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Risk Factors for COVID-19 Adverse Outcomes in ICU Settings of Various Types Repurposed Hospitals

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Summary

Objective: to study the risk factors for COVID-19 adverse outcomes in repurposed hospitals of various types.

Material and methods. A retrospective study was conducted in the ICUs of three repurposed hospitals: a municipal hospital, a federal center and a private clinic. Data of 369 patients were analyzed for the period from April to December 2020. Gender, age, BMI, NEWS score, severity of lung damage based on CT quantification, blood gases and pH, patterns of antibiotic administration during hospital stay (all classes and number of antimicrobials, regardless the sequence of administration), patterns of main drugs administration (glucocorticosteroids, lopinavir/ritonavir, tocilizumab/ solilumab, hydroxychloroquine) were evaluated as risk factors. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated by logistic regression.

Results. Patients from repurposed hospitals of various types were distinguishable in terms of distribution by sex, severity of lung damage, administered therapy, blood gases, and the number of antimicrobials used. Mortality rates were 21.8% in the federal center, 41.4% in the private clinic, and 77.2% in the municipal hospital. The most significant risk factors were: the severity of lung damage based on CT quantification (OR=3.694, 95% CI: 1.014–13.455, P=0.048) — in the federal center, patient's age (OR=1.385, 95% CI: 1.034–1.854, P=0.029) and arterial oxygen tension (OR=0.806, 95% CI: 0.652–0.996) — in the municipal hospital, and patients' age (OR=2.158, 95% CI: 1.616–2.880, P<0.0001), number of antibiotics (OR=1.79, 95% CI: 1.332–2.406, P=0.0001), and blood pH (OR=0.381, 95% CI: 0.261–0.555, P<0.0001) — in the private clinic.

Conclusion. Patient's profiles in municipal, federal, and private ICU settings varied significantly in the first wave of the COVID-19 pandemic. Gender distribution and severity of the diseases were found as the most significant differences among them. Clinical outcomes were also different, with the lowest mortality rate in the federal center and the highest in the municipal hospital. Arterial pO_2, blood pH, and the number of antimicrobials used in the course of treatment were the significant risk factors of fatal outcome (in some hospitals).

Keywords: COVID-19; SARS-CoV-2; ICU; risk factors; logistic regression; hospital repurposing

Conflict of interest. The authors declare no conflict of interest.

Introduction

Despite significant reductions in morbidity and mortality, COVID-19 remains a significant public health problem. Patients admitted to intensive care units are still at high risk of serious complications and death. The 2020–2021 COVID-19 pandemic has provided a wealth of information, the analysis of which will allow important conclusions to be drawn about risk factors in the management of coronavirus infection. A large number of risk factors have been described in the literature, and they vary considerably from country to country and from hospital to hospital. According to a meta-analysis of 40 studies by Y. Li et al., the most significant risk factors for mortality in COVID-19 are male sex (OR = 1.32, 95% CI = 1.18 to 1.48, 20 studies), age (OR = 1.05 for each additional year, 95% CI = 1. 04 to 1.07, 10 studies), obesity (OR = 1.59, 95% CI = 1.02 to 2.48, 4 studies), diabetes mellitus (OR = 1.25, 95% CI = 1.11 to 1.40, 11 studies), and chronic kidney disease (OR = 1.57, 95% CI = 1.27 to 1.93, 6 studies) [1].

According to many studies, age is a risk factor independent of disease severity, hospital type, or department [2, 3]. Gender was found to be a significant risk factor in most published studies, whereas data on smoking and comorbidities are less consistent [3–5]. Among comorbidities, diabetes mellitus, obesity, and cardiovascular disease are the most commonly reported risk factors [6, 7].

A more accurate prognosis of outcome can be obtained from the results of laboratory tests. C-reactive protein, lactate dehydrogenase (LDH), C3, increased CD14+CD16+ monocytes and Th17 cells have been studied as predictors of disease outcome [8–10]. Not all of these markers are available for routine measurement. It is important to find an optimal set of predictors based on clinical and medical history data and routine laboratory tests.

During the 2020–2021 pandemic, coronavirus pneumonia was treated in a variety of hospitals. In addition to city hospitals, converted public and private hospitals were involved. Since the patient populations and treatment efficacy differed in many parameters, it is reasonable to consider patients from different types of hospitals as separate populations unless proven otherwise.

Aim of the present study: to investigate risk factors for adverse COVID-19 outcomes in different types of converted hospitals.

Materials and Methods

A retrospective study of the outcomes of treatment of coronavirus pneumonia in intensive care units of three hospitals involved in the provision of medical care in Moscow in 2020 was conducted. The types of hospitals were abbreviated as follows: city clinical hospital (CCH), converted federal center (CFC), and converted private clinic (CPC). Treatment outcomes for April–June 2020 were obtained from CFC and CCH, and for May–December 2020 from CPC. Inclusion criteria were treatment in the ICU, COVID-19 as the reason for transfer to the ICU, absence of severe neoplastic and neurological disorders not related to infection.

Patients with the minimum required information were selected. For CFC, data were collected on sex, age, duration of ventilatory support, length of ICU stay, BMI, NEWS score, severity on lung CT scan (on admission, initiation of ventilation, last value during hospitalization and «maximum» value during hospitalization), pH, and lactate and glucose levels, arterial blood CO_2 and O_2 pressures before tracheal intubation, number of antibacterial drugs prescribed during treatment (different antibacterial drugs, regardless of the order in which they were prescribed), frequency of administration of major drugs (glucocorticosteroids, lopinavir/ritonavir, tocilizumab/solilumab, hydroxychloroquine).

For CCH, data on sex, age, NEWS score, arterial blood CO_2 and O_2 pressures before tracheal intubation, and number of antibacterial drugs administered during treatment were collected.

For CPC, data were collected on sex, age, duration of mechanical ventilation and ICU stay, pH and lactate levels, arterial blood CO_2 and O_2 pressures before tracheal intubation, number of antibacterial drugs prescribed during treatment, specific drugs prescribed (glucocorticosteroids, lopinavir/ritonavir, tocilizumab/sarilumab, hydroxychloroquine), and tracheotomy.

Statistical analysis of the study results and plotting were performed using the common statistical libraries *sklearn*, *statsmodels*, and *scipy* of Python 3.

Chi-squared test for categorical variables, ANOVA with post hoc comparison by Tukey's test for quantitative parameters (Tukey's HSD test, statsmodels library) were used to assess differences in clinical and laboratory parameters between institutions. Normality of distribution was assessed by the Shapiro–Wilk test (scipy library). Data were described as mean and standard deviation (*SD*), unless otherwise noted.

Logistic regression model with l1 regularization (maximum likelihood estimator of statsmodels library, b. l1 alpha = 1) was used to estimate the studied parameters as risk factors. According to the recommendations for epidemiological data analysis, missing values were imputed by iterative imputation (IterativeImputer function of Ridge Regression in the sklearn library). To assess the accuracy of imputation, we compared the mean and standard deviation in the sample before and after imputation. Covariates whose values could exceed 10 were scaled to a range of 1–10, which was taken into account when interpreting the regression coefficients. Pseudo-R^2, log likelihood and log likelihood ratio *P*-value were evaluated as criteria for model adequacy. A logistic regression model was calculated for all available covariates from individual hospital data. Covariates with a calculated P-value $<$ 0.05 were selected as significant predictors of mortality, and odds ratios (OR = expB), 95% confidence intervals (95% CI) were reported for each factor.

Results и discussion

Patient selection. Based on the inclusion and exclusion criteria, 540 patients were selected from 4 450 ICU patients in the three clinical centers, of whom 369 patients had the required minimum information (sex, age, disease outcome, length of stay in the ICU, and duration of mechanical ventilation) and whose data were used for the study (Fig. 1).

Comparison of different clinical facilities. There were differences in almost all parameters of the patient populations between the different types of clinical centers. The most important for further analysis were the differences in adverse outcome rate between the three institutions. It was 21.8% for CFC, 77.2% for CCH, and 41.4% for CPC (chi-squared differences <0.001 for CFC/CCH and CCH/CPC comparisons, P=0.006 for CFC/CCH, which is below the set threshold, even when multiple comparisons adjustments were applied).

The sex ratio of patients differed significantly between some clinical centers (67.2%, 43.6%, 62.3% of male patients, P=0.003 in CFC, CCH, and CPC,

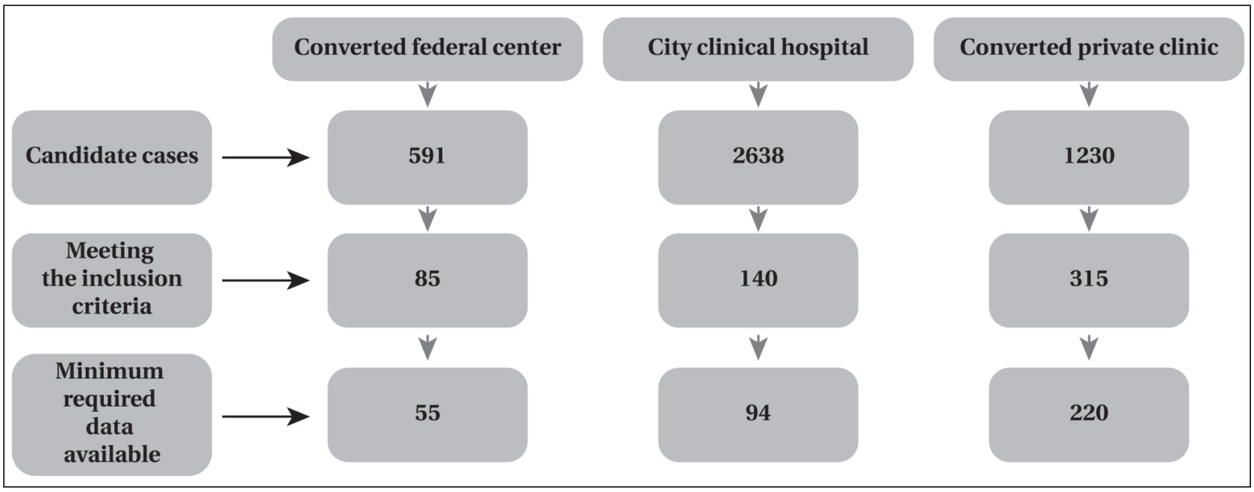

Fig. 1. Flowchart of the patient selection.

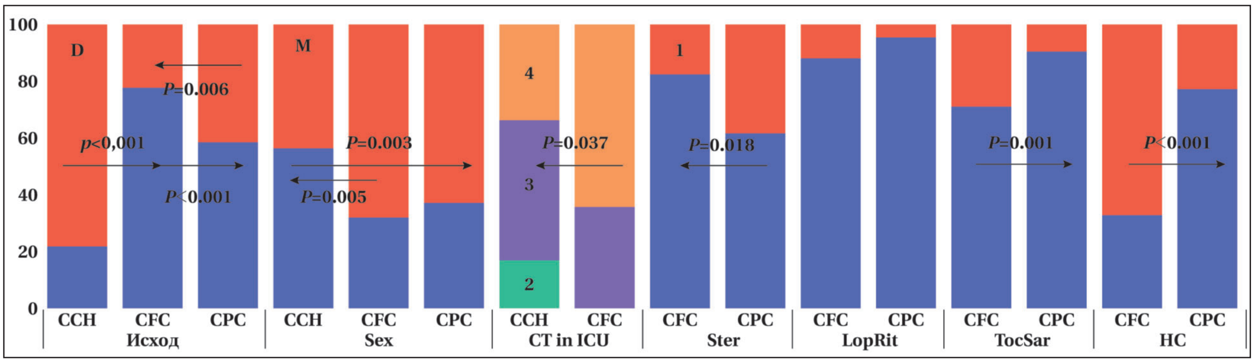

Fig. 2. Comparison of different clinical sites by frequency of categorical variables (%).
Note. CCH — city clinical hospital; CFC — converted federal center; CPC — converted private clinic; CT in ICU — CT severity of pneumonia before intubation (0–4 points); Ster — administration of steroids; LopRit — administration of lopinavir/ritonavir; TocSar — administration of tocilizumab/sarilumab; HC — administration of hydroxychloroquine; D — death; M — male sex. For the administration of drugs, «1» means that the drug was prescribed.

respectively, when compared by chi-squared test in the overall comparison). Pairwise comparisons using the chi-squared test were also significant with P=0.005 for CFC and CCH, P=0.49 for CFC/CPC, and P=0.003 for CCH/CPC. Thus, no gender differences were observed between patients in the ICU of the converted federal center and the private clinic, but significantly fewer males met the study inclusion criteria in the CCH sample.

When comparing the severity of pneumonia on CT scan before tracheal intubation, CFC and CCH differed significantly (P=0.037 with more severe disease in CFC), whereas CT severity on admission did not differ significantly (P=0.10). Hydroxychloroquine (22.3% vs. 66.7%, P<0.001), tocilizumab/sarilumab (10% vs. 39.4%, P=0.001) and steroids were prescribed significantly less often in CPC than in CFC (37.8% vs. 17%, P=0.018). The frequency of prescribing lopinavir/ritonavir was not significantly different (4.1% vs. 11.4%, P=0.11).

The mean age of patients was not significantly different between the three centers (ANOVA P>0.1). The mean NEWS score was significantly higher in CCH than in CFC (6.4±3.1 vs. 4.3±3, p=0.001). Mean pH before tracheal intubation was significantly lower (7.36±0.11 vs. 7.47±0.06, P=0.001) and lactate level was significantly higher (2.09±1.22 mmol/L vs. 1.18±1.19 mmol/L, p=0.001) in CPC compared to CFC. Significant differences were found between patients of the three institutions in O_2 and CO_2 partial pressure before tracheal intubation (P<0.001 and P<0.001, respectively), number of antibiotics administered (P<0.001). The pO_2 in CPC was significantly higher than in CFC (93.7±31.9 mm Hg versus 48.7±11.7 mm Hg, P=0.001) and CCH (93.7±31.9 mm Hg versus 56±18.3 mm Hg, P=0.01), no difference was found between CFC and CCH (P=0.18). Mean pCO_2 was significantly lower in CFC compared to CCH (32.9±11.7 mm Hg vs 56±18.3 mm Hg, P=0.001) and CPC (32.9±11.7 mm Hg vs 42.6±14.1 mm Hg, P=0.001). There were no significant differences between CCH and CPC (P=0.85). The number of antibiotics prescribed was significantly different between CFC and CPC (2.1±1.4 vs.

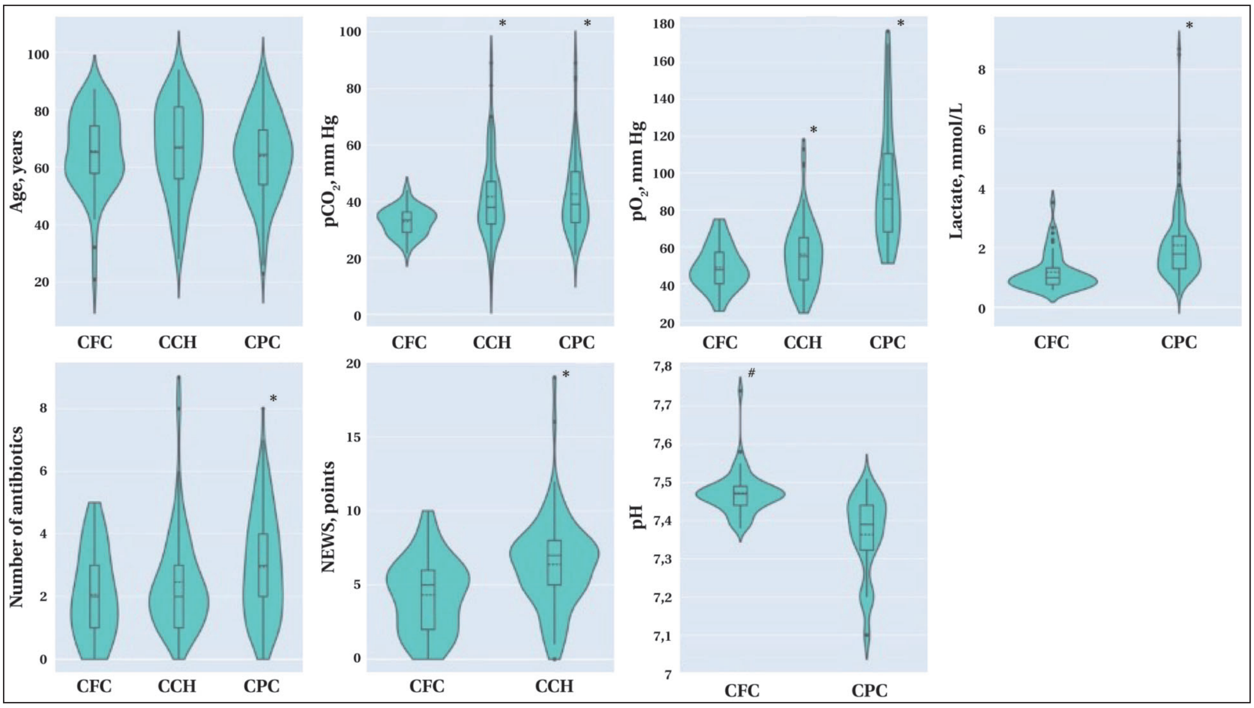

Fig. 3. Comparison of different clinical institutions by mean values of quantitative variables (violin diagrams).
Note. * — the average value is significantly ($P<0.01$) higher than in the CFC group. # — the average value is significantly ($P<0.01$) higher than in the CPC group.

Missing values and imputation quality.

Parameter	Institution	Missing values	Mean before imputation	Mean after imputation	SD before imputation	SD after imputation	SD of imputed means
pCO_2	CFC	1	32.88	32.94	4.82	4.79	4.78
pO_2	CFC	1	48.7	48.7	11.73	11.62	11.62
Last CT severity	CFC	3	2.73	2.75	1.03	1.05	1.00
Lactate	CFC	6	1.19	1.14	0.63	0.65	0.59
Number of antibiotics	CFC	10	2.1	1.93	1.42	1.42	1.28
CT severity on admission	CCH	76	3.17	3.15	0.71	0.96	0.3
pH	CPC	5	7.36	7.36	0.11	0.11	0.10
pCO_2	CPC	120	42.6	43.2	14.1	15.0	9.5
pO_2	CPC	120	93.7	94.7	31.9	32.5	21.5
Lactate	CPC	5	2.1	2.1	1.22	1.22	1.2
Number of antibiotics	CPC	88	2.94	2.66	1.7	1.9	1.3

2.9±1.7, $P<0.001$). The differences between CFC and CCH (P=0.38) and CPC and CCH (P=0.09) were not significant.

Patients in the ICUs of the different types of converted hospitals studied differed significantly in their clinical characteristics. On the one hand, a higher score on the NEWS scale in CCH compared to CFC indicates greater severity of illness. On the other hand, patients in CFC had greater severity on CT scan before tracheal intubation, and the proportion of males was maximal among them. A pH shift towards acidosis in CPC patients compared to CFC patients could also be a sign of greater disease severity.

The reasons for the discrepancy in the characteristics of the samples could be different, since the treatment was performed in 2020, before the full standardization of the treatment of COVID-19 patients. Importantly, the results of the risk factor study need to be interpreted in light of the specifics of the inpatient setting. The results of individual epidemiologic studies may not be applicable because of such differences, so it is better to be guided by the results of meta-analyses.

Analysis of Significant Mortality Factors

Imputation of missing values. Logistic regression methods cannot handle data with missing values, so we iteratively imputed missing values for each criterion used in the model (Table). Conformity of the new sample form to the original data was tested using means and standard deviations (SDs).

The standard deviations of one of the basic methods for imputing missing values, the mean for the parameters (see table), were reported. The mean values for the parameters differed insignificantly, the standard deviations differed significantly less from the baseline values than the mean imputation. A significant improvement was obtained by imputing the parameters with a large number of missing values.

Because of the small number of patients selected for CFC, a number of parameters were not included in the logistic regression model due to uneven class distribution. The following variables were included in the model: age, NEWS score, pCO_2, pO_2, admission lung CT severity score, last available CT severity score, lactate level, and number of antimicrobials administered. For the model, the pseudo-R^2 value was 0.73, LL = –7.88, LLR $P<0.001$. Severity according to the last CT scan was a significant risk factor (p=0.048). With a score of 1 to 4, each additional point increased the risk of death by a factor of 3.694 (OR = 3.694; 95% CI, 1.014–13.455). Most of the other parameters included in the model were not significant due to the wide confidence interval. Due to the proximity of significant differences, the possible importance of pCO_2, pO_2, NEWS, and lactate level should be considered in further studies (Fig. 4, *a*).

Risk factors in CCH. Sex, age, lung CT severity at ICU transfer and pO_2 were included in the model predicting the odds of fatal outcome based on data from CCH. The adequacy of the model can be assessed by pseudo-R^2 = 0.11, LL = –44.27, LLR *p*-value of 0.010. For age, the OR was 1.385, i.e., each year in the model increased the odds of death by a factor of 1.385 (95% CI, 1.034–1.854; P=0.029; 66.7±15.7 years). The other significant predictor was pO_2 56±32 mm Hg, OR = 0.806 (95% CI, 0.652-0.996), indicating that each additional 10 mm Hg of pO_2 in the blood reduced the odds of death by 1.24-fold (Fig. 4, *b*).

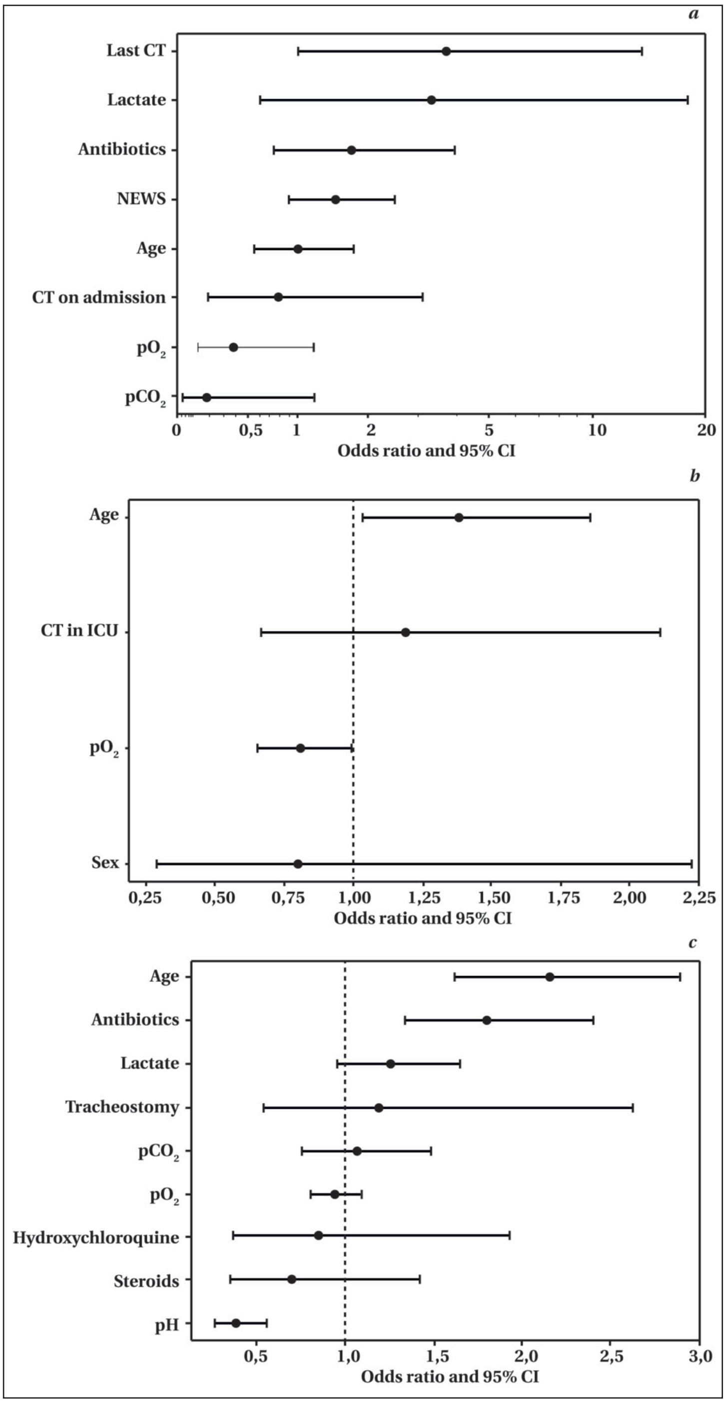

Fig. 4. Forest plot of risk factors for death in the ICU of the CFC (*a*), CCH (*b*), CPC (*c*).

Risk factors in CPC. From the CPC data, age, pH, pCO_2, pO_2, use of steroids, hydroxychloroquine, lactate level, tracheostomy, and number of antimicrobial agents used were included in the logistic regression model. For the model, the pseudo-R2 value was 0.24, LL = –113.95, LLR $P<0.001$. Three risk factors were significant, including pH, age, and number of antibiotics prescribed. For age (63.9±14.4 years), the OR was 2.158 (95% CI 1.616 to 2.880, $P<0.0001$), i.e. each year increased the odds of death by a factor of 2.158. For pH (7.36±0.11), the OR was 0.381 (95% CI 0.261 to 0.555, $P<0.0001$), i.e. a decrease in pH by 1 increased the odds of death by 2.62 times. For the number of antibiotics (2.9±1.7 drugs), the OR was 1.79 (95% CI 1.332 to 2.406, P=0.0001), i.e., each additional antibacterial drug was associated with a 1.79-fold increase in the odds of death (Fig. 4, *c*).

Analysis of blood acid-base balance and blood gases is an important method of assessing patient status in the ICU. Several studies have confirmed that arterial pO_2 and pCO_2 may be predictors of mortality to some extent [11]. However, they, as well as pH, were not included in meta-analyses of significant predictors of COVID-19 outcome [12, 13]. Significant variation in blood gas measurements between clinical centers may be explained by lack of strict adherence to blood collection protocols. Therefore, the use of such parameters as predictors requires strict standardization of techniques.

There is no information in the literature on the relationship between the number of antibacterial agents administered and the risk of mortality in the ICU. A number of studies have shown that the administration of antibacterial drugs itself may be an independent risk factor for adverse outcomes [14]. In ICU patients, a high number of antibiotics indicates the development of septic complications. Interestingly, more antibiotics were prescribed in a private clinic, which was also a significant risk factor for mortality.

The drugs used to treat coronavirus pneumonia in 2020 had no significant effect on the odds of death, regardless of the type of hospitalization. Currently, the failure of most etiologic therapies has been demonstrated in numerous clinical trials. Moiseev S. et al. demonstrated a lack of effect of tocilizumab [15]. The meta-analysis by Amani B. et al. showed no effect of lopinavir/ritonavir [16]. Later, Axfors C. et al. showed a lack of efficacy for hydroxychloroquine in a meta-analysis [17]. The results obtained with the above drugs are consistent with the literature. However, we found no effect of steroids, contrary to the results of many other studies in severe patients [18, 19]. A relatively small number of patients received steroids (treatment was prescribed before the clinical guidelines were updated), which may explain the lack of significant differences.

Ermokhina L. et al. analyzed risk factors in the ICU of Moscow City Hospital No. 68 during the first pandemic wave. With an average mortality of 44.9%, significant risk factors included age and length of stay in the ICU. Mortality did not differ between men and women and did not depend on BMI. None of the etiologic medications affected mortality. The results presented by the authors are similar to those we obtained from the CCH and CPC data [20].

It should be noted that the results of our study were obtained in 2020, during the first wave of the COVID pandemic. Coronavirus strains and approaches to treatment management changed during the second wave and thereafter. For example, in the study by Bychinin M. V. et al., ICU mortality during the «second wave» increased from 50.5% to 62.7% compared to the first wave, and the structure of comorbidity changed slightly [21].

Conclusion

During the first wave of COVID-19, ICUs of different types of hospitals (city, federal and private) received patients with significantly different clinical characteristics. Treatment outcomes were also significantly different.

Arterial blood pO_2 and pH before tracheal intubation were significant predictors of mortality in patients with coronavirus pneumonia in the ICU.

The number of antibiotics administered may be a significant predictor of mortality in some medical centers.

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