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Impact of maternal COVID-19 infection on offspring immunity and maternal-fetal outcomes at different pregnancy stages: a cohort study

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Abstract

Objective To investigate the impact of COVID-19 infection on maternal and neonatal outcomes and immunity in pregnant women in China.

Methods 283 pregnant women with COVID-19 were included in the prospective observational cohort study and divided into five groups based on infection stage. Antibody levels were measured in plasma, umbilical cord blood, and breast milk, and combined with clinical data and 6-month follow-up results. We measured SARS-CoV-2 antibody levels using a chemiluminescence immunoassay and analyzed the data with the Kruskal-Wallis test, $\chi 2$ test, or Fisher's exact test.

Results No significant differences were found in age, BMI, weight change during pregnancy, or the incidence of gestational hypertension, gestational diabetes, gestational hypothyroidism, intrahepatic cholestasis, transaminitis, preterm birth, small for gestational age, neonatal NICU transfers, developmental delays, and hearing damage among the five groups. The incidence of COVID-19 in infants from mothers infected at different stages of pregnancy was significantly lower than in the uninfected group ($P < 0.05$). Maternal and umbilical cord blood showed significantly higher IgG levels in the infected group compared to the uninfected group at different stages of pregnancy ($P < 0.05$). The median transplacental antibody transfer ratio across all infection groups was 1.15 (0.98–1.30), with no significant differences between them. The reinfection group had significantly higher IgA levels during pregnancy compared to other groups ($P < 0.05$).

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Conclusion No adverse outcomes were observed in mothers or infants at any stage of maternal SARS-CoV-2 infection. Antibodies in umbilical cord blood and breast milk may offer passive immunity to newborns for 1–3 months. Reinfection during pregnancy may extend this immunity without raising the risk of adverse outcomes.

Keywords COVID-19, Pregnancy, Infant, Antibody

Introduction

Since December 2019, Corona Virus Disease 2019 (COVID-19) has triggered a global pandemic. After extensive efforts to combat the virus, the current global situation indicates a trend towards normalization, with Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) continuously spilling over between humans and animals due to evolution and recombination [1]. Since late 2022, when the epidemic was lifted, the Omicron variant has become the predominant strain in China [2]. It causes milder symptoms but has an extremely high transmission rate, leading to a sharp increase in infections among vulnerable populations such as pregnant women and newborns [3–4].

The potential adverse effects of the virus on maternal and perinatal outcomes are concerning. Omicron infection may not increase the risk of spontaneous abortion or congenital malformation in the first trimester, but it may raise the likelihood of hypertensive disorders, premature delivery, cesarean sections, and postpartum hemorrhage [5–8]. Vertical transmission is infrequent, and clinical outcomes in offspring generally show positive results [9]. No COVID-19 symptoms were observed in infants aged 1–3 months during follow-up, suggesting possible protection through placental transmission of maternal antibodies [10].

SARS-CoV-2 can trigger the production of protective antibodies in both adults and children, lasting up to 1 year after infection [11–12]. Newborns, with low immunity, receive passive immunity against pathogens through IgG antibodies that cross the placental barrier. Previous studies have shown that newborns can acquire IgG antibodies against the novel coronavirus via the placenta, with a correlation between antibody levels in umbilical cord blood and maternal blood [10, 14–16]. The transplacental antibody transfer ratio is calculated by comparing cord blood IgG levels to maternal IgG levels, ranging from 0.7 to 1.3 across different studies [10, 13–15]. A transfer ratio above 1.0 indicates effective immunity and is influenced by the timing of infection or vaccination [16–17]. The median transfer ratio in previous studies did not consistently exceed 1, leading to controversy over how maternal COVID-19 infection impacts passive immunity for offspring. Therefore, we speculate that SARS-CoV-2 IgG transfer ratios may relate to the stage of infection during pregnancy. Additionally, breastfeeding does not increase transmission risk; IgA antibodies are detectable in breast milk [18–19]. Thus, we aimed to investigate the potential correlation between antibody levels in breast milk and timing of infection.

Previous studies from Western countries mainly focused on early COVID-19 variants, had limited population sizes, and primarily included late-stage infections during pregnancy, with few reports on early-stage infection and delivery. Additionally, the follow-up period for offspring was mostly restricted to three months. In summary, there is a lack of information on maternal and infant outcomes and immunity related to Omicron variant infection in Asian populations, especially since nearly everyone has received three doses of the COVID-19 vaccine. We plan to conduct a larger, longer observational cohort study on pregnant women in China to examine the impact of COVID-19 infection during pregnancy on maternal and infant outcomes. This study will also monitor passive immunity transferred from mothers with COVID-19 to their offspring and analyze differences in outcomes and immunity at different stages of infection—namely the first, second, and third trimesters—which can guide decision-making for pregnant women with COVID-19 as well as public health strategies.

Methods

Study design and patient population

We recruited pregnant women undergoing prenatal examinations and deliveries at the Obstetrics Department of The Third Affiliated Hospital of Chongqing Medical University who were infected with COVID-19 during pregnancy. They were categorized into five groups based on infection stage: first trimester (GA 0 to 13^{+6} weeks), second trimester (GA 14 to 27^{+6} weeks), third trimester (GA 28 to 42 weeks), reinfected group (infected twice during pregnancy), and uninfected group. COVID-19 diagnosis followed the "Guidelines for the Diagnosis and Treatment of COVID-19 Infections (Trial version 10)" [20].

Inclusion criteria: (1) Chinese pregnant women over 18 years old, regardless of COVID-19 diagnosis. (2) Pregnant women and their husbands must be informed and agree to participate by signing relevant consent forms.

Exclusion criteria: (1) COVID-19 infection before pregnancy. (2) Other systemic diseases, such as hematological disorders, malignancies, or conditions requiring transfusions and immunotherapy. (3) Severe pregnancy complications preventing participation in further research. (4) Individuals vaccinated for SARS-CoV-2 within one year prior to delivery. (5) Any family history of inherited

diseases. (6) Individuals unable to cooperate with specimen collection.

This study was approved by The Third Affiliated Hospital of Chongqing Medical University Institutional Review Board [MR-50-23-024191/ 2023(16)]. It's regretful that the registration process was not performed before the start of the study due to the observational nature of the study.

Clinical data collection

We obtained clinical data for mothers and children through medical history inquiries and the electronic medical record system, including age, ethnicity, Body Mass Index (BMI), COVID-19 history, obstetric history, chronic diseases, pregnancy complications, delivery history, medication history, vaccination status, etc. We also collected information on the baby's gender, birth details, and health conditions. Electronic questionnaires or telephone follow-ups were conducted to assess the mother's and baby's health at 1 month, 3 months, and 6 months after delivery; this included checking for COVID-19 infection, postpartum bleeding, feeding methods, growth development, etc. The diagnostic criteria for infant COVID-19 infection are the same as mentioned above.

Sample collection

All individuals were asymptomatic at the time of collection. Approximately 3 mL of maternal and cord blood was collected in a yellow top serum tube during delivery hospitalization. Breast milk samples (0.5–3 mL) were collected through hand expression or a breast pump into a red top tube a few days after delivery. One month postpartum, the mother returned for follow-up to collect another breast milk sample. Samples were transported to our Testing Center as soon as possible. Blood samples were centrifuged, and plasma was extracted and frozen at – 80 °C until analysis.

Laboratory methods

The chemiluminescent immunoassay for detecting antibodies (IgG and IgA) reactive to the SARS-CoV-2 receptor-binding domain (SARS-CoV-2 RBD) spike protein was provided by Autobio (Zhengzhou, China) and Bioscience (Chongqing, China). The relative luminescence unit (RLU) of each sample tube showed a positive correlation with the SARS-CoV-2 antibody titer. The critical value (cut-off) was defined as 10% of the mean positive control luminescence plus the mean negative control luminescence. The Sample to Cut Off Ratio (S/CO) was calculated by dividing the sample's luminescence value by the cut-off. A negative result was indicated if the sample's luminescence value was below the cut-off and its S/CO ratio was less than 1.0. Conversely, a positive result occurred if the sample's luminescence equaled or exceeded the cut-off, with an S/CO ratio reaching or surpassing 1.0. All tests were conducted under stringent biosafety conditions.

Statistical methods

No formal sample size calculation was conducted for this descriptive and exploratory study. All women meeting the inclusion and exclusion criteria were recruited during the enrollment period. Data processing, analysis, and plotting were performed using SPSS 26.0 and GraphPad Prism 8.4 software. Descriptive analysis included frequency with percentage for categorical variables and mean (SD) or median (Q1, Q3) for continuous variables. Kruskal-Wallis test assessed differences in measurement data, while $\chi 2$ test or Fisher's exact test evaluated differences in categorical data. A P-value < 0.05 was considered statistically significant.

Results

Demographics

We identified 290 individuals, with or without COVID-19, who delivered at The Third Affiliated Hospital of Chongqing Medical University during the recruitment period. All participants provided informed consent and their medical history. Seven were ineligible for the study due to withdrawal ($n = 1$) and missed sample collection ($n = 6$). During hospitalization, we collected 252 maternal blood samples, 268 umbilical cord blood samples, and 225 breast milk samples from 283 subjects. At 1, 3, and 6 months postpartum, we followed up with 251, 248, and 241 participants respectively and obtained an additional nine breast milk samples (Fig. 1).

Demographics of the 283 mother-infant dyads are presented in Table 1. The study cohort primarily consisted of women of reproductive age, with 96.1% being Han ethnicity, 26.1% having a chronic health condition, and 59.7% experiencing pregnancy complications. All participants had completed the administration of two doses of inactivated SARS-CoV-2 vaccines (produced by Sinopharm Beijing Biological Products Institute, Sinopharm Wuhan Biological Products Institute, or Beijing Kexing Zhongwei Biotechnology Co., Ltd.) prior to conception. Notably, none of the participants had received a vaccination within one year preceding delivery. There were 110 infections in the first trimester, 85 in the second, and 48 in the third trimester. Additionally, there were 22 cases of reinfection (first and second trimesters) and 18 uninfected cases. At that time, the symptoms of infection included fever, sore throat, cough, nasal congestion, rhinorrhea, myalgia, and fatigue. Notably, all participants experienced upper respiratory tract infections without any manifestations of pneumonia, such as dyspnea or hypoxemia. According to the diagnosis and treatment guidelines [20], all cases were classified as mild. This

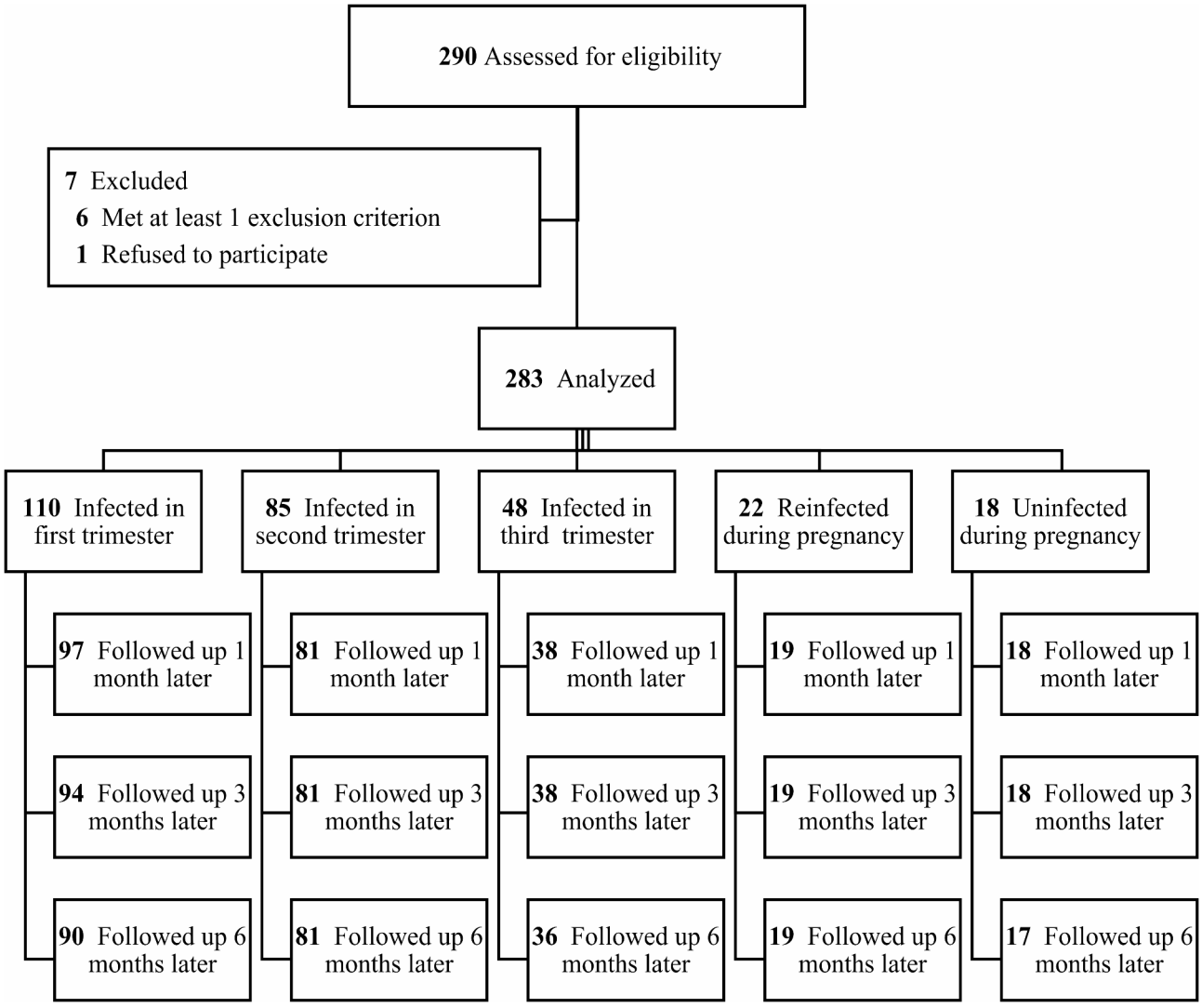

Fig. 1 Study diagram

study included a total of 287 infants, including four sets of twins; all infants were born at >31 weeks gestational age, with 92.7% classified as full-term infants. Forty-one neonates (14.3%) were admitted to the NICU due to conditions such as dyspnea, prematurity, asphyxia, jaundice, and infections. None was diagnosed with COVID-19 during hospitalization.

Maternal clinical outcomes

No significant differences were observed in age, BMI, weight change during pregnancy, or the incidence of gestational hypertension, gestational diabetes mellitus (GDM), gestational hypothyroidism, intrahepatic cholestasis of pregnancy, and transaminitis among pregnant women infected with COVID-19 at different stages (Table 2). Only one woman diagnosed with GDM required insulin therapy; the others managed their glycemic control through dietary modifications and physical activity. Two women diagnosed with hypothyroidism did not receive thyroxine treatment. All women with intrahepatic cholestasis of pregnancy were treated with ursodeoxycholic acid. Only one woman with elevated transaminase received this treatment; the others resolved spontaneously without intervention. A pregnant woman infected with COVID-19 in her second trimester experienced venous thrombosis in both calf muscles (Supplement 1). Additionally, two women with thrombocytopenia and a platelet count exceeding 50 × 10^9/L did not receive any treatment.

The cesarean section rate among the five groups was approximately 50%, with no statistically significant differences observed. There were also no differences in rates of oligohydramnios, placental adhesion, premature rupture of membranes, or postpartum hemorrhage at delivery. During follow-up, the median duration of lochia rubra did not differ between infected and uninfected mothers,

Table 1 Demographics of the 283 mother–infant dyads with COVID-19 in pregnancy

Variable	Mean (SD) or *N* (%)
Mother	
Age(years)	29.7 (4.0)
Ethnicity	
Han	272/283 (96.1)
Miao	5/283 (1.8)
Tujia	4/283 (1.4)
Bai	1/283 (0.4)
Zhuang	1/283 (0.4)
BMI (kg/m^2)	21.3 (2.6)
Chronic health conditions	
Hypertension	4/283 (1.4)
Diabetes	2/283 (0.17)
Obesity	2/283 (0.7)
Infection of HBV or syphilis	15/283 (5.3)
Thyroid disease	18/283 (6.4)
Thalassemia	17/283 (6.0)
Others [a]	16/283 (5.7)
Pregnancy comorbidities	
Hypertension disorder of pregnancy	8/283 (2.8)
Gestational diabetes	56/283 (19.8)
Gestational hypothyroidism	40/283 (14.1)
Intrahepatic cholestasis of pregnancy	4/283 (1.4)
Genital infection	11/283 (3.9)
Fetal growth restriction	19/283 (6.7)
Premature delivery	21/283 (7.4)
Other [b]	10/283 (3.5)
Delivery mode	
Vaginal	134/283 (47.3)
Cesarean section	149/283 (52.7)
Trimester of maternal COVID-19 infection	
First	110/283 (38.9)
Second	85/283 (30.0)
Third	48/283 (17.0)
Reinfection (first and second)	22/283 (7.8)
Uninfected	18/283 (6.4)
Infant	
Sex	
Male	145/287[c] (50.5)
Female	142/287[c] (49.5)
Born weight(g)	3173.6 (411.8)
Gestational age at birth(wk)	39.0 (1.4)
Infant breastfed during birth hospitalization	226/283 (79.9)
Transfer to NICU	
Dyspnea	7/287[c] (2.4)
Premature infant	12/287[c] (4.2)
Neonatal asphyxia	2/287[c] (0.7)
Others [d]	20/287 (7.0)

a. Including ovarian tumors, uterine fibroids, pre-excitation syndrome, arrhythmia, hydronephrosis, and nephropathy

b. Including abnormal aminotransferase during pregnancy, pregnancy-related thrombocytopenia, and thrombosis

c. There were 4 twins

d. Including neonatal sepsis and jaundice

regardless of when infection occurred during pregnancy (Table 2).

The composite rates of adverse perinatal outcomes in mothers, including hypertensive disorders of pregnancy, oligohydramnios, placenta accreta, premature rupture of membranes, and postpartum hemorrhage, were 53.6%, 55.3%, 47.9%, 59.1%, and 22.2%, respectively ($P = 0.106$).

Neonatal clinical outcomes

We analyzed 287 neonates and found no differences in sex, gestational age, or birth weight. The median gestational age and birth weight for each group exceeded 39 weeks and 3,000 g, respectively. Additionally, no statistically significant differences were observed in the incidence of preterm births, small for gestational age infants, or neonatal transfers to the Neonatal Intensive Care Unit (NICU). Newborns admitted to the NICU included those with dyspnea, preterm infants, neonatal asphyxia, jaundice, and sepsis (Table 3). The composite rates of adverse perinatal outcomes in neonates, including preterm births, small for gestational age infants, or neonatal transfers to the NICU, were 28.8%, 33.3%, 22.4%, 22.7%, and 22.2%, respectively ($P = 0.628$).

Follow-ups of Infants

All infants were prospectively monitored for breastfeeding, respiratory tract infections, COVID-19 infection, growth and development, and congenital heart disease at 1 month, 3 months, and 6 months of age. The follow-up results are shown in Table 4. Over 90% of infants were successfully breastfed, except those in the third trimester group. Breastfeeding rates gradually declined across all groups without significant differences between them. The incidence of respiratory tract infections was low at 1 month but increased by 3 and 6 months. At 3 months old, the incidence was significantly lower in the first trimester (18.1%), second trimester (30.9%), and reinfected groups (15.8%) compared to the uninfected group (55.6%) ($P < 0.05$), with the lowest rate observed in the reinfected group (15.8%). At 6 months, infection rates were significantly lower in the second trimester (48.1%) and reinfected groups (36.8%) than in the first trimester group (65.6%) ($P < 0.05$), again with the lowest rate seen in the reinfected group (36.8%). Progressive analyses of respiratory tract infections among infants with confirmed COVID-19 revealed significant disparities between groups at 3 months old; incidence rates for infants from mothers infected during pregnancy were significantly lower: first trimester group (0%), second trimester group (14.8%), third trimester group (7.9%), and reinfected group (0%) compared to uninfected infants (33 0.3%) ($P < 0$ 0.05). There were no significant differences in physical retardation or neurodevelopmental delay among all five groups. The prevalence of congenital

Table 2 Maternal comparison of different trimester of gestational COVID-19 infection

Mean (SD), Median (Q1, Q3) or *N* (%)	First	Second	Third	Reinfection	Uninfected	*P* value
Age(y)	30.0 (27.0,33.0)	30.0 (27.0,32.0)	29.0 (28.0,33.0)	29.0 (27.0,30.5)	30.0 (27.0,31.0)	0.828
BMI (kg/m^2)	21.1 (19.5,22.7)	21.4 (19.7,22.8)	20.7 (19.5,22.5)	21.6 (20.5,23.0)	21.7 (19.6,23.2)	0.256
Weight Gain (kg)	13.0(4.7)	14.6 (4.5)	13.7 (4.2)	14.1 (7.6)	12.8 (5.4)	0.179
Hypertension disorder	5(4.5)	6 (7.1)	0 (0)	1 (4.5)	0 (0)	0.341
Gestational diabetes	17 (15.5)	24(28.2)	9 (18.8)	3 (13.6)	3 (16.7)	0.249
Gestational hypothyroidism	14 (12.7)	18 (21.2)	6 (12.5)	0 (0)	2 (11.1)	0.100
Intrahepatic cholestasis of pregnancy	0 (0)	3 (3.5)	0 (0)	1 (4.5)	0 (0)	0.128
Transaminitis	2 (1.8)	3 (3.5)	1 (2.1)	0 (0)	0 (0)	0.945
Cesarean section	58 (52.7)	42 (49.4)	28 (58.3)	11 (50.0)	10 (55.6)	0.896
Oligohydramnios	23 (20.9)	14(16.5)	7(14.6)	5 (22.7)	2 (11.1)	0.760
Adherent placenta	12 (10.9)	8 (9.4)	4 (8.3)	2 (9.1)	0 (0)	0.769
Premature rupture of membranes	18 (16.4)	17 (20.0)	11 (22.9)	5 (22.7)	1 (5.6)	0.495
Postpartum hemorrhage	1 (0.9)	2 (2.4)	1 (2.1)	0 (0)	1 (5.6)	0.455
Duration of lochia rubra (d)	30.0 (21.5,41.0)	35.0(25.0, 50.0)	30.0 (25.0,40.0)	35.0 (20.0,42.5)	30.0 (15.0,35.0)	0.295

Table 3 Neonatal comparison of different trimester of gestational COVID-19 infection

Mean (SD), Median (Q1, Q3) or N (%)	First	Second	Third	Reinfection	Uninfected	*P* value
Sex(male/female)	59/52	45/42	22/27	8/14	11/7	0.474
Gestational age (wk)	39.4 (39.0,40.0)	39.1 (38.0,39.7)	39.1 (38.8,40.0)	39.2 (39.0,39.8)	39.4 (38.5,40.3)	0.196
Born weight (g)	3300 (2950,3550)	3170 (2880,3410)	3200 (2940,3400)	3030 (2915,3280)	3285 (2983,3589)	0.122
Premature	8 (7.2)	8 (9.2)	2 (4.1)	2 (9.1)	1 (5.6)	0.855
Small for gestational age	9 (8.1)	4 (4.6)	2 (4.1)	2 (9.1)	2 (11.1)	0.573
Transfer to NICU	15 (13.5)	17 (19.5)	7 (14.3)	1 (4.5)	1(5.6)	0.377

heart disease at birth was higher in the second trimester group (28 0.4%) than that of first(trimester)group (12 0.4%), reinfection(group) (0%), and non-infection(group) (5 0.6%) ($P < 0$ 0.05). However, by six-months-old closure rates for cardiac defects were similar across all groups. Follow-ups revealed only one case where hearing screening failed.

Blood antibody levels and ratio of transplacental antibody transfer

We collected blood samples from mothers and umbilical cords at delivery and conducted IgG antibody tests for SARS-CoV-2. In both maternal and umbilical cord blood, IgG levels in the infected group were significantly higher than those in the uninfected groups at different stages of pregnancy, showing a statistical difference. The highest IgG levels were found in samples from the reinfection group. In umbilical cord blood, the reinfection group's IgG levels significantly increased compared to those in the early and late groups. The median transplacental antibody transfer ratio for all infected individuals was 1.15 (0.98, 1.30), exceeding 1 across all four infection groups with no significant differences among them (Fig. 2).

Breastmilk antibody levels

IgA antibody levels specific to SARS-CoV-2 were measured in breast milk samples collected shortly after delivery and one month postpartum. Generally, IgA concentration in breast milk is low. However, the reinfection group showed significantly higher IgA levels during pregnancy compared to other groups, indicating a statistically significant difference. IgA concentration sharply decreases after one month postpartum, resulting in only 9 samples collected at the second time point (Fig. 3).

Discussion

To our knowledge, this study is the first to report on the clinical outcomes and antibody levels in Chinese pregnant women exposed to Omicron variant of SARS-CoV-2 at various stages and their offsprings. We collected maternal blood, umbilical cord blood, and breast milk specimens for a prospective observational study. The study also included pregnant women with a high prevalence of early pregnancy infections and those who experienced secondary infections as research subjects, with follow-up continuing for 6 months postpartum. Fortunately, we did not observe significant effects of SARS-CoV-2 on either the mother or her offspring, regardless of the timing or frequency of maternal infection. Furthermore, mothers with COVID-19 could provide passive immunity to their infants through umbilical cord blood and breast milk for a certain period of time.

The study revealed an elevated risk of COVID-19 infection in infants who were not exposed to SARS-CoV-2 in utero, starting from one month of age. Particularly during the 1–3 month period, there was a significantly higher

Table 4 Infantile comparison of different trimester of gestational COVID-19 infection

N (%)	Breast milk feeding			Respiratory tract infections	COVID-19 infection			Physical development retardation			Neural development retardation			Congenital heart disease		
	1 m	3 m	6 m	1 m	3 m	6 m	1 m	3 m	6 m	1 m	3 m	6 m	1 m	3 m	6 m	0 m	6 m
First	91/97 (93.8)	88/94 (93.6)	62/90 (68.9)	6/97 (6.2)	17/94[a] (18.1)	59/90[a] (65.6)	0/97 (0)	0/94[a] (0)	4/90 (4.4)	2/97 (2.1)	4/94 (4.3)	4/90 (4.4)	0/97 (0)	7/94 (7.4)	3/90 (3.3)	12/97[a] (12.4)	6/90 (6.7)
Second	74/81 (91.4)	69/81 (85.2)	55/81 (67.9)	4/81 (4.9)	25/81[b] (30.9)	39/81[b] (48.1)	0/81 (0)	12/81[bc] (14.8)	6/81 (7.4)	2/81 (2.5)	2/81 (2.5)	4/81 (4.9)	0/81 (0)	0/81 (0)	0/81 (0)	23/81[b] (28.4)	13/81 (16.0)
Third	32/38 (84.2)	30/38 (78.9)	25/36 (69.4)	1/38 (2.6)	11/38[abc] (28.9)	17/36[ab] (47.2)	1/38 (2.6)	3/38[c] (7.9)	3/36 (8.3)	1/38 (2.6)	0/38 (0)	0/36 (0)	0/38 (0)	1/38 (2.6)	1/36 (2.8)	6/38[ab] (15.8)	4/36 (1.1)
Reinfection	18/19 (94.7)	17/19 (89.5)	13/19 (68.4)	0/19 (0)	3/19[ab] (15.8)	7/19[b] (36.8)	0/19 (0)	0/19[ac] (0)	2/19 (10.5)	0/19 (0)	0/19 (0)	0/19 (0)	0/19 (0)	1/19 (5.3)	0/19 (0)	0/19[a] (0)	0/19 (0)
Uninfected	17/18 (94.4)	17/18 (94.4)	15/17 (88.2)	0/18 (0)	10/18[c] (55.6)	7/17[ab] (41.2)	0/18 (0)	6/18[b] (33.3)	3/17 (17.6)	0/18 (0)	0/18 (0)	0/17 (0)	0/18 (0)	0/18 (0)	0/17 (0)	1/18[a] (5.6)	1/17 (5.9)
P value	0.484	0.118	0.566	0.842	0.013	0.041	0.296	0.000	0.291	1.000	0.805	0.744	-	0.065	0.375	0.006	0.164

a, b, c There were statistical differences between groups

incidence of COVID-19 infection in infants born to non-infected mothers, which aligns with their diminished levels of antibodies at birth. The probability of COVID-19 infection in infants aged 3–6 months did not differ significantly, likely due to antibody decay. The available evidence is sufficient to demonstrate that maternal infection can confer passive immunity to offspring against SARS-CoV-2 through placental cord blood, with a duration at least three months.

During the same period, compared with the uninfected groups, the proportion of children in the first trimester, second trimester and reinfected group with respiratory tract infection decreased in the study. Our findings align with the studies conducted by Lidan Hu and Ariana Perez, which have reported a decline in the seasonal incidence of respiratory pathogens during the period of 2019–2021, coinciding with the outbreak of the COVID-19 pandemic [21]. Furthermore, in Chinese regions affected by COVID-19, there have been notable changes in virus epidemiology, clinical characteristics, bacterial infection patterns, and infection spectrum [22–23]. It may be associated with the implementation of lockdown measures during outbreaks, as well as reduced monitoring of other respiratory pathogens during such periods. The ratio of respiratory infections in infants aged 1–3 months significantly increased, especially among mothers who were not infected and infected in the third trimester during pregnancy as we found. Recently, elevated levels of IgG and IgA that exhibit affinity towards other respiratory viruses have been documented in the breast milk of mothers with COVID-19 during the ongoing pandemic. Conversely, breast milk from non-infected mothers demonstrates reduced passive immunity against common respiratory viruses [24]. Additionally, we observed no differences in the ratios of transplacental antibody transfer and breastfeeding rates among the groups, with low levels of SARS-CoV-2 antibodies detected in maternal blood, umbilical cord blood, and breast milk for both the third trimester infected and uninfected groups. It is plausible to hypothesize that pregnant women without any infection or those with late infection may experience reduced exposure to other respiratory viruses, including SARS-CoV-2, due to the implementation of stricter precautionary measures. Consequently, the levels of virus antibodies in the blood of mothers, cord blood, and breast milk diminished, thereby reducing protection against viral respiratory tract infections for the infant.

The development of protective antibodies in individuals infected with SARS-CoV-2 occurs within 1–2 weeks, reaching its peak at 3–4 weeks, and this immune response can persist for up to 1 year following infection [13, 25]. In this study involving pregnant women infected with COVID-19 more than 4 weeks prior to delivery, no significant differences observed in the antibody levels

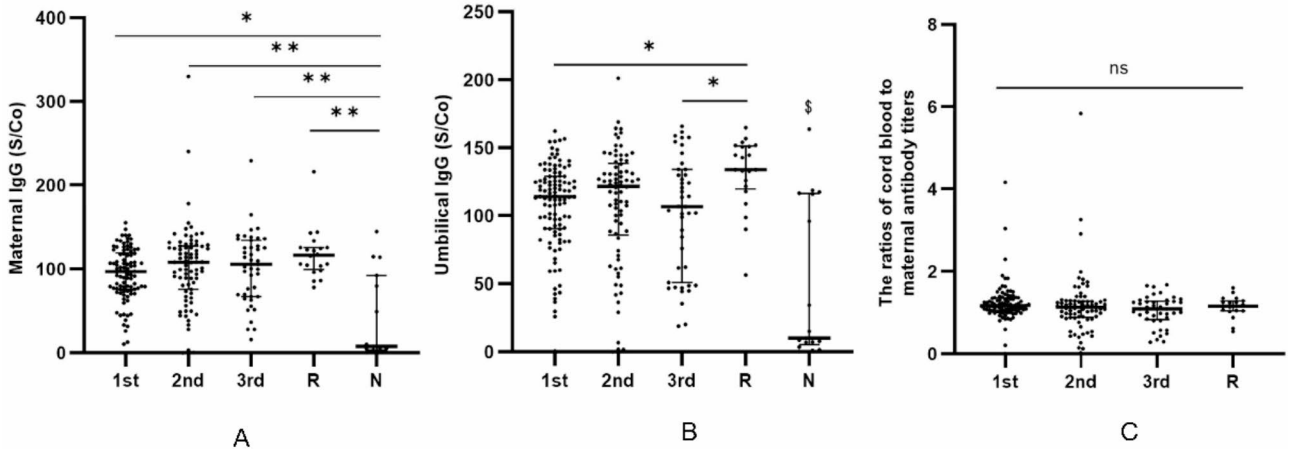

Fig. 2 Maternal blood IgG (**A**) and umbilical cord blood IgG (**B**) levels at delivery for mothers infected with SARS-CoV-2 at different stages of pregnancy. The ratio of transplacental antibody transfer (**C**) for mothers infected with SARS-CoV-2 at different stages of pregnancy. (R: reinfected group; N: uninfected group; $: statistically significant with another four groups)

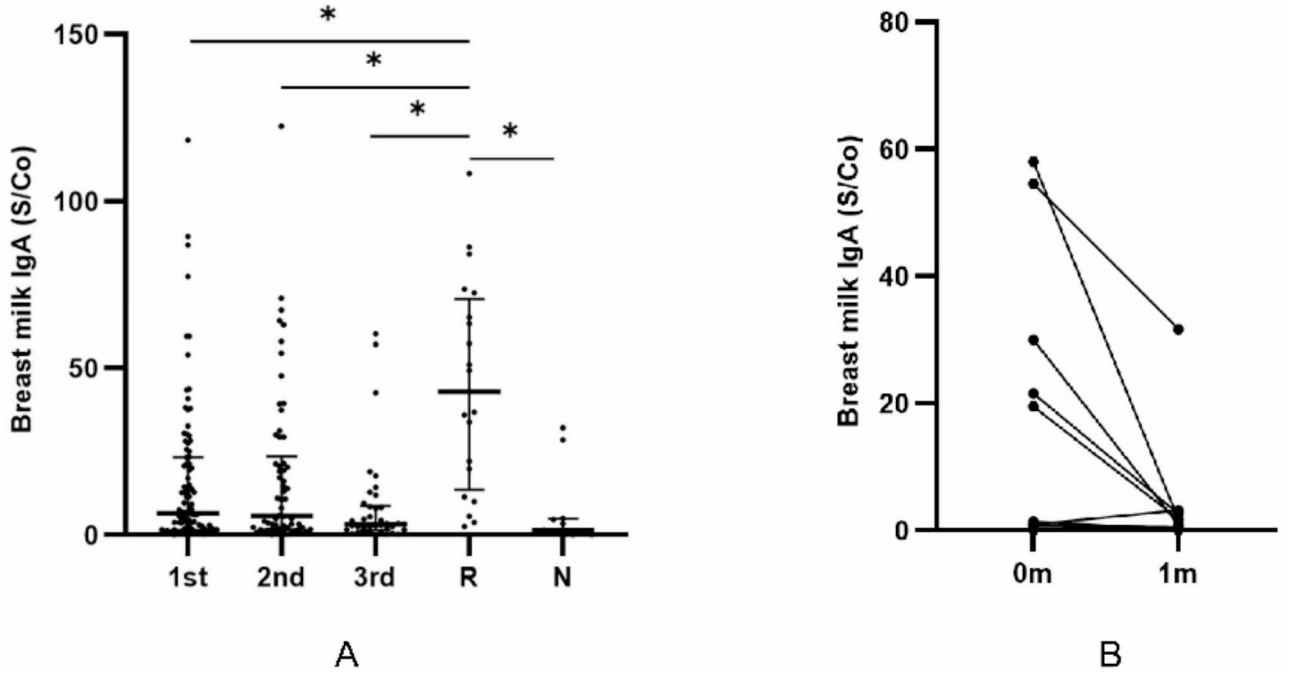

Fig. 3 **A**: Breast milk (colostrum) IgA levels against SARS-CoV-2 for mothers infected at different stages of pregnancy. **B**: The trends of IgA in breast milk at days and 1 month after birth. (R: reinfected group; N: uninfected group)

across different time periods can be easily understood. The transplacental transfer ratio of SARS-CoV-2 IgG has been found to range from 0.7 to 1.3 in several studies [10, 13–15]. In the study conducted by Flannery et al., the ratio of transplacental transfer was found to exceed 1.0. And transfer ratios increased with increasing time between onset of maternal infection and delivery [10]. The median transfer ratios in all groups were found to be greater than 1.0 in our research. However, no significant correlation between its level and time was observed. The truth is, IgG transfer depends on the following: maternal levels of total IgG and specific antibodies, gestational age, placental integrity, IgG subclass, and nature of antigen [26].

Zhang et al. found that reinfection occurred in the presence of varied levels of neutralizing antibodies. And during the secondary infection, some cases displayed secondary immune responses with an increase in serum antibody titers [27]. From December 2022 to January 2023, the reinfection rate of Omicron-to-Omicron subvariants was 9.50% at one year and the severity of Omicron-Omicron reinfection decreased in China [28].

However, there is currently a lack of research on second or multiple infections of COVID-19 during pregnancy. In our study, the reinfection rate among pregnant women was found to be 7.8%, accompanied by milder symptoms and relatively elevated levels of antibodies in blood and milk compared to those observed during a single infection. And there was no increased risk of adverse outcomes for their offsprings.

There is controversy over whether SARS-CoV-2 infection increases the risk of hypertension during pregnancy. Reports indicate that the risk of hypertensive disorders of pregnancy (HDP) rises after COVID-19 infection [8, 29]. Among pregnant women diagnosed with COVID-19, SARS-CoV-2 was more frequently found in the placenta of those suffering from preeclampsia or gestational hypertension. Severe HDP cases were linked to high placental viral load, not necessarily correlating with a positive nasopharyngeal reverse transcription-polymerase chain reaction (RT-PCR) at delivery. Their data suggest that SARS-CoV-2 infection could trigger gestational hypertensive disorders through persistent placental infection and damage [30]. Jiang-Shan Tan et al. provided evidence for a shared genetic predisposition linking COVID-19 infection to increased hypertension risk during pregnancy [31]. Research from the United States and Canada indicates that pregnant women infected with COVID-19 have an equal likelihood of developing HDP compared to uninfected women [32–33]. Similarly, our study found no significant increase in the risk of gestational hypertension among pregnant women at any stage of COVID-19 infection. The variation in outcomes may be due to sample size and variant type.

Similarly, the relationship between gestational diabetes and COVID-19 has sparked controversy in academia. After the pandemic began, GDM prevalence rose during the epidemic's peak but decreased overall year by year [34]. On one hand, SARS-CoV-2 infection may target the pancreas and placenta, leading to β-cell dysfunction and insulin resistance in pregnant women. On the other hand, hormonal and inflammatory changes during pregnancy could increase severe COVID-19 risk for mothers with GDM [35]. Zhongrong He's study suggested that lockdowns were linked to a higher risk of GDM, with the first four months of pregnancy being a sensitive exposure window [36]. Significant disruptions to daily routines caused by the pandemic, such as limited exercise options, suggest a possible link between COVID-19 and increased weight gain during pregnancy [37]. However, a systematic review and meta-analysis indicated that the pandemic had no impact on GDM prevalence [38]. Our research showed consistent findings: as the epidemic progressed and lockdown measures eased, stress on pregnant women decreased, leading to a gradual return of GDM probabilities to normal levels.

The impact of COVID-19 on mothers also includes effects on thyroid and liver function, which have been less reported. During the pandemic, there is an increased risk of elevated free triiodothyronine levels, decreased free thyroxine levels, and isolated hypothyroxinemia in the first trimester [39], possibly due to the "cytokine storm" phenomenon [40]. Our study found no evidence that SARS-CoV-2 infection during pregnancy increases the incidence of intrahepatic cholestasis of pregnancy (ICP). Limited studies exist, and currently, there is no indication that SARS-CoV-2 affects ICP occurrence [41–42]. Coronavirus disease 2019 (COVID-19) associated liver injury (COVALI) encompasses all patients with biochemical liver injury linked to SARS-CoV-2 infection. Pregnant patients show a higher prevalence of COVALI compared to non-pregnant patients and more severely elevated liver enzymes than their non-pregnant counterparts [43]. Fortunately, we did not observe any significant impact of COVID-19 on thyroid or liver function during pregnancy.

For mothers, our study focused on the impact of COVID-19 on pregnancy outcomes, including delivery mode, amniotic fluid, placenta, fetal membranes, and uterine bleeding, in addition to pregnancy complications. We found that the cesarean delivery rate remained unchanged regardless of infection status or timing. These findings align with a U.K. cohort study [44] and a meta-analysis [38]. Additionally, vaginal delivery was not linked to worse maternal or neonatal outcomes compared to cesarean sections [45], although French studies contradicted this notion [46]. Several retrospective studies suggest that exposure to SARS-CoV-2 during pregnancy may lead to oligohydramnios [47–48]. However, while pregnant women infected in the first trimester had a higher incidence of oligohydramnios at delivery in our study, this difference was not statistically significant. There are few studies on placental adhesions related to COVID-19 infection; such infections just before or during early pregnancy could disrupt local endometrial immune responses and lead to abnormal decidualization and trophoblast invasion [49]. The risk of placenta accreta significantly increased with first-trimester infection [50]. In our group, placenta adhesion had the highest incidence during early pregnancy; however, no statistically significant difference was observed. Although research from multiple countries—including China [51], Germany [52], and Spain [53]—indicates an increased risk of premature rupture of membranes due to COVID-19 in pregnant women, a meta-analyse we reviewed concluded that SARS-CoV-2 infection did not significantly raise this risk [54]. Our infected group showed a slightly higher proportion of premature rupture compared to the uninfected group but without statistical significance. Postpartum hemorrhage (PPH) is a leading cause of maternal death

worldwide. A U.S.-based study found that the pandemic increases PPH risk [29], supported by some European studies linking SARS-CoV-2 infection with heightened PPH risk as well [46, 55]. Conversely, several retrospective studies from China and the U.S. indicated no impact from COVID-19 on PPH rates [32, 56]. Our small sample size did not yield significant results regarding lochia duration; while certain individuals experienced longer durations, the comparison revealed no substantial influence from infection at present there is limited literature available on this topic.

We not only focus on maternal health but also pay attention to several pediatric outcomes. Studies from the United States [57], Canada [33], France [46], and Spain [53] suggest that SARS-CoV-2 infection increases the odds of preterm birth compared to uninfected mothers. The INTERCOVID Multinational Cohort Study [58] included subjects from 18 countries, indicating that women with a COVID-19 diagnosis are at higher risk for preterm birth, including iatrogenic cases. Asymptomatic or mild COVID-19 infections during pregnancy do not appear to be associated with small for gestational age infants [59]. However, our study found no significant differences in the proportions of preterm infants, small for gestational age infants, or neonates transferred to NICU across groups. Several relevant meta-analyses [32, 56] support this claim by showing no significant differences in premature birth rates, birth weights, rates of small for gestational age infants, neonatal asphyxia rates, or NICU transfer rates when comparing infected and uninfected groups.

The neurotropism of SARS-CoV-2 has been identified [60]. Marco Massimo et al. reported the presence of SARS-CoV-2 in fetal brain tissue during the first and second trimesters, associated with cortical hemorrhages [61]. Courtney L. McMahon et al. found that SARS-CoV-2 infected blood vessels, neurons, glial cells, and choroid plexus cells, leading to increased gliosis even after viral clearance in the fetal brain [62]. The long-term neurodevelopmental impact on children due to in utero exposure to SARS-CoV-2 remains inconclusive. A multicenter observational study in China reported abnormal brain MRI findings in 3 out of 5 neonates born to mothers with COVID-19 infections; these included delayed myelination, brain dysplasia, and abnormal signals in periventricular white matter but normal physical growth at 44 weeks' postmenstrual age [63]. Hessami et al. conducted a systematic review of infants delivered during the pandemic and found no alteration in their neurodevelopment during the first year due to perinatal exposure to SARS-CoV-2; however, these infants had significant risks for communication delays regardless of maternal infection [64]. Shuffrey and colleagues reported differences in neurodevelopment at 6 months among infants born during the pandemic (independent of maternal COVID infection), showing significantly lower scores in gross motor, fine motor, and personal social subdomains as assessed by the Ages and Stages Questionnaire, 3rd edition [65]. In our study, no delayed neurodevelopment was observed among these offspring; however, longer follow-up is necessary. Additionally, we noted a case of spontaneous cerebral hemorrhage in an infant with suspected vascular malformation whose mother was infected with SARS-CoV-2 during early and mid-pregnancy; thus, its association with this pathogenesis should be considered.

Given that SARS-CoV-2 is considered teratogenic if acquired during the first trimester of pregnancy [66], congenital heart diseases (CHD) were investigated. Gupta et al. found that prenatal detection of critical CHD in newborns requiring cardiac intervention improved during the pandemic [67]. A study on echocardiography suggested that COVID-19 infection in pregnancy may negatively impact fetal cardiac morphology and function, likely due to multisystem inflammatory syndrome (MIS) [68]. Goncu et al. showed that moderate COVID-19 does not seem to adversely affect the fetal heart after recovery [69]. The incidence of CHD in the second-trimester infection group initially increased during the first few days after birth, but this disparity diminished by 6 months postpartum, likely due to a gradual decline in MIS following delivery.

We had a large sample size, especially for cases of infection in the first trimester. However, due to the outbreak, the number of cases in the uninfected and re-infected groups was limited., which may have introduced bias. The absence of selective abortion cases in this study may introduce potential bias in fetal CHD, particularly in the first trimester infection group of pregnancy.

Conclusions

In this cohort study of Chinese pregnancy with SARS-CoV-2 infection, regardless of the stage of maternal infection, we have not observed any adverse clinical outcomes associated with SARS-CoV-2 among mothers and infants, and almost all children who participated in follow-up appeared normal with respect to general physical development, neurodevelopment, and hearing outcomes. Following maternal COVID-19 infection, transplacental transfer of maternal antibodies to the infant was efficient. Antibodies present in umbilical cord blood and breast milk may confer passive immunity to offspring for a duration of 1–3 months. We found that reinfection during pregnancy may not exhibit an elevated risk of adverse outcomes and confers a prolonged duration of passive immunity.

Abbreviations

BMI	Body Mass Index
CHD	Congenital Heart Diseases

COVALI	COVID-19 Associated Liver Injury
COVID-19	Corona Virus Disease 2019
GA	Gestational Age
GDM	Gestational Diabetes Mellitus
HDP	Hypertensive Disorders of Pregnancy
ICP	Intrahepatic Cholestasis of Pregnancy
NICU	Neonatal Intensive Care Unit
PPH	Postpartum Hemorrhage
RLU	Relative Luminescence Unit
RT-PCR	Reverse Transcription-Polymerase Chain Reaction
S/CO	Sample to Cut Off Ratio
SARS-CoV-2 RBD	SARS-CoV-2 Receptor-Binding Domain
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2

Supplementary Information

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Supplementary Material 1

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Author contributions

YS was responsible for the study design, data collection and analysis, and writing of the first draft of the manuscript. XL and NC were responsible for the literature review and theoretical framework construction. LX, MZ, and XL were responsible for specimen collection. Liyan W and SH were responsible for follow-up management. Li W was responsible for patient recruitment. PY and ZY were primarily responsible for the study design, and they provided essential technical support as well as access to necessary resources. JX was responsible for designing the study, provided technical and resource support, and critically revised and edited the manuscript.

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Data availability

The datasets generated and/or analysed during the current study are not publicly available due to privacy protection but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The research had been conducted in strict accordance with the principles outlined in the Declaration of Helsinki. We ensure that all procedures were performed in compliance with relevant laws and institutional guidelines and have been approved by the appropriate institutional committees.
We obtained the necessary ethical approvals (approved by The Third Affiliated Hospital of Chongqing Medical University Institutional Review Board [MR-50-23-024191/ 2023(16)]) and ensured informed consent from all participants.
We have ensured that all participants have provided written informed consent and have the right to withdraw from the study at any time. The collection and processing of research data are in accordance with privacy protection principles, and all personally identifiable information has been removed or encrypted.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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