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Clinical and Morphological Features of Myocardial Infarction in Patients With a New Coronavirus Infection COVID-19

Aim	To analyze fatal outcomes of myocardial infarction (MI) in patients after COVID-19.
Material and methods	Data of pathoanatomical protocols and case histories of 612 patients managed in clinics of the Siberian State Medical University from 01.01.2020 through 31.12.2021 were studied. 68 (11%) of these patients were transferred to the clinics from respiratory hospitals for rehabilitation after the novel coronavirus infection. The main condition for hospitalization was a negative polymerase chain reaction (PCR) test for SARS-CoV-2 virus RNA. 544 (89%) of patients had no history of COVID-19. The incidence of MI was 14% (7/68) in patients after COVID-19 and 10% (74/544) in patients who have not had it. In pathoanatomical protocols and case histories of 81 patients diagnosed with MI, macroscopic and histological changes in the heart, pericardial cavity, coronary arteries, and laboratory results were evaluated. Statistical analysis was performed with a STATISTICA version 10.0 software package.
Results	The patients after COVID-19 had a lower percentage stenosis, more frequent coronary artery thrombosis, and a positive D-dimer. According to our data, MI emerged 10.0 (2.0; 21.0) days after admission to the hospital, had a larger area, always was transmural, and rapidly resulted in death; the time of necrotic changes in all cases did not exceed 24 h. Upon admission to the hospital, the PCR test for SARS-CoV-2 virus RNA was negative, and acute inflammatory changes were stopped at the previous stage of hospitalization.
Conclusion	The risk of coronary thrombosis in patients after COVID-19 remains after the relief of acute inflammatory response and elimination of the infectious agent, thereby creating a risk of MI, that often leads to a fatal outcome.

Keywords	Myocardial infarction; novel coronavirus infection; COVID-19; coronary thrombosis
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Introduction

According to the World Health Organization, cardiovascular mortality increased by 25% during the COVID-19 pandemic [1]. Myocardial infarction (MI), as well as acute cerebral pathology, is the main cause of death in cardiovascular patients. According to the Russian Statistics Agency, the incidence of acute MI in Russia was 141.1 and 133.1 per 100,000 people in 2019 and 2020, respectively. Mortality of MI was 38.8 per 100,000 in 2018 and 39.7 per 100,000 people in 2020 [2]. MI significantly aggravates the course of COVID-19 and increases the rate of death [3–6].

The risk of MI is usually associated in patients with COVID-19 with the acute phase of viral infection. MI occurs mainly within 1 week after the onset of the disease. In this period, much significance is given to the direct damaging effect of the virus on vascular endothelial cells [7] and the so-called cytokine storm [8]. The virus enters cardiomyocytes by binding S-protein with angiotensin-converting enzyme 2 (ACE2) and disrupting signal pathways [9, 10]. The direct mechanism of the virus effect is considered to be the activation, damage, dysfunction, and apoptosis of endothelial cells, blocking of ACE2 receptors, and platelet activation, which leads to hypercoagulation [7, 8, 11]. Pro-inflammatory cytokines (interleukin-1, tumor necrosis factor alpha) activate macrophages that synthesize collagenases, peptidases, and tissue factor [12, 13]. Collagenases destroy the structure of the atherosclerotic plaque cap, which contributes to their destabilization in the coronary arteries [14, 15]. Being a procoagulant, tissue factor leads to the state of hypercoagulation and clotting on unstable plaques [16, 17]. Coronary artery thrombosis, increasing hypoxia, and direct damage to cardiomyocytes in the acute phase of COVID-19 lead to the development of MI [18, 19].

Hypoxia caused by the development of viral pneumonia with the involvement interstitial tissue of the lung is an obvious pathogenetic factor in the development of MI in COVID-19 patients. In such cases, MI occurs in week 2 of the course of the infectious process [20], which is common in patients with severe COVID-19 [21]. The mismatch between increasing hypoxia and the increased need of the myocardium in oxygen due to activation of the sympathetic system, tachycardia, and hypotension plays an important role in the pathogenesis of MI in this period [22].

It should be emphasized that the risk of MI also increases on day 28 after the onset of COVID-19. These terms are explained by secondary nosocomial pneumonia and the aggravation of existing hypoxia [6].

Markers associated with a high risk of death in MI patients were found. Troponin I and D-dimer are considered to be such markers. Elevated troponin I was found more often in the death cases than its normal values [23]. D-dimer is a product of fibrin degradation and a reliable prognostic marker associated with high mortality in COVID-19 [24].

It is of interest to study the clinical and morphological features of MI in patients with the history of COVID-19 in whom acute inflammatory changes, hypoxia, and hypercoagulation have been stopped, and the risk of acute cardiovascular complications has seemingly disappeared.

Objective

Analyze deaths of MI in patients with the history of COVID-19.

Material and Methods

The study was performed following of the Declaration of Helsinki.

Lethal outcomes were studied in 612 patients treated in the Siberian State Medical University (SibMed) clinics from 01.01.2020 to 31.12.2021. Of them, 68 (11%) patients were transferred to the SibMed clinics from respiratory hospitals for post-COVID-19 rehabilitation. 544 (89%) patients had no documented history of COVID-19. The main condition for hospitalization was a negative polymerase chain reaction (PCR) test for SARS-CoV-2 RNA.

The group of patients with COVID-19 history included 37 (54%) male and 31 (46%) female patients; mean age was 72.0 years. The group of patients without COVID-19 history included 276 (51%) male and 268 (49%) female patients; mean age was 71.0 years.

The incidence of MI did not differ in the study groups and was 14% (7/68) in patients with the history of COVID-19 and 10% (74/544) in patients without COVID-19 history.

The duration of treatment in respiratory hospitals of patients admitted to the clinics for post-COVID-19 rehabilitation did not differ between the groups with and without MI (24.0 [21.0; 32.0] days and 30.0 [24.0; 30.0] days respectively).

Patients were treated following the available clinical guidelines.

The reports of pathological studies and data from case records of patients with documented MI were studied. Macroscopic and histological changes in the heart and pericardial cavity were investigated. There were 6 types of atherosclerotic changes in coronary arteries: type I – initial changes, type II – spots and stripes, type III – preatheroma, type IV – atheroma, type V – fibroatheroma, type VI – complicated lesions [25]. Stable plaques with a dense fibrous cap and unstable atherosclerotic plaques with destroyed caps, cap hemorrhage, and clotting in the coronary arteries were analyzed separately [26, 27]. The localization and percentage of stenosis, localization of unstable plaques, and coronary artery thrombosis were taken into consideration. The state of the pericardial cavity, weight and dimensions of the heart, myocardial consistency, localization of postinfarction cardiosclerosis (PICS) and MI were studied. In PICS and MI, the conditional size of the lesion was calculated as the product of the largest length and the largest width of the lesion in millimeters. Histological study of the myocardium took into account the presence of karyopycnosis, karyolysis, loss of transverse striation, cardiomyocyte fragmentation, the severity of inflammatory infiltration, the presence of perivasal and diffuse fine-meshed fibrosis. Comorbidities, complications, immediate cause of death were taken into consideration. Glomerular filtration rate calculated using the CKD-EPI formula was analyzed. Such laboratory data as the levels of high-sensitivity troponin, total fibrinogen, activated partial thromboplastin time (aPTT), and D-dimer were analyzed.

The collected data were processed using Statistica 10.0. Base statistics and non-parametric criteria were used for the data analysis. The frequencies rates of feature detection were determined by descriptive statistics – n (%). They were compared using a paired difference test. Quantitative variables were expressed using the medians and the lower and upper quartiles (Me [LQ; UQ]). The statistical significance of differences between the two samples was determined using the Mann-Whitney test (independent samples). Differences were statistically significant with p less than 0.05.

Results

The investigation of clinical parameters and morphological manifestations of pathological processes in MI in the groups of patients with and without the documented history of COVID-19 allowed identifying

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several features. There were no differences in sex, age, height, weight, body mass index, the presence and severity of obesity (Table 1).

The state of the pericardial cavity, shape, dimensions, weight of the heart, and the contents of the heart chambers also did not differ significantly. The myocardial consistency was more often flabby in the group of patients with the history of COVID-19 (Table 2).

In patients with the history of COVID-19, compared to patients without the history of COVID-19, atherosclerotic plaques type V–VI were detected more often: 1/7 (14%) and 0/74, respectively (p = 0.0006). Unstable plaques were detected in the study groups with approximately the same frequency: in 5/7 (71%) observations in the group with the history of COVID-19 and in 46/74 (62%) cases in the group without the history of COVID-19. However, simultaneous damage of the left and right coronary artery ostia in the group with the history of COVID-19 were found 10 times more often than in the group without the history of COVID-19 (1/5 (20%) and 1/46 (2%) respectively; p=0.025).

Patients with the history of COVID-19, compared to the group of patients without the history of COVID-19, had atherosclerotic lesions with less severe stenosis (80.0 [70.0; 80.0] % and 90.0 [80.0; 90.0] % respectively; p=0.003), stenosis was determined in the left coronary artery ostium more often (5/7 (72%)) than in the group without the history of COVID-19 (29/74 (39%); p = 0.047).

Coronary artery thrombosis was more common among patients with the history of COVID-19 (3/7 (43%) of cases) compared to the group without the history of COVID-19 (9/74 (12%); p = 0.013).

Table 1. Clinical characteristics of patients with myocardial infarction depending on the presence of the history of COVID-19

Parameter	No history of COVID-19 (n = 74)	History of COVID-19 (n = 7)	p
Male	37 (50 %)	5 (71 %)	0.191
Female	37 (50 %)	2 (29 %)	0.283
Age, years	78.0 [65.0; 84.0]	65.0 [60.0; 67.0]	0.069
Height, cm	165.0 [160.0; 174.0]	170.0 [164.0; 176.0]	0.309
Weight, kg	80.0 [61.0; 100.0]	94.0 [60.0; 130.0]	0.401
BMI, kg/m^2	29.0 [24.2; 34.0]	32.0 [20.8; 40.1]	0.516
Obesity	35 (47 %)	4 (57 %)	0.353
Severity of obesity			
I	22 (63 %)	2 (50 %)	0.360
II	7 (20 %)	0	0.257
III	6 (17 %)	2 (50 %)	0.194

BMI, body mass index. Data are expressed as the absolute and relative numbers (n (%)) or the medians and the upper and lower quartiles (Me [LQ; UQ]).

86% (6/7) of patients with the history of COVID-19 and 78% (58/74) of patients without the history of COVID-19 had chronic coronary artery disease. PICS was detected in 86% (6/7) of patients with the history of COVID-19. The incidence of PICS in patients without the history of COVID-19 was 74% (55/74). There were no statistically significant differences. In the group of patients with the history of COVID-19, the area of replacement fibrosis was more often (3/7; 43%) localized in the anterior left ventricular (LV) wall, in the group of patients without the history of COVID-19 – in the anterior (26/74; 35%) and posterior (19/74; 25%) LV walls. Conditional size of PICS zone did not differ in the study groups. Perivasal (6/7; 86%) and diffuse (6/7; 86%) fine-meshed fibrosis was more often found in the myocardium of patients with the history of COVID-19 compared to patients without the history of

Table 2. Morphological characteristics of the pericardial cavity and the heart in patients with myocardial infarction depending on the presence of the history of COVID-19

Parameter	No history of COVID-19 (n=74)	History of COVID-19 (n=7)	p
Volume of pericardial transudate, ml	20.0 [5.0; 60.0]	20.0 [5.0; 60.0] see Table 1	–
Heart weight, g	500.0 [400.0; 680.0]	610.0 [460.0; 940.0]	0.229
Heart shape			
• Cone-shaped	29 (39 %)	2 (29 %)	0.390
• Spherical	45 (61 %)	5 (71 %)	0.332
Heart length, cm	13.0 [12.0; 15.0]	16.0 [13.0; 17.0]	0.128
Transverse heart diameter, cm	13.0 [10.0; 15.0]	13.0 [12.0; 16.0]	0.573
Left ventricular myocardial thickness, mm	18.5 [18.0; 20.0]	20.0 [16.0; 21.0]	0.539
Right ventricular myocardial thickness, mm	3.0 [3.0; 4.0]	4.0 [3.0; 5.0]	0.271
Left ventricular myocardial hypertrophy	74 (100 %)	7 (100 %)	0.500
Right ventricular myocardial hypertrophy	10 (13 %)	2 (29 %)	0.291
Myocardial consistency			
• Elastic	22 (30 %)	0	0.231
• Dense elastic	2 (3 %)	0	0.414
• Flabby	50 (67 %)	7 (100 %)	0.043
Contents of the heart chambers			
• Empty	2 (3 %)	0	0.414
• Liquid blood	12 (16 %)	2 (29 %)	0.332
• Clots	4 (5 %)	0	0.382
• Blood and clots	51 (69 %)	4 (57 %)	0.311
• Left ventricular parietal thrombi	5 (7 %)	1 (14 %)	0.307

COVID-19 (41/74 (55%; p=0.045) and 40/74 (54%; p=0.045), respectively).

Pathological studies in the group of patients with the history of COVID-19 allowed diagnosing acute MI in 14% (1/7) of cases, repeated MI in 57% (4/7), and repeated recurrent MI in 28% (2/7). In the group without the history of COVID-19, acute MI was diagnosed in 24% (18/74), recurrent MI in 7% (5/74), repeated MI in 54% (40/74), and repeated recurrent MI in 15% (11/74) of observations. The number of cases with different variants of MI did not differ in the study groups. Type 1 MI was diagnosed in all cases in the group with the history of COVID-19. In the group without the history of COVID-19, 1 (1%) of 74 patients had type 2 MI.

In both patient groups, MI was more often localized in the anterior LV wall: in 57% (4/7) of cases in the group with the history of COVID-19 and in 31% (23/74) of patients without the history COVID-19. In patients with the history of COVID-19, all cases (7/7; 100%) of MI were characterized by transmural lesions, and necrotic changes corresponded to the term of up to 24 hours in all cases (7/7; 100%), which was consistent with the clinical data and differed significantly from the group of patients without the history of COVID-19 (46% (34/74), p=0.006 and 71% (53/74), respectively, p=0.045). The conditional size of necrotic myocardial changes in the group of patients with the history of COVID-19 was 4.2 times larger than the conditional size of MI in patients without the history of COVID-19 (2500.0 [1645.0; 3600.0] and 600.0 [300.0; 1200.0] respectively; p = 0.0003).

Positive D-dimer was more common among patients with the history of COVID-19 (5/7 (72%) of cases) compared to the group without the history of COVID-19 (4/74 (5%); p = 0.0000). Levels of high-sensitivity troponin, total fibrinogen, international normalized ratio, and aPTT did not differ in the study groups (Figure 1).

Hypertensive heart disease or diabetes mellitus were detected as comorbidities in patients with MI. The frequency of detection of these diseases did not differ in the study groups. Chronic kidney disease (CKD) was diagnosed in 43% (3/7) of patients with the history of COVID-19 and 65% (48/74) of patients without the history of COVID-19. There were no significant differences in stages of CKD and glomerular filtration rate in patients with and without the history of COVID-19 (Table 3).

In the study groups, complications of MI, such as cardiogenic shock, acute heart failure (AHF), acute renal failure (ARF), pulmonary edema, cerebral edema, gastric erosion, thromboembolism, chronic heart failure (CHF), occurred with approximately the same frequency. The histological study of kidney tissue showed that the history of tubulonecrosis was more common in patients with the history of COVID-19 (7/7 (100%)) than in the group of patients without the history of COVID-19 (52/74 (70%); p = 0.045). In patients with the history of COVID-19, tubular necrosis was total in all cases (7/7; 100%), unlike in the group of patients without the history of COVID-19 (29/52 (56%); p = 0.014). CHF stage 3 was detected in patients with the history of COVID-1910 times more often than in the group of patients without the history of COVID-19 (50% (1/2) and 5% (4/74) respectively; p=0.0001).

In MI patients with the history of COVID-19, the most common immediate causes of death were cardiogenic shock (4/7; 57%) and acute cardiopulmonary failure (3/7; 43%); in the comparison group – cardiogenic shock (33/74; 44%). Such conditions as hemorrhagic shock, ARF, CHF, septic shock, hepatic failure, massive pulmonary embolism was registered as the immediate cause of death less often (Figure 2).

The duration of hospital stays different in the study groups. Thus, the duration of hospital stay was longer for patients with the history of COVID-19 that patients without the history of COVID-19 (11.0 [3.0; 22.0] days and 6.0 [1.0; 11.0] days respectively; p = 0.05). Moreover, MI developed in patients with the history of COVID-19 after 10.0 [2.0; 21.0] days from the hospitalization for the rehabilitation for persistent signs of respiratory failure and the onset of MI was registered in the group of patients without the history of COVID-194.0 [0; 10.0] days after the hospitalization.

Table 3. Comorbidities in patients with myocardial infarction depending on the presence of the history of COVID-19

Parameter	No history of COVID-19 (n = 74)	History of COVID-19 (n = 7)	p
Hypertensive heart disease	72 (97 %)	7 (100 %)	0.381
Diabetes mellitus	32 (43 %)	4 (57 %)	0.299
Type of diabetes mellitus			
1	2 (6 %)	0	0.379
2	30 (94 %)	4 (100 %)	0.340
Chronic kidney disease	48 (65 %)	3 (43 %)	0.223
Stages of chronic kidney disease			
S2	5 (10 %)	0	0.331
S3A	8 (17 %)	1 (33 %)	0.314
S3B	15 (31 %)	1 (33 %)	0.478
S4	15 (31 %)	1 (33 %)	0.478
S5	4 (8 %)	0	0.351
Glomerular filtration rate, mL/min/1.73m^2	36.0 [21.0; 45.0]	43.5 [29.0; 54.0]	0.487

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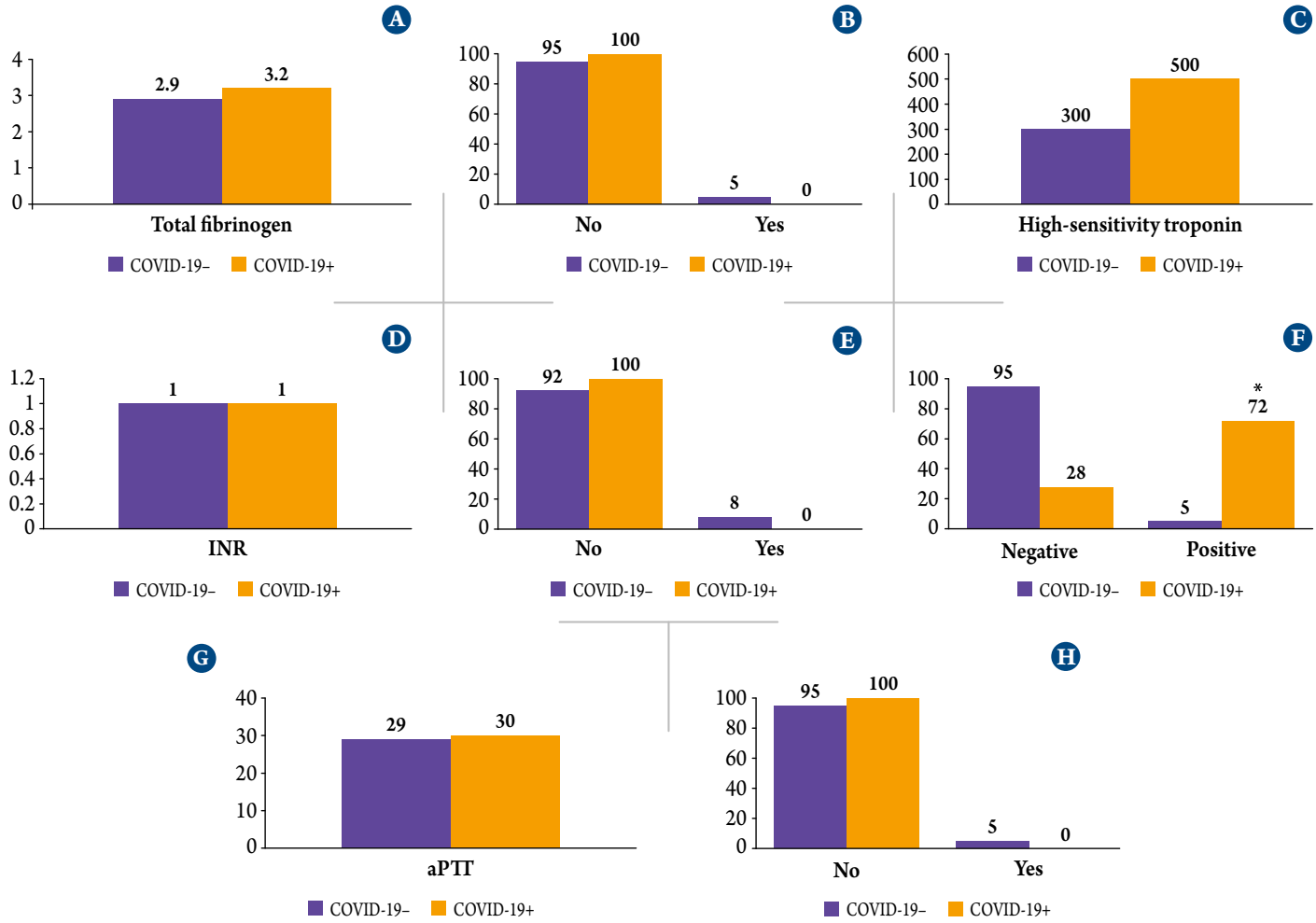
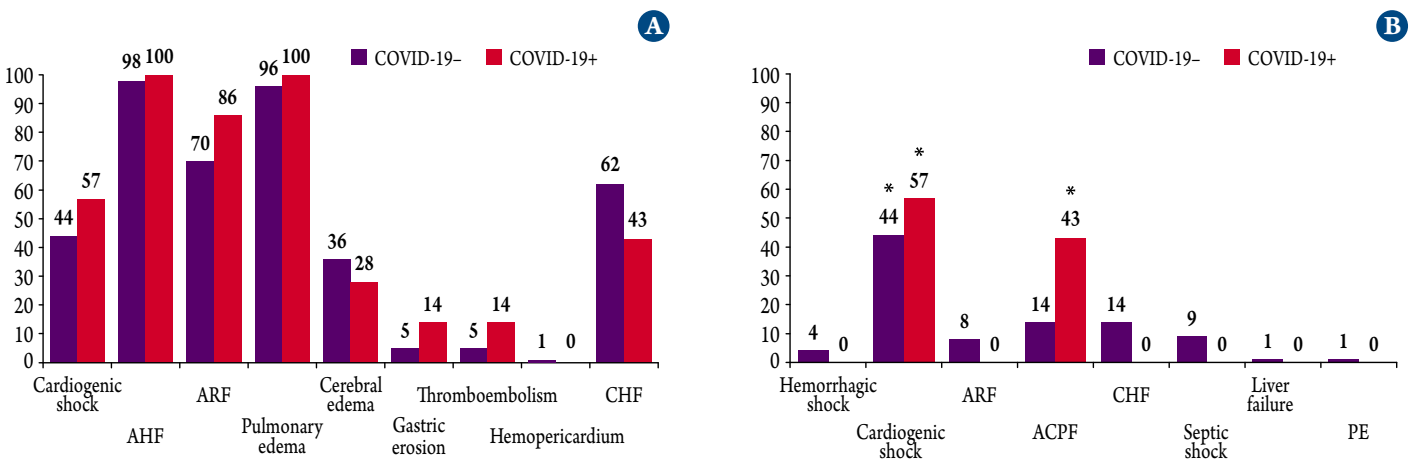
Figure 1. Laboratory data in patients with myocardial infarction depending on the presence of the history of COVID-19



A – total fibrinogen, g/l, Me [Q1; Q3]; **B** – elevated total fibrinogen, n (%); **C** – high-sensitivity troponin, pg/ml, Me [Q1; Q3]; **D** – INR, Me [Q1; Q3], **E** – decreased INR, n (%); **F** – D-dimer, n (%); **G** – aPTT, s, Me [Q1; Q3]; **H** – decreased aPTT, n (%); * – significant differences ($p<0.05$).

Figure 2. Complications and immediate causes of death of patients with myocardial infarction depending on the presence of the history of COVID-19



A – complications of myocardial infarction, n (%); **B** – immediate cause of death, n (%); * – significant differences ($p<0.05$).

Discussion

The groups of patients with and without the history of COVID-19 did not differ statistically significantly in the incidence of MI, sex, age, height, weight, body mass index, and comorbidities. At the same time, signs were discovered during the study that allow describing the features of the etiology, pathogenesis, morphological and clinical manifestations of MI that occur in patients with the history of COVID-19. For example, a smaller percentage of stenosis and more frequent coronary artery thrombosis are indicative of the important role of clotting in the development of MI in the patient population of interest. The tendency to hypercoagulation is also shown by elevated D-dimer levels. All the above is consistent with the available data on the role of clotting in the development of MI in COVID-19.

In patients with the history of COVID-19, MI had larger focus, was always transmural, and caused rapid death – necrotic changes detected in the autopsy study did not exceed 24 hours in all cases. It is possible that such clinical and morphological features may be associated with previous viral damage to cardiomyocytes and kidney tissue.

It should also be pointed out that MI developed in patients with the history of COVID-19 after 10.0 [2.0; 21.0] days from the hospitalization for the rehabilitation for persistent signs of respiratory failure, and the duration of the previous stage of hospital treatment was 24.0 [21.0; 32.0] days.

Conclusion

The study showed that the risk of clotting in the coronary arteries in patients with the history of COVID-19 persists after the relief of signs of the acute inflammatory response and the elimination of the infectious agent, which creates a threat of myocardial infarction. It is possible that the severity of clinical and morphological manifestations of myocardial infarction and its complications in patients with the history of COVID-19 may be due to structural changes in the myocardium and kidneys. The authors hope that the data obtained can be used to determine the strategy of managing such patients during their rehabilitation in medical hospitals.

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