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Programvezető: Dr. Csala Miklós, egyetemi tanár

Témavezető: Dr. Valent Sándor, egyetemi docens

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COVID-19 and pregnancy

PhD thesis

Dorina Supák MD

Division of Moleculare medicine
Semmelweis University

Supervisor: Sándor Valent MD, PhD

Official reviewers: Csaba Demendi MD, PhD
Márton Vezér MD, PhD

Head of the Complex Examination Committee:
Gábor Sobel MD, PhD

Members of the Complex Examination Committee:
Márton Keszthelyi MD, PhD
Márton Vezér MD, PhD

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LIST OF ABBREVIATIONS

ACE-2 - angiotensin-converting enzyme 2

ARDS - acute respiratory distress syndrome

COVID-19 - Coronavirus disease 2019

CRP - C reactive protein

DHA - Docosahexaenoic acid

HELLP - H: hemolysis (the breakdown of red blood cells)

EL: elevated liver enzymes.

LP: low platelet

H1N1- swine flu, is a type of influenza A virus.

IL-1β - interleukin-1β

IL-6 – interleukin-6

IUGR - Intrauterine Growth Restriction

LMWH-prophylaxis - Low-molecular-weight heparins prophylaxis

MERS - Middle East Respiratory Syndrome

nCPAP - Nasal continuous positive airway pressure

NICU - neonatal intensive care unit

NLR – Neutrophil-Lymphocyte ratio

PCR - Polymerase chain reaction

ROC - receiver operating characteristic

ROP - Retinopathy of prematurity

RNA - ribonucleic acid

RT-q-PCR - real-time quantitative polymerase chain reaction

SARS - Severe acute respiratory syndrome

SARS-CoV-2 - Severe acute respiratory syndrome coronavirus 2

TMPRSS2 - transmembrane serine protease 2

TNF-α - Tumor necrosis factor alpha

WHO - The World Health Organization

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1. INTRODUCTION

In my work, I would like to provide a comprehensive picture of the COVID-19 epidemic that is shaking the health sector and the entire world, as well as its implications for pregnancy.

The global outbreak of COVID-19, caused by the new coronavirus SARS-CoV-2, has emerged as one of the most significant public health challenges of the twenty-first century (1, 2). The virus originated in late 2019 and has spread quickly worldwide, picking up thousands of more lives and contaminating millions (3, 4). The pandemic had a massive impact, leading to a huge increase in research on COVID-19. Scientists focused on understanding the virus, how it spreads, and the diseases it causes. This research brought about significant changes in public health policies worldwide (5). COVID-19 has received significant attention owing, in part, to its effect on pregnant women and other high-risk populations by the medical and scientific community (6). A woman's immune system, cardiovascular system, and respiratory system can all change during pregnancy, making it a unique physiological state that may affect how susceptible she is to infections, particularly viral diseases [2, 7, 8]. Pregnant women have historically been recognized as a high-risk population for unfavorable outcomes during pandemics, as the SARS outbreak in 2002–2003 and the H1N1 influenza pandemic of 2009 [9]. In order to guarantee the best possible outcomes for both the mother and the fetus, it is crucial to comprehend how COVID-19 affects pregnancy. Given the intricate interactions between the mother's immune system, placental function, and fetal development, COVID-19 poses unique complications during pregnancy. A higher risk of serious illness, such as respiratory issues, premature birth, and other obstetric difficulties, may exist for pregnant women with COVID-19 (7, 8). The clinical management of pregnant patients is made more difficult by the existence of comorbidities, which include conditions like diabetes, hypertension, and obesity that are known to worsen the severity of COVID-19 (9-11).

Numerous studies have examined the transmission of SARS-CoV-2 from mother to fetus, and found diverse results. Although preliminary findings indicated restricted indications of vertical transmission, further inquiries have recorded instances when the virus has been found in placental tissue, amniotic fluid, and even in the blood of newborns (12, 13). Concerns regarding the possibility of congenital infection and its effects on the

health of newborns have been raised by these findings. The long-term effects for neonates exposed to SARS-CoV-2 in gestation are still mostly unclear, and the overall rate of vertical transmission is still quite low (14-17).

Pregnancy-related immune response regulation strikes a delicate balance between preventing fetal rejection and the requirement to protect the mother. During the second and third trimesters in particular, this immune adaptation entails a change towards an anti-inflammatory state that may impact the mother's response to SARS-CoV-2 infection (18). According to certain research, this immunomodulation may lessen the mother's immune system's ability to fight infection, raising the possibility of serious illness. On the other hand, some studies suggest that expectant mothers might develop a strong immunological response, which could result in hyperinflammatory conditions that have negative consequences (19).

Furthermore, managing COVID-19 in expectant mothers presents particular clinical difficulties. Pregnancy-related safety and effectiveness concerns with immunomodulatory drugs, vaccinations, and antiviral treatments must be carefully considered (20, 21). Pregnant women were not included in the COVID-19 clinical trials, which caused some initial reluctance to administer the vaccine (22). Subsequent research, however, has produced encouraging information on the immunogenicity and safety of COVID-19 vaccinations in expectant mothers, prompting broad vaccination recommendations for this population (23). It has been demonstrated that vaccination lowers the risk of hospitalization, serious illness, and unfavorable pregnancy outcomes (24).

The effect of COVID-19 on mental health during pregnancy is an important field of study. Pregnant women may have increased anxiety and sadness as a result of the pandemic's major stresses, which include social isolation, economic uncertainty, and fear of infection (25-27). During the pandemic, integrated care strategies that address both physical and psychological health are necessary since these mental health issues can have a significant impact on both maternal and fetal well-being (28).

In summary, the relationship between COVID-19 and pregnancy is a complicated and multidimensional field of study with important consequences for the health of expectant mothers and newborns. Comprehending the pathogenesis, therapeutic therapy, and long-term consequences of COVID-19 in expectant mothers is imperative in order to steer

evidence-based practices and guarantee the security and welfare of this susceptible demographic. This thesis aims to contribute to the growing body of knowledge about COVID-19 in pregnancy, offering insights that can help anticipate the intensity of COVID-19 infection among pregnant individuals.

1.1 COVID-19 – the virus and symptoms

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) belongs to the Coronaviridae family, characterized by a positive-sense single-stranded RNA genome, and shares significant genetic similarity with the coronaviruses responsible for the SARS outbreak in 2003 and the Middle East Respiratory Syndrome (MERS) in 2012 (29).

COVID-19 spreads primarily through respiratory droplets and aerosols produced when an infected person coughs, sneezes or speaks; however, it can also spread through contact with contaminated surfaces, followed by touching the face, particularly the mouth, nose, or eyes (3). The virus binds to host cells via the angiotensin-converting enzyme 2 (ACE-2) receptor, which is highly expressed in the lungs, heart, and gastrointestinal tract, among other tissues (30).

COVID-19 can cause symptoms that vary from moderate to severe, with some cases resulting in death or serious illness (31). Usually occurring between two to fourteen days after exposure, the incubation phase is when most symptoms start to show up on the fifth day (32). Fever, dry cough, and weariness are common symptoms that characterize most symptomatic cases. Additional symptoms include headaches, sore throats, nasal congestion, pain in the muscles or joints, and anosmia, or loss of taste or smell. In more severe situations, some people may have gastrointestinal symptoms like vomiting and diarrhea (7, 30, 33). COVID-19 presents a wide range of symptoms and varying degrees of severity, which are affected by multiple factors including age, pre-existing medical conditions, and the amount of virus present in the body. Older adults and individuals with ongoing health issues face a greater risk of experiencing severe outcomes, potentially leading to fatality. Gaining a comprehensive understanding of the diverse manifestations of COVID-19 symptoms and the disease's progression is essential for providing effective patient care and creating new treatment strategies (19, 34).

1.2 COVID-19 - the waves

The COVID-19 outbreak has exhibited multiple distinct phases, each with unique epidemiological characteristics and consequences for public health. The initial phase of COVID-19 emerged in late 2019 and early 2020, following the first reported cases in Wuhan, China. This phase was characterized by swift global transmission due to the highly contagious nature of the SARS-CoV-2 virus, resulting in extensive shutdowns and the enactment of public health protocols worldwide. During this initial phase, most infections were linked to the original variant of the virus, later termed the "wild type" strain(35).

The ongoing circulation of the virus resulted in the accumulation of genetic changes, giving rise to new variants. Towards the conclusion of 2020, numerous countries experienced a second wave, primarily fueled by the Alpha variant (B.1.1.7), which was first detected in the UK. This particular strain exhibited enhanced transmissibility and, according to some research, increased disease severity, leading to a surge in cases and heightened strain on healthcare facilities. Concurrently, this wave coincided with the initiation of vaccination campaigns, introducing a novel element to the pandemic dynamics as populations began developing partial immunity to the virus (36, 37).

The mid-2021 COVID-19 resurgence, primarily fueled by the highly contagious Delta variant (B.1.617.2) first detected in India, marked the pandemic's third wave. This variant's enhanced transmissibility led to new outbreaks, even in regions with moderate vaccination coverage (38). The rise in COVID-19 cases due to virus mutations showed the challenges of the virus adapting to people with partial immunity. This sparked discussions about the need for booster shots and changes in public health plans (39). The subsequent wave, beginning in late 2021 and continuing into 2022, was driven by the Omicron variant (B.1.1.529), initially identified in South Africa. Omicron was notable for its numerous mutations, especially in the spike protein, allowing it to partially evade immunity gained through vaccination or previous infection (40). Although Omicron spread more rapidly, it generally caused less severe illness compared to Delta, leading to a disparity between case numbers and hospitalizations in some regions (41). The emergence of Omicron prompted rapid development and deployment of variant-specific vaccines and treatments (42). In conclusion, the COVID-19 waves have been shaped by the interplay of viral evolution, population immunity, and public health measures. Each

wave has presented unique challenges, necessitating ongoing adaptation of strategies to control the pandemic and protect public health.

1.3 SARS-CoV2 and pregnant women

As we previously mentioned the COVID-19 pandemic, caused by the SARS-CoV-2 virus, has raised significant concerns regarding its effects on pregnant individuals, altering both maternal and fetal health. Pregnant individuals have a bigger risk of severe illness from COVID-19 than their non-pregnant patients, because of physiological changes such as altered immune systems and increased metabolic and respiratory demands. Allotey et al. (2020) highlight that pregnant women with COVID-19 often experience more severe complications, thus necessitating heightened clinical vigilance (7). Several cardiovascular adaptations occur during pregnancy, including changes in blood volume and cardiac output that could complicate the course of COVID-19. According to a meta-analysis, pregnant women with COVID-19 are also much more likely to develop acute respiratory distress syndrome (ARDS), meaning that accurate evaluation as well as administration in this group is important (43). Besides, COVID-19 can result in a disturbed placental function causing serious complications such as placenta abruption and fetal growth restriction (44).

According to some studies, higher levels of stress cause bad physiological adaptations that can compromise maternal health and impair fetal life (22). These findings highlight the necessity of holistic care including emotional and psychological needs both in addition to extent as well as concurrently assessing physical health during the pregnancy pandemic.

During pregnancy the immunological mechanism is a very complex system which we can translate as ‘immuno-tolerance’, so the fetus develops without attacking. Nonetheless, a hyperimmune response in COVID-19 can result in a cytokine storm and worsen the condition of pregnant (12). An excessive inflammatory response in this population could therefore contribute to further maternal health issues and impact fetal viability; as such, care for pregnant women with COVID-19 may be unique.

Concerns about the vertical spread of COVID-19 were also present in everyday life for a long time. Current evidence indicates that vertical transmission is relatively rare.

However, ongoing research is crucial to monitor possible long-term effects on infants born to mothers infected with SARS-CoV-2 (30).

In summary, COVID-19 is a complex disease in pregnant women with physiological, psychological, and immunological effects that pose a risk to fetal health. The increased risk of serious diseases, in addition to the physiological changes associated with pregnancy, necessitates vigilant supervision. More research is needed to ensure that this vulnerable group can receive appropriate care and support during a pandemic.

1.4 Covid-19 treatment for pregnant women

A therapeutic recommendation for pregnant women afflicted with COVID-19 remains accessible on the website of the Royal College of Obstetricians and Gynecologists. Currently, the 16th version is available, which demonstrates the rapidity with which therapeutic recommendations evolved and were refined during the initial years of the pandemic (45).

The most recent recommendations are no longer accessible on the websites of numerous other organizations.

In the subsequent chapter, this study aims to demonstrate how the care protocol was developed at Semmelweis University.

1.5. Covid-19 treatment for pregnant women in Semmelweis University - Protocols

Shortly after the beginning of the epidemic, we published a summary overview of COVID-19 and pregnancy (46). We were still groping in the dark on the subject. There was very little information on this topic in the literature.

Here is a brief summary of our very first recommendations for the start of the pandemic.

• At the time of writing this publication, we were aware of only one case in Hungary. However, based on the genetic characteristics of SARS-CoV-2 and its similarity to other viruses, it was clear that the virus could have a significant impact on pregnant women and their fetuses.

• Recommendations for infection prevention were the same for pregnant and non-pregnant women.

• According to the available data, neither pregnancy nor the postpartum period represents a particular risk, while advanced age and related co-morbidities are significant risk factors.

• The most likely symptoms we expected were: fever (67%), cough (66%), shortness of breath, sore throat, fatigue (7% each) and muscle pain (6%). Laboratory abnormalities known at that time included lymphocytopenia, elevated liver enzymes, and thrombocytopenia.

• Reducing the fever is extremely important.

• We recommended thromboembolic prophylaxis right from the beginning.

Due to the immunosuppressive effect of the steroid, the recommendation was not uniform at first, but we nevertheless recommended its use as steroid prophylaxis.

Nifedipine, indomethacin and non-steroidal anti-inflammatory drugs can be used if they are needed from the point of view of pregnancy.

However, the administration of magnesium sulfate should be considered due to its respiratory depressant effect.

In 2020, when the above notice was published, we did not yet know what awaited us. We saw our first pregnant patient at our clinic in June 2020.

Based on foreign data and experience, we have also continuously developed our treatment protocol.

Our precise house guideline, published on October 1, 2021, recommended the following specific therapy:

- Vitamin C 1 x 1000 mg oral administration
- Vitamin D3 1 x 3000 IU oral administration
- Zinc 1 x 25 mg oral administration
- Dexamethasone from 24+0 week to 34+6 week as steroid prophylaxis: 6 mg dexamethasone every 12 hours for the first two days, then 1x6 mg daily
- Antibiotics if procalcitonin is greater than 0.2

• Azithromycin 1x500 mg oral administration for 3 days

• Ceftriaxone 1x2g intravenously for 5 days

- Quamatel 1 x 40 mg oral administration
- LMWH-prophylaxis (0.01 ml/kg subcutaneous administration)

- O2 therapy: the goal is to reach 95% saturation (nasal tube up to 5l/min, mask 50 above 5l/min, reservoir mask above 10l/min)
- Antipyretic therapy (Paracetamol)
- In case of symptoms appearing within 5 days
• Convalescent fresh frozen plasma intravenously
• Remdesivir intravenously: day 1: 1 x 200 mg, days 2-5: 1 x 100 mg (increased liver function is contraindicated)
- In case of increased liver function, Legalon 2x1 per os
- In case of productive cough, Fluimucil 2 x 200 mg per os
- In case of dry cough, Libexin 2x1 per os and Berodual inhalation 2x a day (1 ml diluted in a 20 ml syringe, half of which is in a nebulizer mask)
- Routine laboratory test: blood count, liver function, kidney function, urine, CRP, procalcitonin, Na+, K+, D-dimer
- Daily ultrasound examination
- Cardiotocography: from the 32nd week twice a day, but continuously if necessary

1.6 The case of a Covid-19 pregnant woman at Semmelweis University

This case of our kidney transplant patient illustrates the potential association between COVID-19 and the development of preeclampsia, leading to the necessity for premature delivery (47).

A 33-year-old white woman who was seven months pregnant whom was made pregnant for the first time with a pre-pregnancy body mass index of 19.3 which was 24.2 at the time of the test. She tested positive for the COVID-19 virus by the year 2021. At the time of admission to the hospital, the symptoms were unremarkable. From the past medical record, she had two episodes of acute pyelonephritis and one of acute necrotizing pancreatitis in the year 2008, which caused sepsis and acute renal failure. The prolonged septic illness with severe consequences ended in chronic kidney failure and required a deceased donor kidney transplantation in 2009. She was diagnosed as suffering from Crohn’s disease in 2011. Before being infected by the SARS-CoV-2 virus, the patient was on medicaments containing 4.5 mg/day tacrolimus and 7.5 mg/day prednisolone. Furthermore, she consumed a food supplement containing folic acid, metafolin, DHA, iodine, vitamins B1, B2, B6, B12, C, D3, E, biotin, niacin, pantothenic acid and DHA

every day during pregnancy. After sustaining a disease of COVID-19, the patient was prescribed an additional 100 mg of aspirin and 0.6 ml subcutaneously enoxaparin-sodium once a day. She tested positive for COVID-19 and four days later she was admitted to the hospital because high blood pressure was coming into play owing to inability to adhere to steroidprophylaxis for the development of the lungs of the fetus. This was referred to as day 1 of admission in the hospital. Basic laboratory tests confirmed the presence of quantitative proteinuria; and, in order to mature the lungs, she had a total of four doses of 6 mg of dexamethasone injected intramuscularly. All the laboratory data are shown in Figures 1 and 2. On the sixth day, on peek of the lung X-ray there was no gross impact but it could not exclude the presence of a slight right bronchopneumonitis (Figure 3). Due to depressed oxygen saturation, non-invasive ventilation was performed with a flow of 2-3 L/min from 5 to 10 days. Anti-SARS-Cov-2 convalescent plasma therapy may be beneficial and safe in immunosuppressed patients and it was done once as suggested by Rodionov et al. (48) However, upon the improvement in respiratory difficulties, biochemical parameters remained indicative of presence of preeclampsia superimposed type. The platelet count was below 150000 platelets/μL in the first 9 days; the lowest level was 104000 platelets/μL. Hemolysis, elevated liver enzymes, and low platelet levels (HELLP) syndrome were absent.

Thirty-five days before her hospital admission, she had been diagnosed with gestational hypertensive disorder. At that time urine didn't contain protein.

There were no signs of the preeclampsia process yet. Methyldopa 3x250 mg was used for hypertension, though it was advised to be taken four times per day. 7 days prior to hospital admission, she received an addition of 40 mg of verapamil to her therapy. In the hospital she was given 2 x 40 mg of verapamil, the dosage of methyldopa was increased to 4 x 250 mg, and additional 25 mg of metoprolol. On the fourth day, she received nifedipine 2 x 20 mg instead of verapamil, metoprolol 2 x 25 mg was given on the 8th day, metoprolol 3 x 25 mg was given on 5th day and then methyldopa treatment was continued on the same 4 x 250 mg dosage. After giving birth and leaving the COVID-ward, she continued to take 4 × 250 mg of methyldopa and 2 × 25 mg of metoprolol (see Figure 4). While she was pregnant her blood pressure was elevated reaching a peak of 176/119 mmHg which highlighted the preeclampsia diagnosis.

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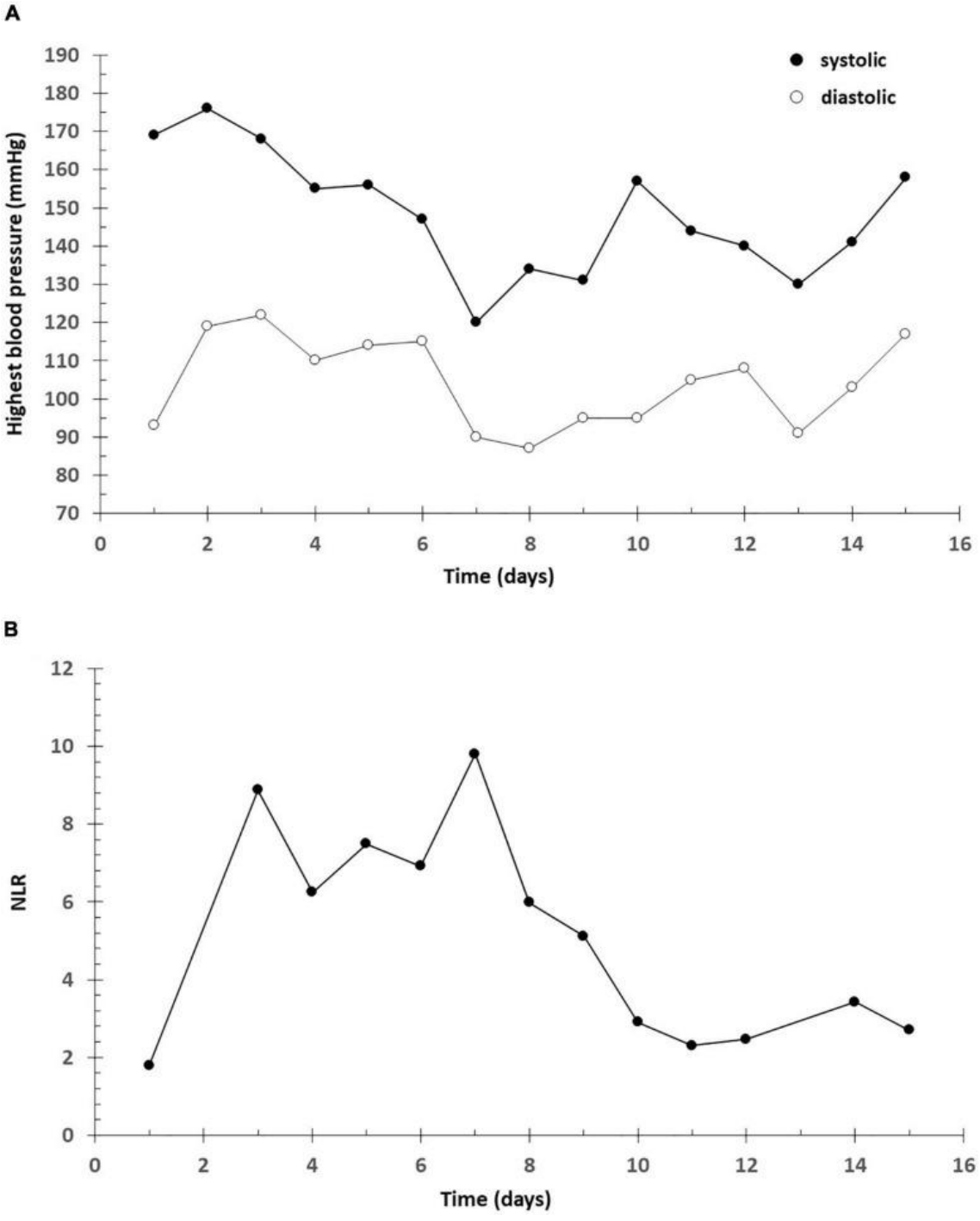

FIGURE 1

Highest blood pressure. NLR. **(A)** Higher blood pressure (mmHg). Systolic (•) and **diastolic (o) blood pressure.** (B) **Neutrophil-Lymphocyte Ratio (NLR). (47)**

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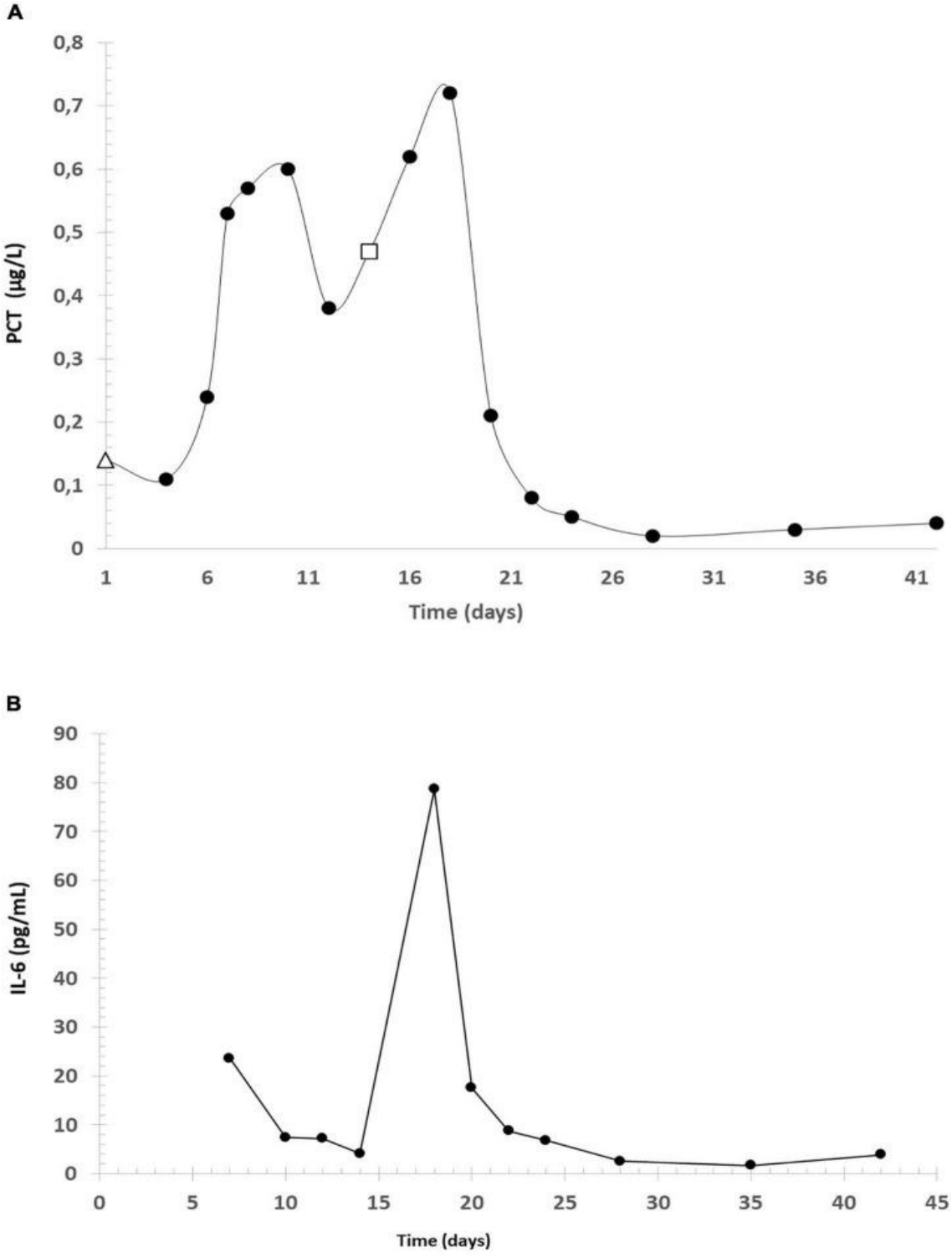

FIGURE 2

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Concentration of PCT and IL-6. (A) PCT (which was measured for the first time on the day of the hospital admission–marked with Δ) during the infection, in μg/L. The last data before the birth was marked with □. **(B)** interleukin-6 (IL-6) concentration. (47)

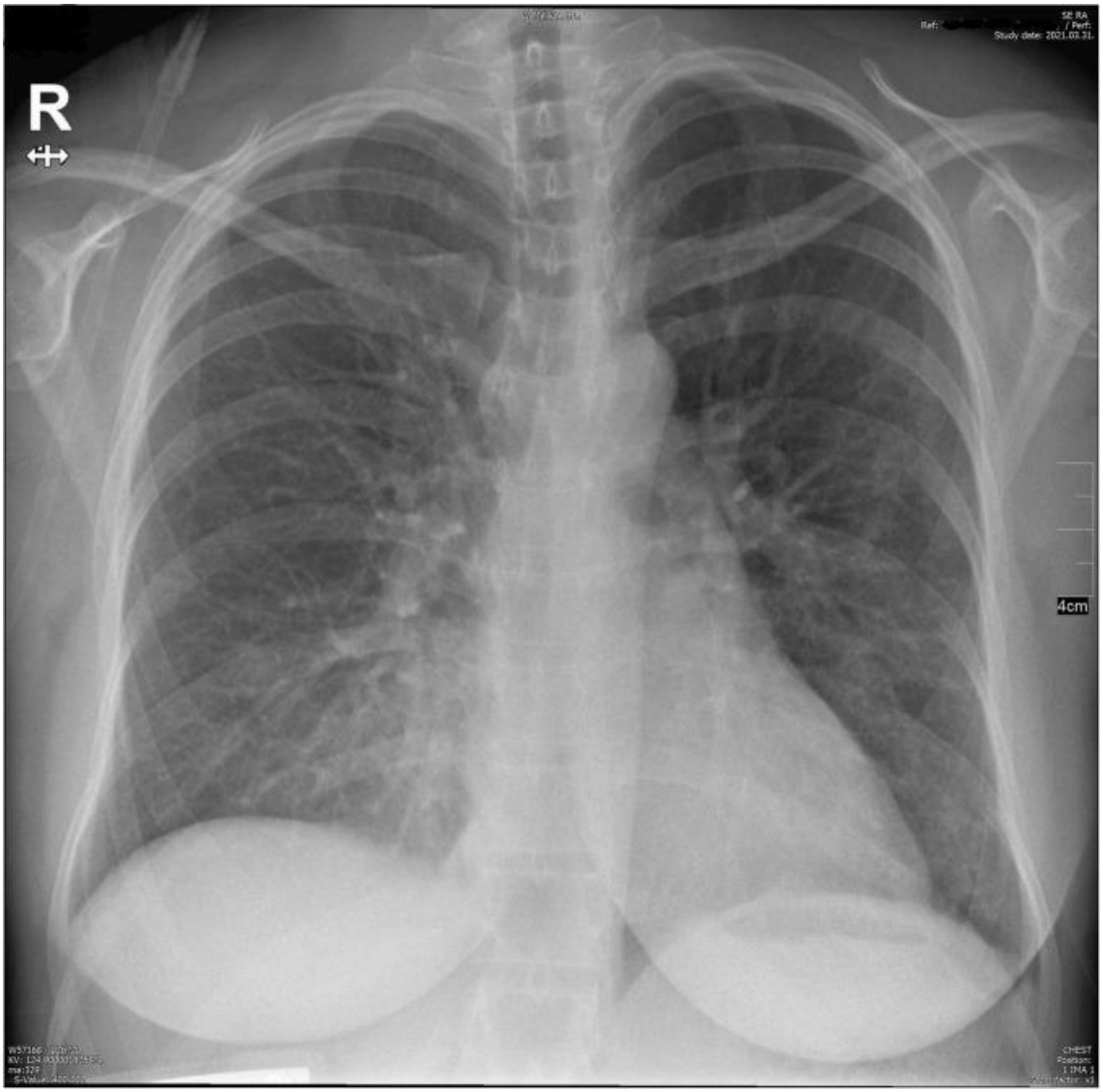

FIGURE 3

Pulmonary X-ray on the 6th day. (47)

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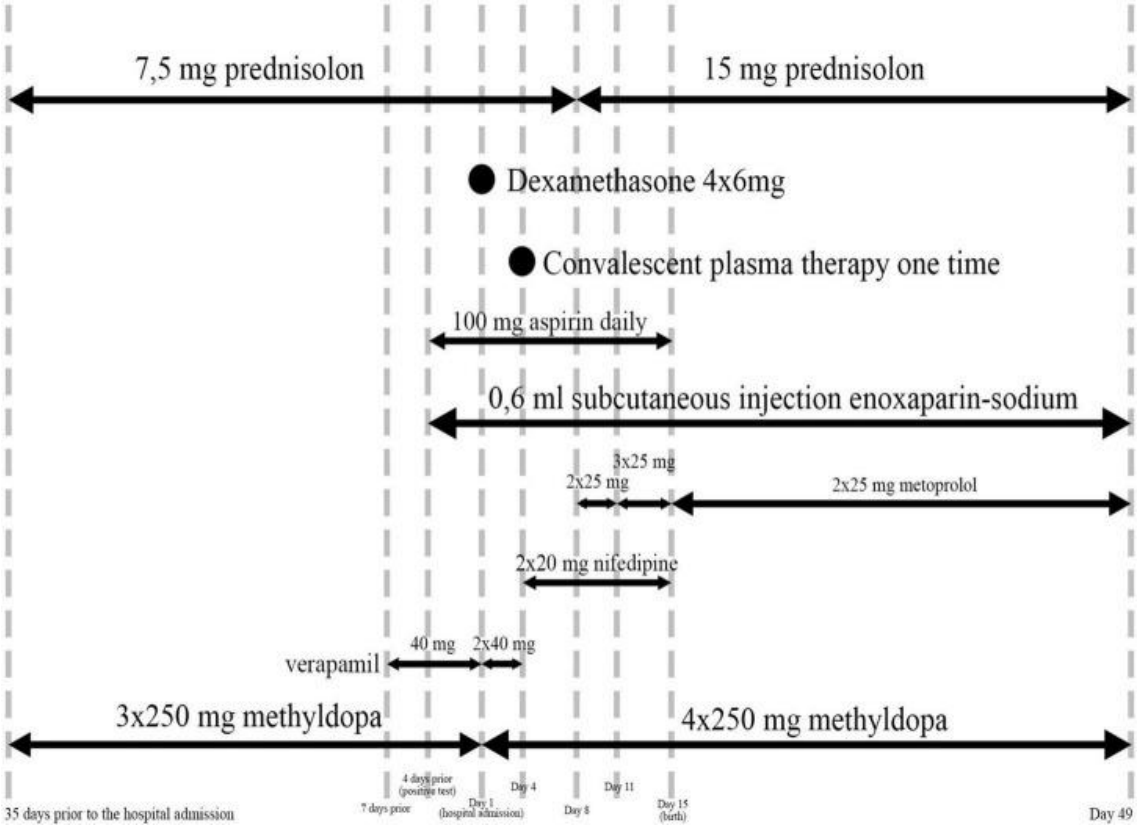

FIGURE 4

Medications. (47)

Fever was recorded on the fifth and sixth. The highest body temperature, 38.4◦C was measured, on the sixth day's morning. Because of the deterioration of the patient"s condition, the cesarean section was performed on day 15th.

Apparently, an obstetric ultrasound examination was carried out daily during her examination, which revealed IUGR and increasing vascular resistance. The first time circulation centralization could be detected was on day 12 which was 3 days before the birth. After we consulted with the neonatologists on the 15th day which is in the 29th gestational week. A cesarean section was done due to the following reasons: preeclampsia, IUGR, and increased vascular resistance. On the day of the cesarean section, the umbilical artery's flowmetry showed the sign of the total diastolic stop. As the previous ultrasonography predicted the birth weight was in the 2.5th percentile (990 g), which confirmed the IUGR diagnosis.

On the day of the birth, the mother presented her first negative PCR test for SARS-CoV-2, two days later she also presented a negative PCR test. The newborn also presented two negative tests on the same day. After the two negative tests, the mother was relocated from the COVID care unit to the standard postnatal unit.

After the operation, the newborn was transferred to the NICU unit of our hospital because he required nCPAP respiration support. This therapy lasted 16 days. In the newborn's first five days, the highest FiO2 was 30%, from the sixth day he mostly received air with 21%

FiO2. We consulted with the ophthalmologists, who found the progression of retinopathy (ROP 3 (+) zona 2 stages on the right eye, ROP 2 (+) stage on the left eye), They advised the laser therapy. We performed a cranial ultrasound examination and 2nd stage intraventricular hemorrhage was found, fortunately, it was not progrediating. The neonate was growing well; 9 days later, his feeding was built up with breast milk. He was released from the hospital with a weight of 1,830 g. The mother would be able to go home on the 49th day but she stayed with his neonate until her son was in the NICU. They were released on the 63rd day from the Semmelweis Univeristy.

This case turned our attention to more detailed research on the relationship between COVID-19 and other pregnancy pathologies. It can be said that preeclampsia is more common among kidney transplant recipients, and pregnancies end in premature birth more often (49). Based on some research, the disease COVID-19 also plays a prominent role in the appearance of preeclampsia-like symptoms (50). In the present patient, the condition was present simultaneously, and this may have contributed to the symptoms of superimposed preeclampsia, which necessitated the termination of the pregnancy.

Based on the INTERCOVID study (which involved 43 institutions in 18 countries), it can be said that among women affected by COVID-19, premature birth and cesarean sections are more common (50).

The disease caused by the pandemic SARS-CoV is characterized by endothelial dysfunction and microvascular damage, which can affect both the maternal organs and the fetus (51, 52). This may explain the deteriorating flow values diagnosed in our patient. In our case report article, we examined the literature on the liver-damaging effect of SARS-CoV-2, as we also measured severely elevated liver enzymes in our patient. We reviewed the relationship between inflammatory parameters (C-reactive protein and

Interleukin-6) and preeclampsia (53). Based on this, we attribute the significant increase in CRP and IL-6 to both preeclampsia and COVID-19 infection. According to some studies, the cytokine storm and elevated IL-6 characteristic of COVID-19 can effectively predict the severity and predictable course of the disease (54). Our case also confirmed this theory, as we found an elevated IL-6 level in our patient, which normalized after recovery. That's when we thought about how to predict the severity of the disease and the expected outcome in pregnant women who are the focus of attention.

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2. OBJECTIVES

Our research aimed to identify the parameters that could be utilized to predict the severity of the disease course in pregnant women.

(1) Our research aimed to identify the parameters that could be utilized to predict the severity of the disease course in pregnant women. The maternal age, elevated inflammatory parameters, and characteristic deviations detected during imaging processes are well known from the literature, is there any other useful predictor?

(2) Can the NLR predict in which case we can expect a fatal outcome?

(3) Can the Neutrophil-to-Lymphocyte Ratio (NLR) provide early insights during hospitalization for identifying pregnant women who may require special attention due to a potentially more severe disease course?

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3. METHODS

3.1 Study design and patient selection

Our patients received treatment at Semmelweis University clinics in Budapest, Hungary. Semmelweis University is a Hungarian COVID-19 center that specializes in the treatment of severe COVID-19 cases in pregnant patients. As a result, the university encountered a higher number of such cases, and nearly all fatal cases involving pregnant COVID-19 patients in Hungary were treated in our clinic. SARS-CoV-2 positivity was confirmed using real-time quantitative polymerase chain reaction (RT-q-PCR) technology. Sampling was completed using nasopharyngeal COVID-19 swabs from the upper respiratory tract.

The data was collected by two independent researchers from the hospital information system (e-MedSolution; Egészséginformatikai Szolgáltató és Fejlesztési Központ, Budapest, Hungary) of Semmelweis University.

Our first study is a case-control study, 45 patients were involved (55). Ten pregnant patients with fatal COVID-19 infections were identified and enrolled, and an additional 15 and 20 patients who survived the disease were enrolled into two control groups. The control groups were defined as follows: (1) pregnant patients who experienced severe symptoms and required respiratory support (invasive or non-invasive) but survived COVID-19 (n = 15); (2) COVID-19 patients who were hospitalized but did not require respiratory support, only closer medical surveillance (n = 20). All available NLR values and comorbidities were collected from the patients enrolled in the study.

The second article is a retrospective cohort study (56). In this study, we compared the NLR values of 123 COVID-19 patients. In the study population, 96 patients had mild/moderate disease, while the remaining 27 patients required mechanical respiratory support. Among the NLR values, we compared the NLR value on the first day after hospital admission with the highest NLR value measured during the hospital stay.

In our study, the predictive value of the first-day NLR values that remained within the normal range was highlighted.

3.2 Data collection

In the initial investigation, data were acquired from 2021 and 2022, which represented the 3rd and 4th waves of the COVID-19 pandemic in Hungary. First, the study comprised all pregnant patients who died at Semmelweis University during the period covering 2021 and 2022. To form the first control group (15 pregnant women), comprising patients in need of respiratory support, individuals were selected from February 2021 to April 2021. For the second control group, we selected 20 pregnant patients who did not require respiratory support during their SARS-CoV-2 infection and had at least three laboratory results from their peripheral blood. These patients were randomly chosen from an online medical database. The percentage of patients from the third wave of the Hungarian COVID-19 pandemic in each selected group was over 70%, implying a probable infection with the beta variant of SARS-CoV-2. This is because the beta variant was the most prevalent during the third wave, while the remaining cases may have been related to the delta variant.

The patients selected for our second study were also treated at Semmelweis University in 2021 and 2022. We divided the patients into two groups: we examined separately the NLR value of the patients who did not require mechanical respiratory support (group 1) and those who required mechanical respiratory support (group 2). Special attention was paid to the number of patients with NLR values in the normal range (NLR<3.5) on the day of hospital admission. We also compared the maternal age between the two groups.

3.3 Statistical methods

After obtaining the neutrophil and lymphocyte values, the quotient was measured between groups using IBM SPSS Statistics 29. The measured variables are presented in tables as mean ± standard deviation (SD). The Kolmogorov–Smirnov test was used to determine if the numerical data matched the normality distribution. Variables were compared using the Wilcoxon rank-sum test and Fisher exact test. Differences were considered statistically significant at $p < 0.05$, in both the Kolmogorov–Smirnov test for the determination of probability and later in other statistical methods. All p values were adjusted using the Holm method. (57)

Receiver operating characteristic (ROC) analyses were also performed to test the sensitivity and specificity of NLR. The ROC analyses were performed in the R for Windows environment (version 4.2.3; R Foundation for Statistical Computing, Vienna, Austria) using the pROC R-library (v1.18.0). The coordinates for the best threshold were identified using Youden's J statistic. Moreover, the effects of various clinical characteristics on NLR values were investigated. The latter analysis was performed using ANCOVA and mixed-effects (R library nlme, version 3.1-163) models.

In the second study, we collected the neutrophil and lymphocyte values (%) from all the laboratory findings of the patients included in our databases and then obtained the NLR by determining their ratio. For each patient, the NLR measured on the day of hospitalization and the NLR measured during the hospital stay were examined.

After collecting the statistical data in a table and then calculating the median and average, the distribution of the data series was checked based on the Kolmogorov–Smirnov test.

Mann–Whitney U-test, chi-square test, and Fisher's exact test were used to compare the datasets. Null hypotheses were accepted when p-values were less than 0.05; the null hypothesis of $p \geq 0.05$ was rejected.

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4. RESULTS

4.1. First study

As previously mentioned, the 45 patients were split up into three groups. Table 1 displays the study participants' age, weeks of gestational age at when the infection began, first-day and peak NLR values. The NLR data for day one and the peak NLR are shown in a box plot, which is another way to view the data for easier comprehension (Figure 5).

Table 1 The patients' neutrophil-to-lymphocyte ratio (NLR) values and ages. Groups 1, 2, and 3 consist of fatal COVID-19 cases, patients who needed mechanical ventilation (either invasive or non-invasive), and patients who were hospitalized but did not need mechanical ventilation, respectively. The data are presented in the table in the format of mean ± SD; after that, in the brackets, the minimums, maximums, and medians are presented. As the presented data show, the ages of the pregnant women in all 3 groups do not differ from each other significantly (55).

Clinical Characteristic	Group 1 (n = 10)	Group 2 (n = 15)	Group 3 (n = 20)
Age (years)	34.60 ± 5.04	31.87 ± 4.90	33.20 ± 7.05
First-day NLR value	14.56 ± 11.34	7.66 ± 4.62	5.97 ± 2.23
Peak NLR during the infection	33.77 ± 14.03	13.35 ± 11.43	7.54 ± 2.86
Gestational age when the infection started (weeks)	31.30 ± 3.09	30.27 ± 5.46	31.05 ± 4.74

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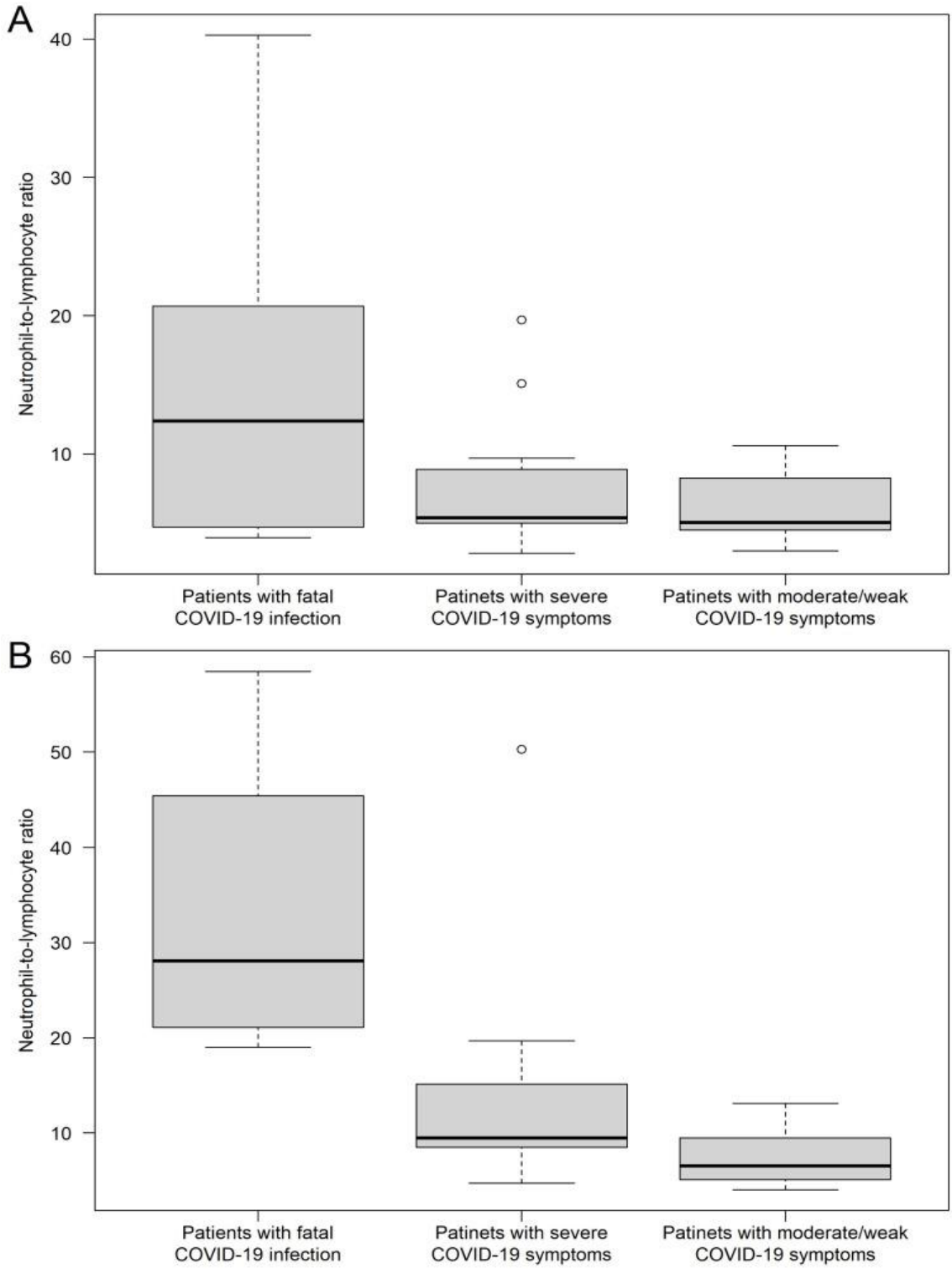

FIGURE 5

The neutrophil-to-lymphocyte ratios (NLRs) are presented for three groups, including the values on the first day of hospital admission (A) and the highest measured value (B). Hollow circles represent outliers (greater/lower 1.5 times the interquartile range above/below the upper/lower quartile) (55).

In order to compare the different groups, we utilized the Wilcoxon rank-sum test. Initial results indicated that there were no significant disparities in age or gestational age at the time of contracting COVID-19. However, upon further analysis, it was observed that the NLR values on the first day of hospitalization were higher in patients who later passed away (14.56 ± 11.34). Nevertheless, no significant differences were noted when comparing this group to those who required ventilation support and recovered (7.66 ± 4.62; p = 0.3926) or to patients with moderate COVID-19 cases (5.97 ± 2.23; p = 0.1288). The values of NLR for fatal COVID-19 cases were notably higher than those of both control groups. Specifically, the peak NLR value for fatal COVID-19 cases was 33.77 ± 14.03, while the ventilated but surviving group had an NLR value of 13.35 ± 11.43 (p = 0.0006). Additionally, the same pattern was observed when comparing the fatal and non-ventilated groups, with a significant difference in peak NLR values (p < 0.0001; Table 2). It is important to mention that no significant difference could be found between the first-day NLR values of the two control groups, but the peak values were significantly higher in the ventilated group (p = 0.0143; Tables 1 and 2).

Table 2 The comparisons' adjusted *p*-values of the groups presented in Table 1; $p < 0.05$ was accepted as a significant difference (55).

Clinical Characteristic	**Groups 1 vs. 2**	**Groups 1 vs. 3**	**Groups 2 vs. 3**
age (years)	$p = 0.5447$	$p = 1.0000$	$p = 1.0000$
first-day NLR value	$p = 0.3926$	$p = 0.1288$	$p = 0.3926$
peak NLR during the infection	$p = 0.0006$	$p < 0.0001$	$p = 0.0143$
gestational age when the infection started (weeks)	$p = 1.0000$	$p = 1.0000$	$p = 1.0000$

To acquire additional data, we also obtained information on the number of comorbidities in the patients, which is depicted in Table 3. The table indicates that 50% of the patients who eventually passed away due to the disease had no comorbidities. In

the ventilated group, this percentage was 53%; however, in the group that did not need ventilation support during their hospital stay, this ratio was even higher at 75%. It is worth noting that none of the patients in the latter group had more than one comorbidity.

Table 3 This table provides a breakdown of the number of comorbidities for patient groups, allowing easy comparison and analysis (55).

Groups	**Patients with 0 Comorbidity in Medical History**	**Patients with 1 Comorbidity in Medical History**	**Patients with 2 Comorbidities in Medical History**
Group 1 (n = 10)	5	4	1
Group 2 (n = 15)	8	5	2
Group 3 (n = 20)	15	5	0

The aim was to determine whether the NLR values could be utilized to predict fatal COVID-19 cases. To achieve this, ROC analyses were carried out for patients who fell into two groups: those who passed away (Group 1) and those who required ventilation support therapy (Group 2). The results revealed that for first-day NLR values, a cutoff of 15.22 had a sensitivity of 50% and a specificity of 93.33%, with an AUC value of 66.0% (Figure 6). For peak NLR values, a cutoff of 18.05 was found to have 100% sensitivity and 86.67% specificity, with an AUC value of 94.0% (Figure 7).

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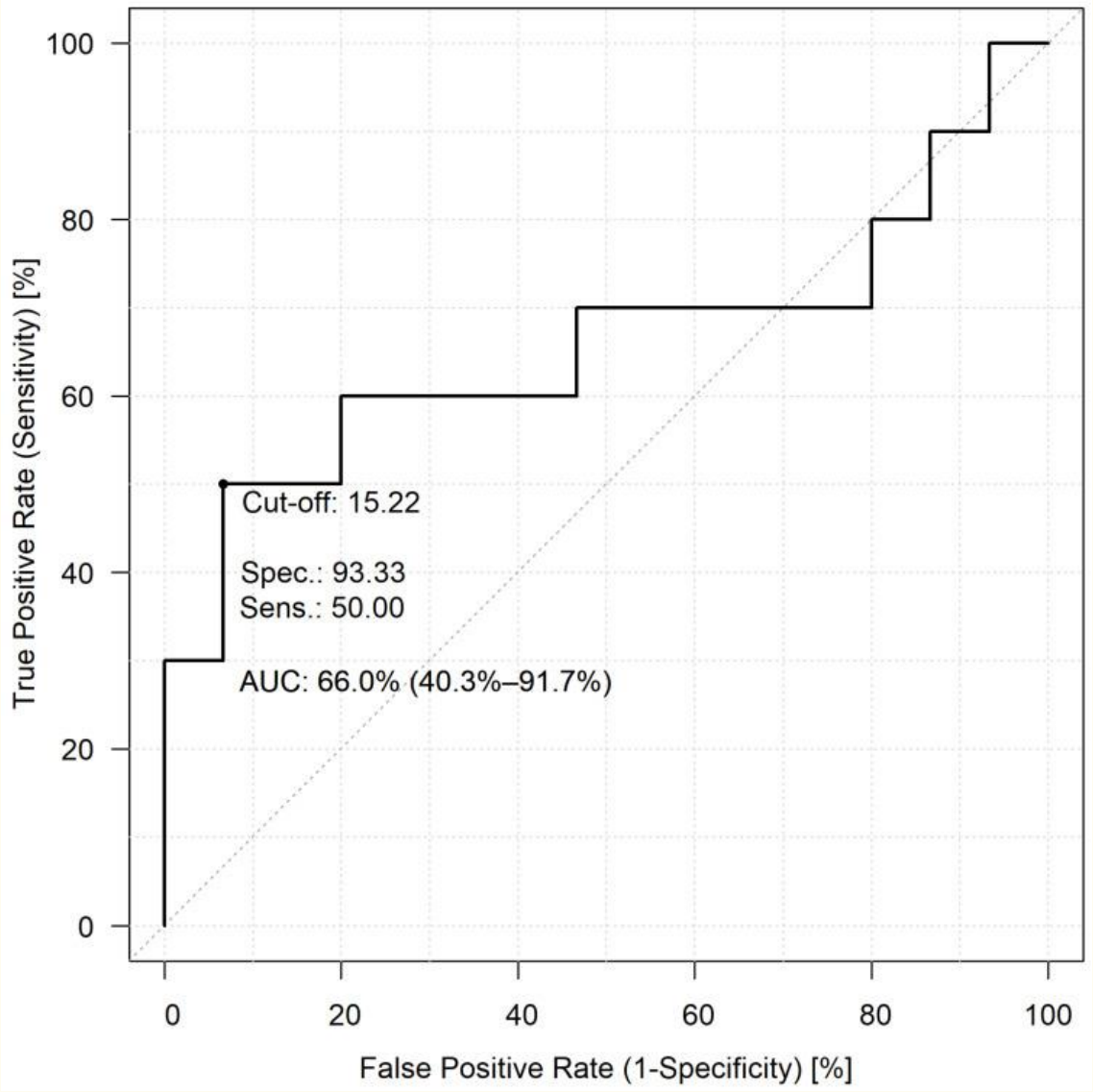

FIGURE 6

The predictive capability of first-day NLR values in patients who lost their life to COVID-19 infection, compared to those patients who needed mechanical ventilation (55).

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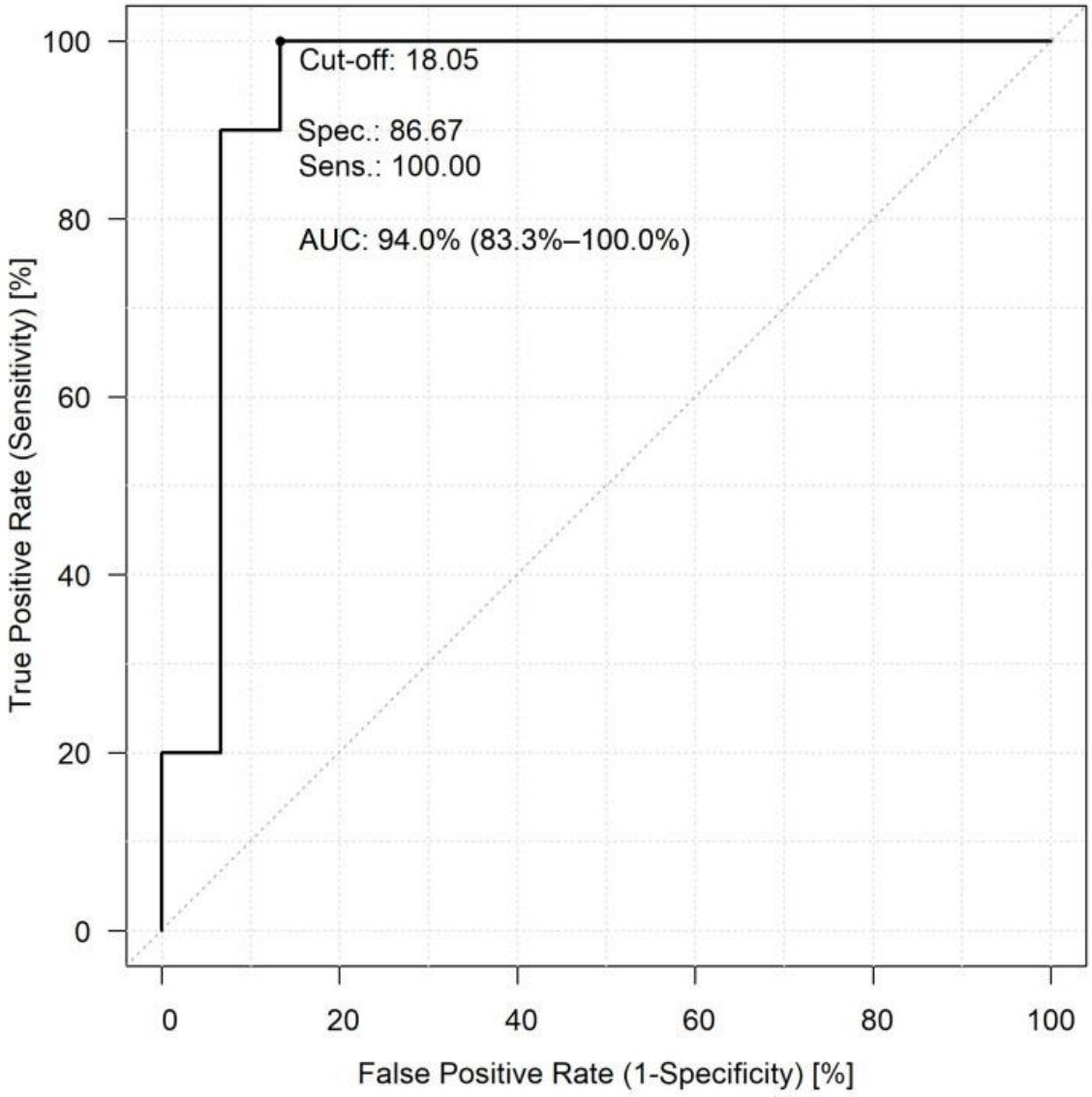

FIGURE 7

The predictive capability of the highest NLR values in patients who lost their life to COVID-19 infection, compared to those patients who needed mechanical ventilation. (55)

Furthermore, the study examined whether any clinical parameters affected NLR values. To achieve this, two different models were constructed for both first-day and peak NLRs. First, an ANCOVA model was used to investigate the effects of age, the gestational week when COVID-19 occurred, and the number of comorbidities. The analysis revealed that none of these factors had a significant impact on NLR values, and the explanatory power of these models was weak, accounting for less than 5% of the variance in both first-day and peak NLR values (Table 4).

Table 4 *p*-values of the ANCOVA models investigating the effect of a few clinical parameters over neutrophil-to-lymphocyte ratio (NLR) (55)

Clinical Characteristic	**Model Investigating D1 NLR**	**Model Investigating Peak NLR**
Age (years)	0.5198	0.8520
Gestational week	0.9482	0.4850
Number of comorbidities		
0 vs. 1	0.0776	0.5020
0 vs. 2	0.4077	0.6700
0 vs. 3	0.9138	0.4760

Second, mixed-effect models were constructed to determine if the number of comorbidities added any additional variance to the NLR values. The results showed that no additional variance was introduced for either the first-day or peak NLR values (Table 5).

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Table 5 *p*-values and random effects of the mixed-effect models investigating the effect of a few clinical parameters over neutrophil-to-lymphocyte ratio (NLR) (55)

Clinical Characteristic	**Model Investigating D1 NLR**	**Model Investigating Peak NLR**
	***p*-Values**	
Age (years)	0.6681	0.3448
Gestational week	0.9742	0.2054
Number of comorbidities		
0 vs. 1	0.1864	0.8583
0 vs. 2	0.6462	0.1610
0 vs. 3	0.7542	0.1649
	Random effect	
Random effect of NLR values	0.0006	0.0006

4.2. Second study

The 123 patients were divided into two groups: light/medium severe patients (group 1), who did not require mechanical respiratory support during COVID-19 (n = 96), and seriously ill patients (group 2), who required mechanical ventilation support at some point during their illness. The data collected from the two groups, including age at the time of infection, NLR on the first day, highest NLR value during the illness, and the number of patients whose NLR remained in the normal range, are summarized in Table 6. We compared the values of the 123 patients using appropriate statistical methods. The p-values were accepted at a significance level of 0.05, so the null hypothesis was accepted at $p<0.05$ and rejected at $p\geq0.05$. The obtained values are shown in Table 6. It is evident from our values that the two studied patient populations can be considered homogeneous with respect to age ($p = 0.91$). However, apart from age, the other values differ significantly between the two patient groups, both on the first day and also the NLR values measured during illness and hospital stay ($p<0.05$). he analysis revealed a significant difference in Neutrophil-to-Lymphocyte Ratio (NLR) values between the patient groups. On the first day of hospitalization, only 1 patient (3.7%) in the severe (2nd) patient group had NLR values within the normal range, whereas 29 patients (30.2%) in the mild/moderate (1st) group maintained NLR values within the normal range. This disparity becomes more pronounced when considering the peak NLR values: 20 patients (20.8%) in the mild/moderate group exhibited peak NLR values within the normal range, while no patients in the severe group had peak NLR values within physiological limits. These differences are statistically significant. In conclusion, all examined variables, except for age, showed significant differences between the two patient groups, which were otherwise homogeneous concerning age.

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Table 6 The patients clinical and laboratory values Group 1 (mild and mediumsevere cases) and Group 2 (severe cases) comparison on p=0.05 significancy level (56)

Clinical Characteristic	**Group 1 (*n* = 96)**	**Group 2 (*n* = 27)**	**p-values**
Age (years)	33.2 ± 3.7	33.3 ± 5.09	0.91
First-day NLR value	5.85 ± 3.75	9.11 ± 5.43	<0.05
Number of patients who had the first day NLR value in the normal range	29 (30.2٪)	1 (3,7 ٪)	<0.05
Peak NLR-value during the illness	6,7±4.02	22.3±16.3	<0.05
Number of patients who had the highest NLR value still in the normal range	20 (20.8٪)	0 (0.0 ٪)	<0.05

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5. DISCUSSION

The SARS-CoV-2 was detected in Wuhan, China at the end of 2019. It caused a pandemic that quickly swept across the world. Since the end of 2019, we know of more than 776 million infected people, while at least 7 million people have died. It's reasonable to conclude that the virus arrived unexpectedly, the healthcare system was unprepared, and the doctors and epidemiologists were also inexperienced due to the lack of prior practice in this type of situation. Pregnant women were treated as a privileged group, as in many other aspects of our lives. The special attention is understandable because there were no clear recommendations regarding the therapy and in these cases, we had to decide on the lives of two or more people. The Semmelweis University Obstetrics and Gynecologist Clinic, especially the staff of the Department of Üllői Street, was under a huge burden, as almost all pregnant women infected with COVID-19 in Hungary were cared for there. We found that healthy pregnant women do not necessarily have to expect a more severe course. On the other hand, the course of some pregnancy pathologies can be aggravated by COVID-19. We can also expect a more severe COVID-19 infection in pregnant women associated with other comorbidities. Every time, we had to face the decision that, with appropriate treatment, the termination of the possible pregnancy should be as late as possible from the fetal point of view, and taking into account both maternal and fetal aspects, the termination of the pregnancy should not take place too late. Our research was therefore directed towards an easy-to-implement, affordable method that has already been used successfully in other diseases, which can predict the severity of the course of COVID-19 in pregnant women, and possibly help to reduce the number of fatal outcomes. The Neutrophil-Lymphocyte ratio proved to be a suitable predictive factor. Due to the retrospective nature of our studies and the sensitivity of the topic, our database could not be expanded afterward, so although we thought it would be informative to also assess the vaccination for our study subjects, we ultimately did not have the opportunity to do so.

SARS-CoV-2 is a newly observed betacoronavirus which was first detected in late 2019 in China. This virus is responsible for the COVID-19 pandemic and caused widespread morbidity and mortality. Structurally, SARS-CoV-2 is an enveloped,

positive-sense single-stranded RNA virus with a 29.9 kilobases long genome. It contains 4 main structural proteins: spike S, envelope E, membrane M, and nucleocapsid N proteins. (58)

The virus can enter the host cell with the help of the spike protein, by binding to the angiotensin-converting enzyme 2 (ACE-2) receptor, which is the key step in infection(3).

The virus uses a really efficient mechanism to enter into the host cell. The host proteases such as transmembrane serine protease 2 (TMPRSS2) can help the spike protein, to create membrane fusion (59).

SARS-CoV-2 belongs to the Coronaviridae family, and the also well-known human pathogen SARS-CoV and MERS-CoV are also included in this family (22).

According to genomic studies the SARS-CoV-2 has about 79% sequence similarity with SARS-CoV and 96% with the bat coronaviruses. Zoonotic origin should be considered, and the intermediate hosts could be pangolins (7).

SARS-CoV-2, similar to other coronaviruses, has also been shown to have acquired immunological escape strategies, so it can inhibit the release and activity of the important anti-viral response, interferon production (36).

This evasion can permit unchecked replication of viruses at the onset of the infection, which may result in elevated disease severity in the targeted populations, particularly those with pre-existing comorbid conditions like cardiovascular diseases, diabetes, etc.(60).

The COVID-19 disease mainly affects the respiratory system. The appearance can vary from asymptomatic to severe, and can even lead to critical illness or death (7). Symptoms of COVID-19 usually appear within 2-14 days of infection. Fever, cough, and shortness of breath may appear, which are among the most common manifestations (30). Some patients often report fatigue, muscle pain, and loss of taste and smell, although these do not occur in all patients (61). In more severe cases, pneumonia, acute respiratory distress syndrome (ARDS), multiple organ failure, or even sepsis or septic shock may develop (7). The elderly and patients with medical conditions such as cardiovascular disease, diabetes, or obesity are at increased risk of severe consequences from the virus (62). Over time, we have recognized that COVID-19 can cause long-term effects, such as “long COVID”. In such cases, symptoms persist for weeks or months after acute infection (63).

Infection caused by SARS-CoV-2 initiates an immunological response process. The functioning of interferons, and proinflammatory cytokines such as IL-6, TNF-α, and IL-1β becomes unregulated, this is also referred to as a cytokine storm, which eventually leads to a hyperinflammatory state (64). The virus can also cause endothelial damage, and lead to coagulopathy and thrombosis in both small and large blood vessels. Finally, it can manifest in multiple organ failure (65). In the disease, inflammation and vascular permeability are increased by modifying the renin-angiotensin system and regulating ACE-2, and then ARDS develops (66). The virus also impairs the functioning of the immune system, the number of lymphocytes, CD4+, and CD8+ cells decreases, which reduces the chance of removing the virus from the body, but increases the chance of superinfection (30). This may be the explanation for the long-lasting viral shedding after the infection, as well as the appearance of chronic symptoms, which we also referred to as long-covid (67).

The virus also affects the nervous system, where we attribute a major role to hematogenous spread. As a result, anosmia is common, but encephalopathy or even stroke may appear (68, 69).

At the time of writing this dissertation, according to the WHO's continuously updated database, more than 776 million people have been infected with COVID-19. In total, more than 7 million people lost their lives due to the infection. In the last 7 days, more than 50,000 cases were reported, the vast majority from Europe.

Our university played a prominent role in the care of pregnant women with COVID-19 in Hungary.

Our first patient who was suffering from COVID-19 in June 2020 was admitted.

We treated approximately in a total of 400 patients. Meanwhile, we lost 10 gravidae.

In the first part of the pandemic, the systematic reviews suggest that the clinical characteristics and severity of COVID-19 disease in pregnant women are generally comparable to those in the general population, but it is really important to provide specialized care for this demographic. Pregnant women warrant particular attention due to their unique physiological state. Furthermore, it is crucial to consider potential pregnancy-related pathologies that may exacerbate the severity of COVID-19 in this population (15).

With the progress of the pandemic and the increase in the number of cases, studies have shown that SARS-CoV-2 infection during pregnancy increases the risk of pathological pregnancies.

Another systematic review and meta-analysis where 438,548 pregnant persons were examined showed that COVID-19 had a connection with an increased risk for preeclampsia, preterm birth, and stillbirth, compared with no SARS-CoV-2 infection during pregnancy (70).

Severe COVID-19 disease (defined as the presence of dyspnoea, respiratory rate of ≥30 breaths per minute and oxygen saturation of 93% or less on room air, or findings consistent with pneumonia) was strongly associated with preeclampsia, gestational diabetes, cesarean delivery, preterm birth, low birth weight, and admission to the neonatal intensive care unit, compared with mild disease (49).

Another systematic review and meta-analysis showed SARS-CoV-2 infected pregnant women have an increased risk for preeclampsia; compared with those who haven't suffered from this infection (71).

Viral infections can cause alterations in the placenta. SARS-CoV-2 is linked to negative outcomes for infants and ongoing inflammatory conditions in the placenta. Recent investigations into SARS-CoV-2-infected pregnancies have identified numerous placental abnormalities, including vascular and inflammatory changes, placental infiltration, thromboembolism, tissue death, and reduced blood flow. These modifications also include indicators of maternal vascular malperfusion, such as heightened fibrin buildup, villous clumping, blood clots between villi, arterial wall thickening, increased syncytial knot formation, and structural changes in placentas (72, 73).

Pregnancies affected by SARS-CoV-2 can result in placental injuries stemming from vascular events, which can be clearly observed using prenatal MRI. Research by Pacu et al. (74) indicated that microvasculopathy, primarily characterized by signs of maternal malperfusion, was commonly found in the placentas of SARS-CoV-2-positive patients.

While many studies have reported on placental and Doppler ultrasound findings in COVID-19-complicated pregnancies (75, 76), the precise effects of SARS-CoV-2 infection on placental observations and Doppler ultrasound measurements remained uncertain during the initial phase of the pandemic.

A meta-analysis published by Chen et al. in 2024 concludes that pregnant women infected with SARS-CoV-2 face a higher likelihood of abnormal Doppler ultrasound parameters and placental findings. These women exhibit increased placental thickness, more placental venous lakes, changes in fetoplacental blood flow, and an abnormal cerebroplacental ratio throughout all trimesters of pregnancy (77).

At this time, we focused our attention on a 33-year-old Caucasian woman, who was 26 weeks pregnant. To highlight from the patient's medical history, she had acute pyelonephritis in 2008, which was also followed by acute necrotizing pancreatitis in the same year. This led to sepsis and then acute renal failure. The prolonged septic condition caused chronic kidney failure, so a kidney transplantation was necessary in 2009. The patient was diagnosed with gestational hypertension one month before the infection was confirmed, and hospital admission became necessary on the 4th day after the positive COVID-19 test. Based on the laboratory and ultrasonography parameters, cesarean section was performed in the 29th week of pregnancy. According to the relevant literature, we can say that the kidney transplant condition predisposed our patient to the development of preeclampsia. The COVID-19 infection probably further accelerated the development of the process (47).

So we came to the conclusion that although the course of COVID-19 disease is not necessarily more severe in healthy pregnant women. On the other hand, the condition of pregnant women complicated by other pregnancy pathologies can be aggravated by a SARS-CoV-2 infection. Also, the course of COVID-19 can be more severe in pregnant women with already known comorbidities.

Then we inquire into the literature on how it is possible to predict the severity of COVID-19 in pregnant women. First to mention is the advanced maternal age, this (≥35 years) is associated with more severe outcomes, e.g. increased risk for hospitalization (50). Additionally, pregnancies associated with other comorbidities like obesity, diabetes, and hypertension need special medical attention. In these COVID-19-associated pregnancies, the inflammatory response can be exacerbated, contributing to worse outcomes (78).

We also find lymphopenia and elevated inflammatory markers: C-reactive protein (CRP), D-dimer, and ferritin, as good laboratory predictive markers (64, 79). Lower oxygen saturation levels can predict the need for respiratory support and ICU admission (80).

Some imaging findings on chest X-rays or CT scans have been associated with more severe disease in pregnant women (81). The multi-organ dysfunction (elevated liver enzymes or the sign of kidney injury) can also predict severe outcomes, indicating a systemic inflammatory response (49).

Earlier studies found NLR is an effective marker for predicting pneumonia in SARS-CoV-2-infected patients (82). It was also described earlier that NLR values are significantly higher in patients who did not survive COVID-19 compared to those who did (83).

The Neutrophil-Lymphocyte ratio can be elevated in COVID-19 and also in physiological, normal pregnancies (30).

The elevated NLR values were diagnosed in preeclampsia and it can work as a predictive factor also and foretell the onset of preeclampsia (84, 85).

Studies have demonstrated a positive correlation between NLR levels and the concentrations of interleukin-6 and interleukin-8 in both liver cirrhosis and ovarian cancer (86, 87). Multiple meta-analyses have indicated that elevated NLR is associated with poorer outcomes in various conditions, including pulmonary embolism, cardiovascular disease, and several types of cancer (88-93). Regarding metabolic disorders, research has shown that NLR serves as a predictive marker for both prediabetes and T2DM. Additionally, in T2DM patients, NLR has been linked to microalbuminuria, cerebrovascular disease, and kidney disease (94-96).

In the previous years, numerous studies described the connection between elevated NLR values and gestational diabetes mellitus and gestational hypertonia (30, 97, 98).

Our first publication shows pregnant women who had died as a result of COVID-19 had higher, but not significantly higher Neutrophil-Lymphocyte values on the first day compared to those who no ventilation was required or mechanical ventilation was sufficient. However, peak NLR values during hospital stay were significantly higher in

patients who had died result of the disease compared to the other two control groups. It is important to note that no significant difference was observed between the first-day NLR values of the two control groups, whereas the peak values were significantly higher in the ventilated group.

Our second study, which uniquely examined the Neutrophil-to-Lymphocyte Ratio (NLR) values of 123 pregnant COVID-19 patients, concluded that the NLR values were significantly different both on the day of hospital admission and in terms of the highest measured value in those with a mild/moderate outcome. It is noteworthy that the number of patients whose NLR values were within the normal range (NLR<3.5) on the day of admission was also significantly lower in the group with severe outcomes. The number of patients in whom the NLR value higher than physiological was never detectable was also significantly different between the two groups.

Finally, we can say the measuring the NLR values could be a useful, easily solved, and cheap method to highlight those pregnant women who specifically require close follow-up.

If we measure extremely high NLR values in pregnant COVID-19 patients at any point during their hospital admission, it is obligatory to monitor the patient so strictly.

To detect the fatal outcome the NLR value is a useful marker.

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6. CONCLUSIONS

Findings

1) In addition to the predictive factors known from the literature, such as advanced maternal age, elevated inflammatory parameters, and characteristic deviations detected during imaging processes, the NLR value can also be a useful factor in terms of pregnant women. It can help the physicians whose pregnant patient requires special attention.
2) It is challenging to anticipate the exact timing of a patient's peak NLR value, it is important to maintain serious monitoring of pregnant COVID-19 patients who has exceptionally high NLR values (defined by our ROC analysis as exceeding 18.05) at any stage of their hospitalization. The extremely elevated NLR levels can be a potential indicator of severe disease progression, increased clinical attention and care can be expected from the physicians.
3) In our other research, we examined the NLR values of 123 pregnant COVID-19 patients. We concluded that cases with mild/moderate outcomes had significantly lower NLR values both on the day of hospital admission and in terms of the highest measured values.

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7. SUMMARY

The global outbreak of COVID-19, caused by the new coronavirus SARS-CoV-2, has emerged as one of the most significant public health challenges of the twenty-first century.

Our research sought to answer the following questions: Can the NLR predict in which case we can expect a fatal outcome? Can the Neutrophil-to-Lymphocyte Ratio (NLR) provide early insights during hospitalization for identifying pregnant women who may require special attention due to a potentially more severe disease course?

Our patients received treatment at Semmelweis University clinics in Budapest, Hungary. The data was collected by two independent researchers from the hospital information system. Our first study is a case-control study, the second one is a retrospective cohort study.

In our initial investigation, we conducted a comparative analysis of three groups The first cohort comprised patients who succumbed to COVID-19. The second cohort consisted of individuals who experienced severe COVID-19 symptoms necessitating mechanical ventilation, while the third cohort included patients who exhibited mild manifestations of the disease. The NLR value of the fatal outcome group measured on the day of admission was elevated, albeit not significantly, compared to the values of the other two groups. However, the peak NLR value observed during hospitalization was significantly higher in the first group, compared to the values of the other two groups. The values of the severe course group were also significantly higher compared to the mild course group. In the second study, the 123 patients were divided into two groups: light/medium severe patients and seriously ill patients. The NLR value demonstrated a statistically significant difference between the two groups across all examined parameters. This difference was observed in the value measured on the day of hospital admission, the peak value measured during hospitalization, as well as in the number of patients whose NLR value remained within the normal range throughout the entire hospitalization period.

We concluded that cases with mild/moderate outcomes had significantly lower NLR values both on the day of hospital admission and in terms of the highest measured values. The Neutrophil-Lymphocyte ratio emerged as a suitable predictive indicator.

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9. BIBLIOGRAPHY OF PUBLICATIONS

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