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# COVID-19 related maternal mortality cases in associated with Delta and Omicron waves and the role of lung ultrasound

## *COVID-19'a bağlı anne ölümü olgularının Delta ve Omikron dalgaları ile ilişkisi ve akciğer ultrasonunun rolü*

**Arzu Bilge Tekin[1], Murat Yassa[2], Pınar Birol İlter[1], Emre Yavuz[1], Betül Önden[1], Canberk Usta[1], Doğuş Budak[1], Osman Samet Günkaya[1], Gül Çavuşoğlu[1], Bilge Doğan Taymur[1], Niyazi Tuğ[1]**

[1]*University of Health Sciences Turkey, Şehit Prof. Dr. İlhan Varank Sancaktepe Training and Research Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Turkey*

[2]*Bahçeşehir University, VM Medical Park Maltepe Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Turkey*

### Abstract

**Objective:** To present coronavirus disease-2019 (COVID-19) related maternal mortality in relation to Delta and Omicron waves and to investigate the role of lung ultrasound (LUS) in estimating mortality.

**Materials and Methods:** This retrospective cohort study was conducted in the obstetrics and gynecology clinic of a tertiary pandemic hospital between March 2020 and January 2022. The hospitalized pregnant women with COVID-19 diagnosis and maternal deaths were studied in relation with Delta and Omicron waves. The relationship between LUS scores of hospitalized patients and maternal mortality was explored.

**Results:** Thousand and sixty-five pregnant women were hospitalized because of COVID-19 infection. Fifty-one (4.79%) of these patients had critical sickness, 96 (9.01%) of them had severe illness, 62 (5.82%) of them were admitted to the intensive care unit and 28 (2.63%) of all hospitalized pregnant women had died. Of the 1.065 patients, 783 (73.5%) were hospitalized before the Delta wave and the maternal mortality rate was 1.28% (10/783), 243 (22.8%) were hospitalized during the Delta wave and the maternal mortality rate was 7% (17/243) [relative risk (RR)=5.478, 95% confidence interval (CI) (2.54-11.8), z=4.342, p<0.001]. During the Omicron wave 39 (3.66%) patients were hospitalized and the maternal mortality rate was 2.56% (1/39). Maternal mortality rates, according to LUS scores, were 0.37% (1/273) for LUS 0, 0.72% (2/277) for LUS 1, 2.58% (10/387) for LUS 2 and 11.72% (15/128) for LUS 3 respectively (LUS 3 vs. others; maternal mortality: RR=8.447, 95% CI (4.11-17.34), z=5.814, p<0.0001). There were no vaccinated patients in the study cohort.

**Conclusion:** The maternal mortality rate was relatively high, particularly during the Delta wave at our referral center. The Delta wave, delayed vaccination and vaccine hesitancy of pregnant women might have important roles in maternal mortality. Higher LUS scores should warn clinicians of an increased risk of maternal death.

**Keywords:** COVID-19, Delta, lung ultrasound, maternal mortality, Omicron

### Öz

**Amaç:** Delta ve Omikron dalgaları ile ilişkili olarak koronavirüs hastalığı-2019 (COVID-19) ile ilişkili anne ölümlerini sunmak ve akciğer ultrasonunun (AUS) hastalık şiddeti-mortalite tahminindeki rolünü araştırmaktır.

**Gereç ve Yöntemler:** Bu retrospektif kohort çalışması, üçüncü basamak bir pandemi hastanesinin kadın hastalıkları ve doğum kliniğinde Mart 2020 ile Ocak 2022 tarihleri arasında yapılmıştır. Hastanede yatan COVID-19 tanılı gebeler ve anne ölümü olguları Delta ve Omikron dalgaları ile ilişkili olarak incelenmiştir. Hastanede yatan hastaların AUS skorları ile anne ölümleri arasındaki ilişki araştırılmıştır.

**PRECIS:** Among pregnant women infected with COVID-19, the highest mortality rate was observed in the Delta wave and higher lung ultrasound scores should warn clinicians of an increased risk of maternal death.

**Address for Correspondence/Yazışma Adresi:** Arzu Bilge Tekin MD,
University of Health Sciences Turkey, Şehit Prof. Dr. İlhan Varank Sancaktepe Training and Research Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Turkey
**Phone:** +90 530 252 56 90 **E-mail:** arzubilgetekin@gmail.com **ORCID ID:** orcid.org/0000-0001-8054-2624
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**Bulgular:** Bin altmış beş hamile kadın COVID-19 enfeksiyonu nedeniyle hastaneye yatırıldı. Bu hastaların 51'inde (%4,79) kritik hastalığa, 96'sında (%9,01) ağır bir hastalık mevcuttu, 62'si (%5,82) yoğun bakıma yatırıldı ve hastanede yatan tüm gebe hastaların 28'inde (%2,63) ölüm gerçekleşti. Delta dalgası öncesinde 783 (%73,5) hasta hastaneye yatırıldı, anne ölüm oranı %1,28 (10/783), Delta dalgası sırasında 243 (%22,8) COVID-19 hasta hastaneye yatırıldı ve anne ölüm oranı %7'di (17/243) [göreceli risk (RR)=5,478, %95 güven aralığı (GA) (2,54-11,8), z=4,342, p<0,001]. Omikron dalgası sırasında 39 (%3,66) hasta hastaneye yatırıldı ve anne ölüm oranı %2,56 (1/39) idi. AUS skorlarına göre anne ölüm oranları, AUS 0 için %0,37 (1/273), AUS 1 için %0,72 (2/277), AUS 2 için %2,58 (10/387) ve AUS için %11,72 (15/128) idi (AUS 3 ve diğerleri; anne ölüm oranı: RR=8,447, %95 GA (4,11-17,34), z=5,814, p<0,0001). Çalışma grubunda aşılı hasta bulunmamaktaydı.

**Sonuç:** Anne ölüm oranı, özellikle sevk merkezimizde Delta dalgası sırasında nispeten yüksekti. Gebelerin Delta dalgası, aşı gecikmesi ve aşı tereddütlerinin anne ölümlerinde önemli rolleri olabilir. Daha yüksek akciğer ultrason skorları, klinisyenleri artan anne ölümü riski konusunda uyarmalıdır.

**Anahtar Kelimeler:** COVID-19, Delta, akciğer ultrasonu, anne ölümü, Omikron

## Introduction

Recent studies and reviews indicate that pregnant women are more likely to are affected by severe illness and intensive care and mechanical ventilation[1-4]. Coronavirus disease-2019 (COVID-19) was associated with a substantial increase in maternal morbidity and mortality[5]. The maternal mortality rates varied widely from 1.35% to 12.3%[6-8]. Variants of concern have begun to be reported by the World Health Organization (WHO)[9] and the pace of the pandemic has increased. Data on maternal mortality associated with the increasing waves of the pandemic have been accumulated recently[7,10-12]. As the pandemic progressed, new genetic variants of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) were identified in the second half of the 2020[5]. In May 2021, the Delta variant was identified as a variant of concern[5], with research indicating that it was more transmissible and that patients with the Delta variant became ill faster and showed higher viral loads in the respiratory tract compared to the other variants[13]. Recently, Delta wave was related to a high maternal mortality rate, particularly for unvaccinated pregnant women[7]. Nowadays, the Omicron variant has taken the place of the Delta variant and it is identified as a more transmissible variant with decreased severity[14].

Diagnosis of COVID-19 is mainly based on the symptoms of the patient, nasopharyngeal polymerase chain reaction (PCR) test results, and chest imaging tests[9,15]. For obstetricians, the lung ultrasound (LUS) is a rapid and safe technique for the triage, diagnosis and follow-up of pregnant women with COVID-19[16,17]. Performing LUS right after the fetal assessment for screening of COVID-19 is feasible until PCR results are acquired. It has the advantage of eliminating the ionizing radiation exposure from chest computed tomography (CT) and pregnant women's concerns about ionizing radiation. LUS is a new thoracic imaging method that is becoming more widely used than other thoracic imaging modalities. Its usage to determine the pulmonary involvement in COVID-19 has increased recently[18]. Abnormal LUS findings were found relevant to early admission into intensive care units (ICU) or ICU and mortality in the pandemic[16,18].

The data on maternal mortality rates during the latest variants of the COVID-19 pandemic needs to be updated. In this study, we aimed to investigate the COVID-19 related maternal mortality in connection to Delta and Omicron waves and the impact of LUS in determining disease severity-mortality in one of Turkey's largest pandemic centers.

## Materials and Methods

This retrospective cohort study was conducted in the obstetrics and gynecology clinic of a tertiary pandemic hospital specialized in the care of pregnant women infected with SARS-CoV-2. At this center, approximately 4.000 women give birth annually and during the pandemic maternal healthcare continued along with the management of pregnant women with COVID-19. The diagnosis and management of the patients with COVID-19 were applied in line with WHO and, the Turkey Ministry of Health recommendations as well as the local protocol of the obstetrics clinic.

All pregnant women who were hospitalized and diagnosed with COVID-19 between March 2020 and January 2022 were included in this study. There were no further exclusion criteria. The patients were divided into three groups: those who were hospitalized before the Delta wave, those who were hospitalized during the Delta wave, and those who were hospitalized during the Omicron wave. The maternal deaths were classified and further analyzed in detail regarding the period of the pandemic. The data of pregnant women who were admitted to the hospital and confirmed as COVID-19 by nasopharyngeal swab reverse transcription-PCR test and LUS or chest-CT were analyzed retrospectively using the hospital electronic health records. The primary outcome of the study was to evaluate the change in the maternal mortality rate associated with the Delta and Omicron waves and to investigate the maternal mortality cases in detail. The study's secondary outcome was to look at the link between initial LUS scores upon diagnosis and maternal mortality.

Electronic health records were used to collect information on the demographic and clinical characteristics, obstetric outcomes, and the laboratory results of COVID-19-diagnosed mothers. Some patients in the study cohort had been included in the previous publications[19-23]. The study was approved by the local ethics committee (University of Health Sciences Turkey, Şehit Prof. Dr. İlhan Varank Sancaktepe Training and Research Hospital - no: 2021/218) and by the Ministry of Health COVID-19 Scientific Research Evaluation Commission. The research was conducted ethically in accordance with the guidelines for human studies and World Medical Association Declaration of Helsinki.

### Hospitalization Criteria

At the time of admission to the hospital and during follow-up in the hospital, pregnant women with COVID-19 were classified as having mild, moderate, severe and critical illness. Mild illness was defined for the pregnant or postpartum cases of COVID-19 who were symptomatic but without lower respiratory tract symptoms (shortness of breath) or abnormal chest imaging (i.e., mainly LUS or occasionally tomography, chest X-ray). Moderate illness was defined for the pregnant or postpartum cases of COVID-19 who were symptomatic with lower respiratory tract symptoms without significant hypoxia (pulse oximetry saturation ≥94% on room air). Severe illness was defined for the pregnant or postpartum cases of COVID-19 who were symptomatic with oxygen saturation <94%, respiratory rate more than 30 breaths per minute, Po2 to the fraction of inspired oxygen <300 mmHg, or lung infiltrates >50%. Critical illness was defined for the pregnant or postpartum cases of COVID-19 who were symptomatic with respiratory failure, septic shock, hyper-inflammatory syndrome, or other organ system dysfunction[24]. Pregnant women who were diagnosed with moderate, severe and critical COVID-19 were hospitalized. Patients with mild disease were hospitalized, if their LUS score 2 or 3 or, there were difficulties in follow-up from home and some of the mild cases were hospitalized because for obstetric reasons. Additionally, asymptomatic pregnant women with positive nasopharyngeal PCR tests who were admitted to the hospital for obstetric reasons were hospitalized.

### Effects of Delta and Omicron Wave

The impact of the Delta and Omicron waves was evaluated based on the Turkey Ministry of Health declarations. According to these declarations, the Delta wave was effective between August 1, 2021 to December 27, 2022 and after that Omicron wave has been effective[25-27].

### Lung Ultrasound

The lung involvement of the patients was scored between 0 and 3 with LUS at the time of the hospital admission as a routine local protocol. LUS scores 0, 1, 2, and 3 were defined as normal, mild lung involvement, moderate lung involvement, and severe lung involvement, respectively[16,17]. LUS scores of hospitalized patients in relation to the clinical severity of all hospitalized patients and with maternal mortality were investigated.

### Statistical Analysis

The data of this study were analyzed with IBM SPSS Statistics version 22.0 (IBM Corporation, Armonk, NY). The normality assumption of the variables was checked using the Shapiro-Wilk test and skewness/kurtosis values. Descriptive statistics were used as mean, standard deviation, median, number, and frequency. The chi-square test and Fisher's Exact test were used to compare categorical variables. Wilcoxon signed ranks tests Mann-Whitney U test and independent samples t-test were used to compare continuous variables according to normality assumptions All tests were 2-sided and the p-value <0.05 was set as statistically significant.

## Results

Overall, there were 1.065 pregnant women hospitalized due to the COVID-19 infection between March 2020 and January 2022. Fifty-one (4.79%) of these patients had critical sickness, 96 (9.01 percent) of them had a severe illness, 62 (5.82 percent) of them were admitted to the ICU and 28 (2.63 percent) of the hospitalized pregnant women had died. Monthly data for the number of hospitalized patients and the maternal deaths between March 2020 and January 2022 are presented in Figure 1.

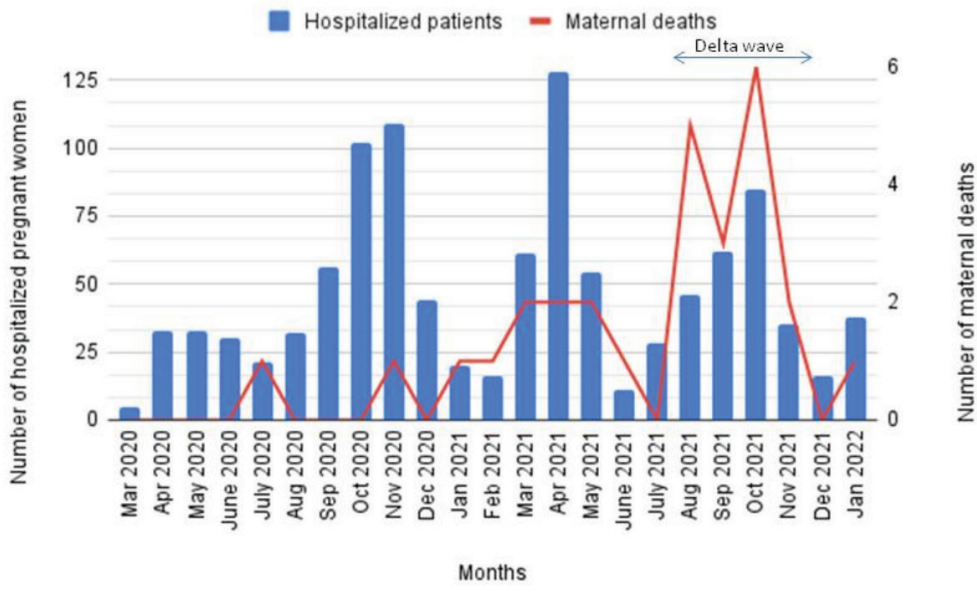


**Figure 1.** Monthly data for the number of hospitalized patients and maternal deaths

Of the 1,065 patients, 783 (73.52%) were hospitalized before the Delta wave with a maternal mortality rate of 1.28% (10/783), 243 were hospitalized during the Delta wave with a maternal mortality rate of 7% (17/243), and 39 (3.66%) patients were hospitalized during the Omicron wave with a maternal mortality rate of 2.56% (1/39) (p<0.001, chi-square=23.71532). There was a significant increase in maternal death with the impact of the Delta wave compared with pre-Delta period [relative risk (RR)=5.478, 95% confidence interval (CI) (2.54-11.8), z=4.342, p<0.001]. The count and the rates of maternal deaths, patients with ICU admission and with severe-critical disease during pre-Delta, Delta, and Omicron waves are summarized in Table 1. There were not any difference between demographic and obstetric characteristics of maternal deaths before and during the Delta wave and these are presented with characteristics of all maternal deaths in Table 2.

**Table 1.** The count and the rates of maternal deaths, ICU admission and severe-critical disease during pre-Delta, Delta and Omicron waves

| | Pre-Delta (n=783) | Delta wave (n=243) | Omicron wave (n=39) | p |
|---|---|---|---|---|
| **Patients admitted to ICU** | 32 (4.1%) | 28 (11.5%) | 2 (5.1%) | **<0.0001** |
| **Patients with severe-critical disease** | 102 (13%) | 43 (17.7%) | 2 (5.1%) | **<0.0001** |
| **Maternal deaths** | 10 (1.28) | 17 (7%) | 1 (2.56%) | **<0.0001** |

ICU: Intensive care unit

**Table 2.** Demographic, obstetric characteristics of the maternal deaths in relation with Delta wave

| | Values[a] | | | p |
|---|---|---|---|---|
| | All (n=28) | Pre-Delta (n=10) | Delta (n=17) | |
| **Age (year)** | 31.19±5.41 | 29.5±5.7 | 31.35±5.05 | 0.505 |
| **BMI (kg/m²)** | 26.6±3.49 | 25.97±3.5 | 27.18±3.68 | 0.443 |
| **Gestational age at birth or abortus (week)** | 30.36±5.06 | 29.3±5.52 | 30.94±5 | 0.505 |
| **Fetal birth weight (gr)** | 1967.46±792.70 | 1898.78±751.26 | 1989.44±852.34 | 0.714 |
| **Nulliparity** | 11 (39.3%) | 4 (40%) | 7 (41.2%) | |
| **Primiparity** | 9 (32.1%) | 4 (40%) | 5 (29.4%) | 0.807 |
| **Multiparity** | 8 (28.6%) | 2 (20%) | 5 (29.4%) | |
| **Second trimester (14-28 week)** | 7 (25%) | 3 (30%) | 4 (23.5%) | |
| **Third trimester (>28 week)** | 21 (75%) | 7 (70%) | 13 (76.5%) | 0.711 |
| **Multiple gestation** | | | | |
| Singleton | 26 (96.4%) | 10 (100%) | 16 (94.12%) | |
| Triplet | 1 (3.6%) | | 1 (5.88%) | |
| **Pregnancy outcome[b]** | | | | |
| Cesarean section | 24 (88.9%) | 9 (90%) | 14 (82.4%) | |
| Vaginal delivery | 2 (7.4%) | | 2 (11.8%) | |
| Miscarriage | 1 (3.7%) | 1 (10%) | | |
| **Preterm** | | | | |
| 34-37 week | 5 (17.9%) | 6 (66.67%) | 2 (11.11%) | |
| <34 week | 20 (71.4%) | 3 (33.33%) | 13 (72.22%) | |
| **Term** | 3 (10.7%) | | 3 (16.67%) | |
| **Positive PCR results at the end of the pregnancy[c]** | 27 (96.4%) | 10 (100%) | 16 (94.12%) | |

Data presented as mean ± standard deviation or n (%).
BMI: Body-mass index, PCR: Polymerase chain reaction, [a]: Only one mother was died during the Omicron wave. Omicron column was removed due to statistical difficulties, [b]: All of the cesarean sections and one labor induction were done due to a rapid deterioration in maternal clinical status. One of the vaginal deliveries was preterm labor. Miscarriage was spontaneous at 18th week. One of the pregnant women died at 23th gestational week under medical induction (due to *in utero mort fetus*), [c]: At the cesarean section, vaginal delivery and abortus

Twenty-seven maternal deaths occurred mainly due to respiratory failure in the ICU and one patient died from acute pulmonary embolism in the inpatient clinic, 5 days after her discharge from the ICU. One of the pregnant women had an intrauterine fetal death during follow-up in the ICU and medical induction for abortion was applied, but, the patient died before the abortion. All the other maternal deaths occurred postpartum. demographic characteristics, obstetric characteristics and outcomes of maternal deaths are presented in Table 2. Twenty-eight babies were born and the 5th minute APGAR score of 7 babies was below 7. Twenty-one babies were followed up in the neonatal ICU primarily due to prematurity. There was no proven vertical transmission to babies according to nasopharyngeal PCR in the first 12 h of babies.

Clinical characteristics of maternal deaths in relation with Delta wave are summarized in Table 3. COVID-19 related imaging techniques, interventions during the follow-up of the disease in relation with Delta wave are presented in Table 4. Twenty-three pregnant women (23/28, 82.14%) admitted to the hospital with severe and two pregnant women (2/28, 7.14%) admitted with critical disease. Three of the pregnant women (3/28, 10.71%) had moderate disease at the time of admission and the LUS scores of these women were LUS-1, LUS-2, and LUS-3 respectively. One of the three pregnant women with moderate disease and LUS-1 score was admitted to the ICU 12 days after the admission to the hospital. LUS scores of all hospitalized patients were evaluated according to mortality and it was found statistically significant ($p<0.001$, chi-square=34.810). The maternal mortality rate, according to LUS scores, were 0.37% (1/273), 0.72% (2/277), 2.58% (10/387) and 11.72% (15/128) for LUS 0, LUS 1, LUS 2 and LUS 3, respectively (LUS-3 vs. others; maternal mortality: RR=8.447, 95% CI (4.11-17.34), z=5.814, $p<0.0001$). Demographic, clinical characteristics and laboratory findings of pregnant women with COVID-19 in relation with LUS scores are presented in Table 5. Additionally, clinical severities and LUS scores of all hospitalized patients in detail are presented in Supplementary Table 1.

The laboratory findings of the pregnant women at the time of hospital admission and at the critical stage of the disease are presented in Table 6. At hospital admission 19 (67.9%) patients presented with lymphopenia.

One maternal death occurred during the Omicron wave. She was 39 years old, her body mass index (BMI) was 27.55 and her parity was 3. She had 31+2nd gestational weeks and was admitted to the hospital with shortness of breath. She had hypothyroidism as co-morbidity. On admission to hospital C-reactive protein level was 18 mg/L and the lymphocyte count was 0.44 /$10^3$ uL. She rejected chest-CT, her chest X-ray revealed pneumonia and her LUS score was 3. After the 5th day of hospital admission, because of rapid deterioration in maternal clinical status cesarean section was performed and she was admitted to the ICU. She passed away due to COVID-19 pneumonia and accompanying acute respiratory distress syndrome (ARDS) after 4 days of follow-up in the ICU.

There were no vaccinated patients in the cohort of this study. Primarily used medications for treating patients are summarized in Supplementary Table 2.

## Discussion

The total mortality rate of pregnant women due to COVID-19 was 2.63% among hospitalized patients, and the maternal deaths occurred in one-fifth of the patients who had a severe or critical illness. Maternal deaths were found to have increased approximately 5 times among hospitalized patients during the Delta wave. Almost all maternal deaths occur postpartum and co-morbidities may not be the determining factor for maternal death. The Delta wave and delayed vaccination may be the main reasons for increased maternal mortality. LUS may play a significant role in identifying critical patients. To the best of our knowledge, this study reports the highest number of maternal deaths from a single center.

The maternal mortality rate has been reported differently in each country, Centers for Disease Control in the United States reported a 0.2% maternal mortality rate from COVID-19[2], on the other hand, in Brazil 12% mortality rate was reported by Takemoto et al.[28]. The maternal mortality ratio (2.63%) was relatively high in our study from the commonly reported mortality rates in the literature[29-31]. However, this rate was among hospitalized patients who belonged to a pandemic referral hospital. In a multinational cohort study, the overall maternal mortality was found to be 1.6% that was 22 times higher than that in COVID-19 diagnosed non-pregnant women[32]. In a multicenter retrospective cohort study in Washington State, mortality due to COVID-19 was found to be 13.6 times higher in pregnant women compared with similarly aged individuals[4]. The study from Brazil emphasized that maternal death in pregnancy or postpartum period is always a tragedy and must be considered preventable[33].

The overall maternal death rate was 2.63%, although it was 1.28% before the Delta wave. The Delta variant had become the predominant variant in many parts of the UK and other countries due to increased transmissibility since February 2021[34]. As the pandemic progressed, the risk of critical illness increased, although this may be associated with the increased number of patients or with the effects of the new variants, the data on the reason for this increase have been scarce and confusing[34]. After the Delta variant spread, the death rate during pregnancy was reported to have increased in Mississippi[35] and in Parkland hospital the morbidity was reported to have increased with the Delta wave[36]. In this study, during the Delta wave, the death rate of pregnant women increased approximately 6 times in our hospital. Another reason for the increase in maternal mortality may be the lack of vaccination in pregnant women. Previously, pregnant women were excluded from COVID-19 vaccine research, and countries did not prioritize vaccinating

**Table 3.** Clinical characteristics of COVID-19 related maternal deaths[a]

| | All (n=28) | Pre-Delta (n=10) | Delta (n=17) | p |
|---|---|---|---|---|
| **Total duration of hospitalization (day)** | 15.86±8.49 | 18.6±9.05 | 14.59±8.19 | 0.309 |
| **Intensive care unit duration (day)** | 10.57±7.94 | 12.7±7.83 | 9.71±8.1 | 0.243 |
| **Symptoms at first admission** | | | | |
| Shortness of breath | 15 (53.6%) | 4 (40%) | 10 (58.8%) | |
| Cough | 7 (25%) | 3 (30%) | 4 (23.5%) | |
| Fever | 2 (7.4%) | - | 2 (11.8%) | |
| Myalgia | 1 (3.6%) | 1 (10%) | - | |
| Malaise | 1 (3.6%) | 1 (10%) | - | |
| Sore throat | 1 (3.6%) | 1 (10%) | - | |
| Diarrhea-nausea | 1 (3.6%) | - | 1 (5.9%) | |
| **Contact history** | | | | |
| Positive | 17 (60.7%) | 8 | 8 | 0.093 |
| Negative | 11 (39.3%) | 2 | 9 | |
| **Co-morbidities[b]** | 14 (50%) | 4 | 9 | 0.516 |
| **Positive PCR test** | 28 (100%) | 10 (100%) | 17 (100%) | |

Data presented as mean±standard deviation or n (%)
PCR: Polymerase chain reaction, [a]: Only one mother was died during the Omicron wave. Omicron column was not added due to statistical difficulties, [b]: There were 5 pregnant women ≥35 years of age, 4 pregnant women with ≥30 kg/m$^2$ body mass index, 3 pregnant women with preeclampsia, 2 pregnant women with asthma, 2 pregnant women with hypothyroidism and 1 pregnant women with scoliosis. Co-morbidities can appear simultaneously in a pregnant woman

**Table 4.** Imaging studies and interventions of COVID-19 related maternal death cases[a]

| | n (%) | | | |
|---|---|---|---|---|
| **Imaging studies** | **All (n=28)** | **Pre-Delta (n=10)** | **Delta (n=17)** | |
| **Chest X-ray** | | | | |
| Pneumonia | 19 (67.9%) | 6 (60%) | 12 (70.6%) | |
| Rejection | 9 (32.1%) | 4 (40%) | 5 (29.4%) | |
| **CT** | | | | |
| Pneumonia | 14 (50%) | 8 (80%) | 6 (35.3%) | |
| Rejection | 11 (39.3%) | 2 (20%) | 8 (47.1%) | |
| Negative | 3 (10.7%) | - | 3 (17.6%) | |
| **Initial LUS score at hospital admission** | | | | |
| LUS 0 | 1 (3.6%) | 1 (10%) | | |
| LUS 1 | 2 (7.1%) | 1 (10%) | 1 (5.9%) | |
| LUS 2 | 10 (35.7%) | 1 (10%) | 9 (52.9%) | |
| LUS 3 | 15 (53.6%) | 7 (70%) | 7 (41.2%) | |
| **Interventions** | | | | **p** |
| Supplemental oxygen need with nasal cannula | 26 (92.9%) | 10 (100%) | 15 (88.2%) | 0.260 |
| Non-invasive mechanical ventilation | 28 (100%) | 10 (100%) | 17 (100%) | |
| Invasive mechanical ventilation | 23 (82.1%) | 9 (%) | 13 (76.5%) | 0.382 |
| ECMO | 10 (35.7%) | 2 (%) | 8 (47.1%) | 0.230 |

LUS: Lung ultrasound, CT: Chest computed tomography, ECMO: Extracorporeal membrane oxygenation, [a]: Only one mother was died during the Omicron wave. Omicron column was not added due to statistical difficulties

**Table 5.** Demographic, clinical characteristics and laboratory findings of pregnant women with COVID-19 in relation with lung ultrasound scores

| n=1.065 | Values | | | |
|---|---|---|---|---|
| Demographic characteristics | LUS score 0/1 n=550 | LUS score 2 n=387 | LUS score 3 n=128 | p |
| Age (year) | 28.65±5.35 | 29.25±5.54 | 30.69±5.47 | 0.001 |
| BMI (kg/m$^2$) | 26.24±3.81 | 26.4±3.78 | 26.87±3.61 | 0.242 |
| Gestational age (week) | 27.3±10.48 | 28.06±9.08 | 29.02±7.72 | 0.155 |
| Parity | 1.25±1.28 | 1.26±1.2 | 1.5±1.28 | 0.117 |
| **Laboratory findings** | | | | |
| Leucocyte count (/10$^3$ uL) | 9.1±5.54 | 8.58±4.19 | 11.54±6.93 | <0.0001 |
| Lymphocyte count (/10$^3$ uL) | 1.5±0.9 | 1.35±0.99 | 1.1±0.82 | <0.0001 |
| C-reactive protein (mg/L) | 3.39±4.94 | 5.87±14.7 | 8.04±7.6 | <0.0001 |
| Lactate dehydrogenase (IU/L) | 210.0 (92) | 238.5 (116.5) | 296.5 (232.5) | <0.0001 |
| **Clinical characteristics** | | | | |
| Duration of hospitalization (day) | 3.78±3.86 | 7.51±4.42 | 11.59±11.45 | <0.0001 |
| Patients admitted to ICU | 4 (0.73%) | 22 (5.68%) | 36 (28.13%) | <0.0001 |
| Patients with severe-critical disease | 10 (1.82%) | 61 (15.76%) | 76 (59.38%) | <0.0001 |
| Maternal death | 3 (0.55%) | 10 (2.58%) | 15 (11.72%) | <0.0001 |
| Supplemental oxygen need with nasal cannula | 24 (4.36%) | 86 (22.22%) | 77 (60.16%) | <0.0001 |
| Non-invasive mechanical ventilation need | 5 (0.91%) | 34 (8.79%) | 47 (36.72%) | <0.0001 |
| Invasive mechanical ventilation need | 3 (0.55%) | 9 (2.33%) | 23 (17.97%) | <0.0001 |
| Extracorporeal membrane oxygenation | 1 (0.18%) | 4 (1.03%) | 10 (7.81%) | <0.0001 |

Variables are reported as mean ± standard deviation or median (interquartile range) depending on distribution characteristics and n (%), LUS: Lung ultrasound, ICU: Intensive care unit

**Table 6.** Laboratory parameters of the maternal deaths at two occasions (hospital admission and critical stage of disease)

| n=28 | At hospital admission Values | During critical stage Values | p |
|---|---|---|---|
| **Leucocyte count (/10$^3$ uL)** | 8.14±3.4 | 19.54±8.17 | **<0.0001** |
| **Neutrophil count (/10$^3$ uL)** | 7.1±3.29 | 16.26±6.96 | **<0.0001** |
| **Lymphocyte count (/10$^3$ uL)** | 0.90±0.33 | 2.07±1.61 | **0.002** |
| **Hemoglobin level (g/dL)** | 10.78±1.35 | 8.93±1.94 | **<0.0001** |
| **Platelet count (10$^3$/mm$^3$)** | 220±84.39 | 268.04±177.89 | **0.191** |
| **Alanine aminotransferase (IU/L)** | 17.2 (32.8) | 25.5 (74.3) | **0.052** |
| **Aspartate aminotransferase (IU/L)** | 30.5 (34.83) | 51.5 (98.77) | **0.009** |
| **C-reactive protein (mg/L)** | 7.77±5.02 | 16.9±14.26 | **0.001** |
| **Lactate dehydrogenase (IU/L)** | 295.5 (173.5) | 678.5 (440.75) | **<0.0001** |
| **Ferritine (ng/mL) (n=14)** | 159.2 (239.2) | 735.6 (5130.78) | **0.003** |
| **D-dimer (mcg/mL) (n=26)** | 1.5 (2.55) | 5.05 (7.43) | **0.004** |
| **Fibrinogen (mg/dL) (n=26)** | 562.28±139.87 | 544.08±290.21 | **0.476** |
| **Procalcitonin (ng/mL) (n=16)** | 0.35 (1.84) | 0.88 (3.87) | **0.776** |

Variables are reported as mean ± standard deviation or median (interquartile range) depending on distribution characteristics

pregnant women[31]. Later, our government, along with a few other countries, promoted COVID-19 vaccination of pregnant women[32]. Despite this, unfortunately, there were no vaccinated patients in the cohort of this study. Vaccine acceptance is low due to the concerns about vaccine safety in our country[37]. Hospitalization and mortality were not considerably increased during the Delta wave in the vaccinated population, according to an Israeli study[38] and Aslam et al.[7] reported recently that at the 4th wave maternal deaths were all in unvaccinated pregnant women. Due to the relatively higher severity of the Delta variant, the vaccine hesitancy and delayed vaccination might have had an outsized influence on the increased mortality rate during the Delta wave in pregnant women. The mortality rate with the onset of the Omicron wave was 2.6% in the study cohort, this rate was lower than the Delta wave but, higher than the pre-Delta period. However there is no statistical significance between pre-Delta period and Omicron wave maternal mortality rates, and the number of patients in the Omicron wave may be insufficient to determine the maternal mortality rate.

All maternal deaths in this study occurred after delivery, except one patient. Maternal deaths were primarily reported postpartum in Iran, Brazil and Mexico, similar to our cohort of maternal deaths[39,40]. In this study, COVID-19 pneumonia and accompanying ARDS were the primary causes of mortality, except for one maternal death, which was caused by pulmonary embolism. All of the hospitalized patients received either 40 mg or 60 mg enoxaparin according to their weight for thrombophylaxis since COVID-19 increases the risk of thrombosis[41]. Similar to the first maternal death reported in the United caused by basilar artery thrombosis[42], one of our maternal deaths occurred due to a hypercoagulative state of the postpartum period that was pulmonary embolism as a complication of deep vein thrombosis. She had been treated with enoxaparin 60 mg twice daily before her death.

In the current study, if we consider age over 35 and BMI over 30 as risk factors, 14 (50%) pregnant women had co-morbidity. There were 3 women with preeclampsia, 2 women with asthma, 2 women with hypothyroidism and one woman with scoliosis. Half of the pregnant women had no co-morbidity, therefore, co-morbidities may not predict maternal death. However, when compared to similar age non-pregnant women, pregnant women have a higher risk of complications-such as severe pneumonia, hospitalizations, admission to an ICU, and invasive mechanical ventilation-and mortality from COVID-19[43]. Although there has been a report that severe infection can be seen in the early stages of pregnancy[19], late stages of pregnancy are often associated with more severe infection and major unfavorable outcomes[44]. Similar to the case series of maternal deaths from Iran[45] maternal deaths in our hospital occurred in the second and third trimesters.

It would be beneficial to identify COVID-19 patients who can worsen to reduce or even eliminate maternal mortality caused by COVID-19. The leading indicators are common symptoms and nasopharyngeal PCR results, although they might be deceptive and delayed in making decisions, particularly when it comes to hospitalization. When we investigated the relation between LUS scores and maternal death rates, the highest maternal mortality rate was observed among the patients an LUS score of 3 (14/118, 11.9%). Besides, a significant correlation was found between clinical severity and LUS scores. ICU admission, mechanical ventilation and mortality were linked to higher LUS scores, according to a recently published review[18].

### Study Limitations

The retrospective nature of this investigation made it difficult to determine the precise number of variant cases. Therefore, the declared period of the Delta and Omicron waves in our country was the basis of our estimation of the maternal mortality rate.

## Conclusion

Maternal death is always a tragedy, and it is important to investigate the risk of mortality and take precautions. The maternal mortality rate was relatively high in our referral center of COVID-19. Maternal mortality occurred in the second and third trimesters of pregnancy by a majority in the postpartum period due to COVID-19 pneumonia and related ARDS except for one case in this study. The use of LUS appears to be valuable in identifying critical patients. The Delta wave, delayed vaccination and vaccine hesitancy of pregnant women may have all played important roles in maternal mortality in our hospital. Developing and improving vaccination strategies for pregnant women and prioritizing them, could be crucial in preventing pandemic related deaths in pregnant women.

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### Ethics

**Ethics Committee Approval:** The study was approved by the local ethics committee (University of Health Sciences Turkey, Prof. Dr. İlhan Varank Sancaktepe Training and Research Hospital - no: 2021/218)

**Informed Consent:** Retrospective study.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Interpretation: M.Y., O.S.G., B.D.T., N.T., Supervision: C.U., N.T., Concept: A.B.T., M.Y., P.B.İ., B.Ö., D.B., O.S.G., Design: A.B.T., E.Y., C.U., G.Ç., B.D.T., N.T., Data Collection or Processing: M.Y., P.B.İ., E.Y., B.Ö., C.U., D.B., O.S.G., G.Ç., B.D.T., N.T., Analysis or Interpretation: A.B.T., M.Y., Literature Search: Writing: A.B.T., P.B.İ., E.Y., C.U.

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**Supplementary Table 1.** LUS scores and the clinical severity of hospitalized patients

| Lung ultrasound scores of hospitalized patients | Clinical severity of patients | | |
|---|---|---|---|
| | Asymptomatic- mild disease | Moderate disease | Severe- critical disease |
| **0-1** | 502 (72.3%) | 38 (17%) | 10 (6.8%) |
| **2** | 175 (25.2%) | 151 (67.4%) | 61 (41.5%) |
| **3** | 17 (3.1%) | 35 (15.6%) | 76 (51.7%) |
| **Total** | 694 (100%) | 224 (100%) | 147 (100%) |

LUS: Lung ultrasound, p<0.0001 (chi-square value=499.039)

**Supplementary Table 2.** Medications used in the treatment of patients

| Medications | | n (%) |
|---|---|---|
| **Anticoagulant** | Enoxaparin 40-60 mg subcutaneously as a prophlaxis | 28 (100%) |
| **Antiviral** | 50 mg ritonavir and 200 mg lopinavir (two tablets twice daily in pregnancy) | 16 (57.1%) |
| | Favipiravir 200 mg (eight tablets twice daily postpartum) | 2 (7.1%) |
| **Antibiotic** | Choice, dose and duration changes with clinical judgement | 27 (96.4%) |
| **Corticosteroids** | 120 mg methylprednisolone daily | 28 (100%) |
| **Convalescent plasma therapy** | | 7 (25%) |