Arterial Hypertension and Severe COVID-19 in Hospitalized Patients: Data from a Cohort Study

Podzolkov V.I., Bragina A.E.*, Tarzimanova A.I., Vasilyeva L.V., Ogibenina E.S., Bykova E.E., Shvedov I.I., Ivannikov A.A., Druzhinina N.A.

I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia

Aim. To assess the association of hypertension with the severe forms and fatal outcomes of Coronavirus disease 2019 (COVID-19).

Material and Methods. This retrospective cohort study involved adult patients (⩾18 years old), admitted to the University hospital №4 of Sechenov University (Moscow, Russia) between 08 April 2020 and 19 November 2020 with clinically diagnosed or laboratory-confirmed COVID-19. The cohort included 1637 patients. The primary outcome was all-cause in-hospital mortality. The secondary outcomes included intensive care unit admission (ICU) and invasive ventilation. Multiple logistic regression was performed to assess the independent association between risk factors and endpoints.

Results. A total of 1637 patients were included in the study. 51.80% (n=848) of the subjects were males. The median age was 59.0 (48.0; 70.0) years and 55.90% (n=915) had pre-existing diagnosis of hypertension. Patients with hypertension had significantly more severe lung injury based on chest CT scan findings as well as lower oxygen saturation (SpO_2). More of them were admitted to ICU and placed on invasive ventilation. The hypertension group also had higher mortality. Age, hypertension, glucose, C-reactive protein and decreased platelet count were independently associated with mortality, hypertension having the strongest association (OR 1.827, 95% CI 1.174-2.846, p=0.008). Age, hypertension, neutrophil count, platelet count, glucose, and CRP were independently associated with ICU admission, with hypertension having the strongest association (OR 1.595, 95% CI 1.178-2.158, p=0.002). Age, hypertension, glucose, CRP and decreased platelet count were independently associated with invasive ventilation, with hypertension having the strongest association (OR 1.703, 95% CI 1.151-2.519, p=0.008).Based on the multiple logistic regression models, odds of death, ICU admission, and invasive ventilation were higher in the hypertension group as compared to the group without hypertension.

Conclusion. Hypertension can be an independent predictor of severe COVID-19 and adverse outcomes, namely death, ICU admission, and invasive ventilation in hospitalized patients.

Keywords: COVID-19, hypertension, mortality, risk factors.

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* Corresponding Author (Автор, ответственный за переписку): anna.bragina@mail.ru

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Introduction

Despite the progress in treatment and prevention, including wide use of various vaccines, the COVID-19 pandemic is still not slowing down. Worldwide spread of the disease with more than 200 million COVID-19 confirmed cases, a mortality rate of around 2.2% globally, the growing data about post-acute sequelae of COVID-19, social distancing determine significance of COVID-19 not only as a statistical indicator, but also as the cause that greatly influences the quality of life all around the world [1]. As stated in the position paper from VAS-European Independent Foundation in Angiology/Vascular Medicine, patients with cardiovascular diseases (CVD), arterial hypertension, diabetes mellitus and obesity are at higher risk of severe COVID-19, disease worsening and death [2]. Special approaches to monitoring and treatment have been proposed for those patients.

The role of hypertension as a risk factor for a severe course and adverse outcomes of COVID-19 has been studied in several large studies and meta-analyses. On the one hand, hypertension is one of the most common comorbidities in COVID-19 patients: 15 to 59% of COVID-19 patients have high blood pressure (BP) [3-8]. A number of meta-analyses conducted early in the pandemic demonstrated the high predictive value of hypertension. In the pooled analysis by G. Lippi (13 studies, 2893 patients), hypertension was associated with an almost 2.5-fold increased risk of severe COVID-19 and mortality [9]. Several other papers have reported similar results [3-5, 10-12]. On the other hand, more recent publications have criticized chosen statistical methods used in these works [4]. In this context, The Hypertension Cardiovascular Outcome Prevention and Evidence in Asia (HOPE Asia) Network reviewed the available evidence in its guidelines and suggested that the following factors for the severe course and adverse outcomes of COVID-19 should be considered, excluding hypertension: diabetes mellitus, smoking, cardiovascular disease (heart failure, stroke, angina, myocardial infarction), chronic obstructive pulmonary disease, chronic kidney disease, cancer (especially chemotherapy and radiation therapy) [13]. However, several meta-analyses have confirmed the association of hypertension with a more severe prognosis in COVID-19 patients. According to Chinese researchers, the proportion of patients with hypertension among critically ill and deceased patients was significantly higher [14]. Another meta-analysis of 34 studies also confirmed the role of hypertension in the development of more severe forms of COVID-19 [15]. To our knowledge, there have been no large studies of the effect of hypertension on outcomes of COVID-19 in the Russian population.

Studies to date have shown conflicting results on the question of whether hypertension can be considered a risk factor for the severe course of COVID-19, and the fact that it remains one of the most prevalent diseases in the population makes it an important question to explore [16-21].

The aim of our study was to assess the predictive value of hypertension as a risk factor for the severe forms and fatal outcomes of COVID-19.

Patients and Methods

This retrospective cohort study involved adult patients (⩾18 years old), admitted to the University hospital №4 of Sechenov University (Moscow, Russia) between 08 April 2020 and 19 November 2020 with laboratory-confirmed SARS-CoV-2 infection, coded as U07.1 by International Classification of Diseases, Tenth Revision (ICD-10), or clinically diagnosed, coded as U07.2, when SARS-CoV-2 polymerase chain reaction (PCR) is unavailable or negative. The cohort included 1637 patients. Data (including pre-existing diagnosis of hypertension) were collected from discharge documents and electronic medical records at the hospital. This study population was previously reported in paper where were explored a different aspect of the issues [22]. The study was approved by the Sechenov University Local Ethics Committee on February 18, 2021 (protocol 04-21). The need for informed consent was waived due to the retrospective nature of the study.

Lung injury was assessed by chest computed tomography (CT) scan. The degree of lung damage was classified as CT-0 to CT-4 according to Consensus Guidelines of Russian Society of Radiology (RSR) and Russian Association of Specialists in Ultrasound Diagnostics in Medicine (RASUDM) [23]. The primary outcome was all-cause in-hospital mortality. The secondary outcomes included intensive care unit (ICU) admission and invasive ventilation.

Continuous variables were presented as median with interquartile range. Categorical variables were presented as frequency (percentage). Differences between groups were assessed by Mann-Whitney U test for continuous variables and by Chi-squared test for categorical variables.

Initially, the univariate logistic regression was performed to determine association of risk factors with outcomes, odds ratio (OR) per unit increase with corresponding 95% confidence interval (CI) and p-value was used as a measure of association. Predictive value of risk factors weas assessed by performing Receiver-operating characteristic (ROC) curve analyses with calculation of Area under the curve (AUC) as a measure of discrimination.

To assess the independent association between risk factors and endpoints multiple logistic regression was performed. Only the variables with AUC significantly greater than 0.5 (95% confidence interval does not include 0.5) were included in the multiple logistic regression models. Again OR with 95% CIs were computed to de-

termine the strength of association. A two-tailed p-value<0.05 was considered statistically significant.

Statistical analysis was conducted using Statistica10.0 (StatSoft Inc., USA).

Results

A total of 1637 patients were included in the study [848 (51.8%) men and 789 (49.2%) women, mean age was 58.8±16.1 years].

55.90% (n=915) had pre-existing diagnosis of hypertension (2.95% (n=27) with stage 1; 33.44% (n=306) with stage 2 and 63.61% (n=582) with stage 3). 99 (10.82%) hypertensives did not take any hypotensive therapy, 67 (7.32%) took monotherapy with angiotensin-converting enzyme inhibitors, 54 (5.90%) – with angiotensin receptor blockers, 93 (10.16%) – with β-blockers, 20 (2.19%) – with calcium channel blockers, 7 (0.77%) – with diuretics, 3 (0.33%) – withmoxonidine, 346 (37.81%) were taking combination therapy, information about therapy of 226 hypertensives was not available. 657 (71.80%) hypertensives had systolic BP on admission (SBP)<140 mm Hg and diastolic BP on admission (DBP)<80 mm Hg.

Baseline characteristics of the study population are shown in Table 1.

In the hypertension group age, time from admission to discharge, body mass index (BMI), systolic BP on admission (SBP), diastolic BP on admission (DBP), neutrophil levels, C-reactive protein (CRP) and glucose concentrations were significantly higher than in the group without hypertension.

As showed in Table 2, patients with hypertension had significantly more severe lung injury based on chest CT scan findings as well as lower oxygen saturation (SpO_2). More of them were admitted to ICU and placed on invasive ventilation. The hypertension group also had higher mortality.

We assessed the association of different factors with primary endpoint (all-cause in-hospital mortality) using univariate logistic regression and ROC curve analysis. Results are presented in Table 3.

Several risk factors were associated with mortality including age, hypertension, SBP on admission, neutrophil count levels, platelet count levels, glucose, CRP, estimated glomerular filtration rate calculated by Chronic Kidney Disease Epidemiology Collaboration equation (eGFR CKD-EPI), SpO_2. The most predictive variables with the highest AUC were hypertension, age, CRP, SpO_2 and decreased eGFR (CKD-EPI).

Multiple logistic regression was performed to assess the independent association of hypertension and several other variables with the primary outcome (Table 4).

The model showed that age, hypertension, glucose, CRP, decreased platelet count and SpO_2 were independently

Table 1. Baseline characteristics of patients

Parameter	Total (n=1637)	Patients with hypertension (n=915)	Patients without hypertension (n=722)	p-value
Age, years	59 (48; 70)	67 (58; 78)	48 (39;58)	0.000
Male, n (%)	848 (51.80)	417 (45.60)	431 (59.70)	0.000
Time from admission to discharge, days	14.0 (12.0; 17.0)	14.0 (12.0;18.0)	14.0 (11.0;17.0)	0.003
Smoking history, n (%)	294 (31.68)	192 (20.98)	102 (14.13)	0.001
BMI, kg/m²	29.7 (25.6; 34.6)	31.2 (27.3;35.4)	27.8 (24.8;31.2)	0.000
SBP, mm Hg	121.0 (117.0; 130.0)	126.0 (120.0;135.0)	120.0 (115.0;130.0)	0.000
DBP, mm Hg	80.0 (71.0; 80.0)	80.0 (73.0;80.0)	80.0 (70.0;80.0)	0.000
Pulse, bpm	90.0 (80.0; 98.0)	90.0 (80.0;97.0)	90.0 (82.0;98.0)	0.015
Diabetes, n (%)	294 (17.96%)	244 (26.84%)	50 (6.97%)	0.000
SpO_2, %	95.0 (92.0;96.0)	94.0 (92.0;96.0)	95.0 (93.0;97.0)	0.000
Neutrophil count, $\times10^9$/l	3.52 (2.50; 5.10)	3.65 (2.59;5.31)	3.40 (2.40;4.90)	0.008
Neutropenia (<1.5×10^9/l), n (%)	97 (5.93)	54 (5.90)	43 (5.96)	0.922
Platelet count, $\times10^9$/l	219.0 (168.0;292.0)	214.0 (164.0;292.0)	224.0 (173.0;292.0)	0.056
Thrombocytopenia (<100×10^9/l), n (%)	42 (2.57)	28 (2.40)	14 (1.94)	0.164
CRP, mg/l	44.1 (13.6;107.4)	51.0 (16.9;120.0)	37.0 (9.2;90.6)	0.000
Glucose, mmol/l	5.10 (4.60;6.00)	5.30 (4.70;6.40)	4.91 (4.50;5.60)	0.000
eGFR (CKD-EPI), ml/min/1.73m²	69.0 (54.5; 81.6)	60.6 (48.5;72.9)	77.5 (68.4;88.0)	0.000

p-values are calculated for testing differences between two groups with and without hypertension; BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure, SpO_2 – oxygen saturation, CRP – C-reactive protein, eGFR (CKD-EPI) – estimated glomerular filtration rate, calculated by Chronic Kidney Disease Epidemiology Collaboration equation.

Table 2. Comparison of the course of COVID-19 in the presence or absence of hypertension

Parameter	Patients with hypertension (n=915)	Patients without hypertension (n=722)	p-value
The degree of lung damage based on chest CT scan findings, n (%):			
• 0 (no lung injury);	7 (0.77)	16 (2.23)	0.000
• 1 (mild);	210 (23.02)	200 (27.75)	
• 2 (moderate);	408 (44.60)	361 (49.93)	
• 3 (severe);	243 (26.54)	129 (17.85)	
• 4 (critical)	47 (5.07)	16 (2.23)	
SpO_2<90%, n (%)	114 (12.46)	37 (5.13)	0.000
ICU admission, n (%)	134 (14.64)	26 (3.60)	0.000
Invasive ventilation, n (%)	86 (9.40)	12 (1.66)	0.000
Death, n (%)	97 (10.60)	8 (1.11)	0.000

CT – computed tomography, SpO_2 – oxygen saturation, ICU – intensive care unit

Table 3. Univariate logistic regression all-cause in-hospital mortality

Parameter	Univariate OR	95% CI	p-value	AUC	SE	95% CI
Age	1.084	1.067-1.102	0.000	0.794	0.023	0.773-0.813
Male sex	0.972	0.798-1.185	0.779	0.507	0.029	0.483-0.532
Hypertension	3.253	2.261-4.681	0.000	0.695	0.021	0.672-0.717
SBP on admission	0.982	0.969-0.996	0.012	0.540	0.032	0.515-0.564
Neutrophil count	1.140	1.093-1.190	0.000	0.675	0.034	0.652-0.698
Platelet count	0.996	0.994-0.998	0.001	0.635	0.031	0.611-0.658
Glucose	1.112	1.053-1.174	0.000	0.663	0.035	0.639-0.687
CRP	1.011	1.009-1.013	0.000	0.786	0.024	0.765-0.806
eGFR (CKD-EPI)	0.956	0.945-0.966	0.000	0.729	0.030	0.706-0.751
SpO_2	0.838	0.804-0.873	0.000	0.738	0.028	0.684-0.792

OR – univariate odds ratio, CI – confidence interval, AUC – area under curve, SE – standard error, SBP – systolic blood pressure, CRP – C-reactive protein, eGFR (CKD-EPI) – estimated glomerular filtration rate, calculated by Chronic Kidney Disease Epidemiology Collaboration equation, SpO2 - oxygen saturation.

associated with mortality, hypertension having the strongest association. AUC for this regression model was 0.914 (SE 0.016; 95% CI 0.884-0.945).

Univariate logistic regression analysis and ROC curve analysis for several variables with ICU admission as an endpoint were performed. Several risk factors were associated with ICU admission including age, male sex, hypertension, neutrophil count, platelet count, glucose, CRP, SpO_2 and eGFR (CKD-EPI). The most predictive variables with the highest AUC were CRP (OR=1.014; 95% CI 1.012-1.016; p=0.000; AUC 0.830), neutrophil count (OR=1.232; 95% CI 1.179-1.289; p=0.000; AUC 0.714),age (OR=1.046, 95% CI 1.034-1.058; p=0.000; AUC 0.689), glucose (OR=1.156, 95% CI 1.097-1.217; p=0.000; AUC 0.667), SpO_2 (OR=0.802, 95% CI 0.770-0.835; p=0.000; AUC 0.728) and hypertension (OR=2.143, 95% CI 1.727-2.660; p=0.000; AUC 0.654).

Multiple logistic regression model demonstrated age, hypertension, neutrophil count, platelet count, glucose, CRP and SpO_2 were independently associated with ICU admission, with hypertension having the strongest association (OR 1.495, 95% CI 1.099-2.036, p=0.011). AUC for this regression model was 0.894(SE 0.013; 95% CI 0.870-0.920).

Univariate logistic regression analysis and ROC curve analysis demonstrated age, hypertension, neutrophil count, platelet count, glucose, CRP, SpO_2 and eGFR (CKD-EPI) were associated with invasive ventilation. The most predictive variables with the highest AUC were CRP (OR = 1.013; 95% CI 1.011-1.015; p=0.000; AUC 0.823), age (OR=1.056; 95% CI 1.041-1.072; p=0.000; AUC 0.723), glucose (OR=1.136, 95% CI 1.073-1.201; p=0.000; AUC 0.685), eGFR (CKD-EPI) (OR=1.035, 95% CI 1.024-1.046; p=0.000; AUC 0.680), SpO_2 (OR=0.834, 95% CI 0.800-0.870; p=0.000; AUC

Table 4. Results of multiple logistic regression analysis examining the association of variables with mortality

Parameter	Estimate	Standard error	OR	95% CI	p-value
Age	0.078	0.013	1.081	1.053-1.109	0.000
Hypertension	0.559	0.230	1.750	1.114-2.748	0.015
SBP on admission	-0.014	0.009	1.733	0.969-1.002	0.094
Neutrophil count	0.028	0.028	1.028	0.973-1.086	0.321
Platelet count	-0.004	0.001	0.996	0.993-0.999	0.003
Glucose	0.068	0.029	1.070	1.010-1.133	0.021
CRP	0.009	0.001	1.009	1.006-1.012	0.000
eGFR (CKD-EPI)	-0.003	0.007	0.997	0.983-1.011	0.698
SpO_2	-0.137	0.026	0.872	0.828-0.918	0.000

Estimate – estimated coefficient in regression model, OR – odds ratio, CI – confidence interval, SBP – systolic blood pressure; CRP – C-reactive protein; eGFR (CKD-EPI) – estimated glomerular filtration rate, calculated by Chronic Kidney Disease Epidemiology Collaboration equation, SpO2 – oxygen saturation.

0.726) and hypertension (OR=2.477, 95% CI 1.824-3.365; p=0.000; AUC 0.669).

The multiple logistic regression model showed that age, hypertension, glucose, CRP, decreased platelet count and SpO_2 were independently associated with invasive ventilation, with hypertension having the strongest association (OR 1.642, 95% CI 1.107-2.435, p=0.014). AUC for this regression model was 0.892 (SE 0.018; 95% CI 0.856-0.927).

Based on the multiple logistic regression models, odds of death, ICU admission, and invasive ventilation were higher in the hypertension group as compared to the group without hypertension (Figure 1).

Discussion

In the analyzed cohort of hospitalized patients with clinically diagnosed or laboratory-confirmed SARS-CoV-2 infection, more than half had hypertension. Hypertension was associated with significantly more severe disease: more severe lung injury based on chest CT scan findings, more frequent need for ICU admission, invasive ventilation, and higher mortality.

Early studies of the predictive value of hypertension as a risk factor for severe COVID-19 were criticized for lack of adjustment for age. Opponents commented about older people having hypertension more often, which probably was the reason behind the association of hypertension with mortality. In the current study, we assessed the potential of hypertension as a predictor for mortality in hospitalized patients after adjustment for age as well as other factors such as male sex, BP on admission, neutrophil count, platelet count, glucose, CRP, and eGFR. Among hospitalized patients, such factors as age, CRP, eGFR, and hypertension had the highest predictive ability. Multiple logistic regression, which included these variables, proved a significant association of hypertension with mortality.

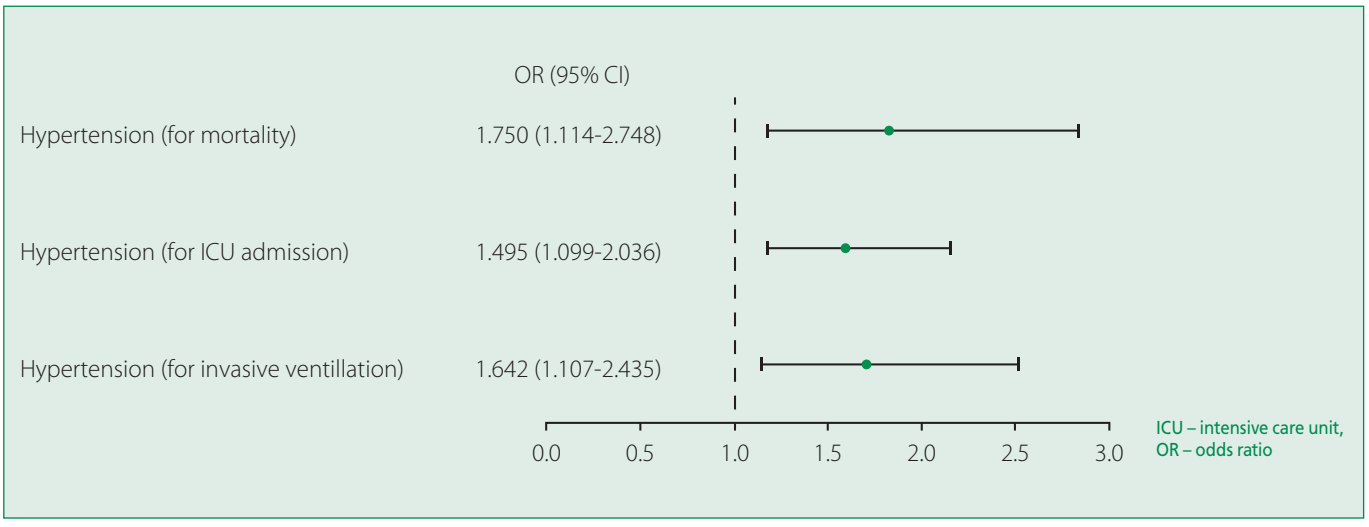

Figure 1. Odds ratios for association of hypertension with mortality, ICU admission and invasive ventilation, based on multiple logistic regression models. Box-plot indicates odds ratio and 95% confidence interval

Moreover, for such factors as SBP on admission, neutrophil count, and eGFR no significant association has been found.

Similar results have been obtained in other studies [24,27]. Rodilla E. et al. showed in their study that hypertension, regardless of prior antihypertensive therapy, was associated with increased mortality [24].

Caillon A. et al. analyzed the data from Wuhan patients and built regression models for mortality and survival. In both models, SBP but not hypertension was significantly associated with outcomes [28]. The differences between these findings and the results of the current study could be due to the relatively small sample size (157 patients versus 1637 patients in our study), which probably resulted in a lack of statistical power. In addition, A. Caillon et al. used a different set of variables. Also, L1 regularization used in the study has a tendency to select one variable from the group of correlated variables, which in the case of SBP and hypertension could lead to the selection of SBP over hypertension.

Guan W.J. et al. in their study of adverse outcomes among hospitalized patients with various comorbidities built a Cox regression model including such factors as age, smoking status and comorbid conditions. Hypertension together with chronic obstructive pulmonary disease, diabetes mellitus, and malignancies have been shown to significantly increase risks of reaching the composite endpoint (death, the admission to ICU or invasive ventilation) [29].

There are studies that showed male sex to be a predictor of mortality in COVID-19 patients [30]. For example, Nasiri et al. in a systematic review and meta-analysis found that males had significantly higher mortality compared to females (OR 3.4; 95% CI 1.2-9.1, p=0.01). In our study, we haven't found the association of male sex with outcomes.

A possible reason for a severe course and poor prognosis of COVID-19 in patients with hypertension could be the presence of target organ damage. Uncontrolled hypertension causes a number of pathophysiological changes in the heart and vessels, particularly endothelial dysfunction, left ventricular hypertrophy, and fibrosis, which in turn can make the myocardium and endothelium more susceptible to SARS-CoV-2 [5]. One more mechanism of cardiovascular damage by SARS-CoV-2 virus may be its affinity for angiotensin-converting enzyme type 2, which is abundant in the heart and endotheliocytes. Other suggested pathogenetic mechanisms include cytokine storm caused by an unbalanced type 1 and type 2 T-helper response, sympathetic hyperactivation, anemia, and hypoxemic cardiomyocyte damage due to respiratory failure [13,31,32].

This study has its limitations. First, it was based on the data from a single hospital. Second, the study was retrospective, so not all parameters could be retrieved from records, which resulted in some missing data.

Conclusions

In this study, we have shown that hypertension can be an independent predictor of severe COVID-19 and adverse outcomes, namely death, ICU admission, and invasive ventilation in hospitalized patients.

Relationships and Activities. None.

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About the Authors:
Valery I. Podzolkov
eLibrary SPIN 8683-2155, ORCID 0000-0002-0758-5609
Anna E. Bragina
eLibrary SPIN 3753-5539, ORCID 0000-0002-2699-1610
Aida I. Tarzimanova
eLibrary SPIN 2685-4078, ORCID 0000-0001-9536-8307
Lyubov V. Vasilyeva
eLibrary SPIN 9111-1333, ORCID 0000-0001-5730-7837
Ekaterina S. Ogibenina
ORCID 0000-0002-2129-818X
Ekaterina E. Bykova
eLibrary SPIN 8932-8731, ORCID 0000-0002-4830-624X
Ilya I. Shvedov
eLibrarySPIN2369-0439, ORCID 0000-0001-9722-6097
Alexander A. Ivannikov
eLibrary SPIN 3934-5062, ORCID 0000-0002-9738-1801
Natalya A. Druzhinina
eLibrary SPIN 6842-0447, ORCID 0000-0001-8397-0210