentations and severity differences of COVID-19 infection during pregnancy compared with the general nonpregnant population, such as what was observed during influenza[49].

The cytokine storm in COVID-19 patients is an uncontrolled immune response and an indicator of a severe clinical course that results in mortality, intensive care unit (ICU) admission, mechanical ventilation, multiorgan failure, and respiratory distress[50,51]. There are several risk factors for cytokine storms, such as advanced age, a weakened immune response, and past medical conditions (obesity, DM, HTN). Cytokine storms are characterized by increased ferritin[52], IL-6, D-dimer, and LDH levels, which are associated with the risk of deterioration and poor prognosis. High ferritin, low iron, low TIBC, and low hemoglobin levels are strongly associated with the risk, severity, and mortality of COVID-19 patients[53]. Surprisingly, we reported significantly lower ferritin levels in pregnant COVID-19 patients[54]. It has been reported that the inflammatory state in COVID-19 patients increases ferritin levels, and high ferritin is associated with high severity of disease and poor outcomes[54,55]. This might be one of the reasons for the total insignificant difference in mortality between pregnant and nonpregnant individuals. Thus, there are still considerable controversies in this context, which indeed require a thorough evaluation and update.

Derangements in coagulation markers such as the PLT, PT, PTT, INR, D-dimer and FDP may be drivers behind the sepsis and disseminated intravascular coagulation (DIC) observed among nonsurvived COVID-19 patients. A total of 20.6% of all participants with a median of 198.5 (124–273) (x 10^3 /uL) and 22.2% of pregnant participants with a median of 202 (125.3–278.7) (x 10^3 /uL) in this study presented with thrombocytopenia. Abnormal D-dimer and FDP levels were observed in both groups. PT, PTT, INR, and D-dimer significantly differed between the two groups (Supplementary Table S2). A prolonged coagulation time increases the risk of thromboembolic events, especially during pregnancy[56]. These alterations also affect neonates[57], which was not evaluated in this study. Acidosis is another complication observed in severe cases of COVID-19. O_2 saturation, blood pH, and pO_2 are factors associated with COVID-19. pH was comparable between the groups with lower PCO_2 and base excess (BE) for the pregnant group (Supplementary Table S2), whereas other studies reported lower PCO_2 and higher BE[39].

Most of the patients in this study (80.34%) were admitted to the ICU and stayed in the hospital for six days on average, and nine patients died, indicating a severe course of the disease. The severity did not differ between the pregnant and nonpregnant groups. The death rate during pregnancy was 4.62%, which was approximately the same as that of nonpregnant individuals (5.61%). Although 1% is a significant mortality rate, the result was not statistically significant. The maternal mortality rate did not significantly increase during pregnancy, and some studies support this finding. The results of an analysis of 110 pregnant patients compared with 234 nonpregnant patients affected by SARS-CoV-2 suggested not only that there were no significant differences between the two groups in terms of mortality, intensive care unit (ICU) admission, or end-organ failure but also that the rate of ARDS in pregnant women was lower[58]. On the other hand, in a multinational cohort study in 2021, 706 pregnant patients with a COVID-19 diagnosis and similar demographic characteristics experienced more adverse outcomes, such as mortality, preeclampsia, and preterm birth, than noninfected pregnant patients did[59]. Nevertheless, it is pivotal to consider that the former paper proposes that COVID-19 is associated with higher rates of maternal death and employs a different method of observational study to compare pregnant patients with other pregnant patients without COVID-19.

Several limitations exist for this study. Publication bias and study heterogeneity are unavoidable in this type of study; therefore, they should be considered when the final dataset is interpreted. Furthermore, the vital role of vaccination must be included in mortality mitigation and in reducing the chances of severe infection. There are several reports that show increased mortality in pregnant COVID-19 patients who are vaccinated[60–62]. However, more studies, as well as a large systematic review and meta-analysis, have shown that the COVID-19 vaccine protects against hospital/intensive care unit admission, intubation, and death in hospitalized pregnant and postpartum women with severe SARS-CoV-2-induced SARS[63,64]. Indeed, unvaccinated pregnant women are more likely to experience severe adverse outcomes.

Conclusion

This study offers crucial insights into the clinical, laboratory, and radiological characteristics of pregnant women with COVID-19, demonstrating no significant difference in disease severity compared with nonpregnant women. Despite initial concerns, both groups presented similar clinical severity and outcomes, challenging the perception of increased vulnerability among pregnant women. This finding is particularly relevant as the pandemic evolves and attention to COVID-19 wanes. Our research also highlights abnormal liver and kidney function markers in pregnant patients, underscoring the necessity for vigilant monitoring. Notably, the higher neutrophil-to-lymphocyte ratio observed in pregnant patients suggests its potential utility as a prognostic indicator. Furthermore, the similarity in radiological findings, such as ground-glass opacities and consolidations, between the two groups reinforces the comparable impact of COVID-19 on both pregnant and nonpregnant women.

Data availability

The raw dataset is available upon request to the corresponding author (Seyed Amir Ahmad Safavi-Naini; sdamirsa@ymail.com), contingent upon receiving ethical approval confirmation, in compliance with the ethical committee's mandate on data sharing. The code used for analyzing this study is accessible in the GitHub repository at https://github.com/Sdamirsa/Tehran_COVID_Cohort/tree/main/COVID19_Pregnancy_wMatch.

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Competing interests

The authors declare no competing interests.

Additional information

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