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## ELECTROCARDIOGRAM QRS COMPLEX DURATION AS A PREDICTOR OF HOSPITAL PROGNOSIS IN PATIENTS WITH COVID-19

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| <i>Aim</i>                  | To determine the effect of major electrocardiographic (ECG) parameters on the prognosis of patients with COVID-19.  |
| <i>Material and Methods</i> | One of systemic manifestations of COVID-19 is heart injury. ECG is the most simple and available method for diagnosing the heart injury, which influences the therapeutic approach. This study included 174 hospitalized patients with COVID-19. Major ECG parameters recorded on admission and their changes before the discharge from the hospital or death of the patient, were analyzed, and the effect of each parameter on the in-hospital prognosis was determined. Results were compared with the left ventricular ejection fraction (LV EF), laboratory data, and results of multispiral computed tomography (MSCT) of the lungs.  |
| <i>Results</i>              | ECG data differed on admission and their changes differed for deceased and discharged patients. Of special interest was the effect of the QRS complex duration at baseline and at the end of treatment on the in-hospital survival and mortality rate. The Cox regression analysis showed that the QRS complex duration (relative risk (RR) 2.07, 95% confidence interval (CI): 1.17–3.66; $p=0.01$ ), MSCT data (RR, 1.54; 95% CI: 1.14–2.092; $p=0.005$ ), and glomerular filtration rate (GFR) (RR, 0.98; 95% CI: 0.96–0.99; $p=0.001$ ) had the highest predictive significance. In further comparison of these three indexes, the QRS duration and GFR retained their predictive significance, and a ROC analysis showed that the cut-off QRS complex duration was 125 ms ( $p=0.001$ ). Patients who developed left bundle branch block (LBBB) in the course of disease also had an unfavorable prognosis compared to other intraventricular conduction disorders ( $p=0.038$ ). The presence of LBBB was associated with reduced LV EF ( $p=0.0078$ ). The presence of atrial fibrillation (AF) significantly predetermines a worse outcome both at the start ( $p=0.011$ ) and at the end of observation ( $p=0.034$ ). A higher mortality was observed for the group of deceased patients with ST segment deviations, ST elevation ( $p=0.0059$ ) and ST depression ( $p=0.028$ ). |
| <i>Conclusion</i>           | Thus, the QTc interval elongation, LBBB that developed during the treatment, AF, and increased QRS complex duration are the indicators that determine the in-hospital prognosis of patients with COVID-19. The strongest electrocardiographic predictor for an unfavorable prognosis was the QRS complex duration that allowed stratification of patients to groups of risk.  |
| <i>Keywords</i>             | COVID-19; electrocardiography; bundle branch block; QTc interval; left ventricular ejection fraction  |
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The end of the COVID-19 pandemic has shifted the focus of interest onto studying the consequences of the novel coronavirus disease. Nevertheless, it is important to continue to study the features of COVID-19 due to the risk of new epidemics resulting from the emergence of new virus subvariants with a highly contagious course of the disease [1, 2].

The involvement of the cardiovascular system is a manifestation of multi-organ damage in COVID-19 in

a significant number of patients [3–7]. Electrocardiography is a routine, simple, and available diagnostic method that is conducted in series for all patients hospitalized. It serves as a tool for identifying various disorders and assessing the patient's prognosis [8, 9].

According to the authors who manage COVID-19 patients, the presence of the rhythm and conduction disorders, the ST-segment displacement, the T-wave inversions, and the QTc interval prolongation are the most

common findings in such patients [8–28]. Both persistent and paroxysmal atrial fibrillation (AF) have also been shown to have an adverse effect on the prognosis in COVID-19 [8–10, 17, 20, 24–26]. QTc prolongation is a known risk factor for severe arrhythmia and sudden death, and its prognostic value for COVID-19 patients is unclear [8, 11, 12, 14, 18, 19, 21, 27, 28]. ST-segment displacement and abnormal T-wave changes of various types are often detected in patients with severe COVID-19 [13–16, 28].

The data regarding the effect of various forms of intraventricular conduction disorders on the hospital prognosis are the most controversial in the available literature [22, 23, 29–31].

The duration of the QRS complex is an important predictor of poor prognosis in patients with COVID-19 [31, 32]. The increase in the QRS complex duration was shown to correlate in patients with COVID-19 during therapy with such phenomena as all-cause death and respiratory failure requiring intubation [31]. In another study, an increase of more than 120 msec was observed in the QRS complex duration in patients with the composite endpoint, including hospital mortality, the need for mechanical ventilation or admission in the intensive care unit ( $p = 0.008$ ) [32].

## Objective

Evaluate the prognostic significance of electrocardiographic (ECG) parameters regarding an unfavorable prognosis of patients with COVID-19 during treatment in an infectious disease hospital.

## Material and Methods

ECG series were performed in 174 patients with confirmed COVID-19 (positive PCR of oral and nasopharyngeal swabs in the age group 18 years and older in combination with a pathognomonic pattern in lung computed tomography scans).

The study was approved by the local ethics committee of the N.I. Pirogov Russian National Research Medical University (Minutes no. 202 dated 23/11/2020). The ethical principles in human clinical trials of the Declaration of Helsinki of the World Medical Association were followed and documented in the informed consent.

The age of patients was 73.0 [51.0; 82.0] years from 30.0 to 97 years, the age of deceased patients ( $n=64$ ) was 79.0 [72.0; 83.0] years from 49 to 92 years and significantly different from the age of discharged patients of 65.0 [55.0; 80.0] years ( $p=0.0001$ ). Concomitant diseases were coronary artery disease ( $n=55$ ), of which postinfarction cardiosclerosis ( $n=32$ ), diabetes mellitus type 1 and 2 ( $n=49$ ), paroxysmal and permanent AF ( $n=45$ ), a history of pulmonary diseases ( $n=19$ ), chronic kidney disease ( $n=102$ ),

arterial hypertension ( $n=128$ ), cancer ( $n=20$ ). Most patients were polymorbid.

This study analyzes the ECG findings of patients with COVID-19 recorded at admission and before discharge or death. Of the total group of 174 patients, the study was conducted once in 8 patients due to death on day 1 of hospital stay, i.e., serial examinations were conducted in 166 patients.

ECG was recorded on the Schiller BR-102 plus device and included automatic analysis of the main intervals (PQ, QRS, QT, QTc, measured by the Bazett formula at a heart rate (HR) of less than 90 bpm or the Friderici formula at a higher HR), assessment of the ST segment displacement, changes at the end of the QRST complex, conduction disorders.

Echocardiography was conducted using the Philips Affiniti-70 device. The effect of echocardiographic indicators on hospital survival and mortality in patients with COVID-19 has been presented previously [6]. Laboratory test results and multislice computed tomograms (MSCT) of the chest were evaluated retrospectively.

## Statistical methods

Non-parametric statistical analysis methods were used in the non-normal distribution. The Mann-Whitney test was used to determine the differences between the two independent variables, and the Kruskal-Wallis test with the Bonferroni correction was used for multiple comparisons. The percentages were compared using Pearson's chi-square test, and Fisher's exact test was used for small values. The data are expressed as the median and interquartile range or the absolute and relative values. The Kaplan-Meier method was used and curves were constructed to study overall survival; the statistical significance of survival was determined for two compared groups using the log rank test and the chi-square test was used for three and more groups. The multivariate Cox regression analysis was used to assess risk factors for the onset of the endpoint in patients with COVID-19. The ROC analysis was performed and the area under the ROC curve was determined to identify the differential margin between the values of the parameters of interest in the independent samples. The cut-off point was the value at which there was a minimum of false-negative and false-positive results. The differences were statistically significant with  $p$  value less than 0.05.

## Results

Significantly different baseline ECG indicators in the groups of the discharged and deceased patients were higher HR ( $p = 0.039$ ), longer duration of the QRS complex ( $p = 0.02$ ); the PQ, QRST, and QTc intervals did not differ in the analyzed groups (Table 1).

Since there were statistically significant baseline (beginning of treatment) differences in HR and the QRS complex duration in the groups, the effect of these parameters on hospital survival was studied. Both parameters were broken down by quartiles, and patients with HR  $\geq 95$  bpm turned out to have lower hospital survival. Among patients with HR  $\geq 95$  and lower HR, 53.5% and 31.3% died, respectively ( $p=0.009$ ). The following ECG indicators of interest were associated with a higher HR: the duration of the QRST complex ( $p<0.0001$ ) and the QTc interval ( $p=0.027$ ), and the duration of the QRS complex did not differ in patients with normal HR and tachycardia ( $p=0.67$ ).

To assess the effect of the QRS complex duration as an independent indicator, we divided patients into four groups by quartiles depending on the values of this indicator: Group 1 with the QRS complex of 0.08 sec ( $n=79$ ), Group 2 – 0.09 sec ( $n=51$ ), Group 3 – 0.10 sec ( $n=21$ ), and Group 4 –  $>0.10$  sec ( $n=18$ ). The study of hospital survival showed that among the four groups presented, the overall survival was similar in Group 1 and Group 2 and significantly different from that in Group 3 and Group 4 ( $p=0.0014$ ). Therefore, we considered it possible to combine Group 1 and Group 2, as well as Group 3 and Group 4.

Of the 131 patients with QRS complex of 0.08–0.09 sec, 39 (29.8%) died in hospital. In the group with the QRS complex  $\geq 0.1$  sec ( $n = 40$ ), hospital mortality was 57.5% ( $n=23$ ). Patients with intraventricular conduction parameters  $<0.10$  sec had the highest hospital survival – 70.23% in Group 1 and 42.5% in Group 2 ( $p=0.0004$ ; Figure 1).

The correlation analysis showed no relationship between the QRS complex duration and the degree of respiratory failure, blood oxygen saturation ( $SpO_2$ ), and the severity of lesions of the pulmonary parenchyma according to MSCT at admission and over time. Weak but significant correlation of the QRS complex duration was revealed with the following indicators: left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic dimension (LVESD), left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), left ventricular mass index (LVMI), the final diastolic size of the right ventricle, the left atrium (LA), right ventricular end-diastolic dimension (RVEDD), left atrium (LA), pulmonary artery (PA), mitral regurgitation, and left ventricular ejection

fraction (LVEF) with  $r$  from 0.2 to 0.3 and  $p$  from 0.0006 to 0.05. There was virtually no correlation between the QRS complex duration and HR at baseline and during treatment ( $r = -0.2$ ;  $p = 0.005$  and  $r = -0.2$ ;  $p = 0.02$ , respectively).

At baseline, 51 patients had QTc prolongation, of whom 14 (27.45%) patients died, and 40.16% of 122 patients died in the group with normal values. There was no statistically significant effect of the QTc interval on hospital survival ( $p=0.13$ ).

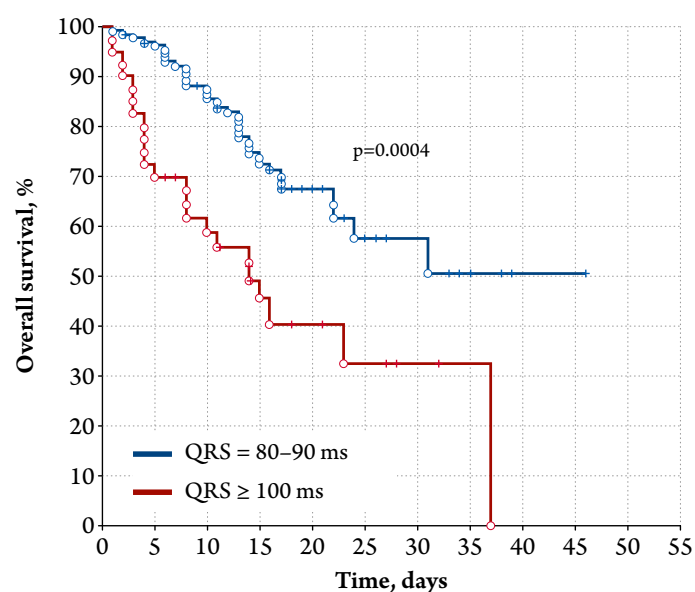
Analysis of the QRS complex before discharge/death showed that the survival rate of patients with a longer duration of the QRS complex was statistically significantly lower than that in patients with normal values ( $p=0.015$ ; Figure 2).

The group with QRS complex  $\leq 0.09$  sec consisted of 126 patients, of whom 39 (30.95%) died, and 50% of patients ( $n=40$ ) died among those with QRS complex  $\geq 0.09$  sec.

The duration of the QTc interval measured at the final stage of treatment was longer in the fatal outcome group (see Table 1). In the assessment of the effect on the hospital prognosis, this indicator predicted low survival in patients with QTc interval  $> 0.44$  sec ( $p = 0.004$ ).

Such intraventricular conduction disorders as bundle branch blocks were detected by the baseline ECG

**Figure 1.** Hospital survival in two groups of patients with COVID-19 depending on the QRS complex duration at admission



**Table 1.** Baseline ECG findings in the discharged and deceased patients with COVID-19

| Baseline ECG data | Discharged (n = 110) | Deceased (n = 64)  | p     |
|-------------------|----------------------|--------------------|-------|
| HR, bpm           | 85.5 [74.0; 94.0]    | 89.0 [76.0; 104.5] | 0.039 |
| PQ, s             | 0.16 [0.16; 0.20]    | 0.16 [0.16; 0.20]  | 0.63  |
| QRST, sec         | 0.38 [0.36; 0.40]    | 0.38 [0.36; 0.41]  | 0.77  |
| QRS, sec          | 0.08 [0.08; 0.09]    | 0.09 [0.08; 0.10]  | 0.002 |
| QTc, sec          | 0.44 [0.43; 0.47]    | 0.46 [0.43; 0.48]  | 0.21  |

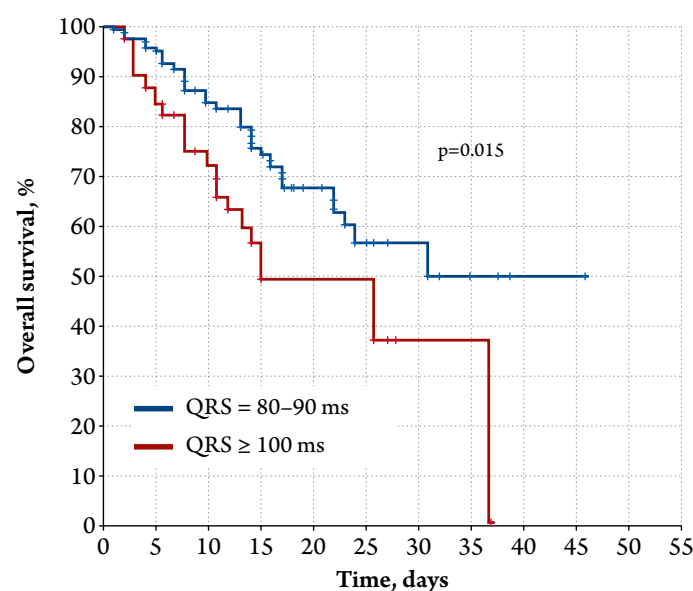
examination in 60 cases. The lowest survival rate was detected in patients with left bundle branch block (LBBB) (Figure 3).

Given the important prognostic role of LVEF for hospital prognosis of patients with COVID-19 [6], we studied the association of this indicator with intraventricular conduction disorders. The QRS complex duration was shown to be associated with LV systolic function regardless of the presence or absence of intraventricular blocks ( $p=0.0025$ ). The QRS complex durations of 0.08 sec ( $n=72$ ), 0.09 sec ( $n=48$ ), 0.10 sec ( $n=18$ ), and more than 0.10 sec ( $n=17$ ) corresponded to LVEF of 55.0 [51.0; 57.0] %, 53.0 [47.5; 57.0] %, 54.0 [44.0; 57.0] %, and 50.0 [34.0; 56.0] %, respectively.

In addition to the studied indicators, the negative effect of AF was shown, which significantly worsened the prognosis. Of the 174 patients, 30 had AF at admission, of whom 17 patients died, which was 56.67%, mortality in the group of patients with sinus rhythm was 32.64% ( $n=47$ ;  $p=0.011$ ). Similar, less yet statistically significant data were obtained when analyzing ECG before discharge or death of the patient. Of the 167 patients, 37 patients had AF, of whom 19 (51.35%) died, and in the sinus rhythm group, the mortality rate was 31.54% ( $n=41$ ;  $p=0.034$ ; Figure 4).

This may be due to the association of AF with abnormal LV systolic and diastolic functions. The comparative analysis of ECGs showing sinus rhythm and AF revealed significantly more dilated heart chambers, worse indicators of global contractility, and a higher degree of pulmonary hypertension in patients with AF, which is likely to cause a more severe prognosis of such patients (Table 2).

**Figure 2.** Hospital survival of patients with COVID-19 depending on the QRS complex duration on the ECG over time



The evaluation of the prognostic significance of indicators affecting the hospital prognosis, the Cox regression revealed the highest relative risk (RR) for three indicators: the QRS complex duration, the severity of changes in MSCT, and reduced renal function.

Regression analysis including only the strongest predictors (the QRS complex duration, percentage of lung damage in MSCT, and glomerular filtration rate (GFR)) showed that in this case, the QRS duration complex (RR 1.2, 95% confidence interval (CI) 1.18-1.27;  $p=0.0003$ ) and GFR (RR 1.0, 95% CI 1.0-0.98;  $p<0.001$ ) were the most powerful predictors of the hospital prognosis.

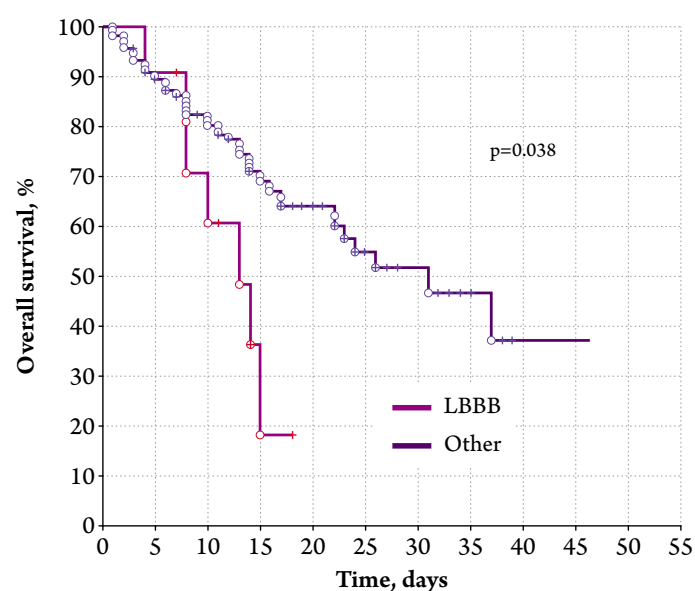
The area under the ROC curve, which corresponded to the correlation between the mortality prognosis and the QRS complex duration, was  $0.619 \pm 0.045$  (95% CI 0.530-0.708).

The cut-off duration of the QRS complex was 125 ms. The resulting model was statistically significant ( $p<0.01$ ). The QRS complex duration equal or less than the cut-off value predicted a high risk of death. The sensitivity and specificity of the method were 67% and 65%, respectively. Consequently, the QRS complex duration on ECG was the most powerful predictor of hospital prognosis in patients with COVID-19.

## Discussion

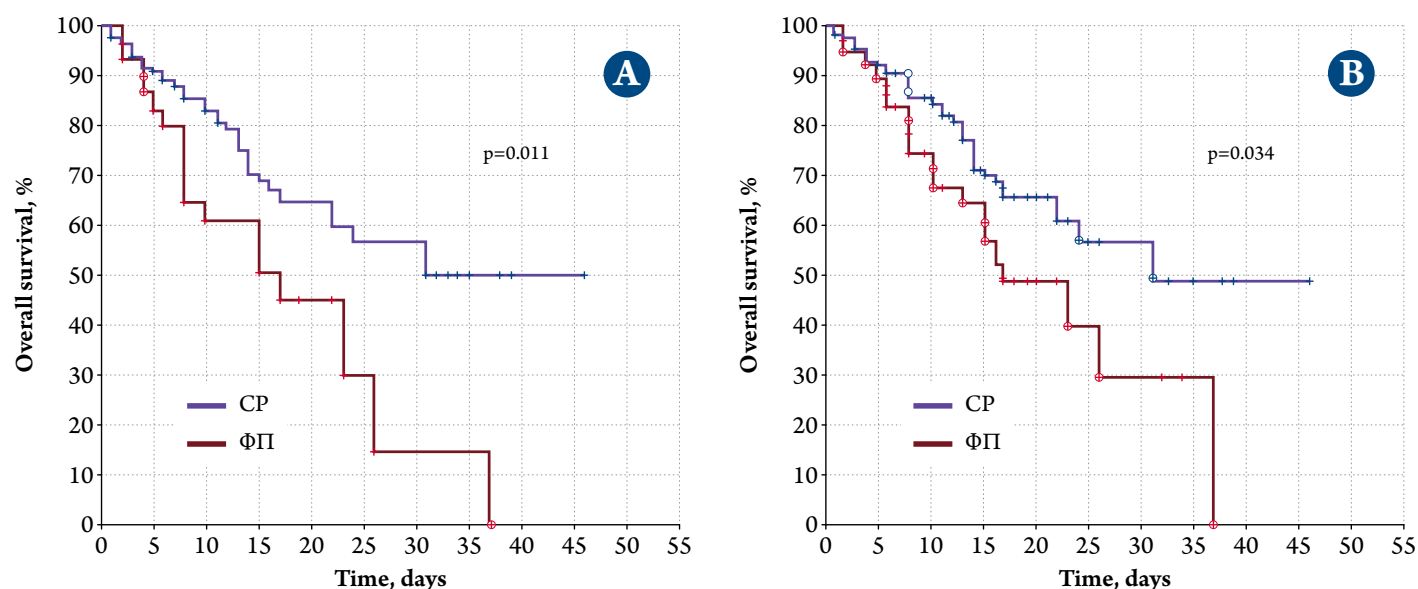
Thus, a highly significant parameter with a negative effect on the hospital prognosis of patients with COVID-19 was a prolonged QRS complex >125 ms. Comparable results were shown in several papers. In a study including 269 patients, longer duration of

**Figure 3.** Hospital survival of patients with COVID-19 depending on the presence of LBBB



LBBB – left bundle branch block.

**Figure 4.** Effect of AF recorded at admission (A) and before discharge/death of patients with COVID-19 (B) on hospital survival



SR, sinus rhythm; AF, atrial fibrillation.

the QRS complex on day 7 of treatment was statistically significantly correlated with a worse prognosis ( $p=0.003$ ), which was defined by the authors as a combination of such factors as all-cause death and respiratory failure requiring mechanical ventilation. However, the duration of the QRS complex was estimated in the cited paper, unlike our study, only as a percentage ratio of values received at baseline and over time. At the same time, the duration of the QRS complex in absolute values did not have predictive significance at the two stages ( $p=0.3$  and  $p=0.2$ , respectively) [31]. Sonsoz et al. [32] concluded that there were more chances to achieve a composite primary endpoint (mortality/need for mechanical ventilation or treatment in the intensive care unit) with a duration of the QRS complex  $>0.12$  sec, however, according to the authors, some parameters were not available for

the analysis due to the retrospective nature of the study. The prolongation of the QRS complex is likely to reflect acute cardiac involvement with impaired interventricular and/or intraventricular synchronization in COVID-19. In severe inflammatory heart disease, there may be a delay in conduction with a predominance of the QRS complex duration  $>120$  ms [33].

A number of studies show higher prevalence of LBBB in deceased patients with COVID-19 [34–36]. The analysis of ECGs of 324 patients showed a statistically significant effect of this parameter on hospital mortality ( $p<0.001$ ) [34]. A similar study evaluating only baseline ECGs of 2,539 patients characterized LBBB as a reliable factor of poor prognosis ( $p=0.016$ ) [35]. In our work, LBBB demonstrated the reliable effect on hospital mortality, and its prognostic role increases with the onset of a new block in ECG during long-term infectious process.

**Table 2.** Comparative characteristics of echocardiographic parameters in patients with sinus rhythm and AF

| Parameter   | Sinus rhythm (n = 133) | AF (n = 25)       | p         |
|-------------|------------------------|-------------------|-----------|
| LVEDD, cm   | 4.8 [4.5; 5.1]         | 5.3 [4.6; 5.5]    | 0.007     |
| LVESD, mm   | 3.5 [3.2; 3.8]         | 3.9 [3.5; 4.3]    | 0.0002    |
| LVEF, %     | 55.0 [50.0; 57.0]      | 48.0 [42.0; 53.0] | 0.0002    |
| LA1, cm     | 4.2 [4.2; 4.4]         | 4.7 [4.4; 5.0]    | $<0.0001$ |
| LA2, cm     | 5.8 [5.4; 6.2]         | 6.5 [6.2; 7.0]    | $<0.0001$ |
| RV, cm      | 3.9 [3.8; 4.1]         | 4.2 [3.9; 4.3]    | 0.007     |
| RA1, cm     | 4.2 [4.1; 4.4]         | 4.7 [4.3; 5.0]    | 0.0001    |
| RA2, cm     | 5.6 [5.1; 6.0]         | 6.2 [5.8; 6.9]    | $<0.0001$ |
| PA, cm      | 2.8 [2.4; 3.0]         | 3.05 [2.8; 3.2]   | 0.04      |
| PASP, mm Hg | 50.0 [45.0; 60.0]      | 58.0 [50.0; 64.0] | 0.02      |

LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; PA, pulmonary artery; LA1 = left atrial transverse dimension; LP2, left atrial longitudinal dimension; RA1, right atrial transverse dimension; RA2, right atrial longitudinal dimension; PASP, pulmonary artery systolic pressure.



**Высокоэластичный  $\beta_1$  – адреноблокатор с вазодилатирующими свойствами<sup>1</sup>**



### Благотворительное воздействие на культуру и творчество личности



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1. *What is the main purpose of the study?*  
 2. *What are the research objectives?*  
 3. *What is the research methodology?*  
 4. *What are the findings of the study?*  
 5. *What are the conclusions of the study?*  
 6. *What are the limitations of the study?*  
 7. *What are the implications of the study?*  
 8. *What are the future research directions?*  
 9. *What are the contributions of the study?*  
 10. *What are the key words of the study?*

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## Conclusions

1. Conventional electrocardiogram recorded over time is an available tool that allows accurately enough stratifying patients with COVID-19 by the risk of adverse hospital outcome.
2. An increase in the QRS complex duration of more than 125 ms and/or left bundle branch block are powerful predictors of a decrease in hospital survival of patients with COVID-19.
3. The prolongation of the QTc interval during infectious process was statistically significantly correlated with lower

survival of patients with COVID-19, its baseline value did not affect the hospital prognosis.

4. Any form of atrial fibrillation reduced hospital survival of such patients.

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