TOPICAL ISSUE

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MEDICAL AND SOCIAL PORTRAIT OF PREGNANT WOMEN WITH COVID-19 IN VARYING SEVERITY

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As a result of a comparative analysis, a number of statistically significant features of the medical and social portrait of pregnant women with COVID-19 of varying severity were identified. An increase in the median age, an increase in the frequency of somatic pathology (chronic arterial hypertension, varicose veins of the lower extremities, overweight, obesity, systemic lupus erythematosus) and polypathies are characteristic as the severity of COVID-19 in pregnant women increases. Mild infection is more common in primigravid women, moderate and severe in pregnant women with a history of childbirth and medical abortion, and extremely severe in multiparous women.

Keywords: new coronavirus infection, COVID-19, pregnancy, social portrait, somatic pathology, gynecological and obstetric history.

Introduction. The COVID-19 pandemic turned out to be a serious challenge with respect to the pregnant women management against the background of SARS-CoV-2 infection manifestation. The available experience of the previous occurrences of the seasonal respiratory infections was insufficient due to the specificity of COVID-19 course and its effect on the body of pregnant women. Research data indicate that during gestation period the severity of COVID-19 course could vary from mild to extremely severe one [3]. Moreover, COVID-19 of any degree of severity could lead to adverse pregnancy outcomes.

Besides, during the gestation period risks of sudden deterioration of a pregnant woman's health condition against the background of primarily stable disease course were noted [1, 8, 9, 11]. During the 1st-4th waves of the pandemic intensive treatment with respiratory support in the intensive care units was required for every 4th pregnant woman with pneumonia [12, 13]. The risk of the adverse maternal and fetal outcome is increasing with the increase in the COVID-19 severity [4, 5, 11]. At the same time the amount of available information about the extremely severe COVID-19 course in the gestation period is limited.

In the meta-analysis by E. R. Smith et al. (2023) that included 12 studies from 12 countries with the participation of 13,136 pregnant women (1,942 women with the confirmed/suspected COVID-19 and 11,194 women without COVID-19 during gestation and at labor) high risk of serious diseases for mothers and newborns, mother lethality against the manifestation of the COVID-19 at any time of the gestation, but more often in the 3rd trimester was determined [10].

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, the mutation and wide circulation of various variants of SARS-CoV-2 virus which retains its high contagiousness persist [2]. The effect of COVID-19 on the gestation course and perinatal outcomes are being actively studied at present time. The data of some studies are contradictory, and the amount of available data is still insufficient for complete understanding of the risks of COVID-19 manifestation during gestation. The data on the specific features of the health and social profile of pregnant women who had SARS-CoV-2-infection of various degree of severity during gestation are limited.

The objective of the study is to analyze the specific features of the health and social profile of pregnant women with COVID-19 of various degrees of severity.

Materials and research methods. A prospective cohort study of 1,476 pregnant women has been performed on the basis of the maternity hospitals of the GBUZ Regional clinical hospital #2, Chelyabinsk, and GAUZ Regional clinical hospital #3, Chelyabinsk, which are the obstetric hospitals of the 2nd level and in general are comparable in terms of the level of equipment and medical care provision to the pregnant, parturient, and puerperant women based on the order of the Ministry of Health of the Russian Federation No. 1130n dated October 20, 2020 "On the procedure for providing assistance in obstetrics and gynecology" and current clinical guidelines in obstetrics and gynecology, approved by the Ministry of Health of the Russian Federation (https://cr.minzdrav.gov.ru/).

The study has been approved by the Ethics Committee of the South Ural State Medical University of the Ministry of Health of the Russian Federation.

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The evaluation of the medical and social characteristics of the studied individuals has been performed based on the labor and delivery records, medical histories of pregnant and puerperant women.

The main group consisted of 1,386 patients with COVID-19 hospitalized over the period from April 2020 to September 2021 (1st-4th wave of COVID-19 pandemic) to the maternity hospital of the GBUZ Regional Clinical Hospital № 2, Chelyabinsk which has been repurposed to a COVID hospital for providing medical assistance to pregnant, parturient, and puerperant women with COVID-19, as well as to the newborns in the territory of the Chelyabinsk City and Chelyabinsk Region. The 1st study group (n=482) included pregnant women with mild COVID-19, the 2nd group (n=718) – those with COVID-19 of moderate severity, the 3rd group – pregnant women with severe COVID-19, and the 4th group (n=21) – patients with extremely severe course of the infection. The comparison group (the 5th group) consisted of 90 pregnant women.

COVID-19 severity was determined in accordance with the existing guidelines (Version 5 (28.12.2021) https://static-0.minzdrav.gov.ru/system/attachments/attaches/000/059/052/original/BMP_preg_5.pdf). The following main group inclusion/exclusion criteria were developed. Inclusion criteria: confirmed COVID-19 case (U07.1), availability and accessibility of medical records to collect the data for the research, written informed consent of the patients to participation in the study and publication of its findings in the open media, follow-up in women's health clinic, reproductive age.

Exclusion criteria: probable/suspected COVID-19, non-accessibility/lack of medical records, lack of written informed consent to participation in the study and/or publication of its findings in open media, multiple pregnancy, decompensation of somatic diseases, malignant neoplasms, psychiatric illnesses, HIV.

The comparison group (study group 5) comprised 90 pregnant women admitted to the maternity hospital of the GAUZ Regional clinical hospital #3, Chelyabinsk over the period from July 2020 to February 2021 in the 3rd trimester for the pre-delivery preparation and delivery. The comparison group was formed using the nested randomization method. A month was selected randomly. Those pregnant women who were admitted to the maternity hospital during this month were included in the study. The inclusion criteria for this group were: negative SARS-CoV-2 test from the oral cavity and nasopharyngeal cavity at hospital admission, no clinical signs of COVID-19/ acute respiratory viral infection over the course of the current gestation, 3rd trimester of gestation.

Statistical processing of the obtained results was carried out using standard methods using the IBM SPSS Statistics 19 program. As indicators of descriptive statistics, the median (Me) and quartiles (Q1; Q3) were calculated for quantitative characteristics, and the absolute and relative frequencies (in %) were calculated for qualitative characteristics. Differences in quantitative and ordinal parameters between three or more groups were assessed using the Kruskal-Wallis test, and subsequent comparisons between two groups were performed using the Mann-Whitney test. To identify differences between groups in terms of qualitative characteristics, the x2 test or Fisher's exact test was used (if the conditions for applying the x2 criterion were violated). Statistical hypotheses were tested at a critical significance level of 0.05.

Results and Discussion. Median age of the pregnant women was 29 (24;33), 31 (27;35), 32 (28;35), 33 (29;36,5), 29 (25;33) years in groups 1-5, respectively (p_{1-5}<0.001; $p_{1,2}$<0.001; $p_{1,3}$<0.001; $p_{1,4}$=0.003; $p_{1,5}$=0.352; $p_{2,3}$=0.310; $p_{2,4}$=0.204; $p_{2,5}$=0.011; $p_{3,4}$=0.392; $p_{3,5}$=0.003; $p_{4,5}$=0.008; $p_{main/comparison(mc)}$=0.132), which is illustrative of the statistically significant increase in the median age of the patients from the 2nd, 3rd, 4th group relative to groups 1 and 5 without statistically significant differences between pregnant women from groups 1 and 5. The data we have acquired are in agreement with the findings of other studies [4, 11, 12]. Patients belonged mainly to East Slavic ethnicity with no statistically significant difference between the studied groups (p_{1-5}=0.325; p_{mc}=0.769).

Patients from the 1st and 2nd group statistically significantly more often were not legally married as compared to pregnant women from the 5th group – 351 (72.8%), 545 (75.9%), 116 (78.9%), 19 (90.5%), 79 (87.8%) cases in the 1st-5th group, respectively (p_{1-5}=0.013; p_{1-5}=0.013; $p_{1,2}$=0.250; $p_{1,3}$=0.161; $p_{1,4}$=0.080; $p_{1,5}$=0.003; $p_{2,3}$=0.458; $p_{2,4}$=0.190; $p_{2,5}$=0.016; $p_{3,4}$=0.376; $p_{3,5}$=0.114; $p_{4,5}$=0.999; p_{mc}=0.007).

There were no statistically significant differences between the groups in terms of the employment pattern (p_{1-5}=0.206; p_{oc}=0.408). As for the substance abuse, then smoking was noted among women with COVID-19 with statistically significant predominance in the 1st and 2nd group – 48 (10.0%), 53 (7.4%), 4 (2.7%), 1 (4.8%), 3 (3.3%) cases in groups 1-5, respectively (p_{1-5}=0.023; $p_{1,2}$=0.137; $p_{1,3}$=0.005; $p_{1,4}$=0.710; $p_{1,5}$=0.044; $p_{2,3}$=0.043; $p_{2,4}$=0.999; $p_{2,5}$=0.189; $p_{3,4}$=0.492; $p_{3,5}$=0.999; $p_{4,5}$=0.573; p_{mc}=0.123). Thus, we did not obtain the risk of COVID-19 severity increase due to smoking in women, although a number of studies point at the increased risk of SARS-CoV-2-infection progressions for smokers relative to those who have never smoked [14, 15].

In general, the prevalence of various kinds of somatic diseases differed statistically significantly only in pregnant women of the 1st, 2nd, and 5th studied group – 311 (64.5%), 504 (70.2%), 119 (81.0%), 19 (90.5%), 78 (86,7%) in 1st -5th group respectively (p_{1-5}<0.001; $p_{1,2}$=0.039; $p_{1,3}$<0.001; $p_{1,4}$=0.014 $p_{1,5}$<0.001; $p_{2,3}$=0.008; $p_{2,4}$=0.044 $p_{2,5}$=0.001; $p_{3,4}$=0.374 $p_{3,5}$=0.254 $p_{4,5}$=0.999; p_{mc}=0.001). This could imply that the very fact of having a somatic disease could have no contribution to the risk of severe COVID-19 development. What is more important is what kind of the somatic disease a pregnant woman has.

In our study the combined somatic pathology (polypathia) was statistically significantly more frequent in group 4 –138 (28.6%), 246 (34.3%), 74 (50.3%), 17 (81.0%), 40 (44.4%) in group 1-5, respectively (p_{1-5}<0.001; $p_{1,2}$=0.039; $p_{1,3}$<0.001; $p_{1,4}$<0.001; $p_{1,5}$=0.004; $p_{2,3}$<0.001; $p_{2,4}$<0.001 $p_{2,5}$=0.058; $p_{3,4}$=0.010 $p_{3,5}$=0.378 $p_{4,5}$=0.003; p_{mc}=0.062). Therefore, polypathia in pregnant women is associated with the risk of extremely severe COVID-19 which has also been demonstrated in other studies [3, 7]. In case of polypathia chronic arterial hypertension (CAH), varicose veins of the lower extremities (VVLE), hypothyroidism were most often registered.

Circulatory system diseases (CAH, VVLE, congenital heart disease, cusp prolapse, thrombophlebitis in past medical history) were observed in 79.0 (16.4%), 166 (23.1%), 45 (30.6%), 10 (47.6%) and 17 (18.9%) cases in the 1st-5th group, respectively. They were registered statistically significantly more often in groups 3 and 4 (p_{1-5}<0.001; $p_{1,2}$=0.005; $p_{1,3}$<0.001; $p_{1,4}$=0.001; $p_{1,5}$=0.560; $p_{2,3}$=0.054; $p_{2,4}$=0.009 $p_{2,5}$=0.366; $p_{3,4}$=0.120 $p_{3,5}$=0.046 $p_{4,5}$=0.006; p_{mc}=0.498). Similar results were obtained by the authors in other studies [3, 4, 12]. Chronic anemia was observed statistically significantly more often in patients with COVID-19 from group 3 and 4 – 11 (2.3%), 8 (1.1%), 14 (19.5%), 3 (14.3%), 5 (5.6%) cases in the 1st -5th groups, respectively (p_{1-5}<0.001; $p_{1,2}$=0.112; $p_{1,3}$<0.001; $p_{1,4}$=0.017; $p_{1,5}$=0.152; $p_{2,3}$<0.001;

$p_{2,4}$=0.003; $p_{2,5}$=0.010; $p_{3,4}$=0.450; $p_{3,5}$=0.275; $p_{4,5}$=0.173; p_{mc}=0.104).

The obtained data are in agreement with the findings of other studies demonstrating a higher risk of incidence and development of severe COVID-19 in pregnant women with anemia [3, 4, 6]. Endocrine system diseases, nutrition and metabolic disorders were registered statistically significantly more often in group 3 and 4 relative to group 1 and 2, and the comparison group (p_{1-5}<0.001; $p_{1,2}$=0.604; $p_{1,3}$=0.001; $p_{1,4}$=0.003 $p_{1,5}$=0.051; $p_{2,3}$=0.002; $p_{2,4}$=0.005; $p_{2,5}$=0.025; $p_{3,4}$=0.196; $p_{3,5}$<0.001; $p_{4,5}$<0.001; p_{mc}=0.011). As for the thyroid diseases (hypothyroidism, hyperthyroidism, autoimmune thyroiditis, nontoxic diffuse-nodular goiter) there were no statistically significant differences between the groups (p_{1-5}=0.174; p_{mc}=0.891). Diabetes mellitus (DM) was registered in 1 (0.2%), 2 (0.3%), 4 (2.7%), 1 (4.8%), 0 (0.0%) cases in the 1st -5th groups, respectively, with higher frequency of occurrence in the 3rd group (p_{1-5}=0.004; $p_{1,2}$=0.999; $p_{1,3}$=0.012; $p_{1,4}$=0.082; $p_{1,5}$=0.999; $p_{2,3}$=0.009; $p_{2,4}$=0.083; $p_{2,5}$=0.999; $p_{3,4}$=0.492; $p_{3,5}$=0.300; $p_{4,5}$=0.189; p_{mc}=0.999).

Most of the studies show high frequency of occurrence of DM in pregnant women with COVID-19, high risk of severe course of the NCI if a patient has this disease [3, 4, 11, 12]. The median of the body mass index differed statistically significantly between the 1st -5th group – 23 (20;27), 24 (21;28), 27 (24;31), 26 (22;32), 21 (19;23.3), respectively (p_{1-5}<0.001; $p_{1,2}$<0.001; $p_{1,3}$<0.001; $p_{1,4}$=0.003 $p_{1,5}$<0.001; $p_{2,3}$<0.001; $p_{2,4}$=0.055; $p_{2,5}$<0.001; $p_{3,4}$=0.966; $p_{3,5}$<0.001; $p_{4,5}$<0.001; p_{mc}<0.001). Obesity of various degrees was noted in 80 (16.6%), 140 (19.5%), 49 (33.3%), 9 (42.9%), 6 (6.7%) patients from 1st -5th group, respectively (p_{1-5}<0.001; $p_{1,2}$=0.203; $p_{1,3}$<0.001; $p_{1,4}$=0.005; $p_{1,5}$=0.016; $p_{2,3}$<0.001; $p_{2,4}$=0.022; $p_{2,5}$=0.003; $p_{3,4}$=0.391; $p_{3,5}$<0.001 $p_{4,5}$<0.001; p_{mc}=0.002).

Thus, patients with COVID-19 had metabolic disorders (excess body weight (BMI=25.0-29.9) and obesity) statistically significantly more often. Women from the 3rd and 4th study group had the highest frequency of these disorders relative to the members of the other groups – 186 (38.6%), 356 (49.6%), 97 (66.0%), 14 (66.7%), 18 (20.0%) cases in 1st -5th group, respectively (p_{1-5}<0.001; $p_{1,2}$<0.001; $p_{1,3}$<0.001; $p_{1,4}$=0.010; $p_{1,5}$=0.001; $p_{2,3}$<0.001; $p_{2,4}$=0.123; $p_{2,5}$<0.001; $p_{3,4}$=0.951; $p_{3,5}$<0.001 $p_{4,5}$<0.001; p_{mc}<0.001). Association between obesity and risk of COVID-19 development, as well as with the risk of severe course of the disease and adverse obstetric outcomes has also been shown in large-scale studies by J. Allotey et al. (2020), M. Jafari et al. (2021), M. La Verde and al. (2021), E. R. Smith and all. (2023) [10, 11, 12, 13].

Compensated systemic lupus erythematosus (SLE) was registered statistically significantly more frequently in the 4th group of patients with COVID-19 – 1 (0.2%), 1 (0.1%), 1 (0.7%), 2 (9.5%), 0 (0.0%) cases in 1-5th group, respectively (p_{1-5}=0.002; $p_{1,2}$=0.999; $p_{1,3}$=0.413; $p_{1,4}$=0.005 $p_{1,5}$=0.999; $p_{2,3}$=0.311; $p_{2,4}$=0.002; $p_{2,5}$=0.999; $p_{3,4}$=0.041 $p_{3,5}$=0.999; $p_{4,5}$=0.034; p_{mc}=0.999). There were no statistically significant differences between the 1st -5th studied groups in terms of the frequency of occurrence of the diseases of the respiratory system (p_{1-5}=0.949; p_{mc}=0.463), digestive (p_{1-5}=0.090; p_{mc}=0.019) and urogenital (p_{1-5}=0.393; p_{mc}=0.527) systems, diseases of the ear and mastoid process (p_{1-5}=0.360; p_{mc}=0.999), infectious and parasitic diseases (p_{1-5}=0.250; p_{mc}=0.412).

A number of specific features of the obstetric-gynecologic anamnesis has been revealed in the studied patients. Among pregnant women with COVID-19 of the 1st group current pregnancy was the first one statistically significantly more often – 162 (33.6%), 163 (22.7%), 24 (16.3%), 0 (0.0%), 31 (34.4%) patients in group 1-5, respectively (p_{1-5}<0.001; $p_{1,2}$<0.001; $p_{1,3}$<0.001; $p_{1,4}$=0.001; $p_{1,5}$=0.904; $p_{2,3}$=0.099; $p_{2,4}$=0.007; $p_{2,5}$=0.018; $p_{3,4}$=0.046; $p_{3,5}$=0.002; $p_{4,5}$=0.002; p_{mc}=0.064). The number of multiparous women increased statistically significantly with increasing severity of COVID-19 – 267 (55.4%), 504 (70.2%), 112 (76.2%), 19 (90.5%), 51 (56.7%) cases in the 1st -5th group, respectively (p_{1-5}<0.001; $p_{1,2}$<0.001; $p_{1,3}$<0.001; $p_{1,4}$=0.001; $p_{1,5}$=0.864; $p_{2,3}$=0.144; $p_{2,4}$=0.044; $p_{2,5}$=0.009; $p_{3,4}$=0.169; $p_{3,5}$=0.002; $p_{4,5}$=0.004; p_{mc}=0.073).

In the groups of patients with moderate and severe COVID-19 the number of women with 3 and more deliveries in the past history increased statistically significantly – 23 (4.8%), 71 (9.9%), 18 (12.2%), 3 (14.3%), 5 (5.6%) patients in group 1-5, respectively (p_{1-5}=0.004; $p_{1,2}$=0.001; $p_{1,3}$=0.001; $p_{1,4}$=0.088; $p_{1,5}$=0.789; $p_{2,3}$=0.392; $p_{2,4}$=0.458; $p_{2,5}$=0.184; $p_{3,4}$=0.730; $p_{3,5}$=0.091; $p_{4,5}$=0.173; p_{mc}=0.340).

On the whole, patients with COVID-19, and in particular pregnant women from the group with extremely severe course of the infection, had Cesarean delivery in the past medical history statistically significantly more often – 81 (16.8%), 153 (21.3%), 35 (23.8%), 10 (47.6%), 4 (4.4%) cases in group 1-5, respectively (p_{1-5}<0.001; $p_{1,2}$=0.054; $p_{1,3}$=0.055; $p_{1,4}$=0.001; $p_{1,5}$=0.002; $p_{2,3}$=0.503; $p_{2,4}$=0.013; $p_{2,5}$<0.001; $p_{3,4}$=0.021; $p_{3,5}$<0.001; $p_{4,5}$<0.001; p_{mc}<0.001).

Patients with COVID-19, in particular those from group 2 and 3 of the study, had therapeutic abortions in the past medical history statistically significantly more often – 119 (24.7%), 226 (31.5%), 50 (34.0%), 6 (28.6%), 16 (17.8%) pregnant women in group 1-5, respectively (p_{1-5}=0.008; $p_{1,2}$=0.011; $p_{1,3}$=0.026; $p_{1,4}$=0.687; $p_{1,5}$=0.156; $p_{2,3}$=0.548; $p_{2,4}$=0.777; $p_{2,5}$=0.007; $p_{3,4}$=0.621; $p_{3,5}$=0.007; $p_{4,5}$=0.360; p_{mc}=0.019). As for the frequency of various gynecological pathologies, then, in general, there were no statistically significant differences in the studied groups (p_{1-5}=0.799; p_{mc}=0.604).

Conclusion. Thus, increase in the median age with increasing infection severity is typical of the pregnant women with COVID-19 in comparison to pregnant women without COVID-19. Pregnant women with severe and extremely sever course of COVID-19 are statistically significantly more often have legal marriage and reside in big industrial cities. Smoking is statistically significantly more often registered among pregnant women with mild and moderate COVID-19. As for the somatic diseases, then pregnant women with COVID-19 in general, and pregnant women with severe and extremely severs course of the infection more often have circulatory system diseases (CAH, VVLE), endocrine system diseases, nutrition and metabolic disorders (DM, obesity, excess body weight), chronic anemia.

The increase in the frequency of obesity correlated statistically significantly with the increase in the severity of COVID-19. SLE is observed statistically significantly more often in pregnant women with extremely severe COVID-19. High frequency of the polypathia is a specific feature of the extremely severe course of the infection in pregnant women. The number of multigravida, multiparous women increases statistically significantly with the severity of COVID-19. On the whole, patients with COVID-19 statistically significantly more often have Cesarean delivery in the past medical history. Women with moderate and severe COVID-19 statistically significantly more often have therapeutic abortions in past medical history.

Increase in the median age, frequency of somatic pathology (CAH, VVLE, excess body weight, obesity, hypothyroidism, SLE) and polypathia is charac-

teristic of the increase in the COVID-19 severity in pregnant women. Mild course of the infection occurs more frequently in primigravidas, moderate and severe ones – in pregnant women with deliveries and abortions in the past medical history, extremely severe – in multiparous women.

References

1. Voropaeva EE, 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. Itogovoe zayavlenie o rabote pyatnadcatogo soveshchaniya Komiteta Mezhdunarodnyh mediko-sanitarnyh pravil (2005 g.) po chrezvychajnoj situacii v svyazi s pandemiej [Internet]. 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 [Final statement on the work of the fifteenth meeting of the International Health Regulations Committee (2005) on the pandemic emergency [Internet]. 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]

3. Voropaeva EE, et al. Kliniko-laboratornye osobennosti i materinskie iskhody u beremennyh s kriticheskim porazheniem legkih pri COVID-19 [Clinical and laboratory features and maternal outcomes in pregnant women with critical lung damage in the COVID-19]. Ural'skij medicinskij zhurnal [Ural Medical Journal. 2024; 1: 90-103 (In Russ.).] DOI: 10.52420/2071-5943-2024-23-1-90-103.

4. Belokrinitskaya TE, et al. Materinskaya smertnost' i near miss pri novoj koronavirusnoj infekcii (COVID-19) u beremennyh Sibiri i Dal'nego Vostoka [Maternal mortality and critical conditions (near miss) in COVID-19 in pregnant women of Siberia and the Far East]. Problemy reprodukcii [Russian Journal of Human Reproduction. 2021; 5: 114-120 (In Russ.).] DOI: 10.17116/repro202127051114.

5. Morozov SP, et al. Prognozirovanie letal'nyh iskhodov pri COVID-19 po dannym komp'yuternoj tomografii organov grudnoj kletki [Prediction of lethal outcomes in COVID-19 cases based on the results chest computed tomography]. Tuberkulez i bolezni legkih [Tuberculosis and Lung Diseases. 2020; 6: 7-14 (In Russ.).] DOI: 10.21292/2075-1230-2020-98-6-7-14.

6. Sinchikhin SP, et al. Svyaz' mezhdu COVID-19 i zhelezodeficitnoj anemiej u beremennyh [Relationship between COVID-19 and iron deficiency anemia in pregnant women]. Ginekologiya [Gynecology. 2021; 6: 592-596 (In Russ.).] DOI: 10.26442/20795696.2021.6.201340.

7. Fus A.V., Podolinny G.I. Polipatii: v poiske faktorov etiopatogeneticheskih riskov [Polypathy: searching for etiopathogenetic risks factors]. Vestnik Rossijskogo universiteta druzhby narodov. Seriya: Medicina [RUDN Journal of Medicine. 2020; 2: 135-144 (In Russ.).] DOI: 10.22363/2313-0245-2020-24-2-135-144.

8. Ishchenko LS, 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]. Yakut Medical Journal. 2023; 1: 80-83 (In Russ.).] DOI: 10.25789/YMJ.2023.81.20.

9. Belokrinitskaya TE, 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]. Akusherstvo i ginekologiya [Obstetrics and Gynecology. 2022; 4: 47-54 (In Russ.).] DOI: 10.18565/aig.2022.4.47-54.

10. Smith ER, et al. Adverse maternal, fetal, and newborn outcomes among pregnant women with SARS-CoV-2 infection: an individual participant data meta-analysis. BMJ Glob Health. 2023; 8(1): e009495. DOI: 10.1136/bmjgh-2022-009495.

11. 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.

12. Allotey J, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ. 2020; 370: m3320. DOI: 10.1136/bmj.m3320.

13. La Verde M, et al. Maternal death related to COVID-19: A systematic review and meta-analysis focused on maternal co-morbidities and clinical characteristics. Int J Gynaecol Obstet. 2021; 154(2): 212-219. DOI: 10.1002/ijgo.13726.

14. Simons D, et al. The association of smoking status with SARS-CoV-2 infection, hospitalization and mortality from COVID-19: a living rapid evidence review with Bayesian meta-analyses (version 7). Addiction. 2021; 116(6): 1319-1368. DOI: 10.1111/add.15276.

15. Gallus S, et al. The role of smoking in COVID-19 progression: a comprehensive meta-analysis. Eur Respir Rev. 2023; 32 (167): 220191. DOI: 10.1183/16000617.0191-2022.

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IMPACT OF COVID-19 ON REMOTE CARDIOVASCULAR ENDPOINTS IN PATIENTS WITH SICK SINUS SYNDROME AND IMPLANTED PACEMAKER

SARS-CoV2, responsible for the COVID-19 pandemic, is still relevant for the medical system throughout the world. In addition to the effect on the respiratory system, cardiac manifestations of COVID-19 are also known in the acute and post-COVID-19 period, including known coronary heart disease, proarrhythmogenic effects including impact on sick sinus syndrome (SSS). Cardiovascular diseases including myocarditis, heart failure, tachyarrhythmias and myocardial infarction, where arrhythmias are widespread were detected among hospitalized patients with COVID-19.

Objective: To investigate the impact of COVID-19 incidence on long-term cardiovascular endpoints in patients with SSS with implanted pacemaker. Methods. In a retrospective, non-randomized, uncontrolled study, 447 patients with SSS were examined, of which 205 patients experienced and 242 - did not have COVID-19. The follow-up period was 30 months and the endpoints were cardiovascular death, myocardial infarction, stroke and cardiovascular hospitalization. Adverse cardiovascular events were monitored using the "Promed" electronic medical record system, as well as during follow-up examinations at the consultative and diagnostic clinic. **Results.** Comparison of the incidence of adverse cardiovascular endpoints in the COVID-19 and control groups showed no differences in all endpoints according to the Chi-square test ($p>0.1$), with the exception of frequency of myocardial infarction in the "COVID-19" ($p=0.040$). The close relationship between tachy-bradicardia, microvascular dysfunction and coronary artery disease, and at the same time the impossibility of modulating the heart rhythm in the presence of vegetative dysfunction and an established pacemaker assumed that autonomic dysfunction in post-COVID patients caused myocardial ischemia and, as a result, an increase of myocardial infarction rate. Conclusion. During long-term follow-up, COVID-19 in patients with SSS increased the risk of myocardial infarction.

Keywords: sinus node weakness syndrome, COVID-19, pacemaker, coronary artery disease, cardiovascular endpoints.

Introduction. SARS-CoV2, the well-known coronavirus responsible for the COVID-19 pandemic, continues to be relevant worldwide. Along with the impact of the disease on the respiratory system, there are also known cardiac manifestations of COVID-19. In addition to other cardiovascular diseases, including myocarditis, heart failure, tachyarrhythmias, and myocardial infarction (MI) [3,13], arrhythmias are widespread among hospitalized patients with COVID-19 [8]. Tachyarrhythmias are the most common rhythm disorders. Scientific publications about bradyarrhythmia, including sinus and atrioventricular node dysfunctions are much less common, despite the fact that they are associated with a worser prognosis. Several observational studies and clinical cases have been published that do not provide data on the long-term prognosis of bradyarrhythmia and sinus node dysfunction in COVID-19 [3]. Recently published reports indicate the involvement of COVID-19 in heart's conduction system damage, especially in the sinoatrial node and atrioventricular node. Although the exact mechanism remains unclear, it is thought to be the result of hypoxemia, inflammation, or direct viral infiltration leading to impaired myocardial function [1-11]. Methods for treating bradyarrhythmia in patients with COVID, especially with regard to the reversibility of the process and the need for constant pacing, are not properly investigated. Despite implantation of pacemaker, mortality in patients with SSS remains high [6]. The clinical consequences of first-time bradyarrhythmia in patients with COVID-19 are unknown, and the treatment approach is controversial without understanding the short-and long-term outcomes [3].

Sinus sick syndrome syndrome (also known as sinus node dysfunction) is a medical condition characterized by a malfunction of the sinus node. This dysfunction can lead to heart failure and bradycardia. Sinus node weakness syndrome most often affects the elderly, but can affect all age groups. Causal factors can be divided into internal and external. Internal factors include idiopathic degenerative fibrosis, cardiomyopathy, and ischemia. External factors include medications, hypothyroidism, autonomic dysfunction, and electrolyte disturbances. Patients usually experience fainting or pre-fainting states, palpitations, dizziness, and fatigue. Treatment consists of eliminating the underlying causes and installing a pacemaker [1].

The aim of the study was to identify the impact COVID of COVID-19 morbidity on long-term cardiovascular endpoints in patients with sick sinus syndrome and an implanted pacemaker.

Materials and methods. In a retrospective longterm controlled study, a comparison of longterm cardiovascular endpoints was performed in patients with SSS and implanted pacemaker in the period from April 2020 по to December 2020. Implantation of the pacemaker was performed in the Department of Arrythmology in the Republic Cardiological Center (Ufa).

Inclusion criteria: established diagnosis of SSS, no indications for permanent

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pacemaker implantation, according to the Clinical Recommendations of Bradiarrhythmias and Conduction Disorders (2020) [2], voluntary informed consent, age 40-85 years old, absence of decompensation. Non-inclusion criteria: unstable coronary heart disease (CHD), MI for 3 months, and stroke for 3 months, chronic heart failure of the IV degree according to the NYHA classification, ejection fraction <35%, severe chronic concomitant diseases, and the presence of a malignant tumor for 5 years. The criterion for exclusion from the study was the patient's refusal to participate in the study.

A total of 607 patients were selected who were admitted during the COVID-19 pandemic and developed severe bradiarrhythmias requiring pacemaker implantation. For the analysis, two groups of patients with SSS were identified: the "COVID-19" group (*n*=205) and the "Control" group (*n*=242), which included patients who did not tolerate COVID-19 during the follow-up period. 160 patients were later completely excluded from the study with a diagnosis of acute respiratory viral infections, without confirmed COVID-19.

The diagnosis of COVID-19 was established based on the presence of detected SARS-CoV-2 RNA using nucleic acid amplification methods and / or detected SARS-CoV-2 class M and G immunoglobulins, in accordance with the current recommendations on COVID-19 of the Ministry of Health of the Russian Federation at the time of the study.

The following unfavorable events were selected as endpoints: MI, stroke, pulmonary embolism (PE), death, and cardiovascular hospitalization. Adverse cardiovascular events were monitored using the “Promed” electronic medical record system, as well as during follow-up examinations in the consultative and diagnostic polyclinic of the Republic Cardiologic Center for the period of 30 months from April 2020 to June 2024.

To analyze the main clinical and demographic characteristics of SSS patients, continuous numerical features were presented in the form of median *Me* and interquartile range (Q1-Q3), for nominal features in the form of absolute and relative frequency (%). Frequency differences were evaluated using nonparametric criteria: for continuous numerical features – the Mann-Whitney criterion, for categorical features – the "Chi-square" criterion with the Yates correction for the rarity of events (if necessary). Differences were considered statistically significant if the significance level of rejecting the null hypothesis of no differences in

Table 1

Clinical and instrumental characteristics of patients with SSS

Sign	of COVID-19 (*n*=205)	Control (*n*=242)	*p*-level of differences
Representation of continuous features: median and interquartile range interquartile			
range of LV EF	62 (58. 64)	62 (58. 64)	0.637
LA	39 (37. 42)	39 (37. 42)	0.879
RV	23 (22. 25)	24 (22. 25)	0.878
BMI	28.2 (25.1 – 32.1)	27.7 (24.7 -30.6)	0.176
Representation of categorical features: absolute frequency and relative frequency (%)			
AH	193 (94.2)	230 (95)	0.988
AF	87 (42.4)	93 (38.4)	0.390
DM	37 (18.1)	38 (15.7)	0.509
CKD	32 (15.6)	35 (14.5)	0.735
IHD	199 (96.6)	238 (98.3)	0.558†
PMIC	40 (19.5)	47 (19.4)	0.981
CHF	198 (96.6)	234 (96.7)	0.842†
stroke in history	19 (9.3)	25 (10.3)	0.708
COPD+ Bronchial Asthma	10 (4.9)	7 (2.9)	0.275
stenting	53 (25.8)	47 (19.4)	0.104

Note: AH – arterial hypertension, CHD – coronary heart disease, BMI – body mass index, LA – anterior-posterior size of the left atrium, - acute cerebrovascular мозгового accident, RV-basal diameter of the right ventricle, PMIC - postmyocardial infarction cardiosclerosis, DM - diabetes mellitus, LV EF-left ventricular ejection fraction, AF – atrial fibrillation, CKD - chronic kidney disease, COPD-chronic obstructive pulmonary disease, CHF-chronic heart failure; † - the "chi-square" test was performed with the Yates correction.

Table 2

Comparison of end point frequencies in patients in the study groups

End point	COVID-19 endpoint (n=205), %	Control (n=242), %	p
Death All-cause death	26 (12.7)	27 (11.2)	0.620
CV death	15 (7.3)	19 (7.9)	0.832
CV hospitalization	71 (34.6)	94 (38.8)	0.359
MI	**24 (11.7)**	**15 (6.2)**	**0.040***
Stroke	14 (6.8)	18 (7.4)	0.804
AF	34 (16.6)	38 (15.7)	0.801
PE	0 (0)	1 (0.4)	0.934†

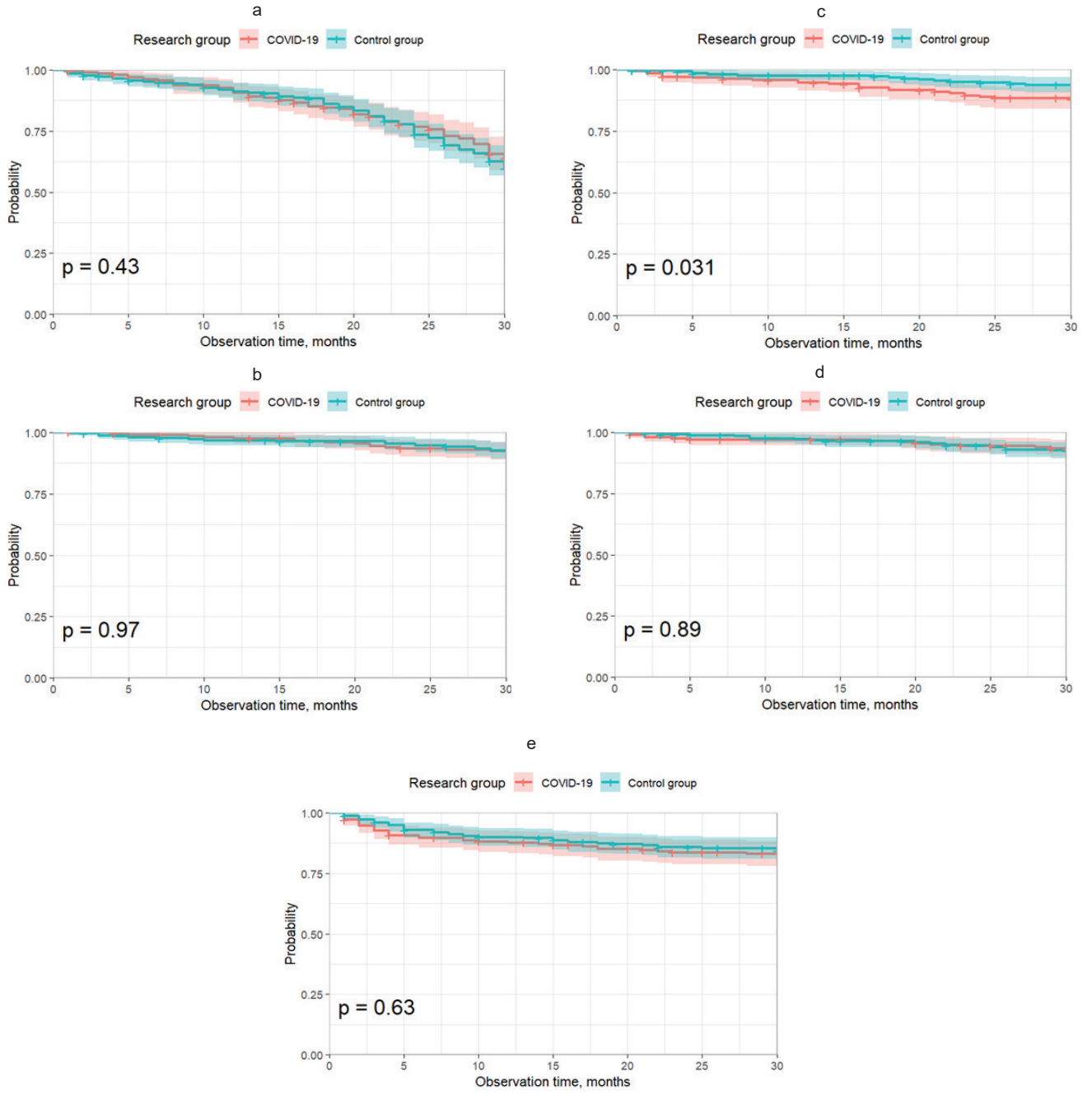
Note: MI – myocardial infarction, PE – pulmonary embolism, AF- new-onset atrial fibrillation, CV hospitalization – cardiovascular hospitalization, CV death – cardiovascular death;† - the chi-square test was performed with the Yates correction. * - differences are statistically significant at p<0.05

Table 3

Results of the Gehan-Wilcoxon test comparing the duration of the period before the end point in patients in the study groups

Endpoint	Number of censored observations		*p*-level
	of COVID-19 differences (*n*=205)	Control (*n*=242)	
CV death	11	8	0.431
CV hospitalization	17	20	0.968
MI	**9**	**10**	**0.031***
Stroke	11	11	0.890
AF	6	8	0.627

Note: MI – myocardial infarction, AF-new-onset atrial fibrillation, CV hospitalization – cardiovascular hospitalization, CV death – cardiovascular death; * - differences are statistically significant at p<0.05.



Kaplan-Meier curves with confidence intervals according to the Greenwood form for end points: a - cardiovascular hospitalization; b - death due to cardiovascular causes; c - myocardial infarction; g - stroke; e - newly diagnosed atrial fibrillation for patients with CVS in the COVID-19 group and the control group during an observation period of 30 months

the study groups was $p<0.05$. The study of differences in the duration of the period before the onset of adverse cardiovascular endpoints in patients with SSS, depending on the presence of a history of COVID-19, was carried out using a survival analysis. In particular, we used Kaplan-Meier multiplication scores with an estimate of the confidence interval for them using the Greenwood formula, and also performed the Gehan-Wilcoxon test for differences in survival. When finding Kaplan-Meier estimates for the endpoints of cardiovascular hospitalization, MI, stroke, atrial fibrillation, censored events were the patient's death before the follow-up period (30 months), for cardiovascular mortality, censored events were deaths from other causes before the end of the follow-up period.

The study was conducted in accordance with the standards of Good Clinical Practice and the principles of the Helsinki Declaration. The study protocol was approved by the Local Ethics Committee of the Bashkir State Medical University of the Ministry of Health of the Russian Federation, Meeting No. 9 of 17.12.2021. Prior to inclusion in the study, all participants received written voluntary informed consent.

Results. Table 1 shows the results of the analysis of clinical and demographic characteristics of patients with SSS in the "COVID-19" (n=205) and "Control" (n=242) groups. As can be seen, the groups did not differ in gender and age composition, the age of patients in the COVID-19 group was 73 (66, 80) years, and in the Control group - 73 (67, 81), according to the main indicators of the structure and functions of the heart