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Research article

THE RISK OF DEVELOPING SEVERE CLINICAL FORMS OF COVID-19 IN HEALTHCARE WORKERS IN THE INITIAL PERIOD OF THE PANDEMIC: NON-OCCUPATIONAL FACTORS AND LABORATORY PROGNOSTIC INDICATORS

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Under the COVID-19 pandemic, healthcare workers were at the highest risk of getting infected with the disease; this necessitates specialized studies in this occupational group.

The aim of the study was to identify non-occupational risk factors and laboratory markers indicating that severe clinical forms of new coronavirus infection would probably develop in healthcare workers in the initial period of the pandemic.

The study included 366 workers who suffered COVID-19 in 2020–2021. The disease was confirmed by examining smears from the pharynx and nose with PCR. Some of the samples were examined using the SARS-CoV-2 whole genome sequencing technology. To determine laboratory prognostic indicators evidencing the development of more severe forms of the disease (pneumonia), a number of healthcare workers underwent laboratory examination during the acute period of the disease, namely: general clinical and biochemical blood tests, immunophenotyping of lymphocytes, analysis of the hemostasis system and cytokine levels. To study non-occupational risk factors of pneumonia, all healthcare workers after recovery were asked to fill in a Google form developed by the authors.

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The most severe clinical forms of COVID-19 were registered in healthcare workers who were older than 40 years, with low physical activity and a body mass index higher than 25.0, had diabetes mellitus and chronic diseases of the genitourinary system.

When analyzing the results of laboratory tests, markers indicating development of pneumonia were identified and their critical values (cut-off points) were determined: the level of lymphocytes (below 1.955·109/l), T-cytotoxic lymphocytes (below 0.455·109/l), T-helpers (below 0.855·109/L), natural killers (below 0.205·109/l), platelets (below 239·109/L), erythrocyte sedimentation rate (above 11.5 mm/h), D-dimer (above 0.325 mcg/ml), total protein (below 71.55 g/L), lactate dehydrogenase (above 196 U/L), C-reactive protein (above 4.17 mg/l), and interleukin-6 (above 3.63 pg/l).

The study identified non-occupational risk factors causing development of severe COVID-19 and established laboratory prognostic indicators.

Keywords: *coronavirus infection, COVID-19, healthcare workers, clinical manifestations, non-occupational risk factors, laboratory markers, prognostic indicators of severe clinical forms.*

The new coronavirus infection (COVID-19) was first detected at the end of 2019 in Wuhan, the People's Republic of China. Over the next few months, it spread rapidly all over the world bringing about significant social and economic losses everywhere it occurred. According to the official statistical data, on January 01, 2023 there were more than 650 million COVID-19 cases registered all over the world and more than 6.5 million deaths caused by the disease[1] [1, 2].

Since the pandemic started, healthcare experts worldwide have been actively investigating the new infection, its epidemiological, clinical and immune-pathological features; they have been developing and implementing new drugs to effectively prevent and treat it [3–8]. This research is especially significant when it comes down to people from occupational groups with higher risks of SARS-CoV-2, healthcare workers included. The latter were the first to face this new disease and became a population group that has suffered the greatest damage. The COVID-19 incidence among healthcare workers has been substantially higher against any other occupational group during all the periods in the pandemic [9–11].

Some studies showed that healthcare workers had several leading risk factors of getting infected with the new coronavirus infection due to their occupational activity. These factors included contacts with infected patients, how close and how long these contacts were, necessity to work with infected biomaterials, insufficient provision with personal protective equipment (PPE) and PPE defects, absence of qualitative instructions prior to work with patients infected with SARS-CoV-2 etc. It is noteworthy that clinical forms with lung involvements were just as frequent in this occupational group as in population in general [11–13].

We should bear in mind that healthcare workers have a specific sex, age, somatic and behavioral 'profile' just as employees of any other organization. Therefore, it is necessary to examine not only occupational risk factors of getting infected but also non-occupational ones in order to identify those able to cause infection and severe clinical course of the disease in future.

Without any doubt, priority tasks the public healthcare has to tackle nowadays are to provide safety for healthcare workers, to develop the most effective prevention programs and new treatment and rehabilitation protocols for them.

Given all the aforementioned, today there is a need in studies that address both clinical COVID-19 symptoms in healthcare workers and non-occupational risk factors of severe clinical forms of the disease as well as studies aimed at identifying laboratory indicators that can be used in clinical practice as markers of the infection clinical course and its outcome.

In this study, our aim was to identify non-occupational risk factors and laboratory markers indicating that severe clinical forms of new coronavirus infection would probably develop in healthcare workers in the initial period of the pandemic.

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[1] Statistika koronavirusa v mire [World coronavirus statistics]. *GOGOV*. Available at: https://gogov.ru/covid-19/world (January 01, 2023) (in Russian).

Materials and methods. The study was accomplished in 2020–2021 during the first and second epidemic rises in the COVID-19 incidence in the Russian Federation. The study design was approved by the Local Committee on Ethics of the European medical center 'UMMC-Health' (The Meeting Report No. 1e dated June 02, 2020). Participation in the study was voluntary and each participating healthcare worker gave a written informed consent to it.

The study included 366 healthcare workers who lived in the Sverdlovsk region and was diagnosed with COVID-19. Among the participants, there were 110 doctors (30.0 %), 93 nurses and 28 hospital attendants (25.4 and 7.7 %, accordingly), 40 administrative and managerial staff (10.9 %), as well as 95 utility workers and technicians (25.9 %). The participants' age varied between 18 and 70 years (the median age was 38 years). Most respondents were women (305 or 83.3 %).

Eighty-five healthcare workers (23.2 %) who had the diseases as pneumonia were included into the test group; the remaining 281 (76.8 %) who had it as an acute respiratory infection (ARI) were included into the reference group. There were no deaths among the participants. The COVID-19 was diagnosed in accordance with the Temporary Methodical Guidelines on Prevention, Diagnostics and Treatment of the New Coronavirus Infection (COVID-19) (Versions 6–8).

To confirm the diagnosis and to later estimate how long the SARS-CoV-2 virus persisted in the body, each healthcare worker had several PCR-tests with a 3–5 day interval between them to detect the virus RNA in smears from the pharynx and nose (2356 samples were tested overall). The tests were performed in the PCR laboratory of the European medical center 'UMMC-Health' using test-systems produced by Saint Petersburg Pasteur Institute, MEDIPALTECH LLC, DNK-Tekhnologia TS LLC and Vector-Best JSC. We analyzed a correlation between the threshold cycle value (Ct) that described a viral load and the disease severity as well as a period in the disease progression. Samples with their Ct value being lower than 30 were sent to Smorodintsev Research Institute of Influenza of the RF Public Healthcare Ministry (the laboratory for molecular virology) where the whole genome sequencing of SARS-CoV-2 was performed (58 samples). These tests were performed using the new-generation genome sequencing (NGS) with Illumina MiSeq device and ARTIC Network modified sequencing protocol. The obtained sequences were aligned with MAFFT v7.453 and deposited in an international (EpiCov GISAID[2]) and Russian (VGARus[3]) virus genome aggregator.

In an acute period in the disease, several healthcare workers underwent additional laboratory tests, 168 people overall including 67 with pneumonia (the test group) and 119 with acute respiratory infection (the reference group). The laboratory tests included total blood count, immune phenotyping of leucocyte sub-populations with flow cytometry (T-lymphocytes including T-helpers and cytotoxic T-lymphocytes, CD-index, B-lymphocytes, NK-cells and TNK-cells), some chemical indicators (amylase, alkaline phosphatase, alanine transaminase (ALT), aspartate transaminase (AST), lactate dehydrogenase (LDH), creatinine kinase (CK), glucose, total protein, creatinine, cholesterol, total bilirubin, urea, C-reactive protein (CRP)), homeostasis indicators (D-dimer) and some cytokines (interferons IFN-α, IFN-β, IFN-γ, C9-components in the complement system, TNF-α, interleukin IL-1β, IL-6, IL-10) identified with ELISA. All the healthcare workers had several points of laboratory control (from one to four). The total number of tests equaled 304 laboratory units (205 in the test group and 99 in the reference one) for total blood count and biochemical blood test; 286 units (195 in the test and 91 in the reference group) for immune phenotyping of lymphocytes; 101 units (49 in the test and 52 in the

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[2] GISAID: database. Available at: https://www.gisaid.org (December 01, 2022).
[3] VGARus (Virus Genome Aggregator of Russia): the Russian platform for aggregating information about virus genomes. Available at: https://genome.crie.ru/app/index (December 19, 2022).

reference group) to estimate D-dimer levels; 288 units (190 in the test and 98 in the reference group) to estimate IL-6 levels in the cytokine profile and 84 units (43 in the test and 41 in the reference group) to estimate other indicators in it (IL-1β, IL-10, TNF-α, IFN-α, IFN-β, IFN-γ). Units of measurement and reference values of the analyzed indicators are provided in Table 2. Laboratory tests were accomplished in the clinical and diagnostic laboratory of the European medical center "UMMC-Health" using Sysmex XN 1000 and Roller 20 PN / ALIFAX hematology analyzers, Beckman Coulter AU680 clinical chemistry analyzer, STA Compact Max homeostasis analyzer (DIAGNOSTICA STAGO S.A.S., France), BD FACSCanto II flow cytometer; all the tests relied on using original reagents provided by the manufacturers of the equipment. Cytokines were analyzed with Cobas e411 (Roche, Switzerland) with original reagents Elecsys IL6, Thermo Scientific Well-Wash automated microplate washer, IEMS incubator / shaker, Multiskan Ascent microplate reader and the following reagents: Human Complement C9 ELISA Kit, VeriKine Human IFN Beta ELISA Kit, Human IFN gamma ELISA Kit, Human IFNα ELISA Kit, Human TNFα ELISA Kit, Human IL-1β ELISA Kit, Human IL-10 ELISA Kit.

To examine clinical symptoms and identify non-occupational risk factors of severe COVID-19, all the participants were offered to fill in a Goggle form developed by the authors to clarify some clinical data and medical records. This Google form was made of 66 questions combined into several information blocks, namely personal details, potential risk factors (anthropometric parameters, blood group and Rh factor, intake of antiviral drugs, smoking, alcohol intake, physical activity, doing sports, chronic diseases, vaccination against several communicable diseases), clinical COVID-19 symptoms, therapy-related issues, consequences of the disease and rehabilitation. When analyzing vaccination records (hepatitis B, diphtheria, tetanus, measles, rubella, flu, and pneumococcal infection), we additionally took data from the participants' vaccination certificates.

The study involved using epidemiological, clinical, immunological, molecular-genetic and statistical methods. We estimated how data were distributed based on Shapiro – Wilk test and Kolmogorov – Smirnov test. Quantitative data were given by median (Me), the first and third quartiles (Q1–Q3), minimum and maximum values (Min–Max); categorical data were given by a share and frequency in percent (%). When comparing quantitative indicators, we estimated statistical significance of differences with Mann – Whitney test; categorical indicators were compared with chi-square test (χ^2). Correlations between indicators were analyzed as per Spearman's coefficient and estimated as per the Chaddock scale. Differences were considered statistically significant at $p \leq 0.05$. Probability of an outcome depending on impacts of various risk factors was estimated by drawing up a fourfold contingency table and calculating odds ratio (OR) with 95 % confidence interval (95 % CI). We created ROC-curves to identify laboratory markers of severe COVID-19 forms and their threshold values. Only prognostic models with statistical significance ($p < 0.05$) as well as those with specificity and sensitivity higher than 50 % were considered in the study. All the data were statistically analyzed with Microsoft Office 2016 and IBM SPSS Statistics, Version 26.

Results. The respondents most often mentioned the following clinical COVID-19 symptoms typical for any ARI: running nose (211 or 57.7 %); cough (189 or 50.3 %), which was non-productive (dry) in most cases (up to 85 %), as well as sore throat (133 or 36.3 %); 'tightness' and pain in the chest (101 or 27.6 %); shortness of breath (80 or 21.9 %). Among general infection symptoms, many healthcare workers mentioned apparent weakness and elevated fatigability (289 or 79.0 %), muscle and joint pains (188 or 51.3 %) and fever (279 or 76.2 %) which did not exceed 37.5 °C in 47.7 % of the cases, varied between 37.5–38.5 °C in 33.7 % and was higher than 38.5 °C in 18.6 % of the cases. Some healthcare workers had neurological symptoms in-

cluding anosmia (265 or 72.4 %), headache (210 or 57.4 %) and not so frequent dizziness (83 or 22.7 %) and eyeball pains (97 or 26.5 %). In other cases, gastrointestinal tract was involved since the participants had some dyspeptic symptoms including qualms or retching (37 or 10.1 %), diarrhea (66 or 18.0 %), changes or losses of taste (176 or 48.0 %). In some rare cases, the participants mentioned some skin symptoms including skin rush with various morphological elements, loss of coordination, excessive sweating, heart rhythm disorders, acute sense of smell, metallic taste in the mouth, cramps in lower extremities and sleeping disorders. In singleton cases, the disease involved panic attacks, elevated anxiety and irritability or apathy.

Clinical symptoms of the coronavirus infection could persist for 1–28 days in the infected healthcare workers ($Me = 10$ days). Together with investigating clinical symptoms of the disease, this study involved estimating a viral load by analyzing the threshold cycle value in PCR in different periods of the disease and in different clinical forms as well as duration of the SARS-CoV-2 virus persistence in patients' bodies. We established that the Ct value did not have any statistically significant differences in workers with different clinical forms of COVID-19: the median Ct value equaled 24.8 in the participants who had COVID-19 as ARI and 26.6 in those who had pneumonia ($p = 0.136$). It was noted that an increase in the threshold cycle value (a decline in a viral load) occurred simultaneously with progression of the disease; Spearman's correlation coefficient between the Ct value and a day in the disease equaled 0.410 (the direct moderate correlation according to the Chaddock scale), $p < 0.001$.

After major COVID-19 symptoms disappeared, most healthcare workers still had the virus RNA in their smears from the pharynx and nose detected by PCR-tests. This indicated they were still 'epidemiologically dangerous' as potential sources of the virus and they could not be allowed to return to their workplaces since they could still spread the infection. Bearing in mind that the SARS-CoV-2 virus persisted in the infected healthcare workers for a long time, their absence from a workplace varied between 13 and 45 days (the median absence equaled 22 days). Different periods during which the virus was excreted into the environment were established for different clinical forms of the disease. Thus, when COVID-19 progressed as ARI, this period varied between 13 and 34 days ($Me = 21$ days); when the lungs were involved, between 14 and 45 days ($Me = 24$ days). Whole-genome sequencing of the SARS-CoV-2 virus from the infected healthcare workers established B.1.1 to be the prevailing strain in the first and second epidemic rises in the incidence (up to 50 % of the analyzed samples); such genetic variants as B.1, B.1.1.397, B.1.1.317, B.1.1.387, B.1.1.409, B.1.1.141, B.1.1.274 were identified in most remaining cases and several others were identified in singleton cases.

Next, we analyzed non-occupational risk factors that could cause severe forms of the coronavirus infection in the examined healthcare workers (Table 1). We established a statistically significantly higher risk of the severe disease for healthcare workers older than 40 years, with BMI indicating overweight (higher than 25.0) and with low physical activity due to absence of any regular training. Sex, blood group, Rh-factor, smoking and alcohol intake, intake of various antiviral drugs and vitamins were not identified as potential risk factors of pneumonia for the examined healthcare workers. Among chronic diseases, genitourinary pathology and diabetes mellitus had certain influence on a probability that the disease would progress in its severe form with the lung involvement. Our analysis of vaccination records did not establish any effects produced by previous vaccinations against hepatitis B, diphtheria, tetanus, measles, rubella, flu, and pneumococcal infection on a risk of pneumonia in patients infected with SARS-CoV-2.

The next stage in the study involved laboratory tests; the examined healthcare workers gave their consent to them. The test results are given in Table 2.

Table 1

Risk factors causing COVID-19 pneumonia in healthcare workers

No.	Risk factor	COVID-19 clinical form				OR	95 % CI	χ^2	p
		Pneumonia (test group)		ARI (reference group)					
		abs	%	abs	%				
1	2	3	4	5	6	7	8	9	10
1	**Age, years**								
1.1	18–19	0	0.0	2	0.7	–	–	–	–
1.2	20–29	10	11.8	61	21.7	0.48	0.23–0.99	4.13	**0.043**
1.3	30–39	22	25.9	105	37.4	0.59	0.34–1.01	3.79	0.052
1.4	40–49	31	36.5	66	23.5	1.87	1.11–3.15	5.65	**0.018**
1.5	50–59	16	18.8	35	12.4	1.63	0.85–3.12	2.21	0.138
1.6	Older than 60 years	6	7.0	12	4.3	1.70	0.62–4.68	1.09	0.298
1.7	*Older than 40 years	53	62.4	113	40.2	2.46	1.49–4.01	12.91	**<0.001**
2	**Sex**								
2.1.	Men	17	20	43	15.3	1.38	0.74–2.58	1.05	0.306
2.2	Women	68	80	238	84.7	0.72	0.39–1.35	–	–
3	**Body mass index**								
3.1	Below 18.5	2	2.4	18	6.4	0.35	0.08–1.55	2.08	0.150
3.2	18.5–24.9	37	43.5	147	52.3	0.70	0.43–1.15	2.01	0.156
3.3	25–29.9	28	32.9	79	28.1	1.26	0.75–2.17	0.74	0.392
3.4	30–34.9	12	14.1	25	8.9	1.68	0.81–3.51	1.96	0.162
3.5	35–39.9	6	7.1	11	3.9	1.86	0.67–5.20	1.46	0.228
3.6	Above 40	0	0.0	1	0.4	–	–	0.30	0.582
3.7	*Above 25	116	41.3	46	54.1	1.678	1.030–2.734	4.36	**0.037**
4	**Blood group**								
4.1	0	28	32.9	95	33.8	0.96	0.57–1.61	0.02	0.883
4.2	A	28	32.9	109	38.8	0.78	0.46–1.29	0.95	0.329
4.3	B	20	23.5	52	18.5	1.36	0.76–2.43	1.04	0.308
4.4	AB	9	10.6	25	8.9	1.21	0.54–2.71	0.22	0.638
5	**Rh-factor**								
5.1	Rh+	72	84.7	236	84.0	1.06	0.54–2.07	0.03	0.874
5.2	Rh-	13	15.3	45	16.0	0.95	0.48–1.85		
6	**Blood group and Rh-factor**								
6.1	0, Rh+	24	28.2	80	28.5	0.99	0.58–1.69	0.002	0.967
6.2	0, Rh-	4	4.7	15	5.3	0.88	0.28–2.71	0.05	0.818
6.3	A, Rh+	25	29.4	91	32.4	0.87	0.51–1.48	0.27	0.606
6.4	A, Rh-	3	3.5	18	6.4	0.65	0.18–2.29	0.99	0.318
6.5	B, Rh+	16	18.8	44	15.7	1.25	0.66–2.35	0.48	0.490
6.6	B, Rh-	4	4.7	8	2.8	1.69	0.49–5.74	0.71	0.400
6.7	AB, Rh+	7	8.2	21	7.5	1.11	0.46–2.71	0.05	0.817
6.8	AB, Rh-	2	2.4	4	1.4	1.67	0.30–9.27	0.35	0.555
7	**Intake of various antiviral (prevention) drugs**								
7.1	No regular intake of polyvitamins	54	63.5	183	65.1	0.22	0.13–0.36	0.07	0.788
7.2	No regular intake of vitamin C	77	90.6	255	90.7	0.98	0.43–2.26	0.002	0.965
7.3	No regular intake of vitamin D	72	84.7	228	81.1	1.29	0.66–2.49	0.56	0.454
7.4	No regular intake of zinc	82	96.5	267	95.0	1.43	0.40–5.11	0.31	0.578
8	**Bad habits**								
8.1	Smoking	15	17.6	61	21.4	0.77	0.41–1.45	0.65	0.419
8.2	Alcohol intake	67	78.8	233	82.9	0.77	0.42–1.41	0.74	0.390

End of the Table 1

1	2	3	4	5	6	7	8	9	10
9	**Doing sports and overall physical activity**								
9.1	No sports or training	58	68.2	153	54.5	1.79	1.08–3.01	5.08	**0.025**
9.2	Insufficient physical activity (less than 5000 steps a day)	23	32.9	53	72.6	1.56	0.87–2.81	2.27	0.132
10	**Chronic diseases**								
10.1	Cardiovascular pathology	14	16.5	35	12.5	1.39	0.71–2.72	0.91	0.341
10.2	Bronchopulmonary pathology	7	8.2	17	6.0	1.39	0.56–3.48	0.51	0.476
10.3	Diseases of the nervous system	7	8.2	14	5.0	1.71	0.67–4.39	1.28	0.259
10.4	Gastrointestinal pathology	24	28.2	64	22.8	1.33	0.77–2.31	1.07	0.303
10.5	Genitourinary pathology	14	16.5	16	5.7	3.27	1.52–7.01	10.07	**0.002**
10.6	Diabetes mellitus	5	5.9	1	0.4	17.5	2.02–151.96	12.36	**<0.001**
10.7	Oncological diseases	1	1.2	3	1.1	1.10	0.11–10.75	0.01	0.933
10.8	Autoimmune diseases	2	2.4	7	2.5	0.94	0.19–4.63	0.01	0.943
10.9	Allergic diseases	7	8.2	34	12.1	0.65	0.29–1.53	0.98	0.323
10.10	Herpesviral infection	7	8.2	20	7.1	1.17	0.48–2.82	0.12	0.730
10.11	Pregnancy	0	0.0	6	2.1	–	–	1.845	0.175
11	**Vaccinations against**								
11.1	Viral hepatitis B	85	100.0	279	99.3	–	–	0.61	0.436
11.2	Diphtheria	85	100.0	279	99.3	–	–	0.61	0.436
11.3	Tetanus	85	100.0	279	99.3	–	–	0.61	0.436
11.4	Measles	85	100.0	280	99.6	–	–	0.30	0.582
11.5	Rubella	63	74.1	230	81.6	0.64	0.36–1.13	2.44	0.118
11.6	Pneumococcal infection	7	8.2	45	16.0	0.47	0.20–1.09	3.24	0.072
12	**Flu vaccination**								
12.1	Regular	40	47.1	142	50.5	0.87	0.54–1.41	0.32	0.575
12.2	Periodical	34	40.0	95	33.8	1.31	0.79–2.15	1.09	0.296
12.3	No vaccination	11	12.9	44	15.7	0.80	0.39–1.63	0.377	0.540

Table 2

The results of laboratory tests obtained for healthcare workers with different clinical forms of COVID-19

№	Indicator	Units of measurement	Reference levels	COVID-19 clinical form						p
				Pneumonia (test group)			ARI (reference group)			
				Me	Q1–Q3	Min–Max	*Me*	Q1–Q3	Min–Max	
1	2	3	4	5	6	7	8	9	10	11
1.	**Total blood count**									
1.1	Leucocytes	$10^9/l$	4.5–10.2	5.81	4.63–7.26	1.84–37.73	5.42	4.56–6.81	2.66–9.62	0.104
1.2	Lymphocytes	$10^9/l$	1–6.5	1.49	0.99–2.15	0.15–4.61	1.97	1.58–2.37	0.68–3.94	**<0.001**
1.3	Neutrophils	$10^9/l$	1.8–7.7	3.23	2.27–4.73	0.54–34.07	2.74	1.85–3.65	1.03–5.44	**0.001**
1.4	Eosinophils	$10^9/l$	0–0.7	0.04	0.01–0.14	0.0–0.5	0.07	0.03–0.13	0.0–1.29	**0.014**
1.5	Basophils	$10^9/l$	0–0.2	0.02	0.01–0.03	0.0–0.53	0.03	0.02–0.04	0.01–0.3	0.099
1.6	Monocytes	$10^9/l$	0–0.95	0.50	0.35–0.69	0.12–1.45	0.51	0.41–0.68	0.25–1.49	0.243
1.7	Red blood cells	$10^{12}/l$	3.8–5.3	4.49	4.11–4.84	2.47–5.62	4.59	4.34–4.89	3.73–5.54	**0.010**
1.8	Hematocrit	%	34–47	39.5	36.5–42.4	23.5–52.2	39.5	37.0–43.3	30.8–47.9	0.332
1.9	Hemoglobin	g/l	115–155	137	126–147	74–175	137.5	128–152	96–166	0.21
1.10	Mean corpuscular hemoglobin concentration	g/l	310–370	347	338–354	279–379	348	341–354	303–372	0.497
1.11	Mean corpuscular hemoglobin contents	pg	26–34	30.6	29.7–31.4	22.6–35.1	30.3	29.1–31.1	20.8–31.0	0.055

End of the Table 2

1	2	3	4	5	6	7	8	9	10	11
1.12	Mean corpuscular volume	fl	73–101	87.7	85.5–90.2	72.6–107.1	86.7	83.7–89.4	68.6–97.3	**0.004**
1.13	Corpuscular anisocytosis	fl	37–54	40.9	39.2–44.6	34.2–71.0	40.0	38.5–42.2	33.2–47.0	**0.001**
1.14	Corpuscular anisocytosis, %	%	11.6–14.8	12.9	12.3–13.8	11.0–21.2	12.6	12.1–13.4	11.3–18.0	**0.044**
1.15	Normoblasts	10^9/l	0.03	0.0	0.0–0.003	0.0–0.3	0.0	0.0–0.0	0.0–0.01	**0.001**
1.16	Platelets	10^9/l	142–424	226	184–280	25–540	253	198–301	112–584	0.054
1.17	Mean platelet volume	fl	7–13	10.8	10.1–11.5	8.7–14.6	10.3	9.8–10.7	9.1–12.2	**<0.001**
1.18	Giant platelet count	%	13–43	30.5	25.3–36.5	15.0–56.8	27.3	22.3–30.8	16.9–42.6	**<0.001**
1.19	Platelet distribution width	fl	9–17	12.6	11.2–13.9	9.1–25.3	11.7	10.6–12.8	9.0–16.2	**<0.001**
1.20	Thrombocrit	%	0.17–0.35	0.24	0.19–0.29	0.06–0.59	0.25	0.20–0.30	0.12–0.56	0.162
1.21	ESR	mm/h	0–20	23	10–37	2–108	7	4–13	2–41	**<0.001**
2.	**CD-typing of lymphocyte sub-populations**									
2.1	T-lymphocytes	10^9/l	0.80–2.20	1.13	0.70–1.64	0.09–4.11	1.47	1.15–1.91	0.64–2.97	**<0.001**
2.2	T-helpers	10^9/l	0.60–1.60	0.69	0.41–0.97	0.01–1.93	0.92	0.71–1.12	0.36–1.98	**<0.001**
2.3	Cytotoxic T-lymphocytes	10^9/l	0.19–0.65	0.41	0.24–0.58	0.03–2.44	0.49	0.37–0.62	0.03–1.66	**<0.001**
2.4	CD-index	a.u.	1.0–2.5	1.70	1.20–2.50	0.0–4.80	1.85	1.40–2.40	0.30–4.10	0.203
2.5	NK-cells	10^9/l	0.15–0.60	0.15	0.09–0.24	0.02–1.57	0.24	0.17–0.34	0.06–0.97	**<0.001**
2.6	B-lymphocytes	10^9/l	0.10–0.50	0.16	0.11–0.25	0.0–0.83	0.19	0.13–0.26	0.07–0.53	**0.019**
2.7	TNK - cells	10^9/l	0.01–0.85	0.03	0.01–0.06	0.0–1.0	0.03	0.01–0.07	0.0–0.57	0.590
3	**Biochemical blood test**									
3.1	Alkaline phosphatase	U/l	30–120	62	51–78	25–243	63	52–76	29–174	0.942
3.2	Amylase	U/l	28–100	57	50–73	15–260	62	51–78	21–139	0.277
3.3	AST	U/l	6–36	27	21–35	13–109	21	19–27	11–66	**<0.001**
3.4	ALT	U/l	7–55	26	17–37	7–198	18	14–30	4–162	**<0.001**
3.5	CK	U/l л	0–171	81.5	51–148	11–3152	70	50–93	15–661	**0.016**
3.6	LDH	U/l	0–247	233	188–317	79–752	184.5	161–200	125–286	**<0.001**
3.7	Total protein	g/l	66–83	68.9	63.2–73.5	50.0–83.5	73.2	69.8–75.5	64.2–92.3	**<0.001**
3.8	Urea	mmol/l	2.8–7.2	5.0	3.9–7.9	2.5–69.4	4.4	3.7–5.0	2.1–8.9	**<0.001**
3.9	Total bilirubin	µmol/l	5–21	9.7	6.9–13.5	2.6–128.4	8.2	6.0–10.9	2.5–28.2	**0.002**
3.10	Cholesterol	mmol/l	1.8–5.2	4.1	3.4–4.9	1.7–9.1	4.4	3.8–5.1	2.7–7.7	0.058
3.11	Glucose	mmol/l	4.1–5.9	5.2	4.5–6.3	1.2–21.9	5.1	4.5–4.7	2.5–15.7	0.336
3.12	Creatinine	µmol/l	53–97	86	73–101	45.0–311.0	78	70–86	9.4–116.0	**<0.001**
3.13	CRP	mg/l	0–5	9.12	3.1–24.1	0.29–257.1	1.98	0.7–4.8	0.16–39.7	**0.001**
4	**Homeostasis indicators**									
4.1	D-dimer	µg/ml	0–0.5	0.40	0.27–0.59	0.10–1.80	0.29	0.21–0.37	0.06–2.0	**<0.001**
5	**Cytokine profile**									
5.1	IL-6	pg/ml	0–7	6.32	2.48–16.14	1.50–339.3	2.86	1.5–6.27	1.50–81.0	**<0.001**
5.2	IL-1β	pg/ml	0	0.0	0.0–0.0	0.0–15.0	0.0	0.0–0.0	0.0–0.49	0.721
5.3	IL-10	pg/ml	7.9–12.9	2.68	1.78–3.59	1.22–155.0	1.72	1.58–2.23	1.15–109.0	**0.018**
5.4	TNF-α	pg/ml	0	0.0	0.0–0.166	0.0–19.8	0.0	0.0–0.063	0.0–0.66	0.327
5.5	IFN-α	pg/ml	0	0.0	0.0–0.20	0.0–35.1	0.0	0.0–0.35	0.0–48.4	0.961
5.6	IFN-β	pg/ml	1.2–150	5.33	0.0–17.42	0.0–5645	2.29	0.0–19.76	0.0–7839	0.634
5.7	IFN-γ	pg/ml	0–188.9	0.0	0.0–0.0	0.0–35.6	0.0	0.0–0.0	0.0–1.0	0.052
5.8	C9-component in the complement system	µg/ml	43.7–53.9	67.1	37.8–125.0	5.86–300.0	40.9	26.6–59.4	10.24–123.4	**<0.001**

Having analyzed the laboratory test results, we established statistically significant differences in some indicators but not all of them had prognostic value. To identify prognostic laboratory markers, we performed ROC-analysis with creating ROC-curves, calculating areas under them (AUC) and identifying optimal classification thresholds (cut-off points) considering maximum sensitivity and specificity of the created models.

Creating ROC-curves for total blood count indicators revealed that erythrocyte sedimentation rate, levels of platelets and lymphocytes had prognostic value as regards predicting more severe COVID-19 forms.

The ROC-curve for ESR had the AUC equal to 0.759 ± 0.029 (95 % CI: 0.702–0.816), $p < 0.001$. ESR at the cut-off points was determined as equal to 11.5 mm/hour. The healthcare workers with ESR higher than 11.5 mm/hour were at a higher risk of pneumonia; in case ESR was below 11.5 mm/hour, this risk was low. The model sensitivity equaled 70.0 %; the model specificity, 72.4 %.

The ROC-curve built for the platelet level had the AUC = 0.566 ± 0.033 (95 % CI: 0.491–0.621), $p = 0.054$. The cut-off point for this indicator was determined as equal to $239 \cdot 10^9$/l. The healthcare workers with the platelet level lower than $239 \cdot 10^9$/l were at a higher risk of pneumonia; in case the platelet level was above $239 \cdot 10^9$/l, this risk was low. The model sensitivity equaled 55.5 %; the model specificity, 54.5 %.

The AUC for the ROC-curved built for the lymphocyte level equaled 0.671 ± 0.031 (95 % CI: 0.611–0.731), $p < 0.001$. The threshold value for the lymphocyte level was taken at $1.955 \cdot 10^9$/l. Lymphocyte levels below $1.955 \cdot 10^9$/l indicated elevated risks of pneumonia whereas levels higher than $1.955 \cdot 10^9$/l meant these risks were low. The model sensitivity and specificity equaled 67.0 % and 52.7 % accordingly.

The results obtained by immune phenotyping of lymphocytes made it possible to create statistically significant models ($p < 0.05$) with their specificity and sensitivity being higher than 50 % for relationships between a probability of COVID-19 pneumonia and levels of T-helpers, cytotoxic T-lymphocytes (CTL) and NK-cells.

The ROC-curve for T-helpers had the AUC = 0.675 ± 0.030 (95 % CI: 0.613–0.736), $p < 0.001$. The level of T-helpers at the cut-off point equaled $0.855 \cdot 10^9$/l. The healthcare workers with their level of T-helpers below $0.855 \cdot 10^9$/l were at a higher risk of pneumonia; in case the level was above $0.855 \cdot 10^9$/l, this risk was considered low. The model sensitivity equaled 64.9 %; the model specificity, 58.0 %.

The AUC of the ROC-curve for the relationship between likelihood of pneumonia and the number of cytotoxic T-lymphocytes (CTL) equaled 0.626 ± 0.033 (95 % CI: 0.561–0.690), $p < 0.001$. The threshold CTL value dividing the healthcare workers into groups with low and high likelihood of pneumonia equaled $0.455 \cdot 10^9$/l. If the CTL level was lower than $0.455 \cdot 10^9$/l, a risk of pneumonia was high; if the CTL levels exceeded $0.455 \cdot 10^9$/l, this risk was estimated as low. The model sensitivity equaled 61.1 %; the model specificity, 58.0 %

The AUC of the ROC-curve for NK-cells equaled 0.691 ± 0.031 (95 % CI: 0.630–0.752), $p < 0.001$. The threshold NK-cells level equaled $0.205 \cdot 10^9$/l. The NK-cells level below $0.205 \cdot 10^9$/l allowed estimating a risk of pneumonia as elevated and if this level was higher than $0.205 \cdot 10^9$/l, this risk was low. The model sensitivity equaled 65.4 %; the model specificity, 64.0 %.

Next, we analyzed the results of biochemical blood tests. Prognostic models with sufficient sensitivity, specificity and statistical significance were obtained for a relationship between likelihood of more severe COVID-19 forms and levels of total protein, C-reactive protein (CRP) and lactate dehydrogenase (LDH).

The AUC of the ROC-curve for total protein equaled 0.726 ± 0.029 (95 % CI: 0.618–0.784), $p < 0.001$. The level of total protein at the cut-off point was 71.55 g/l. the healthcare workers with the total protein level equal to or below 71.55 g/l were at an elevated

risk of pneumonia; the total protein level higher than 71.55 g/l indicated a low risk. The model sensitivity and specificity equaled 67.6 % and 66.7 % accordingly.

The ROC-curve for C-reactive protein had the AUC = 0.774 ± 0.027 (95 % CI: 0.720–0.827), $p < 0.001$. The threshold CRP level was equal to 4.17 mg/l. The healthcare workers with the CRP level higher than 4.17 mg/l were at an elevated risk of pneumonia; in case the CRP level was lower than 4.17 mg/l, a risk of more severe COVID-19 forms was low. The model sensitivity equaled 67.7 %; the model specificity, 69.5 %.

The ROC-curve for lactate dehydrogenase had the AUC = 0.754 ± 0.029 (95 % CI: 0.697–0.810), $p < 0.001$. The LDH level at the cut-off point equaled 196 U/l. the healthcare workers with the LDH levels higher than 196 U/l had an elevated risk of pneumonia; this risk was low in case the LDH levels was below 196 U/l. The model sensitivity equaled 68.4 %; the model specificity, 67.4 %.

The analysis of the D-dimer level in the healthcare workers with different clinical forms of the coronavirus infection identified the AUC value as equal to 0.711 ± 0.051 (95 % CI: 0.611–0.811) and the model was statistically significant ($p < 0.001$). The threshold D-dimer level equaled 0.325 μg/ml. The healthcare workers with the D-dimer level higher than 0.325 μg/ml were at an elevated risk of pneumonia; in case the D-dimer levels was below 0.325 μg/ml, this risk was considered low. The model sensitivity equaled 63.3 %; the model specificity, 63.5 %.

The next step in the study involved analyzing the cytokine profile of the examined healthcare workers. Statistically significant prognostic models ($p < 0.05$) with satisfactory sensitivity and specificity were obtained only for interleukin-6. The AUC of the ROC-curve for IL-6 equaled 0.658 ± 0.032 (95 % CI: 0.595–0.722). The relationship was statistically significant ($p < 0.001$). The IL-6 level at the cut-off point was equal to 3.63 pg/l. The healthcare workers with the IL-6 level exceeding 3.63 pg/l had an elevated risk of pneumonia and if the IL-6 level was lower than 3.63 pg/l, severe forms of the infection were less likely. The model sensitivity equaled 64.6 %; the model specificity, 64.5 %.

It is worth noting that the outlined threshold levels of the examined laboratory markers are within their reference ranges and it is vital to monitor these markers in dynamics when treating patients with COVID-19. They all have significant prognostic value and in case they tend to grow or decline against their cut-off points, it is necessary to assess risks of more severe COVID-19 forms and make relevant adjustments of a selected therapy.

Discussion. In this study, clinical symptoms of the coronavirus infection were analyzed in healthcare workers as a group with high occupational risks during the first and second COVID-19 pandemic 'wave' in the Russian Federation. Both waves developed predominantly due to B.1.1 SARS-CoV-2 genetic variant. We analyzed viral loads in dynamics during the disease and established how long the virus persisted in patients. The study also involved identifying non-occupational risk factors and prognostic laboratory indicators of more severe COVID-19 forms in healthcare workers.

Among non-occupational risk factors, we highlighted an age older than 40 years, low physical activity, BMI higher than 25 and some comorbidities. In general, our study results correlate well with data reported by some other authors; still, there are some nuances.

Thus, S. Molani and others [14] analyzed data on 6906 hospitalized adults with COVID-19 who were employed by public healthcare institutions in five western states in the USA. The authors reported elevated risks of the severe disease for people older than 50 years with high body mass index and in general this is in line with our findings. Although, our study established greater likelihood of pneumonia for people from occupational risks groups who were older than 40 years.

In their study, L. Kim with colleagues [15] analyzed data on 2491 adults hospitalized with confirmed COVID-19 in a period between March 01 and May 02, 2020. They took data from the COVID-NET, a hospital-based

surveillance system aimed to track COVID-19-associated hospitalization. It contains data provided by 154 emergency hospitals located in 74 counties of 13 states. The authors applied multifactorial analysis to estimate relationships between age, sex, and comorbidities and hospitalization in an intensive care unit (ICU) and in-hospital mortality. The following factors were established to be associated with hospitalization in ICU: age groups 50–64, 65–74, 75–84 and ≥ 85 years against an age group 18–39 years (adjusted risk rates (aRR) were 1.53, 1.65, 1.84 and 1.43 accordingly); male sex (aRR was 1.34); obesity (aRR was 1.31); immune suppression (aRR was 1.29) and diabetes mellitus (aRR was 1.13). Factors that made a death more probable included age of 50–64, 65–74, 75–84 and ≥ 85 years against 18–39 years (aRR was 3.11, 5.77, 7.67 and 10.98 accordingly); male sex (aRR was 1.30); immune suppression (aRR was 1.39); renal failure (aRR was 1.33); chronic bronchopulmonary diseases (aRR was 1.31); cardiovascular diseases (aRR was 1,28); neurological disorders (aRR was 1.25) and diabetes mellitus (aRR was 1.19). The data reported in this study correspond to our results as regards influence of age and certain comorbidities on a risk of more severe clinical forms of the coronavirus infection.

Another study was accomplished by J.Y. Ko with colleagues [16] using the COVID-NET database. They analyzed data on 5416 adults with the coronavirus infection and calculated adjusted rates of hospitalization frequency and their 95 % confidence intervals. Hospitalization was shown to be more frequent among people with three or more comorbidities (against their total absence) (5.0 [3.9–6.3]), severe obesity (4.4 [3.4–5.7]), chronic kidney disease (4.0 [3.0–5.2]), diabetes mellitus (3.2 [2.5–4.1]), essential hypertension (2.8 [2.3–3.4]) and bronchial asthma (1.4 [2.3–3.4]). This is interesting as regards complex analysis of simultaneous effects produced by several risk factors, which could be accomplished in future estimations of data on healthcare workers.

F. Zhou with colleagues [17] accomplished their study in Wuhan; it involved analyzing data on 191 patients, 137 of them re-covered and 54 died in hospital. Multifactorial regression analysis showed elevated likelihood of severe clinical forms, including fatal ones, for elderly people (OR = 1.10, 95 % CI: 1.03–1.17; p = 0.004) with higher scores in the Sequential Organ Failure Assessment (SOFA) (OR = 5.65, 95 % CI: 2.61–12.23; p < 0.001) and the D-dimer level higher than 1 µg/l (OR = 18.42, 95 % CI: 2.64–128.55; p = 0.003). This corresponds to our data as regards estimating a prognostic value of the D-dimer level in infected people but attention should be paid to the fact that its threshold level is lower for people from occupational risk groups with a certain age, sex and somatic 'profile'.

The systemic review coauthored by Y.-D. Gao with colleagues [18] confirmed several risk factors that could cause COVID-19 progression to its severe and even critical stage. These factors included older age; male sex; such comorbidities as essential hypertension, diabetes mellitus, obesity, chronic pulmonary diseases, heart, liver and kidney diseases, cancer, clinical immune deficiencies, local immune deficiencies such as early ability to secret type I interferon, and pregnancy. This corresponds to our study results as per some indicators (age and chronic diseases) identified for a specific population group with high occupational risks of infection.

It should be noted that male sex was a risk factor identified in all the studies outlined above but we did not have the same finding in our research. This is probably due to the sex-related profile of our participants, which corresponds to common sex structure of healthcare workers; probably, similar research should be accomplished on wider samples made of healthcare workers.

In addition, we were not able to establish any influence of blood groups and Rh-factors on the disease prognosis. Still, the issue has been discussed actively in other literature sources. According to the systemic review by Y. Kim and others [19], many studies report that the blood group (B) can indicate higher susceptibility to the SARS-CoV-2-induced infection and the blood group (0) and negative Rh-factors can act as protectors. The authors

also point out that effects produced by a blood group and Rh-factors on clinical outcomes remain unclear and probably there is no relationship between a blood group and the COVID-19 severity or mortality at the moment. Given that, the authors of the review do not recommend to use these indicators as prognostic markers when treating COVID-19 patients.

Analysis of patients' vaccination history was a significant issue in assessing risks of severe clinical forms of the disease. In our study, we did not identify any statistically significant influence of previous vaccinations against several communicable diseases on likelihood of pneumonia in the analyzed healthcare workers infected with the SARS-CoV-2 virus. This concerns vaccinations against viral hepatitis B, diphtheria, tetanus, measles, rubella, pneumococcal infection and flu. However, several studies reported that flu vaccination that was made in an epidemiological season prior to the disease reduced both risks of the infection and its more severe clinical forms. Thus, A. Conlon with colleagues [20] showed in their study that likelihood of getting infected with SARS-CoV-2 was lower among patients who were vaccinated against flu as compared with those who did not get flu vaccination ($OR = 0.76$, 95 % CI: 0.68–0.86; $p < 0.001$). COVID-19 patients with flu vaccination were less likely to need hospitalization ($OR = 0.58$, 95 % CI: 0.46–0.73; $p < 0.001$) or artificial ventilation ($OR = 0.45$, 95 % CI: 0.27–0.78; $p = 0.004$) and had to spend considerably less time in hospital ($OR = 0.76$, 95 % CI: 0.65–0.89; $p < 0.001$).

The study by M. Candelli with colleagues [21] established a lower risk of death over 60 days after getting infected with the coronavirus for patients who had previously been vaccinated against flu against those without flu vaccination ($p = 0.001$). The authors believe flu vaccination can possibly reduce the COVID-19 mortality.

We have come across some articles that estimated a relationship between flu vaccination and the COVID-19 incidence among healthcare workers [22, 23]. The first study was accomplished by N. Massoudi and others [22] in Iran in 2020 and analyzed data on 261 healthcare workers. The authors showed that flu vaccination in 2019 allowed reducing likelihood of the coronavirus infection among healthcare workers in 2020. However, N. Massoudi with colleagues assessed only the risk of getting infected but not the disease progression or risks of its more severe clinical forms. The other study was accomplished in Italy by M. Belingheri with colleagues [23] with analyzing data on 3520 healthcare workers. The authors could not establish any relationship between flu vaccination and the risk of getting infected with SARS-CoV-2.

Some studies focus on investigating a relationship between vaccination against pneumococcal infection and the COVID-19 incidence. The systemic review coauthored by several authors under supervision by H. Im [24] analyzed several studies that reported vaccination against pneumococcal infection to be able to prevent severe COVID-19 clinical forms by preventing incidence and mortality caused by comorbid / secondary infections and superinfections.

Another study [25] involved systemic reviewing and meta-analysis to estimate a relationship between seasonal flu vaccination, vaccination against pneumococcal infection and COVID-19 and its clinical outcomes. Overall, the meta-analysis covered 38 observational studies with significant heterogeneity. Flu vaccination and vaccination against pneumococci were associated with lower risks of getting infected with SARS-CoV-2 ($OR = 0.80$, 95 % CI: 0.75–0.86 and $OR = 0.70$, 95 % CI: 0.57–0.88 accordingly). When data on flu vaccination were adjusted as per age, sex, comorbidities and socioeconomic indicators, the aforementioned relationship with a risk of SARS-CoV-2 became weaker. However, this does not concern vaccination against pneumococcal infection, which retained the same association with the risk of infection even after adjustments as per all these confounders. When it comes down to more severe observation points, such as hospitalization in an intensive care unit or death, available data do not confirm any association between such severe

COVID-19 incomes and flu vaccination or vaccination against pneumococcal infection.

Literature data on a role played by flu vaccination and vaccination against pneumococcal infection in COVID-19 progression are so heterogeneous that this requires additional profound analytical investigation. We have not found any open access publications on other vaccinations from the National calendar and therefore have not been able to compare our data with results of other studies.

Our analysis of laboratory markers identified in the analyzed healthcare workers with COVID-19 established several ones with prognostic value including levels of D-dimer, total protein, CRP, LDH, IL-6, ESR, platelets, lymphocytes, T-helpers, CTL and NK-cells. We compared our findings as regards laboratory tests with other research articles and found some interesting points. Some of them were in line with data obtained by other researcher but still there were certain peculiarities.

Thus, Y.-D. Gao with colleagues [18], along with investigating somatic risk factors, gave some attention to analyzing results of laboratory tests obtained for COVID-19 patients. They revealed several laboratory indicators to be important for monitoring of the disease progression. These indicators included lactate dehydrogenase, procalcitonin, C-reactive protein, proinflammatory cytokines such as interleukins IL-6, IL-1β, glycoprotein Krebs von den Lungen-6 (KL-6) and ferritin. Levels of LDH, CRP and interleukin-6 have been highlighted in our study as effective prognostic laboratory markers in healthcare workers able to point at likelihood of lung-involving clinical forms of the coronavirus infection. However, attention should be paid to prognostic value of procalcitonin, ferritin and KL-6 when planning additional investigations on occupational risk groups.

The systemic review accomplished by M. Palladino [26] confirmed that lower levels of platelets, lymphocytes, hemoglobin, eosinophils and basophils and an elevated level of neutrophils and neutrophils to lymphocytes ratio as well as elevated levels of platelets and lymphocytes were associated with unfavorable clinical outcomes in COVID-19 patients.

The meta-analysis by B.M. Henry with colleagues [27] covered 21 research articles. It identified the most effective prognostic indicators of more severe COVID-19 clinical forms, namely, levels of leukocytes, lymphocytes, platelets, IL-6 and ferritin in blood serum.

Other studies established that the D-dimer level in patients with COVID-19 correlated with an unfavorable outcome of the disease and was quite a precise biomarker to predict the clinical course of the infection [28–30]. ROC-analysis established the threshold D-dimer level that allowed identifying whether patients were at a risk of the lung involvement, namely 0.370 μg/l [31]; this is quite close to our threshold level. Another study established an optimal threshold D-dimer level for predicting mortality among COVID-19 patients as equal to 1.5 μg/l [32].

Some studies highlighted the interleukin-6 level as an effective prognostic laboratory indicator and this is well in line with our study results [33, 34].

Data obtained by PCR-based diagnostics were given special attention in analyzing the results of laboratory tests. The threshold cycle value, which is considered to be inversely proportionate to a viral load, was shown to have no associations with severity of clinical symptoms of the infection but still it had a statistically significant relationship with duration of the disease and grew simultaneously with it. However, different opinions on the matter can be found in literature.

Thus, M.E. Brizuela with colleagues [35] analyzed data on 485 patients in their study and established that the viral load with SARS-CoV-2 in smears from the airways, which was identified as per the threshold cycle, correlated authentically with moderate and severe cases and with age.

B. Mishra and others [36] showed in their study that a share of a high viral load (Ct < 25) was considerably higher in middle-aged and elderly people against young patients (44.6 % and 43.7 % against 32.2 %, $p < 0.001$).

H.C. Maltezou with colleagues [37] established that patients with a higher viral load tended to have more severe COVID-19 clinical forms and more often needed treatment in

ICU. The authors also detected a higher viral load in elderly patients and those with chronic cardiovascular diseases, essential hypertension, chronic bronchopulmonary diseases, immune suppression, obesity, and neurological pathology. The authors suggest using the Ct value to reveal patients who are at elevated risks of severe infection and death.

However, some other studies yielded contrary results. Thus, A. Karahasan Yagci with colleagues [38] reported that a viral load was not a factor associated with a risk of hospitalization or death. The authors mentioned even lower Ct values in patients with mild clinical COVID-19 variants. Similar data were reported in the study by J.F. Camargo and others [39].

I. Saglik with colleagues [40] did not identify any clear correlation between viral load with SARS-CoV-2 and severe clinical symptoms or deaths among COVID-19 patients either. The authors established that a Ct value in patients grew with time since the moment the disease started and this is in line with our study results. The Ct values were the lowest during the first five days after the first symptoms occurred; then, they grew considerably during the second and third week of the disease. Sex, age, or comorbidities did not have any significant differences in patients with low (≤ 25) and high (> 25) Ct values.

I. Saglik with colleagues also noted that levels of neutrophils, platelets and especially lymphocytes were considerably lower in patients with a high viral load. Estimation of the correlation between the Ct value and levels of prognostic laboratory indicators is a promising research trend and should be considered in future investigations of the issue.

P.P. Salvatore with colleagues [41] reported finding in their study similar to those by I. Saglik et al. as regards the Ct dynamics during the disease. The threshold cycle values were the lowest just after symptoms had occurred and had a significant correlation with a time period since this occurrence ($p < 0.001$);

seven days after the first symptoms occurred, the average Ct value equaled 26.5 and 21 days after it was 35.0.

The present study involved whole-genome sequencing of 58 SARS-CoV-2 viruses isolated from the examined healthcare workers. B.1.1. was established to be a prevailing genetic variant; others were identified in singleton cases. SARS-CoV-2 detected in the healthcare workers in this study corresponded to a range of circulating genetic variants of the virus identified in the Sverdlovsk region and the Russian Federation at the initial stage in the pandemic according to the results of SARS-CoV-2 whole-genome sequencing available in the Russian (VGARus)[4] and international (EpiCov GISAID)[5] databases [42]. These results are significant for the complex analysis of the situation and organization of a system for molecular-genetic monitoring of communicable and parasitic diseases in the Russian Federation.

The healthcare workers were examined with the PCR method in dynamics to identify persistence of the SARS-CoV-2 virus in their bodies. It was established to vary between 13 and 45 days (the median was 22 days) and had certain peculiarities for different clinical forms of the infection. Similar data were reported by some other publications by other authors. Thus, Y. Wang with colleagues [43], who accomplished their study during the first pandemic 'wave', showed that duration of the virus persistence correlated with severity of the disease. Patients who had COVID-19 as ARI excreted the virus for 10 days in most cases (81.8 %) whereas patients with severe clinical forms of the disease who needed artificial ventilation excreted the virus for a longer period in 66.7 % of the cases, up to 20–40 days and this is quite similar to our data. X. Zhang and others [44] established in their study that persistent excretion of the virus RNA could be observed in 5.4 % of patients for longer than 45 days. The authors also noted the peak vial

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[4] VGARus (Virus Genome Aggregator of Russia): the Russian platform for aggregating information about virus genomes. Available at: https://genome.crie.ru/app/index (December 19, 2022).
[5] GISAID: database. Available at: https://www.gisaid.org (December 01, 2022).

load was higher in patients with the severe disease against those who had it in milder forms.

However, it is noteworthy that the aforementioned publications were predominantly accomplished on general populations without any emphasis on specific cohorts or occupational groups. It is quite difficult to find open-access studies with their focus on investigating various aspects of the COVID-19 incidence among healthcare workers who were at higher risks of getting infected during the COVID-19 pandemic. This makes our study more valuable and offers some areas for further profound investigations among occupational groups with higher risks of infection.

Conclusion. In this study, we analyzed clinical symptoms of COVID-19 in healthcare workers during the initial stage in the pandemic (the first and second epidemic rises in the incidence); described clinical forms of the coronavirus infection and outlined its prevailing symptoms (common ones for communicable diseases, symptoms of acute respiratory infections, damage to the gastrointestinal tract, skin symptoms). The Ct value in PCR tests was shown to have no associations with severity of COVID-19 clinical symptoms; still, it had a direct correlation with a period starting from the moment the disease started. Whole-genome sequencing identified several genetic variants of the SARS-CoV-2 virus in the examined medical workers (predominantly B.1.1 and some others in singleton cases including B.1, B.1.1.397, B.1.1.317, B.1.1.387, B.1.1.409, B.1.1.141, B.1.1.274). The identified genetic variants corresponded to those circulating in the region and the country as a whole at the initial stage of the pandemic. We established how long they persisted in a patient's body (between 13 and 45 days, the median was 22 days).

In addition, we identified non-occupational risk factors of COVID-19 clinical forms with the lung involvement (age older than 40 years, low physical activity, overweight, diabetes mellitus, and diseases of the genitourinary system) as well as laboratory markers with cut-off points that were associated with more severe COVID-19 in the examined healthcare workers (erythrocyte sedimentation rate higher than 11.5 mm/hour; levels of platelets lower than $239 \cdot 10^9$/l, lymphocytes below $1.955 \cdot 10^9$/l, T-helpers below $0.855 \cdot 10^9$/l, cytotoxic T-lymphocytes lower than $0.455 \cdot 10^9$/l, NK-cells below $0.205 \cdot 10^9$/l, D-dimer higher than 0.325 µg/ml, total protein below 71.55 g/l, C-reactive protein higher than 4.17 mg/l, lactate dehydrogenase higher than 196 U/l, interleukin-6 higher than 3.63 pg/l).

It is advisable to use our data on non-occupational risk factors of severe non-communicable diseases when developing recommendations on identifying whether a person is occupationally fit for a specific medical specialty. Laboratory indicators identified in the present study can be widely used in clinical practice including operative adjustment of treatment protocols.

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