Clinical Characteristics and Outcomes of COVID-19 During Pregnancy—a Retrospective Cohort Study

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Abstract
The course of COVID-19 has been shown to be worse in pregnant women compared with their non-pregnant counterparts. The aim of this study is to share our experience treating pregnant women with COVID-19 and to establish a cohort for future studies of the long-term effects of the disease. We reviewed medical records of all SARS-CoV-2-positive pregnant women who were treated at our hospital for any reason, be it COVID-19 related or not, between April 2020 and February 2021. We extracted data regarding medical history, course of pregnancy, delivery, and neonatal outcomes. A total of 193 SARS-CoV-2-positive pregnant women were treated at our establishment during the study period, half of which were asymptomatic. Sixteen were hospitalized for COVID-19 symptoms, the most common being fatigue/malaise (58%) and cough (48%). Three women required mechanical ventilation and extracorporeal membrane oxygenation treatment. One hundred forty-four SARS-CoV-2-positive women were delivered during the study period. Of them, 24 (17%) underwent induction of labor, and four (17%) were due to symptomatic COVID-19. One hundred fifteen (80%) experienced vaginal delivery, and 29 (20%) underwent cesarean delivery. Neonatal outcomes were favorable; only 2% of 5-min Apgar scores were <7, and all umbilical cord pH levels were >7.1. Six infants tested positive for SARS-CoV-2; they were all asymptomatic, and none required treatment for viral infection. COVID-19 during pregnancy is a disease with potential substantial adverse maternal and neonatal outcomes. There is still much unknown regarding the long-term effects of the disease on parturients and their offspring.

Keywords SARS-CoV-2 · COVID-19 · Pregnancy · Delivery · Neonatal outcomes

Background
In December 2019, a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in China, rapidly spreading worldwide and causing the ongoing coronavirus disease (COVID-19) pandemic [1]. The first case of COVID-19 in Israel was diagnosed in February 2020 [2].

The course of COVID-19 has been shown to be worse in pregnant women compared with their non-pregnant counterparts [3]. They more often suffer from severe respiratory morbidity, coupled with a higher likelihood to be admitted to an intensive care unit (ICU), and require mechanical ventilation. In addition, preterm birth and cesarean delivery were more common in pregnant women diagnosed with COVID-19 [4], more often related to maternal condition rather than fetal indications or as a result of spontaneous onset of preterm delivery.

There is still much debate regarding the rate of vertical transmission of SARS-CoV-2 to the fetus, and its possible mechanisms—transplacental or during passage thru the birth canal. Current literature demonstrates this to be a rare event occurring in approximately 2% of the cases, with no clear indication that this is associated with fetal or neonatal adverse outcome [5, 6].

As the impact of COVID-19 in pregnancy and the COVID-19-associated adverse outcomes—maternal, fetal, and neonatal—remain under debate, women and caregivers alike are still puzzled by the management of pregnant COVID-19 patients. Therefore, we aimed to describe our
experience in a large tertiary center, in treating pregnant women with COVID-19, and to establish a cohort for future studies of the long-term effects of the disease.

Methods

We retrospectively reviewed the medical records of all SARS-CoV-2-positive pregnant women who were treated at our medical center for any reason, be it COVID-19 related or not, between 4 April 2020, and 8 February 2021.

Setting

The Helen Schneider Hospital for Women is part of Rabin Medical Center, a tertiary hospital located in the center of Israel. As such, we treat a large number of pregnant women, for obstetric and non-obstetric conditions, with approximately 8000 deliveries a year. For this reason, as soon as the pandemic reached the state of Israel, our staff began the process of preparing a dedicated area for the treatment of pregnant COVID-19 patients, naming the new wing Delivery Room C, which consists of a triage, delivery room and in-patient antepartum, and postpartum hospitalization rooms. We treated our first pregnant COVID-19 patient on 4 April 2020.

SARS-CoV-2 Testing

We routinely screen all pregnant women for SARS-CoV-2 if they are in labor, admitted for hospitalization or surgery, quarantined due to exposure to a known COVID-19 patient, and/or if they have signs or symptoms suspected to be related to COVID-19. The diagnosis of SARS-CoV-2 was made using a real-time reverse transcriptase-polymerase-chain-reaction (RT-PCR) assay of a nasopharyngeal swab specimen. This was done using a kit by Seegene (Songpa-gu, South Korea).

Data Collection

Data was retrieved from the hospital’s comprehensive computerized maternal, fetal, and neonatal medical database, including records from the emergency room triage, delivery room charts, maternal–fetal hospitalization records, and nursery care. The collected data included maternal demographics, medical and obstetric background, antepartum evaluation of pregnancy and COVID-19 clinical and laboratory parameters, as well as all birth and perinatal outcomes.

Definitions

Birthweight percentiles were calculated by a nationally accepted, gender specific, and reference growth curve [7]. Large for gestational age (LGA) newborn was defined as birthweight above the 90th percentile for gestational age and small for gestational age (SGA) if birthweight was below the 10th percentile.

Disease severity was classified as mild, severe, or critical according to the Wu et al. classification [8].

Statistical Analysis

Data was presented as mean and standard deviations for continuous variables and as numbers and percentages for categorical variables. Data was collected and analyzed using Excel software (Microsoft, Washington, USA, 2016).

Ethics Approval

The study was approved by the institutional review board of Rabin Medical Center (approval no. 331–20-RMC). Informed consent was waived due to the study’s retrospective design.

Results

A total of 193 pregnant women with a positive SARS-CoV-2 test were treated at our medical center between 4 April 2020 and 8 February 2021. Over the 10-month study period, over 5300 SARS-CoV-2 tests were obtained at the obstetric emergency department and the fetal-maternal medicine unit at Helen Schneider Hospital for Women, and the number of COVID-19 diagnoses per month varied significantly (Fig. 1). At the time of writing this manuscript, no fatalities have been recorded. Patient characteristics are presented in Table 1. The mean age of the patients at the time of SARS-CoV-2 diagnosis was 30.9 ± 6 years (range 17–50). Most of the women were healthy; only 15% of patients had a diagnosis of at least one chronic illness: 11 had thyroid disorders, 5 had pregestational diabetes (type 1 or type 2), 4 had inflammatory bowel disease, 3 had chronic hypertension, 3 had asthma, 3 had antiphospholipid antibodies syndrome. A single patient each had one of the following: congenital adrenal hyperplasia, aortic stenosis, Goucher disease, chronic myelogenous leukemia, factor XI deficiency.

The patients had an average of 2 ± 1.9 live children, with 24% nulliparous, and 10% grand-multiparous, i.e., more
than four prior deliveries. Ninety-four percent of pregnancies were spontaneous.

Twenty-seven women (14%) had gestational diabetes mellitus, of them 6 were treated with insulin. One woman developed mild preeclampsia without severe features and did not require treatment with magnesium sulfate. One woman was diagnosed with atypical hemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome, which warranted intravenous magnesium treatment for 24 h.

Forty-seven percent of women were asymptomatic at the time of diagnosis, and 43% experienced at least one symptom defining them as a COVID-19 patient. The most common symptoms were fatigue/malaise (58%), followed by cough (48%) and fever (36%). Signs and symptoms are shown in Table 2.

Of all 193 patients, 16 were hospitalized due to COVID-19 symptoms, the rest were either discharged or admitted for unrelated medical or obstetric issues. Chest x-rays were performed for 21 women, 18 of which were positive for typical COVID-19 findings, and the remaining 3 were normal. Six women were medically treated for COVID-19: 5 received low molecular weight heparin (enoxaparin), 3 received steroid treatment (dexamethasone), and one was treated with antibiotics for superimposed bacterial pneumonia. None of the patients received anti-viral medications or other specific COVID-19 medications. Three patients required intubation and mechanical ventilation, all three of which also required extracorporeal membrane oxygenation (ECMO) treatment.

We reviewed laboratory test results obtained within two weeks of SARS-CoV-2 diagnosis. Not all tests were performed for all patients, and so group size varies (Table 3).

Six patients (4.5%) had recorded leukocytosis > 15 K/µL, and 25% had lymphopenia < 1 K/µL. Twenty percent of patients had anemia with hemoglobin < 10 g/dL, and 27% had some degree of thrombocytopenia, below 150 K/µL. Seven patients (6.7%) had increased international normalized ratio (INR) > 1.1. Two patients (1.9%) had hypofi-brinogenemia < 200 mg/dL, one of them was diagnosed...
with disseminated intravascular coagulation (DIC) following excessive bleeding during emergency cesarean delivery due to non-reassuring fetal heart rate (NRFHR) and was treated with blood products. D-dimer levels were recorded for 64 patients, 21 of which (33%) had an increased level $>3300$ ng/mL.

Elevated liver enzymes—aspartate aminotransferase (AST) and alanine aminotransferase (ALT)—were seen in 23% and 14% of patients, respectively. Lactate dehydrogenase (LDH) was elevated among 36% of patients. None of the patients had an increased level of creatinine. The average maximal level of C-reactive protein (CRP) was $5.2$ mg/dL, and it was increased, above pregnancy-related norms, in 36% of women.

Table 4 shows the delivery outcomes of our population. One hundred forty-four SARS-CoV-2-positive women delivered their infants at our center during the study period. Of them, 24 (17%) underwent induction of labor, 20 for obstetric indications such as post-date gestational age, diabetes, and estimation of large or small for gestational age fetuses. Four were induced due to symptomatic COVID-19 disease. Of women with recorded deliveries, 111

| Table 3 | Laboratory testing results |
|---------|----------------------------|
| $N$ | Maximum | Minimum | Rate |
| Complete blood count | | |
| White blood cells (K/micL; normal range 4.5–11) | 132 | 9.8 ± 3.7 | |
| Leukocytosis > 15 K/micL | 6 (4.5) | |
| Lymphocytes (K/micL; normal range 1–4.8) | 132 | 1.4 ± 0.7 | |
| Lymphopenia < 1 K/micL | 33 (25) | |
| Hemoglobin (g/dL; normal range 12–16) | 132 | 11 ± 1.6 | |
| Anemia < 10 g/dL | 27 (20.5) | |
| Platelets (K/micL; normal range 150–450) | 132 | 189 ± 68 | |
| Thrombocytopenia < 150 K/micL | 35 (27) | |
| Coagulation function | | |
| International normalized ratio (INR) | 105 | 0.97 ± 0.08 | |
| Increased > 1.1 | 7 (6.7) | |
| Fibrinogen (mg/dL; normal range 200–530) | 103 | 584 ± 146 | |
| Hypofibrinogenemia < 200 mg/dL | 2 (1.9) | |
| D-dimer (ng/mL) | 64 | 3378 ± 6300 | |
| Increased > 3300 ng/mL | 21 (32.8) | |
| Biochemistry | | |
| Creatinine (mg/dL; normal range 0.51–0.95) | 114 | 0.52 ± 0.11 | |
| Increased > 0.9 mg/dL | 0 (0) | |
| Aspartate aminotransferase (U/L; normal range 0–31) | 111 | 31 ± 27 | |
| Increased > 31 U/L | 25 (23) | |
| Alanine aminotransferase (U/L; normal range 0–34) | 111 | 23 ± 21 | |
| Increased > 34 U/L | 16 (14) | |
| Lactate dehydrogenase (U/L; normal range 230–480) | 110 | 500 ± 210 | |
| Increased > 600 U/L | 24 (21.8) | |
| Other | | |
| C-reactive protein (mg/dL; normal range 0–0.5) | 61 | 5.2 ± 5.4 | |
| Increased > 0.5 mg/dL | 22 (36.1) | |

Data presented, by the relevance of the specific laboratory testing, as either minimum ± standard deviation or maximum ± standard deviation for continuous variables and as number (percent) for categorical variables.
(77%) experienced normal vaginal delivery, 4 (3%) had an assisted vaginal delivery using vacuum extraction, and 29 (20%) underwent a cesarean delivery. The primary indications for cesarean delivery were: previous cesarean delivery (11, 38%), NRFHR (6, 21%), breech presentation (4, 14%), severe COVID-19 disease (3, 10%), maternal request (2, 7%). Other reasons indicated for a single patient each were triplet pregnancy, suspected uterine scar dehiscence, and medically indicated (presence of arachnoid cyst). Twelve deliveries (8%) were preterm, three of them due to severe COVID-19 disease, all of which underwent a cesarean delivery without a trial of labor.

Nine women experienced spontaneous abortions; of them, three were mid-trimester miscarriages at or beyond 14 gestational weeks. Two women underwent mid-trimester termination of pregnancy, one due to a diagnosis of cystic hygroma and hydrops fetalis, and one for early severe fetal growth restriction.

One hundred forty-four deliveries resulted in the birth of 147 live infants. Neonatal outcomes are summarized in Table 5. The mean gestational age at birth was 38.3 ± 2.6 weeks. Twelve percent of infants were LGA and 5% were SGA. The vast majority of patients gave birth to a singleton infant, one woman had twins, and one woman had triplets.

One additional woman had a monochorionic-diamniotic twin pregnancy, complicated by twin-to-twin transfusion syndrome (TTTS) diagnosed at 16 gestational weeks. This patient underwent laser treatment at week 20. At the time of the procedure, while diagnosed with positive nasopharyngeal maternal SARS-CoV-2, amniocentesis was performed, and amniotic fluid was negative for SARS-CoV-2. Following the procedure, one twin died in utero and expulsion of the dead fetus. This fetus was not taken into account regarding neonatal outcomes, due to the early time of its demise.

At our establishment, neonates born to mothers who have a positive COVID-19 diagnosis at the time of birth are routinely tested for SARS-CoV-2. Swabs are obtained 24 and 48 h after delivery. Our cohort consists of 59 neonates with a documented SARS-CoV-2 test, and six of these infants (10.2%) tested positive. All six infants were asymptomatic, and none of them required treatment for viral infection.

### Discussion

This was is a descriptive study of all pregnant patients with a confirmed COVID-19 infection treated at our facility, a tertiary medical center.

This cohort may demonstrate an underestimation of disease prevalence among pregnant women, as asymptomatic women who were not hospitalized were not tested, and as reviewed earlier, 47% were diagnosed due to routine screening despite being asymptomatic. However, the strength of this study is the testing of all women admitted to the hospital for any reason, regardless of COVID-19 symptoms. Using this method of SARS-CoV-2 screening, we gain a good estimation of disease prevalence among our population.

Approximately 3% of SARS-CoV-2 tests obtained at our establishment during the study period were positive, a larger proportion than that described among a large cohort of pregnant women in Italy [9]. Forty-seven percent of patients included in our cohort were asymptomatic, a higher proportion than has been described in the literature regarding both pregnant [10] and non-pregnant patients [11]. Symptomatic illness in pregnancy has been shown to be associated with adverse maternal and neonatal outcomes such as higher rates of cesarean delivery, preterm delivery, and low birthweight [4, 12]. However, asymptomatic infection is of unclear clinical significance regarding future maternal and neonatal health [3].

It is difficult to estimate the proportion of asymptomatic COVID-19 infections in the non-pregnant population, as they do not undergo routine screening for the disease [11].

Four patients with severe illness were treated in the ICU at our hospital:

1. A 29-year-old generally healthy woman, gravida 2 para 1 with a history of a single cesarean delivery and an uneventful pregnancy course, was diagnosed with COVID-19 upon admission to the hospital. Her only symptom was a cough. She underwent emergency cesarean delivery at 38 weeks due to NRFHR during active labor. Her surgery was complicated by excessive bleeding and dis-

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**Table 5  Neonatal outcomes**

| Sex, female | 84 (57) |
| Birthweight, grams | 3135 ± 600 |
| Percentile | 54.9 ± 28.3 |
| Large for gestational age | 17 (11.6) |
| Small for gestational age | 8 (5.4) |
| 1-min Apgar score < 7 | 5 (3.4) |
| 5-min Apgar score < 7 | 3 (2) |
| Umbilical cord pH* | 7.3 ± 0.06 |
| pH < 7.2 | 6 (4.1) |
| pH < 7.1 | 0 (0) |
| NICU hospitalization | 15 (10.3) |

Data presented as mean ± standard deviation for continuous variables and number (percent) for categorical variables

*Data available for only 99 of the patients

NICU, neonatal intensive care unit
semianated intravascular coagulation (DIC), and when conservative measures did not suffice, she underwent a cesarean hysterectomy. She did not require mechanical ventilation. She was discharged on post-operative day 7.

2. A 33-year-old generally healthy woman, gravida 7 para 5 with a history of four cesarean deliveries and a normal pregnancy follow-up, was diagnosed with COVID-19, 18 days before hospital admission. Her symptoms were malaise/fatigue, shortness of breath, and cough. Examination in the emergency department revealed severe dyspnea and oxygen saturation of 82% in room air. Upon admission, disease severity required intubation and mechanical ventilation. Immediately following intubation, she underwent emergency cesarean delivery at 31 weeks. The neonate’s birthweight was 1900 g (75th percentile); 1-min and 5-min Apgar scores were 3 and 8, respectively; umbilical cord pH was 7.32. The neonate was treated in the neonatal ICU (NICU). Following surgery, the patient’s condition deteriorated, and she was put on ECMO. She was treated with ECMO for 1 month. At the time of writing this manuscript, she is stable, beginning the process of rehabilitation.

3. A 35-year-old gravida 7 para 6 with obesity and chronic hypertension and a history of four cesarean deliveries was diagnosed with COVID-19 at 29 gestational weeks and was hospitalized for treatment at a different facility. Her symptoms at diagnosis were cough and shortness of breath. When her condition deteriorated, she was transferred to our medical center for further treatment and to consider availability of an ECMO machine in our institution. Upon admission to our hospital, her oxygen saturation was 85% in room air. Disease severity required intubation and mechanical ventilation. Immediately following intubation, she underwent emergency cesarean delivery at 31 weeks. The neonate’s birthweight was 1620 g (33rd percentile); 1-min and 5-min Apgar scores were 1 and 2, respectively; umbilical cord pH was 7.27. The neonate was treated in the NICU. Following surgery, her condition deteriorated, and on post-operative day 9, she was put on ECMO. He was treated with ECMO for 1 month and was recently discharged from the hospital.

4. A 40-year-old generally healthy gravida 4 para 1 with gestational diabetes mellitus was diagnosed with COVID-19 at 26 gestational weeks. Her only symptom at diagnosis was a cough. Her oxygen saturation was 93% in room air. She was initially treated in the fetal-maternal medicine COVID-19 ward, but a week later her condition deteriorated, and she was transferred to ICU, where she was intubated and mechanically ventilated. On the same day, she underwent emergency cesarean delivery at 28 weeks. The neonate’s birthweight was 780 g (8th percentile); 1-min and 5-min Apgar scores were 5 and 6, respectively; umbilical cord pH was 7.32. The neonate was treated in the NICU. Following surgery, her condition further deteriorated and was put on ECMO on the same day. One week later, the patient was hemodynamically unstable due to intra-abdominal hemorrhage, and she underwent a laparotomy for hemoarteris and intra-abdominal packing. The following day she developed compartment syndrome, and underwent an additional laparotomy for hemoarteris and intra-abdominal packing. Two days later, she underwent final surgery for abdominal closure. This patient was treated with ECMO for 13 days and was mechanically ventilated for a total of 3 weeks. At the time of writing this manuscript, she is stable and is expected to be discharged from the hospital to begin the process of rehabilitation.

An interesting point regarding severe COVID-19 illness is its relative rarity among our cohort. Only four patients (2%) required ICU admission, and no fatalities were recorded—much less than has been reported in similar studies, that have shown an ICU admission rate of 11% and a mortality rate of 0.8% [13]. A possible explanation for this could be the relative homogeneity of our population, compared with larger, multinational studies.

All three patients treated with ECMO were diagnosed with the UK variant of SARS-CoV-2 (B.1.1.7 lineage), which has not been shown to be associated with greater disease severity [14]. Regarding this diagnosis, it should be noted that only patients admitted to the ICU were screened for the viral variant, so it may be a misrepresentation of its prevalence.

The use of ECMO for severe cardiopulmonary failure during pregnancy and the postpartum period is not common practice, as conditions warranting its use are uncommon and smaller medical facilities do not have the ability to use this modality. The largest study of this practice includes 97 patients, most of them peripartum or postpartum [15]; however, only 39% of these patients were treated for respiratory failure, and the rest were treated for cardiac failure.

During the COVID-19 pandemic, our establishment’s ECMO team treated many patients suffering from respiratory failure, among them the three women described above. The decision to treat these with ECMO was made by a multidisciplinary team, and although not entirely contra-indicated in pregnancy [16], the decision was made to deliver the neonates prior to ECMO treatment in all three cases, allowing for simpler management of these patients.

We reviewed laboratory results of tests obtained within 2 weeks of COVID-19 diagnosis and disregarded blood tests that were taken over 2 weeks after infection for the purpose of this analysis. Previous studies have demonstrated that levels of inflammation markers are generally higher among
pregnant women with COVID-19 compared with a non-pregnant cohort [17].

D-dimer has been used as a biomarker for severe COVID-19 disease, and elevated D-dimer has been shown to be a marker for increased risk of disease complications and of mortality in adult and pediatric populations [18]. The use of D-dimer during pregnancy is controversial and its interpretation is challenging, as it is physiologically elevated in pregnancy, and there are no widely accepted cutoff values for its use. Gutiérrez García et al. attempted to set a trimester-specific normal range of D-dimer [19], demonstrating a cutoff of approximately 3300 ng/mL in the second and third trimesters of pregnancy as the upper normal limit. We defined elevated D-dimer levels as being ≥ 3300 ng/mL in accordance with this study. Elevated D-dimer does not seem to correlate with disease severity among our cohort; of the 21 women with increased levels of D-dimer, only ten (48%) were symptomatic patients. Of the four women treated in the ICU, D-dimer was only slightly elevated (4344 ng/mL) in one patient. One patient who suffered from DIC and required a massive transfusion of blood products expressed an extremely high D-dimer level (50,422 ng/mL); she had no respiratory symptoms and did not require oxygen supplementation or mechanical ventilation.

Neonates born to mothers with a COVID-19 diagnosis at the time of birth are routinely tested for SARS-CoV-2 24 and 48 h after delivery. It should be noted that during the pandemic, our department allowed for early discharge from the maternity ward after only 36 h, and so in many cases, infants did not complete the second test. Of 59 infants with documented tests, six infants (10.2%) were positive for SARS-CoV-2. Four of them had an initial negative test, and tested positive after 48 h. Three of them were breastfed; we have no information regarding breastfeeding in the remaining three. All six infants were asymptomatic, and none of them required treatment for viral infection. As the vertical transmission of the virus has been deemed negligible [5, 13], they were most probably infected after birth, due to close contact with infected parents or asymptomatic hospital staff. No obvious risk factors were identified; all mothers of infected infants were generally healthy with no chronic illnesses, and all infants were singleton, born at term, with appropriate for gestational age birthweights, and normal umbilical cord pH and Apgar scores. Five of these mothers were asymptomatic.

Over the 10-month study period, the number of COVID-19 diagnoses per month varied significantly (Fig. 1). One of the possible explanations for this phenomenon is correlation with nationwide lockdowns in Israel, taking place between 14 March and 4 May 2020, 18 September and 17 October 2020, and 27 December 2020 until 7 February 2021. The number of infections was reduced immediately following every one of these three lockdowns. Similar trends have been demonstrated in other countries with government-issued nationwide lockdowns [20].

Vaccination of the Israeli population began on 20 December 2020, and according to the Israeli Ministry of Health, nearly nine million vaccine doses have been administered to date, vaccinating approximately 50% of our population [21]. There is currently no reliable data regarding the rate of vaccination among pregnant women in Israel. We expect to see a decline in the number of new COVID-19 cases as the proportion of vaccinated individuals grows in the near future.

To summarize, this is a descriptive study of a single center’s experience with COVID-19 during pregnancy, a disease with potential substantial adverse maternal and neonatal outcomes. As this is an ongoing pandemic with no known cure at this time, the aim of this study was to share our experience managing pregnant women with a COVID-19 diagnosis and to establish a cohort for future studies on the long-term effects of the disease, both maternal and neonatal.

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Author Contribution S. Dollinger: project development, data collection, data analysis, manuscript writing.
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All authors read and approved the final manuscript.

Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code Availability Not applicable.

Declarations

Ethics Approval The study was approved by the Institutional Review Board of Rabin Medical Center (approval no. 331–20-RMC). Informed consent was waived due to the study’s retrospective design.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Competing Interests The authors declare no competing interests.

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