Impact of PostCovid-19 on Perinatal Outcomes

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Article

Impact of PostCOVID-19 on Perinatal Outcomes

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Abstract: Severe Acute Respiratory Syndrome-Related Coronavirus 2 (SARS-CoV-2) infection during pregnancy was associated with a number of adverse pregnancy outcomes, including miscarriage, preeclampsia, preterm birth, and stillbirth. The virus persistence can last for a long time, and the consequences of a previous coronavirus infection are currently under study. This study aimed to establish the clinical features of the course of pregnancy and childbirth in women with a history of asymptomatic coronavirus disease 2019 (COVID-19). This study was conducted in the Regional Perinatal Center N3 of Turkestan city, Kazakhstan from August to September 2021. A total of 229 participants were enrolled comprising individuals with (n=133, exposed group) or without a history of COVID-19 (n=96, unexposed group). There is a statistically significant strong relationship between a history of COVID-19 and the development of oligohydramnios (φ=0.743, $p<0.001$); medium strength between a history of COVID-19 and the presence of anemia, abnormal development of the placenta, cord entanglement, low birth weight and stillbirth ($p<0.001$). The past COVID-19 infection in pregnant women have long-term consequences in the form of placenta abnormal development and oligohydramnios, and as a result, the development of adverse perinatal outcomes.

Keywords: COVID-19; pregnancy; placenta; stillbirth; oligohydramnios

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic has affected all categories of patients, including pregnant women [1,2]. The risk of infection with Severe Acute Respiratory Syndrome-Related Coronavirus 2 (SARS-Cov-2) in pregnant women is 15 times higher than in non-pregnant women, while clinically expressed forms of the disease proceeded with intoxication, fever, damage to the vascular endothelium, lungs, heart, kidneys, gastrointestinal tract, central and peripheral nervous system, which led to maternal and perinatal mortality and morbidity [3]. Pregnancy is an independent risk factor for adverse outcomes in women with SARS-CoV-2. Pregnancy alters the immune system's response to viral and bacterial infections in general, including COVID-19, with the development of more severe clinical symptoms. The impact of SARS-CoV-2 infection on the course and outcomes of pregnancy is unfavorable [4]. Thus, it was shown that the perinatal mortality rate was about 4%, the main factors determining adverse perinatal outcomes with maternal COVID-19 infection are early gestational age, the presence of mechanical ventilation in the mother, and low birth weight [5]. Pregnant women with SARS-CoV-2 infection had significantly higher odds of developing preeclampsia compared to women without infection (pooled odds ratio [OR], 1.62; 95% confidence interval [CI] 1.45–1.82), with both asymptomatic and symptomatic SARS-CoV-2 infection significantly increasing the risk of preeclampsia [6]. A meta-analysis showed that SARS-CoV-2 infection was associated with preterm birth, stillbirth, and lower birth weight compared with no SARS-CoV-2 infection [7]. In a large population-based study, a diagnosis of COVID-19 increased the risk of very preterm (<32 wk), preterm (<37 wk), and early (37 and 38 wk) birth, especially among people with comorbidities [8]. An increased risk of stillbirth has been associated with virus infection when pregnant individuals were infected during early (<20 wk) and mid-pregnancy (21–27 wk), suggesting potential fetal vulnerability to SARS-CoV-2 infection in early pregnancy [9].

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Angiotensin-converting enzyme-2 and transmembrane serine protease 2, which play an active role in the entry of the SARS-CoV-2 into the cell, are also co-expressed in the placenta, indicating that the placenta is an increased-risk organ for the COVID-19 [10].

This creates conditions for the penetration of the coronavirus into the placenta cells with the subsequent development of placental dysfunction, including feto-maternal vascular malperfusion [11,12]. There have also been reports of the development of severe oligo- and anhydramnios in SARS-CoV-2-positive pregnant women [13–15].

All the consequences of COVID-19 are associated with complex pathological changes that arise as a result of the effect of the SARS-CoV-2 coronavirus on the human body. There are increasing reports of a cohort of women with asymptomatic or mildly symptomatic infection, in most cases not attracting attention (mild to moderate cold/flu-like symptoms). The course and outcome of pregnancy in clinically silent forms of COVID-19 (mild form) and in individuals with an asymptomatic history (post-COVID-19) remain poorly understood. The seroprevalence of SARS-CoV-2 in pregnant women at the time of delivery in between April-June 2020 was 4.5-14%, however the extent and duration of protection conferred by SARS-CoV-2 IgG antibodies remain unknown [16]. The seroprevalence of SARS-CoV-2 in women in June 2021 in Republic of Kazakhstan was 50% [17].

The virus persistence can last for a long time, and the consequences of a previous (including asymptomatic) coronavirus infection (post-COVID) are currently under study [18,19]. The findings from an integrative review indicated that there were four pathophysiological categories of post-COVID syndrome involved: virus-specific pathophysiological variations, oxidative stress, immunologic abnormalities, and inflammatory damage [20,21]. Therefore, the purpose of this study was to determine the impact of past COVID infection on the course and outcomes of pregnancy.

2. Materials and Methods

2.1. Data Collection

This study was conducted in August to September 2021 in the Regional Perinatal Center N3 of Turkestan city, Kazakhstan. Pregnant women hospitalized for delivery and suspected of being infected with coronavirus (having contact with patients with coronavirus infection) were examined for the presence of antibodies against coronavirus. A total of 229 participants were enrolled comprising individuals with (n=133, exposed group) or without antibodies against coronavirus (n=96, unexposed group). Data were collected from the medical records of participants hospitalized for delivery aged between 18-42 yr old. The serum samples were examined for SARS-CoV-2 antibodies detection using enzyme-linked immunosorbent assay (ELISA), Vector-Best, Novosibirsk, Russian Federation). The ELISA detects the antibodies class G immunoglobulins (IgG) and class M (IgM) to the SARS-CoV-2 receptor-binding domain of spike glycoprotein (S-protein). The IgG antibody test shows the level of immune response and indicates recent or past exposure to the virus (including subclinical or asymptomatic infection).

Inclusion criteria: pregnant women hospitalized for delivery, over the age 18, unvaccinated against COVID-19, had SARS-CoV-2 IgG seropositive antibodies.

Exclusion criteria: comorbidity (kidney and blood diseases, systemic autoimmune diseases, thyroid disorders, malignancies, chronic inflammatory disease, tuberculosis, diabetes mellitus); the presence of IgG antibodies against Herpes simplex virus, Cytomegalovirus, Toxoplasma gondii, Chlamydia trachomatis, Ureaplasma urealyticum; vaccinated against coronavirus.

Procedures and Laboratory Measurements. A structured checklist tool was developed before the actual data collection. Data were collected from the medical records of participants. The demographic information, including age, body mass index, parity, current pregnancy, laboratory parameters (general blood count, urinalysis, C-reactive protein), ultrasound examination of the placenta and fetal membranes, birth outcomes (vaginal birth or cesarean section, emergency or planned births), perinatal outcomes (Apgar score at 1 and 5 min, fetal weight) were extracted from their records. A body mass index of 18.5-24.9 was regarded as normal, 25-30 - overweight, and more than 30 - obesity.

Pregnancy hypertension was diagnosed when systolic blood pressure was above 140 mm Hg and/or diastolic blood pressure > 90 mm Hg. Reference intervals for the main parameters of the

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clinical blood test are as follows: mild anemia - Hb 100-109 g/l; moderate - Hb 70-99 g/l; severe - Hb below 70 g/l. Leukopenia was detected at values below $4*10^9$/l, leukocytosis - above $10*10^9$/l. Trombocytopenia was detected at values < $150*10^6$/l and trombocytosis - > $400*10^6$/l. Proteinuria was considered in the presence of protein in the urine ≥0.3 g/day or ≥0.3 g/l in a double urine test.

The amniotic fluid volume can be assessed by ultrasound device Voluson E8. The most commonly used ultrasound criteria for oligohydramnios single deepest pocket <2 cm and amniotic fluid index<5 cm, for anhydramnios - absence of amniotic fluid [22]. To date, the main echographic sign and criterion for oligohydramnios is a decrease in the amniotic fluid index (AFI), which is calculated as the sum of the vertical dimensions of the maximum pockets of amniotic fluid, defined in four quadrants. Oligohydramnios is a condition with an AFI < 10 cm (for up to 34 wk) or < 8 cm (for > 34 wk). Moderate oligohydramnios - AFI > 5 cm, critical oligohydramnios - AFI < 5 cm. Intrauterine growth restriction (IUGR) is diagnosed when ultrasound-estimated fetal weight is below the 10th percentile for gestational age with deranged Doppler parameters [23].

Sample size.

The sample size for unmatched cohort study was determined using special tool "Epi infoTM" (http://www.cdc.gov/epiinfo) via the following methodology: Two-sided confidence level - 95%; Power - 80%, Ratio (Unexposed : Exposed) – 0,5, Percent outcome in unexposed group – 5%, Risk ratio – 4; Odds ratio – 4,75. Percent outcome in exposed group – 20%, The preliminary calculation resulted in the sample size of n = 201 (134/67). The percentage of errors α – 5% and β – 20%, samples loss – 10%. Since the predicted response is 90%, the sample will need to be increased by 10%, the sample size will be 201*110% ≈ 211 people.

2.2. Ethics Approval

This study was approved by the Ethical Committee of Al Farabi Kazakh National University, Kazakhstan (Code: IRBA492/IRB 00010790). Only clinical data collected during routine clinical care was used in this project, and therefore informed consent were not collected.

2.3. Statistical Analysis

Statistical analysis was done using IBM Statistical Package for the Social Sciences, version 26, SPSS Inc., USA. All quantitative indicators were coded and converted to nominal. Categorical variables were shown as absolute values (n) and percentages (%). A Chi-square test or Fisher's exact test were performed for the variables. A comparison of nominal data was carried out using the Chi-square test. If the obtained value exceeded the critical value, it was concluded that there was a statistical relationship between the studied risk factor and the outcome at the appropriate level of significance. In the case of the analysis of four-field tables with the expected phenomenon in at least one cell less than 10, we calculated the Chi-square with the Yates correction, which makes it possible to reduce the probability of an error of the first type, i.e. detecting differences where there are none. The statistical significance was set at $p < 0.05$.

The strength of the connection was estimated by the criterion φ. Interpretation of the obtained values of statistical criteria according to the recommendations of Rea & Parker: < 0.1 - insignificant, 0.1-0.2 - weak, 0.2-0.4 - medium, 0.4-0.6 - relatively strong, 0.6-0.8 is strong, and 0.8-1.0 is very strong. The OR and 95% CI were used to estimate the associations between the underlying factors and perinatal outcomes. Statistical significance was defined as $p < 0.05$.

3. Results

The clinical characteristics of the exposed and unexposed groups are presented in Table 1. When comparing participants of both groups, no differences were found in age, body mass index, or parity of childbirth. The current pregnancy was complicated in both groups. The presence of hypertensive conditions (without proteinuria, or preeclampsia) was approximately the same between exposed and unexposed groups. It should be noted that mild anemia was more often in the unexposed group

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(p=0.038). When studying laboratory parameters, no statistically significant differences were found. However, thrombocytopenia was more common in the unexposed group (p=0.019).

Table 1. - Demographic and clinical characteristics of groups.

Variables	Exposed (n=133)	Unexposed (n=96)	P-value
Age at delivery (yr):			
18-28	60 (45.1)	49 (51.0)	0.545
>29	73 (54.9)	47 (49.0)	0.560
BMI:			
18.5-24.9 (reference weight)	39 (29.3)	38 (39.6)	0.216
25-30 (overweight)	62 (46.6)	38 (39.6)	0.448
> 30 (obesity)	32 (24.1)	20 (20.8)	0.630
Parity:			
Nulliparous	43 (32.3)	27 (28.1)	0.588
Multiparous	90 (67.7)	69 (71.9)	0.721
Anemia in pregnancy:	76 (57.14)	80 (83,3)	**0.027**
Mild - Hb 100-109 g/l	55 (41.35)	60 (62.5)	**0.038**
Moderate - Hb 70-99 g/l	21 (15.79)	20 (20.8)	0.408
Hypertension in pregnancy:			
Hypertension without proteinuria	23 (17.3)	9 (9.4)	0.125
Preeclampsia	12 (9.02)	8 (8.3)	0.886
Leukocytes:			
Leukocytosis	62 (46.6)	42 (43.8)	0.763
Leukopenia	4 (3.0)	1 (1.0)	0.067
Thrombocytes:			
Thrombocytopenia	5 (3.4)	13 (13.5)	**0.019**
Thrombocytosis	16 (12.0)	5 (5.2)	0.10
CRP (mg/L):			
<5	111 (83.5)	86 (89.6)	0.64
>6	22 (16.5)	10 (10.4)	0.24
Proteinuria	29 (21.8)	12 (12.5)	0.112

Note. BMI: Body mass index, Hb: Hemoglobin, CRP: C-reactive protein.

Table 2 shows the perinatal outcomes. There were no differences in terms and methods of delivery in both groups (p=0.606). In the exposed group, the weight of newborns < 2500 g, entanglement of the umbilical cord, and intrauterine growth restrictions were significantly more frequent compared with the unexposed group (p=0.006). Differences were also found in the assessment on the Apgar scale, in the exposed group low scores (up to 3) and average scores (4-6) at 1 minute were recorded significantly more often compared to the unexposed group (p<0.001) and average scores (4-6) at 5 minutes (p=0.014).

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Table 2. - Perinatal outcomes.

Variables	Exposed (n=133)	Unexposed (n=96)	P-value
Gestation period			
Term (38 wk)	104 (78.2)	69 (71.9)	
Premature (< 38 wk)	27 (20.3)	27 (28.1)	0.606
Overdue (> 41 wk)	2 (1.5)	0 (0)	
Birth outcome			
Vaginal delivery	85 (63.9)	70 (72.9)	0.44
Cesarean section	48 (36.1)	26 (27.1)	0.25
Fetus			
Weight of the child (over 2500 g)	91 (68.4)	93 (96.9)	**0.026**
Weight of the child (up to 2500 g)	33 (24.8)	1 (1.0)	**<0.01**
Stillbirth	9 (6.8)	2 (2.1)	0.11
Entanglement of the umbilical cord	43 (32.3)	4 (4.2)	**<0.01**
Intrauterine growth restriction	10 (7.5)	0	**0.006**
Apgar for 1 min			
0-3	16 (12.0)	3 (3.13)	**0.022**
4-6	21 (15.8)	1 (1.04)	**<0.001**
7-10	96 (72.2)	92 (95.83)	0.068
Apgar for 5 min			
0-3	13 (9.8)	3 (3.1)	0.06
4-6	8 (6.0)	0	**0.014**
7-10	112 (84.2)	93 (96.9)	0.34

Note. Data presented as n (%). Chi-square test.

Table 3 shows the state of the placenta and amniotic fluid in the case and unexposed groups. In the case group, abnormalities in the development of the placenta in the case group were significantly more common compared to the unexposed group (p=0.005). The early maturation of the placenta was more often recorded in the exposed group compared to the unexposed group (p=0.014).

In our study, one of the important signs of the consequences of coronavirus infection deserves special attention - in the exposed group, oligohydramnios (86.4% versus 11.5%, p<0.01) and absolute oligohydramnios (ahydroamnios) (9.0% versus 0%) were significantly more often observed compared to the unexposed group (p=0.003).

Table 3. - The state of the placenta and amniotic fluid.

Variables	Exposed (n=133)	Unexposed (n=96)	P-value
Abnormalities of the placenta:	23 (17.29)	4 (4.17)	**0.005**
Early maturation	8 (6.02)	0	**0.014**
Placentitis	7 (5.26)	1 (1.04)	0.092
Placenta previa	3 (2.26)	0	0.133
Placenta accreta	4 (3.01)	0	0.08
Placental abruption	1 (0.75)	3 (3.13)	0.22
Oligohydramnios:	115 (86.4)	11 (11.5)	**<0.001**

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Moderate	103 (77.4)	11 (11.5)	**<0.001**
Critical (anhydramnios)	12 (9.0)	0	**0.003**

Note. Data presented as n (%). Chi-square test.

The next step was to study the correlation between the presence of a history of COVID-19 and perinatal outcomes (Table 4).

Table 4. - Associations between a history of COVID-19 and pregnancy outcomes.

Variables	**φ**	**p-value**	**OR (95%CI)**
Anemia	0.254	<0.001	-
Proteinuria	0.128	0.053	2.038 (0.981-4.234)
Anomalies of the placenta	0.254	0.011	-
Entanglement of the umbilical cord	0.343	<0.001	10.967 (3.71-31.83)
Intrauterine growth restriction	0.184	0.005	1.803 (1.602-2.030)
Low birth weight	0.356	<0.001	35.225 (4.718-262.983)
Stillbirth	0.293	<0.001	-
Oligohydramnios	0.743	<0.001	46.995 (21.463-102.899)

A weak relationship was found between a history of COVID-19 and intrauterine growth restriction (φ=0.184, p=0.005, OR=1.803 95%, CI (1.602-2.030). There is a statistically significant relationship of medium strength between a history of COVID-19 and the presence of anemia (φ=0.254, p<0.001), abnormal development of the placenta (φ=0.254, p<0.011), cord entanglement (φ=0.343, p<0.001, OR=10.97 95% CI (3.78-31.83), low birth weight (φ=0.356, p<0.001), OR=35.225 95% CI (4.718-262.983) and stillbirth (φ=0.293, p≤0.001). Correlation analysis revealed a statistically significant strong relationship between a history of COVID-19 and the development of oligohydramnios (φ=0.743, p<0.001, OR=46.995 95% CI (21.463-102.899).

4. Discussion

Since the World Health Organization (WHO) declared the COVID-19 pandemic, the entire world has faced an unprecedented global crisis. Kazakhstan was affected by the wave caused by the Delta variant of COVID-19 that started in June and reached its peak in mid-August 2021 [17]. The COVID-19 pandemic has affected all categories of patients, including pregnant women. SARS-CoV-2 infection during pregnancy has been associated with a range of adverse pregnancy outcomes, such as early pregnancy loss, preterm delivery, preeclampsia, fetal death, vertical transmission, intrauterine growth restriction, and congenital structural anomalies. COVID-19 is characterized by multisystemic damage to the body, the severity of which varies from asymptomatic carriage to death.

A significant proportion of COVID-19 cases are asymptomatic, and this large group of asymptomatic cases may include a number of people who test positive for SARS-CoV-2 IgG, including pregnant women.

The effects of coronavirus on organs and systems persist long time after infection. Between 2% and 13% of people experience long-term symptoms after COVID-19 infection, and there is a risk of developing this condition during pregnancy. Identifying the association between adverse fetal outcomes and SARS-Cov-2 during pregnancy is critical for prognosis, early intervention, and prevention of complications.

In our study, a retrospective analysis of birth histories in 133 patients with a history of COVID-19 (main group) in the period August-September 2021 was carried out in comparison with 96 patients in the same period in 2019 (before COVID-19 pandemic). And the first cohort was pregnant women during the pandemic had SARS-CoV-2 IgG seropositive antibody, while they did not receive

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vaccinations. The consequences of COVID-19 infection were observed in SARS-CoV-2 seropositive IgG pregnant women: a significant increase in the incidence of low birthweight newborns (24.8% versus 1.04%, $p<0.01$) with intrauterine growth restriction (7.5% versus 0%), placenta abnormalities (17.3% versus 4.2%, $p=0.005$) with developing of oligohydramnios. One of the important signs of the consequences of coronavirus infection deserves special attention - the development of oligohydramnios (86.4% versus 11.5%, $p<0.01$) and absolute oligohydramnios (ahydroamnios) (9.0% versus 0%). A statistically significant moderate-strength association was found between a history of COVID-19 and anemia, placental abnormalities, low birth weight, and stillbirth ($\varphi=0.293$, $p\leq0.001$); a significant strong association was found for the development of oligohydramnios ($\varphi=0.743$, $p=0.000$).

The research on pregnant women with COVID-19 infection results in SARS-CoV-2 placentitis. SARS-CoV-2 placentitis, manifested by increased fibrin deposition, trophoblast necrosis, and intervillositis, prevents blood perfusion in the intervillous space, which leads to the destruction of the placental parenchyma [24]. A study of pregnancy outcomes in patients with COVID-19 showed an increased risk of stillbirth compared with uninfected women, especially during the Delta's variant predominance [14]. During the period of circulation of the delta variant of the virus compared to pre-delta period, stillbirths (0.7% vs. 0.4%; adjusted prevalence ratio 1.55; 95% confidence interval 1.14–2.09) and preterm births (12.8% vs. 11.9%; adjusted prevalence ratio 1.14; 95% confidence interval 1.07–1.20) were recorded more frequently [25].

Women infected with coronavirus who have not been vaccinated are much more likely than pregnant women in general to have stillborn children or infants who die in the first month of life [26].

However, our results are comparable to a case-control study, which reported an increase in the umbilical artery and uterine artery resistance index in pregnant women with a history of COVID-19 at 3 wk compared to women not exposed to SARS-CoV-2 in history [27], as well as another study which found a case of intrauterine growth restriction associated with severe oligohydramnios and loss of fetal movement in a term pregnancy with a history of positive SARS-CoV-2 at 32 wk gestation [14]. In contrast, when analyzing the results of ultrasound it was found no difference in the amniotic fluid index between women who tested positive for SARS-CoV-2 and uninfected controls [28]. However, there is persistence of the virus with a long-term effect, resulting in placental insufficiency ultimately leads to damage to the organs of the fetus leading to extensive intervillous deposition of fibrinoids with subsequent formation of placental infarction and ischemia [29]. Pregnant women infected with COVID-19 have a higher incidence of obstetric complications, including a 25% increased risk of premature birth and intrauterine growth restriction [29].

Highly immunogenic viral infection such as SARS-CoV-2 can interrupt the normal course of pregnancy. COVID-19 causes uncontrolled systemic inflammation. In pregnant women infected with SARS-CoV-2, Treg/Th17 cell imbalance has the potential to be associated with adverse pregnancy outcomes such as pregnancy loss, preterm birth, and pre-eclampsia [30]. In this regard, different results are possible depending on individual immune susceptibility and gestational age at the onset of infection, which can bidirectionally determine both obstetric complications and the duration and/or severity of the infectious disease [31].

It has been established that not only the active form of coronavirus infection has a significant negative impact on the human body, but also an important role is played by a long-term (more than 12 weeks) post-COVID syndrome, which is characterized by both general clinical manifestations and damage to the vascular wall and endothelium, a tendency to hypercoagulation and microthrombosis. Coronavirus infection suffered before pregnancy contributes to an increase in the incidence of preeclampsia and placental insufficiency in the second trimester by 52.4 and 86.9%, respectively, and in the third trimester - placental insufficiency and fetal hypoxia by 2 times compared to healthy women [32]. It was also found that patients with a history COVID-19 had various symptoms of thrombohemorrhagic syndrome [33]. They are based on dysfunction of endothelial cells, provoked both directly by the virus and by the developing cytokine storm, and subsequently by autoimmune damage [34,35].

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The history of COVID-19 elevated risks of the formation of abnormal development of the placenta and oligohydramnios, and as a result, the development of adverse perinatal outcomes with low birthweight; these require more careful monitoring of pregnancy.

The limitation of this study was in impossibility to test the placenta for the presence of SARS-CoV-2 by polymerase chain reaction. In this case, there would be direct evidence of the influence of the transferred asymptomatic form of COVID-19 on the development of placental insufficiency.

5. Conclusions

This study examined the course of pregnancy in patients with a history of asymptomatic COVID-19. According to the results of this study, there were no significant differences between groups in assessing risk factors (age, BMI), the course of pregnancy, the presence of hypertensive conditions (preeclampsia), the timing and outcomes of labor (vaginal delivery or cesarean section), as well as laboratory parameters. However, differences were found in such parameters as placental abnormalities, low birth weight, intrauterine growth restriction, cord entanglement, and oligohydramnios (up to anhydramnios).

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Institutional Review Board Statement: This study was approved by the Ethical Committee of Al Farabi Kazakh National University, Kazakhstan (Code: IRB A492/13/10/2022).

Informed Consent Statement: Only clinical data collected during routine clinical care was used in this project, and therefore informed consent were not collected.

Data Availability Statement: Clinical-pathological data is available.

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