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The value of indicators characterizing the state of the cardiovascular system in assessing the hospital prognosis of COVID-19 patients

Background Heart damage is one of complications of the novel coronavirus infection. Searching for available predictors for in-hospital death and survival that determine the tactic of managing patients with COVID-19, is a challenge of the present time.

Aim To determine the role echocardiographic (EchoCG) parameters in evaluation of the in-hospital prognosis for patients with the novel coronavirus infection, COVID-19.

Material and methods The study included 158 patients admitted for COVID-19. EchoCG was performed for all patients. The role of left ventricular (LV) ejection fraction (EF) was analyzed in various age groups. EchoCG data were compared with the clinical picture, including the severity of respiratory failure (RF), blood oxygen saturation (SpO2), data of computed tomography (CT) of the lungs, and blood concentration of troponin. Comorbidity was analyzed, and the highest significance of individual pathologies was determined.

Results LV EF ≤40% determined the worst prognosis of patients with COVID-19 ($p<0.0001$), including the age group older than 70 years ($p=0.013$). LV EF did not correlate with the degree of lung tissue damage determined by CT upon admission ($p=0.54$) and over time ($p=0.23$). The indexes that determined an adverse in-hospital prognosis to a considerable degree were pericardial effusion ($p<0.0001$) and pulmonary hypertension ($p<0.0001$). RV end-diastolic dimension and LV end-diastolic volume did not determine the in-hospital mortality and survival. Blood serum concentration of troponin I higher than 165.13 μg/l was an important predictor for in-hospital death with a high degree of significance ($p<0.0001$). Th degree of RF considerably influenced the in-hospital mortality ($p<0.0001$). RF severity was associated with LV EF ($p=0.024$). The SpO2 value determined an adverse immediate prognosis with a high degree of significance ($p=0.0009$). This parameter weakly correlated with LV EF ($r=0.26$; $p=0.0009$). Patients who required artificial ventilation (AV) constituted a group with the worst survival rate ($p<0.0001$). LV EF was associated with a need for AV with a high degree of significance ($p=0.0006$). Comorbidities, such as chronic kidney disease, postinfarction cardiosclerosis and oncologic diseases, to the greatest extent determined the risk of fatal outcome.

Conclusion EchoCG can be recommended for patients with COVID-19 at the hospital stage to determine the tactics of management and for the in-hospital prognosis.

Keywords COVID-19; echocardiography; left ventricular ejection fraction; troponin; pericardial effusion; pulmonary hypertension

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Introduction

When a patient is admitted to hospital, the main task that is presented to a physician is to determine the immediate and long-term prognosis. During the COVID-19 pandemic, predictors associated with hospital survival and mortality taking the form of high-mortality diseases are of particular salience. At present, several indicators are known to determine the unfavorable prognosis of such patients: senior age, various comorbidities, as well as certain laboratory indicators [1–27]. Some studies associate deaths attributed to COVID-19 with a damaged heart due to

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viral fulminant myocarditis in 5% to 25% of cases [28–33]. Several authors also point to acute myocardial damage being associated with increased blood levels of troponin [16, 24, 25, 27, 34, 35].

As well as biological markers of myocardial damage and acute cardiovascular failure, the significance of echocardiography in both acute and chronic disease is analyzed. Currently, indications for the use of echocardiography within the diagnostic algorithm of COVID-19 treatment are not specified other than the examination being recommended «in case of probable clinical benefit» [32, 36–39].

However, there are studies showing that more frequent use of echocardiography in COVID-19 patients resulted in changes in their management [40–43]. Low left ventricular ejection fraction (LVEF) detected by echocardiography turned out to be a reliable and independent risk factor for hospital deaths [40, 43].

Several trials have also demonstrated a high predictive value of right ventricular (RV) performance [44–48]. For example, according to Mahmoud-Elsayed et al. [47], 74 examined patients had RV dilation (41%) and dysfunction (27%). No decrease in LV systolic function was observed.

Thus, the available information about echocardiographic parameters in the COVID-19 setting and their role in patient prognosis is currently inconsistent.

Objective

To determine the role of echocardiographic parameters in assessing hospital prognosis in COVID-19 patients.

Material and methods

Examinations were carried out on 158 patients who underwent echocardiography in the first days after admission to the Russian Academy of Sciences Central Clinical Hospital, in which the Department of Hospital Therapy No.1 of the N.I. Pirogov Russian National Research Medical University is operating.

Inclusion criteria

Patients aged 18 years and older with COVID-19 confirmed by a positive polymerase chain reaction (PCR) oropharynx/nasopharynx swab and a typical computed tomography (CT) pattern, for whom normal access for echocardiography was permitted.

Exclusion criteria

Patients with unconfirmed COVID-19 or poor echo window (PEW).

The study was approved by the ethics committee of the N.I. Pirogov Russian National Research Medical University.

Patients signed the informed consent drawn up following the Declaration of Helsinki of the World Medical Association to participate in the study.

Patient characteristics

The mean age of patients whose ages ranged from 30.0 to 97 years was 73.0 [51.0–82.0] years. The median age of the deceased patients aged between 54 and 92 (n=45) of 80.0 [73.0–85.0] years differed to a statistically significant extent from the median age of the discharged patients (n=113) of 65.0 [54.0–80.0] years ($p<0.0001$). Female patients had a statistically significant greater age than male patients – 76.0 [68.0–83.0] years versus 66.0 [54.0–80.0] years, respectively ($p=0.0004$).

Concomitant diseases were coronary artery disease (CAD) (n=34), including postinfarction cardiosclerosis (n=28), diabetes mellitus (DM) type 1 and type 2 (n=34), atrial fibrillation (n=26), pulmonary diseases (n=2), chronic kidney disease (CKD) mainly in combination with DM (n=29) and arterial hypertension (AH) (n=43). Most patients had more than one comorbidity (AH with concomitant DM and/or postinfarction cardiosclerosis).

All patients underwent the relevant examinations: laboratory tests, SARS-CoV-2 oropharynx/nasopharynx swab, chest CT scan, electrocardiography, pulse oximetry. Echocardiography was performed using a Philips Affiniti-70 device with the patient lying on the left side and the probe in parasternal and apical position. The main echocardiographic parameters were LVEF calculated using the Simpson method, left ventricular mass index (LVMI), left ventricular end-diastolic volume index (LVEDVI), right ventricular end-diastolic dimension (RVEDD), pericardial effusion and pulmonary artery systolic pressure (PASP).

A total of 45 patients died during the hospital stay from April 15, 2020 to June 15, 2020. The deceased patients stayed in hospital from 2 days to 37 days; the median stay was 11.5 [6.5–15.5] days. Autopsy data are available for all the deceased patients. Correlations between hospital survival/mortality and echocardiographic parameters, comorbidity, ventilation and gas exchange rates were studied.

Nonparametric statistical analysis methods were used. The Mann–Whitney test was used to determine differences between the two independent variables, while the Kruskal–Wallis test was used for multiple comparisons. The Bonferroni correction was used in multiple comparisons. The percentages were compared using Pearson's chi-square test; Fisher's exact test was used for small values. The data are presented as the median and interquartile range (Me [25th percentile; 75th percentile]) or the absolute values and percentage. The Kaplan-Meier estimator was used to study the survival rate. The statistical significance of survival in three or more groups was determined using the chi-square test by comparing two groups with the log-rank test and the Gehan–Wilcoxon test. The effect of each indicator on the cumulative survival of patients was divided into deciles, after which the cut-off points were determined. ROC analysis was performed to identify the differential margin between the values of the parameters of interest in the independent samples by calculating the area under the ROC curve. The cut-off point was the value at which there was a minimal number of false-negative and false-positive results.

The differences were statistically significant with $p<0.05$.

Results

The effect of LV systolic function in COVID-19 patients on hospital survival was studied. The worst survival rate was detected in patients with LVEF ≤ 40% ($p<0.0001$). For further research, the patient groups were identified based on LVEF according to chronic heart failure (CHF) classification: LVEF ≥50% (n=112), median 56.0% (53.0–58.0); LVEF 40–49% (n=29), median 45.0% [43.0–48.0]; LVEF <40% (n=16), median 33.0% [28.0–37.0]. Figure 1 shows that the survival curves diverge significantly in these groups ($p=0.0002$). The best survival rate was observed in the group of patients with preserved LVEF; the worst survival rate corresponds to LVEF<40%.

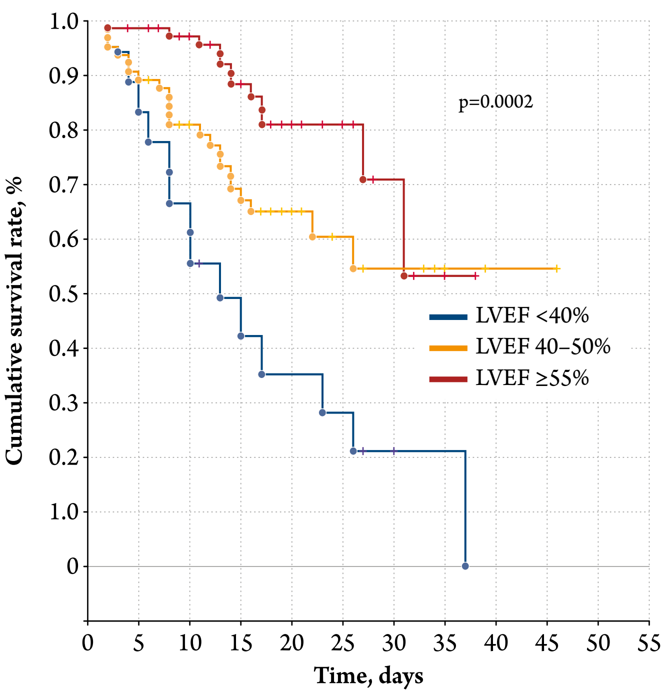
The statistical significance of survival differences between the groups with LVEF ≥50% and LVEF of 40–49% was equal to 0.017 according to the log-rank test and 0.003 between the groups with LVEF 40–49% and LVEF<40%; according to the Gehan-Wilcoxon test – 0.008 and 0.042, respectively. Hospital mortality was also higher in the group of patients with reduced LVEF (Table 1).

Understanding the influence of age on hospital survival and mortality in COVID-19 patients, we also divided the range of values of this indicator into deciles. The Kaplan-Meier survival curves for patient groups aged 70 to 79 years, 80 to 89 years, and 90 years and older almost did not diverge (Figure 2).

Moreover, there was almost no difference in mortality in these age groups. Figure 3 shows that17 (48.6%) of 35 patients aged 70 to 79 years, 19 (46.3%) of 41 patients of 80 to 89 years, and 5 (45.5%) of 1190 years and older died. Male or female sex did not affect hospital survival (log-rank test 0.48, Gehan–Wilcoxon test $p=0.65$).

Thus, given similar mortality and survival rates, the group of patients of 70 years and older was separated to

Figure 1. Hospital survival in COVID-19 patients in three groups depending on LVEF



LVEF – left ventricular ejection fraction

Figure 2. Hospital survival in COVID-19 patients (n=158) depending on age decades

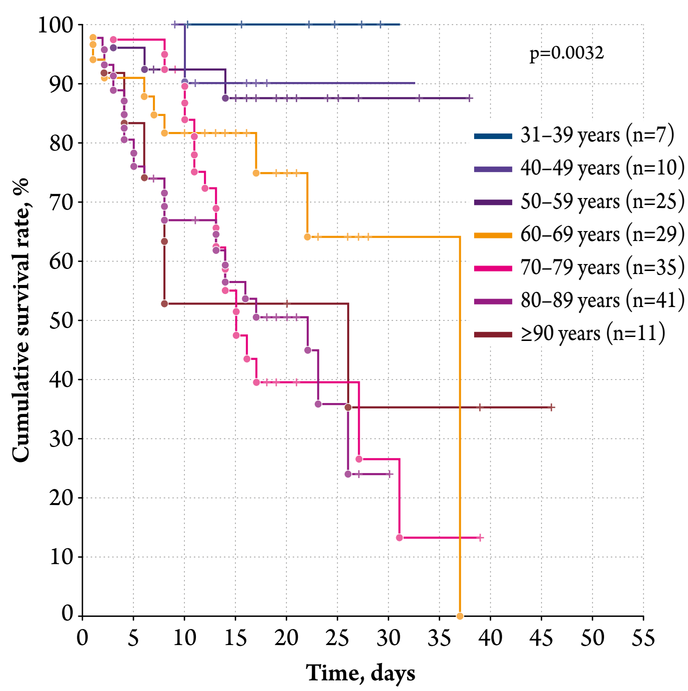


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Table 1. Hospital mortality in three groups of patients with COVID-19 depending on LVEF

LVEF, %	Total of patients	Deceased patients, n	Deceased patients, %
<40	18	14	77.8
40–49	65	22	33.9
≥ 50	75	12	16.0

LVEF, left ventricular ejection fraction, p<0.0001.

Figure 3. Hospital mortality in COVID-19 patients (n=158) in different age groups

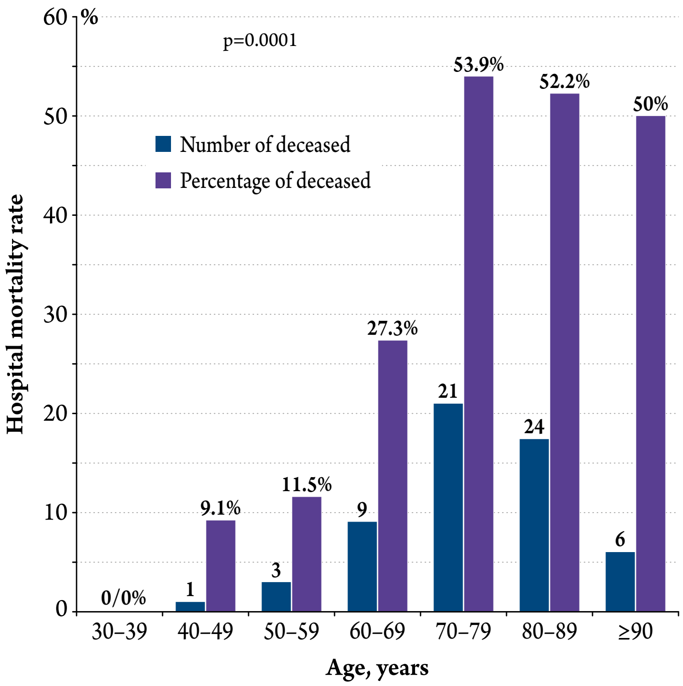
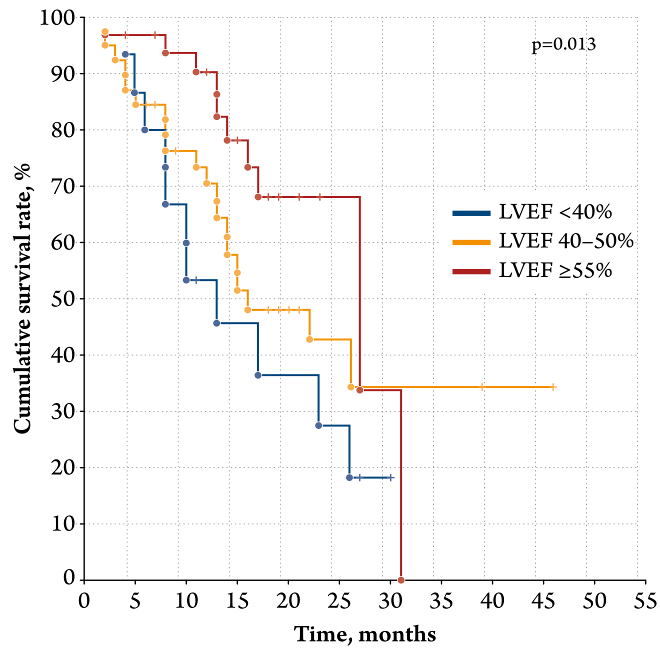


Figure 4. Hospital survival in COVID-19 patients aged 70 years and older depending on LVEF



LVEF, left ventricular ejection fraction.

analyze the effect of LV systolic function. The number of patients decreased to 53 with LVEF≥50%, median 56.0% [53.0–58.0]; 18 with LVEF 40–49%, median 45.0% [43.0–48.0]; and 15 with LVEF <40%, median 33.0% [28.0–37.0]. However, it turned out that LVEF determines hospital survival in older patients similarly to the group as a whole, although with a lower significance with p=0.013 (Figure 4).

The area under the ROC curve (Figure 5), which corresponded to the correlation between the mortality prognosis and LVEF, was 0.753±0.045 with a 95% confidence interval (CI) of 0.664–0.842. The resulting model was statistically significant (p<0.001). The threshold value of LVEF at the cut-off point was 52.5%. When LVEF is equal or less, this value predicts a high risk of death. The sensitivity and specificity of the methods were 70.5% and 70.2%, respectively.

Thus, LVEF was an indicator of hospital survival in patients with COVID-19, including in the older age group.

When comparing the intensity of the pulmonary parenchyma damage shown by CT scan in different stages of the disease with LVEF, no significant correlation was identified (Table 2). Each patient underwent CT scanning on the day of admission, over time, or if his/her condition worsened (n=128). Interestingly, the correlation between LVEF and CT findings (damaged tissue percentage) was not found.

The similar distribution of patients with different CT severity scores in the groups of patients formed according to LVEF did not differ to a statistically significant extent (Figure 6).

Figure 6 shows that the distribution of patients with different degrees of lung damage was also similar and did not differ statistically significantly between patients with different LVEF.

Thus, LVEF also comprised an indicator that determined hospital survival and mortality in patients with COVID-19 regardless of age and severity of lung damage.

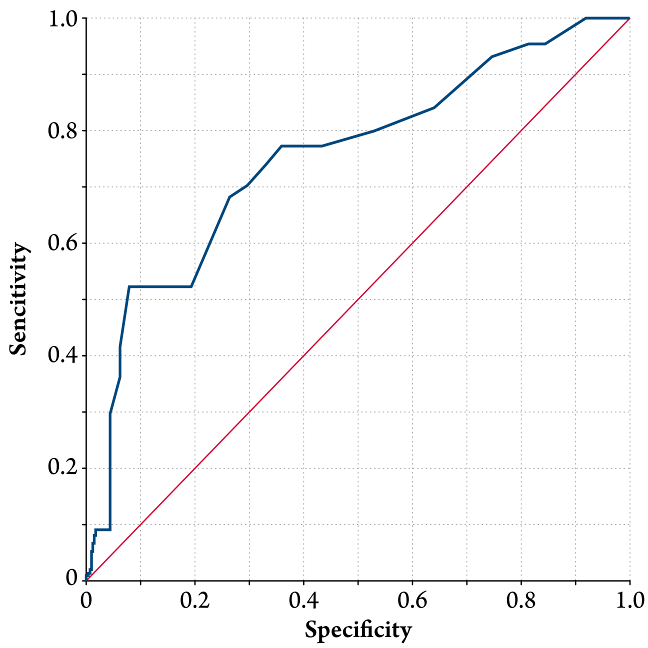
Of other statistically significant standard echocardiographic parameters that determined hospital survival was the presence of pericardial effusion (log-rank test 0.0002, Gehan–Wilcoxon test, p=0.005) and PASP>60 mm Hg. (p<0.0001 according to the log-rank test and the Gehan–Wilcoxon test). The area

Table 2. Correlation coefficients of LVEF and severity of lung damage according to CT

Parameter	n	r	p
LVEF and CT at admission	158	–0.049	0.54
Changes in LVEF and CT	128	–0.100	0.23

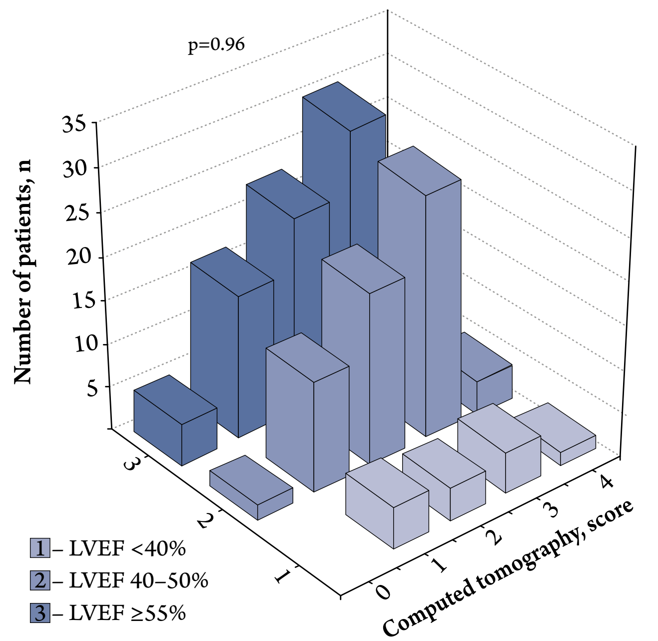
LVEF, left ventricular ejection fraction; CT, computed tomography.

Figure 5. ROC-curves of the correlation between death prognosis and LVEF



Area under the curve is 0.753.
LVEF, left ventricular ejection fraction

Figure 6. Distribution of the lung damage severity scores according to CT in groups of patients with different LVEF



LVEF – left ventricular ejection fraction;
CT – computed tomography

under the ROC curve, which corresponded to the correlation between the mortality prognosis and PASP, was 0.752±0.044 with a 95% CI of 0.666–0.839. The resulting model was statistically significant ($p<0.001$). The threshold value of PASP at the cut-off point was 52.5 mm Hg. If PASP was equal to or above this value, a high risk of death was predicted. The sensitivity and specificity of the methods were 70.5% and 67%, respectively.

Parasternal RVEDD with correlated with moderate power and statistically highly significantly with PASP ($r=0.62$; $p<0.0001$) but did not affect hospital survival. No effect of LVEDV on hospital prognosis was detected.

When assessing the effect of the serum levels of troponin I on hospital survival, the entire range of indicators was divided into four groups: Group 1 up to 100 μg/L (n=38), Group 2 from 100 to 999 μg/L (n=28), Group 3 from 1000 to 9999 μg/L (n=14), Group 4 more than 10,000 μg/L (n=5). The similarity of survival curves in Group 3 and Group 4 allowed their combination into a single group of 19 patients. A total of 85 patients were analyzed for troponin I levels. Survival curves diverged from the acceptable level of significance ($p=0.0038$), with the worst survival being observed in patients with troponin I >1000 μg/L. The correlation between troponin levels and LVEF was assessed to reveal a moderately strong correlation with high statistical significance ($r=-51$; $p<0.0001$). The assessment of hospital mortality in patients with COVID-19 showed a significant dependence of mortality on the serum levels of troponin I. 11 (29.0%) of 38 patients having troponin I up to 100 μg/L, 19 (67.9%) of 28 patients with troponin I of 100 to 999 μg/L, and 18 (94.7%) of 19 patients with troponin I of 1000 μg/L and above died ($p<0.0001$).

The area under the ROC curve corresponding to the correlation between the mortality prognosis and serum levels of troponin I was 0.849±0.042 with a 95% CI of 0.766–0.993. The resulting model was statistically significant ($p<0.001$). The threshold value of troponin I at the cut-off point was 165.13 μg/L. If troponin I was equal to or above this value, a high risk of death was predicted. The sensitivity and specificity of the method were 74.4% and 77.5%, respectively.

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Table 3. Number of patients with RD in patients with different LVEF

RD	LVEF, %		
Grade I	0	10	15
Grade II	8	34	45
Grade III / ARDS	10	21	15

DN – respiratory distress; LVEF – left ventricular ejection fraction; ARDS – acute respiratory distress syndrome (p=0.02)

The severity of respiratory distress (RD) can be expected to significantly influence hospital survival (p<0.0001). Since the survival rates in patients with RF grade III and acute respiratory distress syndrome (ARDS) were similar, these patients combined into one group, which also determined the worst survival rate. Unlike CT findings, the severity of RD was weakly associated with LVEF (Table 3). There were 44.4% of patients with RD grade II and 55.6% of patients with RD grade III/ARDS in the group with reduced LVEF, with 52.3% and 32.3% of such patients, respectively in the group with mid-range LVEF 40–49%, and 60% and 20%, respectively, appearing in the group with preserved LVEF (p=0.024).

Although oxygen blood saturation (SpO2) as shown by pulse oximetry when breathing room air determined hospital survival in patients with high statistical significance (p=0.0009), the curves diverged weakly. The correlation of this indicator with the echocardiographic parameters of interest was also weak: with LVEF (r=0.26; p=0.0009); c RVEDD (r=–0.21; p=0.007); PASP (r=–0.30; p=0.0003). SpO2 did not correlate with serum levels of troponin I. The area under the ROC curve corresponding to the correlation between the mortality prognosis and oxygen blood saturation was 0.656±0.049 with a 95% CI of 0.559–0.752. The resulting model was statistically significant (p=0.002). The threshold value of oxygen blood saturation at the cut-off point was 89.5%. If oxygen blood saturation was equal to or above this value, a high risk of death was predicted. The sensitivity and specificity of the method were 36.4% and 83.3%, respectively.

A total of 56 patients required assisted ventilation, of whom 11 patients received non-invasive high-flow mask ventilation and 45 patients required mechanical ventilation. The lowest survival rate was detected in patients who required mechanical ventilation (p<0.0001). The survival and mortality rates in the group of patients who did not receive mechanical ventilation did not differ between patients on high-flow ventilation and those who did without it. The number of patients with different LVEF in these groups differed to a statistically significant extent: 12 (66.7%) of 18 patients with reduced LVEF, 20 (31.3%) of 64 patients with mid-range LVEF and 12 (16%) of 75 patients with preserved EF received mechanical ventilation (p=0.0006).

Autopsy data analysis was performed for 45 patients. Postinfarction cardiosclerosis (11 of 45) and LV hypertrophy (p=0.065) were most often detected in patients with reduced and mid-range LVEF. Thromboembolism was detected only in 3 cases; acute coronary syndrome was identified in 4 autopsies in patients with reduced and mid-range LVEF.

The most prognostically unfavorable concomitant pathologies were a history of MI (4 of 6 patients in this group died); CHF with a history of myocardial infarction (6 of 10 patients died); cancer (9 of 16 died); and CKD of various stages (14 of 25 patients died). SD type 1 and type 2 and atrial fibrillation (AF) in combination with AH are also prognostically unfavorable (8 of 19 patients and 5 of 12 patients died, respectively). Thus, CKD, postinfarction cardiosclerosis and cancers had the most negative impact on prognosis. However, hospital survival and mortality in patients with COVID-19 were not shown to be affected by essential hypertension, DM without kidney damage, isolated AF, chronic obstructive pulmonary disease and or bronchial asthma in remission.

Discussion

Thus, in the study group of COVID-19 patients, cardiovascular damage was an important factor for short-term hospital prognosis; the hospital mortality and survival rate were determined by cardiovascular indicators in these patients. An independent role of LVEF was detected: a lower hospital survival rate was demonstrated for patients with LVEF<52%.

Similar results have been presented in several papers. In a study that included a retrospective analysis of electronic medical records of both inpatient and ambulatory patients with COVID-19, Ghany et al. [43] also showed that LV systolic function<40% is a significant predictor of mortality. According to the author, the limitations to this study consisted in an inability to identify all deaths as a result of the delayed provision of information at the time of the analysis owing to the lack of large-scale diagnostic testing for COVID-19 in all patients.

There are several studies that, unlike our study, included only patients who required intensive care and had initially poor prognosis, as well as experiencing higher hospital mortality due to reduced LV systolic function [49, 50].

Rath et al. [40] detected a higher hospital mortality rate in patients with LVEF<50%, impaired RV function, and tricuspid regurgitation higher than grade I, however, the study was carried out in patients with a low total mortality rate (13%), unlike in our study with the total mortality rate of 28.5%.

When analyzing the results obtained, mid-range and reduced LVEF associated with higher hospital mortality was explained by the fact that lung damage in patients with COVID-19 with a history of cardiac pathology was likely to result in acute decompensation of CHF. In this situation, a decrease in LVEF<52% is clinically significant and determines a poor prognosis. The difference between the survival curves for patients with LVEF more and less than 50% was highly significant (p=0.009).

Of all echocardiographic factors, PASP and the presence of pericardial effusion were of greatest significance.

The assessment results of the effect of pulmonary hypertension on hospital survival were similar to those reported by most other authors. According to Pagnesi et al. [51], while high pulmonary artery pressure is associated with higher hospital mortality (41.7% vs. 8.5%, p<0.001), RV dysfunction did not affect hospital mortality (17.2% vs. 11.7%, p=0.404). Literature analysis regarding pericardial effusion in patients with COVID-19 showed that these pathologies mainly describe individual clinical situations [52–54]. In the trial carried out by Rodríguez-Santamarta et al. [55], which included 37 patients of whom 33% had pericardial effusion, there was no correlation between pericardial effusion and hospital mortality; the total mortality was 18.9%. In our study, we divided patients according to the presence and absence of any amount of fluid; however, even such a distribution turned out to determine the hospital prognosis.

Our data on high hospital mortality in patients with RD grade III and ARDS were anticipated and consistent with similar findings by numerous authors. The ROC curve analysis showed that the sensitivity of SpO2 was lower than in the study using the ROC-analysis of the sensitivity and specificity of LVEF, troponin I, and PASP. In such cases, SpO2 is most likely to reflect lung damage caused by viral pneumonia in combination with pulmonary congestion due to acute decompensated CHF [56]. Our work also showed that reduced LV systolic function and mortality are mainly associated with such diseases as postinfarction cardiosclerosis and CHF.

The medical history and clinical pattern of a patient's severe condition did not always allow the disease to be interpreted as decompensated CHF. On the basis of autopsy data, it is not possible to identify a correlation between reduced LV systolic function and the effect of coronavirus due to the absence of obvious signs of acute myocarditis and small percentage of diffuse myocardial damage. Moreover, the correlation analysis of the systolic dysfunction severity and the time from disease onset to echocardiography did not reveal any correlation between these indicators (r=0.007; p=0.93). At the same time, the very close dependence of survival on the serum level of troponin I and the correlation between the troponin I levels and LVEF do not entirely exclude the effect of severe intoxication on the state of the myocardium. However, most cases of LV dilatation in our study were interpreted by pathologists as tonogenic dilatation; reduced LVEF was explained by the presence of postinfarction cardiosclerosis. It appears that a decrease in LVEF in many COVID-19 cases is a manifestation of the previous CHF and its decompensation resulting from severe viral pneumonia. Our study showed that a special approach should be applied to those patients.

Thus, the significance of echocardiographic indicators was demonstrated.

There are currently many techniques for echocardiography using easy-to-use portable devices. Given the limitations of using standard echocardiography in pandemic settings, it may be useful to consider the introduction of focal echocardiography. In this case, the determination of LVEF and presence of pericardial effusion, as well as PASP measurement, will not take much time [57].

Conclusions

1. Left ventricular ejection fraction and serum levels of troponin I were found to be the most significant indicators of the condition of the cardiovascular system and predictors of hospital survival and mortality in patients with COVID-19.
2. Left ventricular ejection fraction, which is independent of sex, age and severity of lung damage, determines poor hospital prognosis.
3. Pulmonary artery systolic pressure and pericardial effusion are predictors of hospital survival and mortality.

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4. Autopsy data showed that patients with intermediate and reduced left ventricular ejection fraction most often have changes indicative of a history of myocardial infarction and / or left ventricular hypertrophy.
5. Focal echocardiography can be recommended as a standard examination to make a hospital prognosis in case of inpatient treatment.

No conflict of interest is reported.

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