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# In-Hospital Mortality in Unvaccinated Pregnant versus Non-Pregnant Patients with Coronavirus Disease 2019 and the Impact of Disease Severity on Acute Pregnancy Outcomes: A Retrospective Cohort Study

## Aşılanmamış Hamile ve Hamile Olmayan Koronavirüs Hastalığı 2019 Hastalarında' Hastane İçi Ölüm Oranları ve Hastalık Şiddetinin Akut Gebelik Sonuçları Üzerindeki Etkisi: Retrospektif Kohort Çalışması

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ABSTRACT

**Background:** This study evaluated the impact of pregnancy on in-hospital mortality among unvaccinated patients with Coronavirus Disease 2019 (COVID-19), and assessed how clinical severity influences pregnancy outcomes and maternal rescue interventions.

**Materials and Methods:** This retrospective study was conducted at Dursun Odabaş Medical Center, Van Yüzüncü Yıl University Faculty of Medicine, a tertiary referral center in Eastern Türkiye from May 2020 to October 2021. The cohort comprised 108 hospitalized women aged 18 to 45 years with COVID-19, of whom 54 were pregnant patients matched one-to-one by age and admission date. Disease severity was classified according to World Health Organization guidelines. The primary endpoint was in-hospital mortality, and the secondary endpoint was a composite adverse pregnancy outcome, defined as fetal death or delivery before 37 weeks' gestation.

**Results:** There was no significant difference in in-hospital mortality between the pregnant and non-pregnant groups (9.3% vs. 7.4%, p = 1.000). Multivariate analysis identified baseline oxygen saturation (adjusted odds ratio [aOR]: 0.907, 95% confidence interval [CI]: 0.832–0.988, p = 0.026) and lactate dehydrogenase levels (aOR: 1.004, 95% CI: 1.000–1.008, p = 0.040) as independent predictors of mortality, whereas pregnancy was not a significant predictor (aOR: 1.141, 95% CI: 0.180–7.240, p = 0.889). Severe COVID-19 among pregnant patients was associated with a significantly higher risk of composite adverse pregnancy outcomes than non-severe cases (62.5% vs.26.7%, p = 0.008). After adjusting for maternal age, severe disease remained an independent risk factor for adverse outcomes (aOR: 5.24, 95% CI: 1.46–18.76, p = 0.011), whereas maternal age was not a significant predictor. Severe disease most frequently resulted in iatrogenic preterm delivery to address maternal hypoxia.

**Conclusion:** In this unvaccinated cohort, pregnancy did not independently increase COVID-19 mortality. However, severe respiratory disease increases physiological vulnerability. Iatrogenic preterm delivery to relieve maternal hypoxia shifts the morbidity risk to the fetus. To reduce maternal health deterioration and adverse perinatal outcomes, proactive respiratory management, timely delivery interventions, and preventive measures against disease transmission, including vaccination, are critically important.

**Keywords:** COVID-19, critical illness, hospital mortality, pregnancy, premature birth

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***Preliminary findings regarding the pregnant cohort of this study were presented in part as an oral presentation at the 4th International Health Sciences Congress (VUSAK 2025), December 15–16, 2025, Van, Türkiye.**

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ÖZ

**Amaç:** Bu çalışmada, aşılanmamış bir kohortta gebeliğin Koronavirüs Hastalığı 2019 (COVID-19) hastalarında hastane içi mortalite üzerindeki etkisi ile klinik şiddetin gebelik sonuçları ve maternal kurtarma stratejileri bağlamındaki rolü incelendi.

**Gereç ve Yöntemler:** Mayıs 2020-Ekim 2021 arasında Türkiye'nin doğusunda üçüncü basamak bir sevk merkezi olan Van Yüzüncü Yıl Üniversitesi Tıp Fakültesi Dursun Odabaş Tıp Merkezin'de yürütülen bu retrospektif çalışmaya, yaş ve yatış tarihine göre bire bir eşleştirilmiş, 18-45 yaş aralığındaki 54'ü gebe toplam 108 hastaneye yatırılan COVID-19 kadın hasta dahil edildi. Hastalık şiddeti Dünya Sağlık Örgütü rehberine göre sınıflandırıldı. Birincil sonlanım noktası hastane içi ölüm; ikincil sonlanım noktası ise fetal ölüm veya 37. haftadan erken doğumu içeren bileşik olumsuz gebelik sonucuydu.

**Bulgular:** Hamile ve hamile olmayan gruplar arasında hastane içi ölüm oranlarında (%9,3'e karşı %7,4, p = 1,000) anlamlı fark saptanmadı. Çok değişkenli analizde, başlangıç oksijen satürasyonu (düzeltilmiş odds oranı [aOR]: 0,907, %95 güven aralığı [GA]: 0,832–0,988, p = 0,026) ve laktat dehidrogenaz düzeylerinin (aOR: 1,004, %95 GA: 1,000–1,008, p = 0,040) ölümü bağımsız olarak öngördüğü, gebeliğin ise öngörmediği (aOR: 1,141, %95 GA: 0,180–7,240, p = 0,889) doğrulanmıştır. Ancak hamile hastalarda, şiddetli COVID-19, şiddetli olmayanlara kıyasla, bileşik olumsuz gebelik sonucu riskinde önemli ölçüde artışla ilişkilendirildi (%62,5'e karşı %26,7, p = 0,008). Çok değişkenli lojistik regresyon modelinde anne yaşına göre ayarlama yapıldıktan sonra şiddetli hastalık olumsuz sonuçlar için bağımsız risk faktörü olarak kaldı (aOR: 5,24, %95 GA: 1,46–18,76, p = 0,011), anne yaşı ise anlamlı bir öngörücü değildi. Şiddetli hastalık, öncelikle maternal hipoksiyi yönetmek için iyatrojenik erken doğuma yol açtı.

**Sonuç:** Aşılanmamış bu kohortta, gebeliğin COVID-19 mortalitesini bağımsız olarak artırmadığı saptanmıştır. Ancak şiddetli solunum hastalığı fizyolojik kırılganlık yaratır. Anneyi hipoksiden kurtarmak için gereken iyatrojenik erken doğum, morbiditeyi fetüse kaydırmaktadır. Anne sağlığının kötüleşmesini ve olumsuz perinatal sonuçları azaltmak için proaktif solunum yönetimi, zamanında doğum müdahaleleri ve aşılama da dahil hastalık bulaşmasına karşı koruyucu önlemlerin uygulanması kritik öneme sahiptir.

**Anahtar Kelimeler:** COVID-19, kritik hastalık, hastane içi mortalite, gebelik, preterm doğum

## Introduction

Severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2) continues to pose a significant clinical threat despite the pandemic's transition to an endemic phase after the World Health Organization's (WHO) emergency declaration was lifted (1,2). Multinational INTERCOVID studies and current guidelines from the American College of Obstetricians and Gynecologists consistently identify pregnancy as a critical determinant of maternal morbidity and classify it as a high-risk condition, irrespective of the pandemic phase (3,4). Physiological changes during pregnancy, including mechanical restrictions due to diaphragmatic elevation and increased metabolic oxygen consumption, decrease tolerance to hypoxic stress during viral pneumonia (3,5). This physiological vulnerability results in complex clinical scenarios that, in severe cases, often necessitate iatrogenic preterm delivery or maternal rescue strategies to optimize maternal lung function and prevent fetal hypoxia (3,5).

Although substantial data exist regarding the obstetric effects of Coronavirus Disease 2019 (COVID-19), the current literature is increasingly confounded by the emergence of hybrid immunity resulting from widespread vaccination and prior infections (6). The presence of immunological memory complicates the accurate characterization of the natural progression of the virus during pregnancy. Consequently, data derived from a vaccine-naive population offer a distinct clinical reference point at this stage of the pandemic. Analysis of this cohort is valuable for documenting intrinsic maternal-fetal outcomes and the unmodified clinical consequences of COVID-19 (7).

The hospital conducting this study is Dursun Odabaş Medical Center, Van Yüzüncü Yıl University Faculty of Medicine, a tertiary referral center in Eastern Türkiye, serving a diverse patient population from a broad geographical region and managing numerous critical cases. This study examines the clinical course of SARS-CoV-2 infection in a strictly vaccine-naive population by comparing pregnant and age-matched non-pregnant women. The primary objective is to determine whether pregnancy independently influences intensive care unit (ICU) admission rates and in-hospital mortality among unvaccinated patients with severe disease. The secondary objective is to evaluate the impact of disease severity, as indicated by oxygenation requirements, on pregnancy outcomes. Specifically, the study investigates how severe respiratory compromise alters obstetric management and whether it is associated with a composite adverse pregnancy outcome, defined as fetal death or preterm birth before 37 weeks of gestation.

## Materials and Methods

### Study Design, Setting, and Population

This single-center, retrospective cohort study was conducted at Dursun Odabaş Medical Center, Van Yüzüncü Yıl University Faculty of Medicine, a tertiary referral center in Eastern Türkiye, between May 2020 and October 2021. Hospitalized unvaccinated pregnant women with confirmed

COVID-19 were compared with a matched cohort of non-pregnant women.

A 1:1 matched cohort design minimized selection bias. Each eligible pregnant patient (n = 54) was paired with a consecutive unvaccinated non-pregnant female control (n = 54), matched by age (± 3 years) and admission date. Temporal matching controlled for variations in viral virulence and in the standard of care. The final cohort comprised 108 participants.

**Eligibility Criteria**

Inclusion criteria were: (1) female patients aged 18 to 45 years; (2) SARS-CoV-2 infection confirmed by reverse transcription-polymerase chain reaction; (3) unvaccinated against COVID-19; and (4) hospitalization exceeding 24 hours in a ward or an ICU. Exclusion criteria included receipt of any COVID-19 vaccine, incidental asymptomatic positivity (such as during routine obstetric screening), active malignancy, pre-existing immunosuppression, or incomplete outcome data. No patients had a documented history of COVID-19 infection; however, prior undocumented asymptomatic infections could not be excluded due to the retrospective design.

**Data Collection and Definitions**

Two independent investigators extracted data from electronic medical records and physical charts using a standardized case report form. Variables with more than 20 missing values were excluded from analysis.

Patients were classified as severe or non-severe according to WHO interim guidance (8). Radiographic criteria were omitted because imaging was postponed for over half of pregnant patients to protect maternal and fetal safety. Consequently, imaging findings were excluded from severity criteria to ensure consistency and reduce bias in cohort comparisons. The severe group included both severe and critical COVID-19 cases, defined as the presence of clinical signs of pneumonia (fever, cough, or difficulty breathing) and at least one of the following: respiratory rate exceeding 30 breaths per minute, severe respiratory distress (such as the use of accessory muscles or inability to speak in full sentences), or oxygen saturation ($SpO_2$) below 90% on room air. Patients meeting the criteria for acute respiratory distress syndrome, sepsis, or septic shock were also included. The non-severe group comprised mild and moderate COVID-19 cases. These patients did not meet the criteria for severe or critical disease. Mild cases were characterized by symptoms without signs of viral pneumonia or hypoxemia, whereas moderate cases were defined by clinical signs of pneumonia, with an $SpO_2$ of 90% or higher on room air, and the absence of severe respiratory distress.

Pandemic periods were stratified by dominant variant proxies, based on national epidemiological data, due to the absence of routine genomic sequencing: the Pre-Delta Period (May 2020–June 2021) and the Delta Variant Period (July 2021–October 2021) (9).

The primary study endpoint was all-cause in-hospital mortality. Secondary endpoints were severe respiratory morbidity, defined as ICU admission or invasive mechanical ventilation, and, for the pregnant cohort, an "In-hospital Composite Adverse Pregnancy Outcome," defined as fetal death or preterm birth before 37 weeks of gestation during acute infection. These outcomes were combined because both reflect clinically significant pregnancy compromise during acute maternal hypoxia and systemic inflammation associated with severe COVID-19.

**Ethical Considerations**

The study received approval from the Van Yüzüncü Yıl University Non-Interventional Clinical Research Ethics Committee (decision number: 2024/01-19, date: 12.01.2024). A waiver of informed consent was granted due to the retrospective design, use of de-identified data, and minimal risk to participants. The study was conducted in full compliance with the Declaration of Helsinki.

**Statistical Analysis**

Data analysis was conducted using IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, NY, USA). Normality of continuous variables was assessed with the Shapiro-Wilk test and visual inspection. Descriptive statistics for continuous variables are reported as mean ± standard deviation for normally distributed data and as median (interquartile range) for non-normally distributed data. Categorical variables are presented as frequencies (n) and percentages (%). Comparisons of normally distributed data were performed using the independent-samples t-test with Welch's correction for unequal variances, whereas the Mann-Whitney U test was used for non-normally distributed data. Categorical variables were analyzed using Pearson's chi-square test or Fisher's exact test when expected cell frequencies were less than 5. A hierarchical testing strategy addressed multiplicity, with in-hospital mortality as the primary confirmatory outcome and severe respiratory morbidity and composite pregnancy outcomes as key secondary endpoints. A multivariable logistic regression model identified independent predictors of in-hospital mortality. To minimize overfitting due to the limited number of mortality events, only three independent variables were included, following the "events per variable" rule. Pregnancy status (the primary hypothesis), baseline $SpO_2$, and baseline lactate dehydrogenase (LDH) levels, all of which

demonstrated the strongest univariate associations, were selected for the final model. A second multivariable logistic regression model evaluated the independent association between COVID-19 disease severity (severe vs. non-severe) and composite adverse pregnancy outcomes. Maternal age, which showed a statistically significant difference in univariate analyses ($p < 0.05$), was included to adjust for potential confounding. Effect sizes were quantified using Cohen's d for continuous variables and odds ratios (ORs) and adjusted ORs (aOR) with 95% confidence intervals (CIs) for categorical outcomes and for regression models. A post-hoc power analysis was performed using G*Power (version 3.1) (10). Power calculations were conducted for mortality, composite pregnancy outcomes, and all other analyses. Statistical significance was defined as $p < 0.05$. Analyses stratified by pandemic period were exploratory. Statistical significance was defined as a two-tailed p value of <0.05.

## Results

A total of 108 unvaccinated female patients hospitalized with confirmed SARS-CoV-2 infection were included in the final analysis. The selection process, which applied exclusion criteria and used a 1:1 consecutive matching protocol, is illustrated in the study flowchart (Figure 1). The final cohort consisted of 54 pregnant women and 54 age-matched non-pregnant controls.

Baseline demographic and clinical characteristics, and admission laboratory findings for the pregnant and non-pregnant groups are summarized in Table 1.

### Comorbidities and Clinical History

Comorbidities were present in 13.0% (n = 7) of pregnant women and 11.1% (n = 6) of non-pregnant women (Table 1). The distribution of specific conditions differed between groups. Multimorbidity was more frequent in the pregnant cohort: one patient had three concurrent conditions (hypothyroidism, type 2 diabetes mellitus, and cardiovascular disease), and three patients had two comorbidities (hypothyroidism with gestational diabetes [n = 2] and hypothyroidism with cardiovascular disease [n = 1]). The remaining pregnant patients had isolated conditions, including Behçet's disease, hypothyroidism, and asthma. In contrast, all comorbidities in the non-pregnant group were single conditions, including diabetes mellitus (n = 2), asthma (n = 2), multiple sclerosis (n = 1), and cerebral palsy (n = 1).

### Comparison of Admission Findings

Cough and dyspnea were the most common presenting symptoms, with no significant difference in symptom

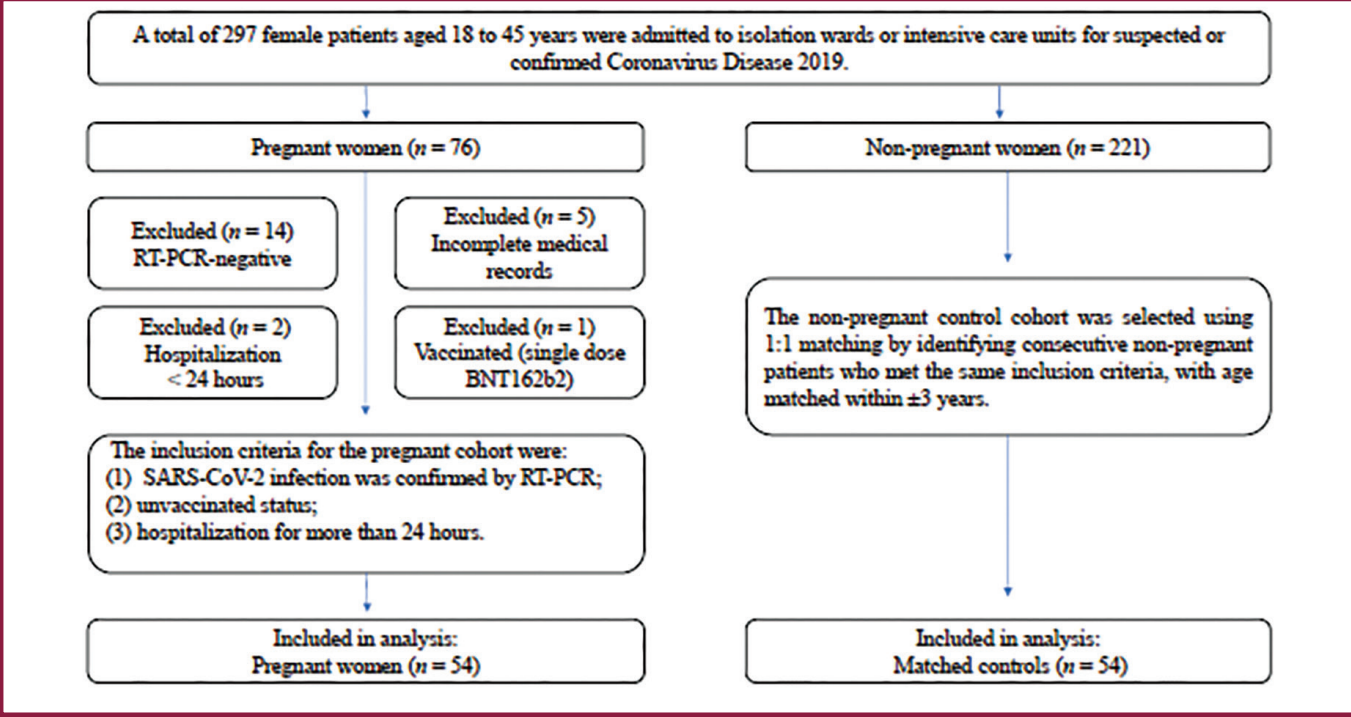



**Figure 1.** Flowchart of the study population selection process. COVID-19, Coronavirus Disease-2019, RT-PCR, reverse transcription-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome Coronavirus-2.

**Table 1. Baseline demographic characteristics, clinical features, and laboratory findings of pregnant and non-pregnant women diagnosed with COVID-19.**

| Variables | Non-pregnant (n = 54) | Pregnant (n = 54) | p value |
|---|---|---|---|
| **Demographics** | | | |
| Age (years) mean ± SD | 30.2 ± 6.9 | 30.2 ± 7.1 | 0.989 |
| **Comorbidities** | | | |
| Any comorbidity n (%) | 6 (11.1) | 7 (13.0) | 1.000 |
| **Vital signs at admission** | | | |
| $SpO_2$% median (IQR) | 90 (83.5-93.0) | 92 (89.8-93.3) | **0.040** |
| Fever (>38°C) n (%) | 18 (33.3) | 15 (27.8) | 0.531 |
| **Symptoms at admission** n (%) | | | |
| Cough | 28 (54.9) | 24 (44.4) | 0.441 |
| Dyspnea | 24 (44.4) | 22 (40.7) | 0.697 |
| Fatigue | 20 (37.0) | 17 (31.5) | 0.543 |
| **Laboratory findings[a] (at admission)** median (IQR) | | | |
| White blood cell (/μL) | 6.9 (4.6-10.4) | 9.2 (6.6-12.3) | **0.004** |
| Lymphocyte (/μL) | 1.3 (0.8-1.9) | 1.1 (0.8-1.4) | **0.049** |
| NLR (neutrophil/lymphocyte) | 4.1 (1.8-6.9) | 7.5 (3.8-12.2) | **0.001** |
| C-reactive protein (mg/L) | 22.0 (5.9-72.2) | 31.0 (10.5-76.3) | 0.638 |
| Ferritin (ng/mL) | 126 (64-261) | 89 (30-191) | 0.068 |
| LDH (U/L) | 315 (215-489) | 293 (226-470) | 0.794 |
| D-dimer (μg/mL) | 0.57 (0.41-1.58) | 1.63 (1.05-2.43) | **<0.001** |

Data are presented as mean ± standard deviation (SD) for age and as median (IQR) for other continuous variables. Categorical variables are reported as frequencies (n) and percentages (%). Statistical analyses were performed using Student's t-test for normally distributed variables, Mann-Whitney U test for non-normally distributed continuous variables, and Chi-square test or Fisher's exact test for categorical variables. Statistically significant values ($p < 0.05$) are indicated in bold. a, the laboratory panel includes key inflammatory and prognostic markers associated with the severity of Coronavirus Disease-2019. IQR, interquartile range; COVID-19, Coronavirus Disease-2019; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; $SpO_2$, oxygen saturation.

frequency between pregnant and non-pregnant women. Pregnant women had a significantly higher median $SpO_2$ on admission than non-pregnant women (92% *vs.* 90%, p = 0.040). Fever rates were similar between the groups.

Significant differences in hematological and coagulation parameters were observed at admission. Pregnant women had higher white blood cell counts (p = 0.004) and neutrophil-to-lymphocyte ratios (NLRs) (p = 0.001) but lower lymphocyte counts (p = 0.049) than non-pregnant women. D-dimer levels were substantially higher in the pregnant group (median 1.63 vs. 0.57 μg/mL, p < 0.001), indicating a large effect size. Other inflammatory markers, including C-reactive protein (CRP), ferritin, and LDH, did not differ significantly between groups.

A post-hoc power analysis was performed for admission parameters that showed significant differences between the study groups (Table 1). Effect sizes (Cohen's d) and corresponding statistical power were as follows: d = 0.38 (power = 51%) for $SpO_2$, d = 0.54 (power = 81%) for white blood cell count, d = 0.31 (power = 35%) for lymphocyte count, d = 0.66 (power = 94%) for NLR, and d = 1.12 (power > 99%) for D-dimer levels.

### Comparison of Clinical Course

Despite variations in $SpO_2$ at admission, all patients in both groups ultimately required supplementary oxygen therapy during hospitalization. Table 2 presents a comparison of maximal disease severity, respiratory support requirements, and clinical outcomes during hospitalization. No statistically significant differences were found between pregnant and non-pregnant women in terms of disease progression (p = 0.336), need for invasive mechanical ventilation (p = 0.507), or ICU admission rates (p = 0.620). In-hospital mortality rates were also similar between the groups (9.3% vs. 7.4%, p = 1.000). Multivariable logistic regression analysis was performed to assess the independent effects of pregnancy and clinical markers on mortality. Baseline $SpO_2$ (aOR: 0.907, 95% CI: 0.832–0.988, p = 0.026) and baseline LDH levels (aOR: 1.004, 95% CI: 1.000–1.008, p = 0.040) were identified as significant independent predictors of mortality.

**Table 2. Maximal disease severity, respiratory support requirements, and clinical outcomes during hospitalization were compared between pregnant and non-pregnant women with COVID-19.**

| Variables | Non-pregnant (n = 54) | Pregnant (n = 54) | p value |
|---|---|---|---|
| **Maximal disease severity[a]** | | | |
| Non-severe (moderate), n (%) | 25 (46.3) | 30 (55.6) | Ref. |
| Severe (severe or critical), n (%) | 29 (53.7) | 24 (44.4) | 0.336 |
| **Maximal respiratory support** | | | |
| NIMV[b], n (%) | 11 (20.4) | 11 (20.4) | 1.000 |
| Invasive mech. ventilation, n (%) | 4 (7.4) | 6 (11.1) | 0.507 |
| **Clinical outcomes** | | | |
| ICU admission n, (%) | 9 (16.7) | 11 (20.4) | 0.620 |
| In-hospital mortality, n (%) | 4 (7.4) | 5 (9.3) | 1.000 |
| **Hospital course** | | | |
| Length of stay (days) median (IQR) | 7.0 (4.0 – 11.0) | 6.0 (3.8 – 10.0) | 0.535 |

Data Interpretation: All variables reflect either the most severe status observed or cumulative outcomes recorded during the hospital stay. [a], Maximal disease severity: Classified according to the highest severity level reached during hospitalization. For example, a patient admitted with moderate disease who progresses to severe disease is classified as "Severe." [b], NIMV includes high-flow nasal oxygen (HFNO) and BiPAP/CPAP. Continuous variables are presented as median (IQR). Categorical variables are reported as frequencies (n) and percentages (%). Statistical analyses were performed using the Mann-Whitney U test for non-normally distributed continuous variables and the chi-square or Fisher's exact test for categorical variables. ICU, intensive care unit; IQR, interquartile range; NIMV, non-invasive mechanical ventilation; COVID-19, Coronavirus Disease-2019.

After adjustment for these clinical and laboratory markers, pregnancy status was not independently associated with increased risk of death (aOR: 1.141, 95% CI: 0.180–7.240, p = 0.889). A post-hoc power analysis indicated very small effect sizes for ICU admission (Cohen's h = 0.096, power = 6.8%) and in-hospital mortality (Cohen's h = 0.069, power = 5.4%; $\alpha$ = 0.05, two-tailed), reflecting similar rates of these outcomes in both cohorts.

All five pregnant patients who died were in the late second or third trimester (gestational age ⩾ 27 weeks). Four of these patients had no known comorbidities, while one had a history of gestational diabetes mellitus and hypothyroidism.

Although genomic sequencing was not performed, a pooled analysis of the entire cohort (n = 108) showed higher mortality during the period epidemiologically associated with the Delta variant surge than during the pre-Delta period (8/48 vs. 1/60; p = 0.007). Given the limited number of events and wide CIs (OR: 11.80, 95% CI: 1.42–97.57), this result should be considered exploratory and hypothesis-generating rather than definitive.

### Comparison of Maternal Characteristics and Obstetric Outcomes According to Disease Severity

Table 3 presents a comparison of maternal characteristics and obstetric outcomes between pregnant patients with non-severe disease (n = 30) and those with severe disease (n = 24).

Delivery Outcomes: Among the 33 patients who delivered during hospitalization, significant differences in delivery timing were observed. Patients with severe COVID-19 delivered at a lower median gestational age than those with non-severe disease (31.0 vs. 37.5 weeks, p = 0.004), resulting in a higher rate of preterm delivery in the severe group. No statistically significant differences were found between the groups regarding gestational age at admission, parity, or mode of delivery (cesarean section rates).

A post-hoc power analysis was performed for characteristics that significantly differed between the disease severity groups (Table 3). Effect sizes (Cohen's d) and corresponding statistical power were as follows: d = 0.51 (power = 73%) for maternal age at admission, d = 1.16 (power = 90%) for maternal age at delivery, and d = 0.81 (power = 83%)for gestational age at delivery.

### Association Between Maternal Disease Severity and In-Hospital Adverse Outcomes

Table 4 presents the analysis of "In-hospital Composite Adverse Pregnancy Outcomes," evaluating the association between maternal disease severity and pregnancy prognosis. Women with severe COVID-19 had significantly higher odds of experiencing an adverse event during hospitalization, defined as fetal death or preterm birth, compared to those with non-severe disease (OR: 4.58; 95% CI: 1.44–14.57; p = 0.008). The post-hoc analysis, based on the observed differences and sample size (n = 54), indicated a statistical

**Table 3. Maternal characteristics, obstetric history, and perinatal outcomes in pregnant women are compared according to COVID-19 disease severity groups.**

| Variables | Non-severe | Severe | p value |
|---|---|---|---|
| **Maternal characteristics** | **(n = 30)** | **(n = 24)** | |
| Maternal age (years) median, (IQR) | 27.5 (21.8 – 34.0) | 34.0 (27.3 – 37.0) | **0.010** |
| Comorbidities (any), n (%) | 3 (10.0) | 4 (16.7) | 0.687 |
| Gestational age at admission (weeks) median, (IQR) | 34 (29 -38) | 31 (28 -36) | 0.102 |
| **Trimester of pregnancy** n (%) | | | |
| First trimester (<12 weeks) | 0 | 1 (4.2) | |
| Second trimester (13–27 weeks) | 5 (16.7) | 4 (16.7) | |
| Third trimester (≥28 weeks) | 25 (83.3) | 19 (79.2) | |
| **Obstetric history** | | | |
| Gravidity median (IQR) | 2.0 (1.0 – 4.0) | 2.5 (1.0 - 4.8) | 0.368 |
| Multiparity n (%) | 19 (63.3) | 15 (62.5) | 0.950 |
| **Delivery status, n (%)** | | | |
| Undelivered | 14 (46.7) | 7 (29.2) | |
| Delivered | 16 (53.3) | 17 (70.8) | |
| **Characteristics of deliveries**[a] | **(n = 16)** | **(n = 17)** | |
| Maternal age at delivery (years) median (IQR) | 25.5 (21.0 – 31.5) | 35.0 (29.5 – 37.5) | **0.003** |
| Gestational age at delivery (weeks) median (IQR) | 37.5 (32.0 – 38.0) | 31.0 (28.0 – 36.0) | **0.004** |
| **Mode of delivery, n (%)** | | | |
| Cesarean section | 11 (68.8) | 14 (82.4) | 0.438 |
| Vaginal delivery | 5 (31.3) | 3 (17.6) | Ref. |
| **Birth outcome types n (%)** | | | |
| Live birth deliveries | 14 (87.5) | 14 (82.4) | 1.000 |
| Term delivery (≥37 weeks) | 8 | 2 | |
| Preterm delivery (<37 weeks) | 6 | 12 | |
| Fetal death, stillbirth[b] | 2 (12.5) | 3 (17.6) | Ref. |

Continuous variables are presented as median (IQR). Categorical variables are reported as frequencies (n) and percentages (%). Statistical analyses were performed using Mann-Whitney U test for non-normally distributed continuous variables, and Chi-square or Fisher's exact tests for categorical variables. Statistically significant values ($p < 0.05$) are indicated in bold. a, Delivery analysis: Calculations of delivery characteristics and birth outcomes were restricted to the subgroup of patients who delivered during hospitalization (non-severe: n = 16; severe: n = 17). b, Stillbirth: Defined as fetal death occurring at or after 22 weeks of gestation. Five stillbirths occurred between 27 and 32 weeks of gestation. IQR, interquartile range; COVID-19, Coronavirus Disease-2019.

power of 76.9% (1-β = 0.769). A favorable in-hospital course, defined as discharge with ongoing pregnancy or uncomplicated term delivery, occurred in 73.3% (n = 22) of the non-severe group and in 37.5% (n = 9) of the severe group. Analysis of live preterm birth phenotypes showed that most preterm deliveries in the severe group (75%, 9/12) were iatrogenic. These interventions were primarily required for complications such as non-reassuring fetal status (n = 5) and hypertensive disorders, such as preeclampsia or HELLP syndrome (n = 2), rather than for spontaneous preterm labor.

To address the significant age differences between severity groups, a multivariable logistic regression model was constructed, adjusting for maternal age as a potential confounder. The analysis demonstrated that severe COVID-19 remained a robust, independent predictor of composite adverse pregnancy outcomes (aOR: 5.24, 95% CI: 1.46–18.76, p = 0.011). In contrast, maternal age was not independently associated with an increased risk of these adverse events (aOR: 0.98, 95% CI: 0.89–1.07, p = 0.598). The post-hoc statistical power was 72% (1-β = 0.72).

### Neonatal Outcomes

Among the 54 pregnant women in the cohort, one twin pregnancy was identified. Twenty-one women with singleton pregnancies were discharged with ongoing pregnancies, while 33 women (32 with singleton pregnancies and one with a twin pregnancy) delivered during hospitalization. Five singleton pregnancies resulted in fetal death or stillbirth. A

**Table 4. Association between maternal COVID-19 severity and in-hospital composite adverse pregnancy outcomes.**

| Variables | Non-severe (n = 30) | Severe (n = 24) | p-value | OR (95% CI) |
|---|---|---|---|---|
| **A. Favorable in-hospital course[a] n (%)** | **22 (73.3)** | **9 (37.5)** | **Reference** | **1.00** |
| A1. Discharged undelivered (ongoing pregnancy) | 14 | 7 | | |
| A2. Term birth (≥37 weeks) | 8 | 2 | | |
| **B. Composite adverse pregnancy outcomes[b] n (%)** | **8 (26.7)** | **15 (62.5)** | **0.008** | **4.58 (1.44 - 14.57)** |
| B1. Fetal death, stillbirth[c] | 2 | 3 | | |
| B2. Phenotypes of live preterm birth | 6 | 12 | | |
| a. Spontaneous phenotype | 2 | 3 | | |
| a1. Spontaneous labor (intact membranes) | 2 | 2 | | |
| a2. Premature rupture of membranes (PPROM) | 0 | 1 | | |
| b. Iatrogenic (indicated) phenotype | 4 | 9 | | |
| b1. Non-reassuring fetal status (NRFS) | 3 | 5 | | |
| b2. Placental abnormalities (abruption/previa) | 1 | 2 | | |
| b3. Hypertensive disorders (preeclampsia/HELLP) | 0 | 2 | | |

Categorical variables are expressed as frequencies (n) and percentages (%). Statistical analyses were performed using Pearson's chi-square test. Associations are presented as odds ratios (ORs) with 95% confidence intervals (CIs). PPROM, preterm premature rupture of membranes; NRFS, non-reassuring fetal status; HELLP, Hemolysis, Elevated Liver enzymes, and low platelet syndrome. a, favorable in-hospital course: defined as continuation of pregnancy until discharge (ongoing pregnancy) or delivery at term (≥37 weeks) without complications during the index hospitalization. b, composite adverse pregnancy outcome (in-hospital): Defined as the occurrence of fetal death or preterm birth (<37 weeks) during the hospitalization period. In this cohort, all recorded fetal deaths occurred after 22 weeks of gestation. c, Stillbirth: Defined as fetal death occurring at or after 22 weeks of gestation. Five stillbirths occurred between 27 and 32 weeks of gestation.

total of 29 live neonates were delivered from 27 singleton pregnancies and one twin pregnancy. The mean birth weight of live neonates was 2439 ± 924 g, and the mean 5-minute APGAR score was 7.76 ± 1.57. Low birth weight, defined as less than 2500 g, was observed in 13 infants (44.8%). Subgroup analysis showed that six neonates weighed between 1500 and 2500 g, six weighed between 1000 and 1500 g, and one weighed less than 1000 g. Overall, 51.7% (15/29) of neonates required admission to the neonatal ICU (NICU) due to low birth weight or respiratory distress, and 10.3% (3/29) required intubation. In the case of the twin pregnancy, the mother developed severe COVID-19 complicated by HELLP syndrome and underwent cesarean section at 28 weeks of gestation. Both twins, with birth weights of 1350 g and 1600 g, were admitted to the NICU for low birth weight. Among the remaining 11 singleton neonates with low birth weight, 9 were born to mothers diagnosed with severe COVID-19.

## Discussion

This study assesses the clinical consequences of SARS-CoV-2 infection in an unvaccinated population to clarify maternal and fetal outcomes without the confounding influence of vaccine-induced immunity. Multivariable analyses indicate that pregnancy status does not independently increase the risk of in-hospital mortality or ICU admission compared to age-matched non-pregnant controls. Instead, baseline disease severity, particularly initial $SpO_2$ and LDH levels, independently predicts fatal outcomes. Although pregnancy is not an independent risk factor for mortality, the severity of respiratory failure is a critical determinant of adverse pregnancy outcomes. After adjustment for maternal age in the multivariable model, severe disease remains a significant predictor of composite adverse outcomes, primarily due to fetal death and the need for maternal rescue through iatrogenic preterm birth.

### Mortality and Clinical Course

The lack of a statistically significant difference in mortality between the pregnant and non-pregnant groups (9.3% vs. 7.4%; p = 1.000) should be interpreted with caution, particularly given the heterogeneity in the existing literature. Multivariable analysis clarifies the relationship between pregnancy and COVID-19 mortality, indicating that clinical outcomes are primarily determined by the severity of the initial presentation, specifically, baseline hypoxia and tissue damage indicated by LDH, rather than by pregnancy status. These results suggest that pregnant patients do not have a higher risk of in-hospital mortality when baseline clinical and laboratory severity is comparable to that in

non-pregnant patients. This observation aligns with studies indicating that pregnancy increases morbidity but does not necessarily elevate the independent risk of mortality across all cohorts (11,12). Conversely, large-scale surveillance data have demonstrated an increased mortality risk associated with pregnancy (13). The observed discrepancy likely reflects a Type II error rather than a true absence of clinical risk, as maternal mortality is a relatively rare endpoint that typically achieves statistical significance only in large population-based studies. Smaller sample sizes may lack sufficient power to detect this difference (13).

The observed 9.3% mortality rate in the pregnant cohort is likely attributable to several external factors beyond statistical variation. Selection and referral biases were present because the tertiary center exclusively cared for hospitalized patients with severe disease. Additionally, the latter phase of the study coincided with the Delta variant surge, which is associated with increased virulence (14,15). Comparable studies of unvaccinated pregnant populations during the Delta wave reported maternal mortality rates up to 7% (14,15). Therefore, the elevated mortality rate in this study should be interpreted as the consequence of a highly virulent variant affecting a high-risk, unvaccinated population, rather than being attributed solely to pregnancy physiology (14,15).

Although pregnancy may not be a primary determinant in the onset of severe disease, it appears to induce physiological fragility following infection. Large-scale multinational cohort studies have demonstrated that infected pregnant women face a significantly higher risk of mortality and intensive care admission compared to non-infected pregnant women (3,16). Consistent with these findings, the present study indicates that severe respiratory compromise directly threatens fetal survival and frequently necessitates iatrogenic preterm delivery as a maternal rescue strategy (5,17).

The pregnant cohort in this study exhibited significantly higher leukocyte counts and D-dimer levels, which likely reflect the physiological leukocytosis and hypercoagulability characteristic of pregnancy rather than increased infection severity (12,18). The literature indicates that pregnancy induces a hypercoagulable state through enhanced thrombin generation, potentially increasing thromboembolic risk during viral infection (5). In contrast, no significant differences were observed in key inflammatory markers, including CRP, Ferritin, and LDH. This finding aligns with previous reports indicating comparable or lower inflammatory indices in pregnant cohorts compared to non-pregnant controls (12,19). Overall, these results suggest that pregnancy does not exacerbate SARS-CoV-2-induced systemic hyperinflammation. Instead, maternal vulnerability appears to result from physiological adaptations and altered immunity that increase susceptibility to respiratory and thromboembolic complications (6).

**Disease Severity and the "Maternal Rescue" Paradigm**

Consistent with established literature, advanced maternal age was more prevalent in the severe disease group, reaffirming its status as a known risk factor for both severe infection and adverse obstetric outcomes (16). However, multivariate analysis indicates that disease severity, rather than maternal age, is the primary determinant of adverse pregnancy outcomes (aOR: 5.24, p = 0.011). This finding aligns with a systematic review demonstrating that women with severe COVID-19 experience significantly higher risks of preterm birth and perinatal complications compared to those with non-severe disease, irrespective of demographic profile (20). These results suggest that clinicians should maintain a high index of suspicion for severe respiratory symptoms regardless of maternal age, ensuring that younger patients receive the same level of aggressive management as older high-risk patients.

In this cohort, the cesarean section rate was 88.2% among patients with severe disease, underscoring the clinical necessity of managing critical maternal hypoxia. The increased metabolic demands of active labor, such as elevated oxygen consumption and cardiac output, often surpass the physiological reserves of patients with severe respiratory compromise (17). As a result, the high incidence of surgical delivery should be considered a necessary "maternal rescue" intervention (5). This approach aims to promptly reduce diaphragmatic elevation and improve maternal respiratory mechanics. The decision-making process is further supported by the INTERCOVID study, which found that most preterm births among infected women were medically indicated to preserve maternal health (3).

In this study, 51.7% of neonates required NICU admission, a rate within the broad range (20.8%–86.4%) reported in the literature (21,22). Prematurity and low birth weight were the primary reasons for admission, consistent with meta-analyses indicating that neonatal morbidity is mainly attributable to iatrogenic preterm birth due to worsening maternal health, rather than direct viral infection (16,23). Additionally, the higher incidence of low birth weight among neonates born to mothers with severe COVID-19 supports findings from large-scale multinational studies that directly associate maternal disease severity with increased neonatal morbidity (3).

Exploratory analysis identified a significantly higher mortality rate during the Delta variant surge compared to the pre-Delta period. This trend was observed across the entire cohort, affecting both pregnant and non-pregnant women,

suggesting a generalized increase in viral virulence rather than pregnancy-specific susceptibility. This observation aligns with previous studies demonstrating the heightened pathogenicity of the Delta variant (B.1.617.2) compared to earlier strains (14,15,24). However, these results should be interpreted with caution. The wide CIs are due to the limited number of mortality events and to classification based on epidemiological timelines rather than on genomic sequencing. Although the data indicate increased severity during the Delta wave, large-scale studies incorporating genomic surveillance are required to accurately quantify variant-specific mortality risks.

### Study Limitations

This study has several limitations inherent to its retrospective design. First, the single-center, tertiary-care setting likely introduced referral bias, resulting in a cohort with greater disease severity than the general population. Second, while the sample size was sufficient to detect differences in composite outcomes, it may not have provided adequate statistical power to confirm differences in mortality between groups, increasing the risk of a Type II error. Third, although the study aimed to evaluate an immunologically naive cohort by excluding patients with a documented history of COVID-19, the retrospective design did not allow for identification of prior undocumented asymptomatic infections. Consequently, unrecognized natural immunity in some patients remains a limitation and may represent an unmeasured confounder. Fourth, viral variant classification was based on epidemiological timelines rather than genomic sequencing; therefore, attributing outcomes to the Delta variant constitutes a temporal proxy rather than a confirmed virological association. Finally, the absence of a non-infected pregnant control group limits the ability to quantify baseline risk relative to infection-attributable risk. The primary strength of this study is its internal comparison of disease severity within a unique cohort of vaccine-naive patients, which provides a valuable clinical reference for understanding the direct impact of SARS-CoV-2 on maternal physiology without the influence of prior immunization.

## Conclusion

In this unvaccinated cohort, pregnancy increased physiological vulnerability to severe respiratory compromise. Although pregnancy did not independently increase mortality risk compared with non-pregnant controls, maternal survival often depended on a "maternal rescue" strategy. This strategy required frequent iatrogenic preterm deliveries, which shifted morbidity to the fetus, to relieve maternal hypoxia. These results suggest that pregnant women may lack the physiological reserve needed to withstand severe viral pneumonia without adverse outcomes. Due to the physiological vulnerabilities associated with severe respiratory disease, proactive respiratory management and timely maternal rescue strategies are essential. Integrating these clinical interventions with rigorous preventive measures, particularly vaccination, is critical to reducing adverse maternal and fetal outcomes. Further research on specific viral variants may help refine clinical management for both mothers and fetuses.

### Ethics

**Ethics Committee Approval:** The study received approval from the Van Yüzüncü Yıl University Non-Interventional Clinical Research Ethics Committee (decision number: 2024/01-19, date: 12.01.2024).

**Informed Consent:** A waiver of informed consent was granted due to the retrospective design, use of de-identified data, and minimal risk to participants.

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### Footnotes

### Authorship Contributions

Surgical and Medical Practices: Ş.İ., E.K., Concept: Ş.İ., E.K., Design: Ş.İ., E.K., Data Collection or Processing: Ş.İ., Analysis or Interpretation: Ş.İ., E.K., Literature Search: Ş.İ., Writing: Ş.İ.,

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