Acta Biomed. 2021 Sep 2;92(4):e2021318. doi: 10.23750/abm.v92i4.11558.

18. Global Measles Outbreaks. CDC report from December 8; 2023. Available from: https://www.cdc.gov/globalhealth/measles/data/ global-measles-outbreaks.html. Accessed December 10, 2023

19. Holt E. War in Ukraine impacts immunisation. Lancet Microbe. 2024 Feb;5(2):e108. doi: 10.1016/S2666-5247(23)00337-3. Epub 2023 Oct 17.

20. Orsini D, Martini M. Measles: a new danger for Ukraine's children! The need for an effective and timely vaccination prevention campaign for an insidious disease that comes from afar. J. Prev Med Hyg. 2023 Jun 1; 64(2):E204-E208. doi: 10.15167/2421-4248/jpmh2023.64.2.2996.

21. Paules CI, Marston HD, Fauci AS. Measles in 2019 - Going Backward. N Engl J Med. 2019 Jun 6;380(23):2185-2187. doi: 10.1056/NEJMp1905099.

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ERYTHROPOETIN AS A PREDICTOR OF EXTREMELY SEVERE COURSE OF NEW CORONAVIRUS INFECTION COVID-19 IN PREGNANT WOMEN

A comparative analysis of medical, social, clinical and laboratory parameters in pregnant women with a new coronavirus infection (NCI) COVID-19 of varying severity was carried out. For the first time, the level of serum erythropoietin was studied in this category of patients; for the first time, a statistically significantly lower level of erythropoietin was detected in pregnant women with extremely severe COVID-19. The threshold value of serum erythropoietin level was determined to predict the development of extremely severe COVID-19 in pregnant women.

Keywords: new coronavirus infection, COVID-19, pregnancy, extremely severe course, serum erythropoietin/

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Introduction. On 5th May, 2023 World Health Organization officially announced that Novel Coronavirus Infection (NCI) COVID-19 pandemic **no longer constitutes a public health emergency of international concern.** However, there is still a wide circulation of various SARS-CoV-2 virus variants [4]. NCI COVID-19 is a predominately respiratory disease with multisystem damage, especially in case of extremely severe disease course, accompanied by pronounced hypoxic effect on all the tissues and organs with the development of multiple organ dysfunction with potential early damage to the kidney parenchyma [9]. The decrease in oxygen saturation of the tissues stimulates the synthesis of erythropoietin (EPO) a glycoprotein hormone. Up to 90% of EPO in the body of an adult person is produced by peritubular fibroblasts of renal interstitium [5]. EPO activates the production of nitrogen oxide in the endothelium, thus effecting the lung vasoconstriction and improving the oxygen supply to the brain, heart and other organs and tissues [12]. Under physiological regulation EPO is capable of reacting against the pro-inflammatory cytokines TNFα and IL-1β, producing an anti-inflammatory effect [3, 13, 14]. Numerous studies have presented the data on adverse pregnancy outcomes in patients with NCI of various severity. Against the background of steady NCI course pregnant women may have sudden development of critical state. The majority of studies testify to a high risk of fetus distress in pregnant women with severe COVID-19, which is associated with the necessity of preterm labor, premature fetus birth, or potential prenatal/intrapartum fetus death [1, 10, 11, 15, 19]. That is why the studies devoted to the analysis of the NCI effect on pregnancy remain highly relevant. The determination of early predictors of the progression of the COVID-19 severity during gestation is of utmost importance.

The aim of the study: to assess the level of blood serum erythropoietin in pregnant women with novel coronavirus infection COVID-19 of various severity; determine its threshold value to predict extremely severe course of COVID-19 during gestation.

Materials and methods. A comparative prospective cohort study has been performed with subsequent retrospective analysis of the data from medical records (labor and delivery record, health card of

Laboratory parameters in pregnant women of the 1st-5th studied groups upon admission to the hospital

	1st group (n=7)	2nd group (n=21)	3rd group (n=10)	4th group (n=7)	5th group (n=20)	p (significance criterion)*,**
C-reactive protein (CRP), mg/l (N=0-5)	8 (5; 23)	25 (16; 39)	53 (20.3; 75)	45 (24; 84)	0 (0; 1.2)	p_{1-5}<0.001; $p_{1.5}$=0.001; $p_{2.5}$<0.001; $p_{3.5}$<0.001; $p_{4.5}$<0.001; $p_{1.2}$=0.044; $p_{1.3}$=0.006; $p_{1.4}$=0.009; p_{oc}<0.001
Procalcitonin (PCT), ng/ml (N≤0.1)	0.07 (0.06; 0.54)	0.08 (0.06; 0.16)	0.15 (0.08; 0.53)	0.25 (0.09; 0.92)	0.07 (0.06; 0.08)	p_{1-5}=0.004; $p_{2.5}$=0.095; $p_{3.5}$=0.004; $p_{4.5}$=0.001; $p_{2.4}$=0.013; p_{oc}=0.005
Ferritin, ng/ml (N=6-159)	46 (30; 87)	114 (60.5; 163)	110 (82.5; 283)	406 (112; 475)	14.5 (6.3; 37.8)	p_{1-5}<0.001; $p_{1.5}$=0.014; $p_{2.5}$<0.001; $p_{3.5}$<0.001; $p_{4.5}$<0.001; $p_{1.2}$=0.024; $p_{1.3}$=0.022; $p_{1.4}$=0.006; $p_{2.4}$=0.041; p_{oc}<0.001
D-dimer, ng/ml	646 (502; 950)	607 (405; 1116.5)	2063.5 (572.5; 2562)	3000 (1873; 3000)	252.5 (164;305)	p_{1-5}<0.001; $p_{1.5}$<0.001; $p_{2.5}$<0.001; $p_{3.5}$<0.001; $p_{4.5}$<0.001; $p_{1.4}$=0.017; $p_{2.4}$<0.020; p_{oc}<0.001
Lactate dehydrogenase (LDG), u/l (N=195-450)	324 (308; 480)	512 (363.5; 635.5)	617.5 (546.3; 700.3)	926 (592; 1469)	243.5 (89.8; 443.3)	p_{1-5}<0.001; $p_{2.5}$=0.001; $p_{3.5}$=0.002; $p_{4.5}$=0.001; $p_{1.2}$=0.015; $p_{1.3}$=0.002; $p_{1.4}$=0.004; $p_{2.4}$=0.014; p_{oc}<0.001
Erythropoietin (EPO), mlU/ml (N=8-30)	23 (17; 35)	16 (7.2; 21.5)	21 (12.8; 27.5)	4.7 (4.4; 9.3)	16.5 (11; 23.5)	p_{1-5}=0.002; $p_{4.5}$=0.001; $p_{1.2}$=0.046; $p_{1.4}$=0.002; $p_{2.4}$=0.005; $p_{3.4}$=0.002; p_{oc}=0.584

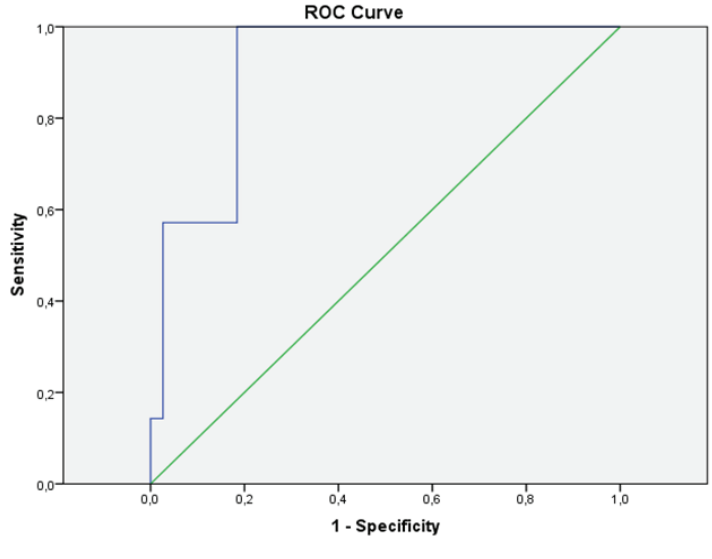
Note: * - subscript number denotes the number of the compared groups, ** - pmc – criterion of significance p between the main group and the comparison group

a pregnant and puerperant woman) of 65 pregnant women. Continuous sampling method has been used in the study. Medical and social, clinical and laboratory parameters were analyzed. The main group consisted of 45 patients with NCI hospitalized during the 3-4th wave of COVID pandemic (July 2021 – September 2021) to the maternity hospital of the State Budgetary Healthcare Institution Regional Clinical Hospital № 2, Chelyabinsk which has been repurposed to a COVID hospital for providing medical assistance to pregnant, parturient, and puerperant women with NCI, as well as to the newborns in the territory of the Chelyabinsk City and Chelyabinsk Region. The comparison group included 20 pregnant women with no indications of NCI/acute respiratory viral infection (ARVI) during the current pregnancy admitted to the maternity hospital of the State Budgetary Healthcare Institution Regional Clinical Hospital #3, Chelyabinsk in August-September 2021 in the 3rd trimester of gestation. At admission the pregnant women from the comparison group had negative SARS-CoV-2 PCR test from the oral and nasopharyngeal cavity, had no clinical signs of ARVI over the course of the current gestation. The COVID-19 severity was determined in accordance with the existing guidelines (Version 4(05.07.2021

r. https://static-0.minzdrav.gov.ru/system/attachments/attaches/000/057/333/original/05072021_MR_Preg_v4.pdf, accessed on 26.10.2023). Patients with mild NCI comprised the 1st group (n=7), medium – the 2nd group (n=21), severe – the 3rd group (n=10), extremely severe – the 4th group (n=7), pregnant women of the comparison group - the 5th studied group (n=20). Main group inclusion criteria were: confirmed COVID-19 case (U07.1), antenatal care, availability and accessibility of the medical records to collect necessary data on gestation course. The non-inclusion criterion was probable/suspected COVID-19 case (U07.2/Z03.8). To evaluate the laboratory parameters the blood was sampled from the median cubital vein upon the studied patients' admission to the in-patient department. Blood serum EPO concentration was determined with ELISA technique with the use of the Erythropoietin-EIA-Best (Vector-Best, Russia) test-system. Optical density of the samples was registered on the photometer «Multisrkan ORIGINAL» (Labsystems, Finland). Statistical processing of the obtained results was performed in the IBM SPSS Statistics 19 software package. To describe quantitative data median and quartile were used, for qualitative data we used absolute and relative frequency. The data were analyzed with the use of non-parametric criteria depending on the type of the data and amount of comparison groups (Kruskal-Wallis test, Mann-Whitney test, Fisher's exact test). ROC-analysis was performed to assess the diagnostic significance of the serum erythropoietin level. The differences were considered statistically significant at $p< 0.05$.

Results and Discussion. Gestational age median upon admission was 29.4 (25.0; 39.0), 25.0 (19.5;37.0), 32.0 (26.8; 35.3), 32.0 (27.0; 32.4) and 40.0 (39.3;40.0) weeks ($p_{1-5}<0.001$; $p_{1,2}=0.395$; $p_{1,3}=0.961$; $p_{1,4}=0.949$; $p_{2,3}=0.409$; $p_{2,4}=0.770$; $p_{3,4}=0.768$; $p_{oc}<0.001$) for the 1st -5th group, respectively, without statistically significant differences between groups 1-4, with the predominance of NCI manifestation in the 3rd trimester of the gestation. Women from the 1st-4th group were hospitalized on the 6 (5;9), 6 (4,5;7), 3.5 (3;5,3), 4 (3;5) day, respectively, from the onset of NCI manifestation ($p_{1-4}=0.044$; $p_{1,2}=0.788$; $p_{1,3}=0.063$; $p_{1,4}=0.080$; $p_{2,3}=0.027$; $p_{2,4}=0.053$; $p_{3,4}=0.799$). The median of the lung tissue involvement according to the initial computer tomography (CT) was 0 (0; 0), 24 (16; 31), 31 (19; 56), 32 (15; 36) % ($p_{1-4}<0.001$; $p_{1,2}<0.001$; $p_{1,3}<0.001$; $p_{1,4}=0.001$; $p_{2,3}=0.143$; $p_{2,4}=0.670$; $p_{3,4}=0.591$) in the 1st - 4th group, respectively. There was no statistically significant differences between the parameter values in groups 2-4. The median of the maximum lung tissue involvement based on the CT data in the dynamics was 0 (0%), 25 (20;34), 53.5 (47.3;56.0) and 100.0 (84.0;100.0) in the 1st -4th group, respectively ($p_{1-4}<0.001$; $p_{1,2}<0.001$; $p_{1,3}<0.001$; $p_{1,4}=0.001$; $p_{2,3}=0.143$; $p_{2,4}=0.670$; $p_{3,4}=0.591$). The median of the hospital stay length was 5 (5; 8), 10 (7.5; 13.5), 15.5 (12.3; 16), 27 (23; 36) and 7 (6; 9) days in the 1st-5th group, respectively ($p_{1-5}<0.001$; $p_{1,2}=0.003$; $p_{1,3}=0.002$; $p_{1,4}=0.002$; $p_{2,3}=0.051$; $p_{2,4}<0.001$; $p_{3,4}=0.016$; $p_{oc}=0.001$). It shows the statistically significant increase in the length of the hospital stay with the increase in the NCI severity. One woman from the 2nd group underwent COVID-19 vaccination prior to the current pregnancy planning. In general, medical and social characteristics of the pregnant women of the 1st-5th group did not differ statistically significantly. The median of the age of the studied women was 31.0 (28.0; 36.0), 31.0 (27.5; 34.0), 31.0 (25.8; 33.5), 33.0 (29.0; 37.0) and 34.0 (30.5;36.8) in the 1st-5th group, respectively ($p_{1-5}=0.407$; $p_{oc}=0.086$). In general, in terms of the presence of somatic disease (4 (57.1%), 14 (66.7%), 10 (100.0%), 6 (85.7%), 18 (90.0%) cases, $p_{1-5}=0.060$; $p_{oc}=0.314$) and exacerbations of the course of the current gestation (6 (85.7%), 17 (81.0%), 8 (80.0%), 6 (85.7%), 18 (90.0%) cases, $p_{1-5}=0.945$; $p_{oc}=0.711$) no statistically significant differences between the pregnant women from the 1st-5th group were obtained.

We have registered high levels of the markers of the acute phase of the inflammation – C-reactive protein and ferritin, marker of the tissue destruction - LDH with the statistically significant difference in pregnant women with NCI, with much higher values in case of extremely severe course of the process (Table 1). It fully agrees with the results of other studies [7, 17, 18]. The level of procalcitonin that shows the risk of the development of COVID-19 complications (bacterial infection or septic state) was statistically significantly higher in the main studied group and it correlated with the NCI severity. The highest values of procalcitonin were registered in case of the extremely severe course of the process which agrees with the published papers data [2]. Statistically significantly high level of D-dimer in pregnant women with COVID-19 was observed, especially in those who had extremely severe course of the infection, relative to the healthy pregnant women, which is in line with the data of published studies [2, 8, 16]. According to the conclusions of the meta-analysis presented in Gungor Baris et al. (2021), the increase in the D-dimer level in dynamics is typical of more severe NCI COVID-19 and is associated with the risk of the lethal outcome [16]. No statistically significant differences between the levels of C-reactive protein, procalcitonin, ferritin, D-dimer, LDH was observed in women of the 3rd and 4th group. In our study for the first ever the level of the serum EPO in pregnant women with COVID-19 was analyzed upon admission to the hospital (Table 1). Statistically significantly lower levels of EPO were registered in group 4 relative to those in pregnant women from group 1-3 ($p_{1,4}=0.002$; $p_{2,4}=0.005$;



ROC-curve of the parameter "Blood serum erythropoietin, mIU/ml" in predicting extremely severe course of NCI COVID-19 in pregnant women

$p_{3,4}$=0.002) and women in the comparison group (p_{1-5}=0.002; $p_{4,5}$=0.001). Our results are similar to those presented in the studies by Yağcı S. et al. (2021), Viruez-Soto A. et al. (2021), Revin V.V. et al. (2022), who observed and reported low levels of serum EPO in non-pregnant patients (men/women) in the group of patients with severe COVID-19 course that required referring the patients to the intensive care unit, and in the group of people who died of NCI [6, 20, 21].

Table 1 Laboratory parameters in pregnant women of the 1st-5th studied groups upon admission to the hospital.

As a result of the conducted ROC-analysis, we esTableished that it is possible to predict the onset of the extremely severe course of NCI COVID-19 in pregnant women with 100% sensitivity and 81.6% specificity when the level of erythropoietin is ≤ 10.5 mIU/ml (on the 4th day from the onset of the disease). The score of the area under the ROC-curve was 0.920 with $CI_{95\%}$ [0.819; 1.000] (p=0.001). It testifies to high discriminating power of the method and possibility of its usage in practical activities (fig. 1).

Fig.1 ROC-curve of the parameter "Blood serum erythropoietin, mIU/ml" in predicting extremely severe course of NCI COVID-19 in pregnant women.

Conclusion. Statistically significantly lower level of blood serum erythropoietin is registered in pregnant women with extremely severe NCI. The development of extremely severe NCI COVID-19 could be predicted when the level of blood serum erythropoietin is ≤10.5 mIU/ml on the 4th day from the disease onset

References

1. Voropaeva E.E. [et al.]. Blagopriyatnyj iskhod krajne tyazhelogo techeniya novoj koronavirusnoj infekcii COVID-19 pri beremennosti s total'nym porazheniem legkih, ostrym miokarditom i infarktom miokarda [Favorable outcome of the extremely severe course of the new coronavirus infection COVID-19 during pregnancy in the presence of overall lung damage, acute myocarditis, and myocardial infarction]. Akusherstvo i ginekologiya [Obstetrics and Gynecology. 2021; 10: 179-186 (In Russ.).]. DOI: 10.18565/aig.2021.10.179-186.

2. Vremennye metodicheskie rekomendacii. Profilaktika, diagnostika i lechenie novoj koronavirusnoj infekcii (COVID-19) [Temporary methodological recommendations. Prevention, diagnosis and treatment of new coronavirus infection (COVID-19). Version 18 (26.10.2023) [Internet] (In Russ.).] URL: https://static-0.minzdrav.gov.ru/system/attachments/attaches/000/064/610/original/VMR_COVID-19_V18.pdf

3. Zakharov Yu.M. Neeritropoeticheskie funkcii eritropoetina [Non-erythropoietic properties of erythropoietin]. Rossijskij fiziologicheskij zhurnal im. I.M. Sechenova [Russian Journal of Physiology. 2007; 93(6):592-608 (In Russ.).]

4. Itogovoe zayavlenie o rabote pyatnadcatogo soveshchaniya Komiteta Mezhdunarodnyh mediko-sanitarnyh pravil (2005 g.) po chrezvychajnoj situacii v svyazi s pandemiej [Final statement on the work of the fifteenth meeting of the International Health Regulations Committee (2005) on the pandemic emergency [Internet. (In Russ.).] URL: https://www.who.int/ru/news/item/05-05-2023-statement-on-the-fifteenth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic

5. Lykov A.P. Eritropoetin: funkcii i terapevticheskij potencial [Erythropoietin: function and therapeutic potential]. Sibirskij nauchnyj medicinskij zhurnal [Siberian scientific medical journal. 2023; 43 (3): 29-39 (In Russ.).] DOI: 10.18699/SSMJ20230203.

6. Revin V.V. [et al.]. Morfofunkcional'naya harakteristika eritrocitov i uroven' eritropoetina v krovi u pacientov kak prediktory tyazhelogo techeniya COVID-19 [Morphofunctional characteristics of erythrocytes and blood erythropoietin level in patients as predictors of severe course of COVID-19]. Byulleten' eksperimental'noj biologii i mediciny [Bulletin of Experimental Biology and Medicine. 2022; 173 (1):57-61 (In Russ.).] DOI: 10.47056/0365-9615-2022-173-1-57-61.

7. Gareyeva A.I. [et al.]. Opyt vedeniya beremennyh s tyazheloj i krajne tyazheloj formami COVID-19 [Experience in managing severe and extremely severe COVID-19 in pregnant women]. ZHurnal akusherstva i zhenskih boleznej [Journal of Obstetrics and Women's Diseases. 2022; 71 (1):11-22 (In Russ.).] DOI: 10.17816/JOWD72169.

8. Ishchenko L.S. [et al.] Osobennosti gemostaza u beremennyh zhenshchin pri manifestacii novoj koronavirusnoj infekcii COVID-19 v tret'em trimestre gestacii [Peculiarities of hemostasis in pregnant women during manifestation of new coronavirus infection COVID-19 in the third trimester of gestation]. YUzhno-Ural'skij medicinskij zhurnal [South Ural medical journal. 2021; 3: 60-74: 2021 9 (In Russ.).]

9. Lykov A.P. Eritropoetin: funkcii i terapevticheskij potencial [Erythropoietin: function and therapeutic potential]. Sibirskij nauchnyj medicinskij zhurnal [Siberian scientific medical journal]. 2023; 43 (3): 29-39 (In Russ.).] DOI: 10.18699/SSMJ20230203.

10. Revin V.V. [et al.]. Morfofunkcional'naya harakteristika eritrocitov i uroven' eritropoetina v krovi u pacientov kak prediktory tyazhelogo techeniya COVID-19 [Morphofunctional characteristics of erythrocytes and blood erythropoietin level in patients as predictors of severe course of COVID-1]. Byulleten' eksperimental'noj biologii i mediciny [Bulletin of Experimental Biology and Medicine. 2022; 173 (1): 57-6 (In Russ.).]. DOI: 10.47056/0365-9615-2022-173-1-57-61.

11. Gareyeva A.I. [et al.]. Opyt vedeniya beremennyh s tyazheloj i krajne tyazheloj formami COVID-19 [Experience in managing severe and extremely severe COVID-19 in pregnant women]. Zhurnal akusherstva i zhenskih boleznej [Journal of Obstetrics and Women's Diseases. 2022; 71 (1): 11-22 (In Russ.).] DOI: 10.17816/JOWD72169.

12. Ishchenko L.S. [et al.] Osobennosti gemostaza u beremennyh zhenshchin pri manifestacii novoj koronavirusnoj infekcii COVID-19 v tret'em trimestre gestacii [Peculiarities of hemostasis in pregnant women during manifestation of new coronavirus infection COVID-19 in the third trimester of gestation]. YUzhno-Ural'skij medicinskij zhurnal [South Ural medical journal. 2021; 3: 60-74 (In Russ.).]

13. Golota A.S. [et al.]. Reabilitaciya v usloviyah pandemii COVID-19 [Rehabilitation during the COVID-19 pandemic]. Klinicheskaya praktika [Clinical Practice. 2022; 13(1):42-65 (In Russ.).] DOI: 10.17816/clinpract79364.

14. Belokrinitskaya T.E. [et al.]. COVID-19 u beremennyh Sibiri i Dal'nego Vostoka: itogi 2 let pandemii [COVID-19 in pregnant women of Siberia and the Russian Far East: 2-year results of the pandemic]. Obstetrics and Gynecology [Akusherstvo i ginekologiya. 2022; 4: 47-54 (In Russ.).] DOI: 10.18565/aig.2022.. 2022. №4. S. 47-54. DOI: 10.18565/aig.2022.4.47-54.

15. Ishchenko L.S. [et al.]. Chastota i iskhody ekstremal'no rannih prezhdevremennyh rodov u beremennyh zhenshchin s novoj koronavirusnoj infekciej COVID-19 [Frequency and outcomes of extremely early preterm birth in pregnant women with new coronavirus infection COVID-19]. Yakutskij medicinskij zhurnal [Yakut Medical Journal. 2023; 80-83 (In Russ.).] DOI: 10.25789/YMJ.2023.81.20.

16. Beleslin-Čokić B.B. [et al.]. Erythropoietin and hypoxia increase erythropoietin receptor and nitric oxide levels in lung microvascular endothelial cells. Cytokine. 2011; 54(2): 129-35. DOI: 10.1016/j.cyto.2011.01.015.

17. Broxmeyer H.E. Erythropoietin surprises: an immune saga. Immunity. 2011; 34(1): 6-7. DOI: 10.1016/j.immuni.2011.01.004.

18. Choi D. [et al.]. Erythropoietin protects against diabetes through direct effects on pancreatic beta cells. J Exp Med. 2010; 207(13): 2831-2842. DOI: 10.1084/jem.20100665.

19. Jafari M. [et al.]. Clinical characteristics and outcomes of pregnant women with COVID-19 and comparison with control patients: A systematic review and meta-analysis. Rev Med Virol. 2021; 31(5): 1-16. DOI: 10.1002/rmv.2208.

20. Gungor B. [et al.]. Elevated D-dimer levels on admission are associated with severity and increased risk of mortality in COVID-19: A systematic review and meta-analysis. Am J Emerg Med. 2021; 39: 173-179. DOI:10.1016/j.ajem.2020.09.018.

21. Liu D. [et al.]. Pregnancy and Perinatal Outcomes of Women With Coronavirus Disease (COVID-19) Pneumonia: A Preliminary Analysis. AJR Am J Roentgenol. 2020; 215(1): 127-132. DOI: 10.2214/AJR.20.23072.

22. Turan O. [et al.] [et al.] Clinical characteristics, prognostic factors, and maternal and neonatal outcomes of SARS-CoV-2 infection among hospitalized pregnant women: A systematic review. Int J Gynecol Obstet. 2020; 151(1): 7-16. DOI: 10.1002/ijgo.13329 ijgo.13329.

23. Vallejo V., Ilagan J.G. A Postpartum Death Due to Coronavirus Disease 2019 (COVID-19) in the United States. Obstet Gynecol. 2020; 136(1): 52-55. DOI: 10.1097/AOG.0000000000003950.

24. Viruez-Soto A. [et al.] Low serum erythropoietin levels are associated with fatal COVID-19 cases at 4,150 meters above sea level. Respir Physiol Neurobiol. 2021; 292(103709): 1-5. DOI: 10.1016/j.resp.2021.103709.

25. Yağcı S. **[et al.].** The relationship between serum erythropoietin, hepcidin, and haptoglobin levels with disease severity and other biochemical values in patients with COVID-19. Int J Lab Hematol. 2021; 43 (Suppl 1): 142-151. DOI: 10.1111/ijlh.13479.