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LEADING ARTICLE

COVID-19 and cardiovascular diseases

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Abstract

The new infectious disease caused bySARS-CoV-2 virus (COVID-19) is commonly seen in patients with cardiovascular risk factors and cardiovascular diseases (CVDs) that can affect the course of infectious process. At the same time, the virus can cause additional damage of heart and vessels, lead to cardiovascular complications and aggravate the course of CVDs. This review article presents the main findings on interaction between these pathologies as well as recommendations for the management of patients with COVID-19 and cardiovascular diseases.

Key words: *COVID-19, cardiovascular diseases.*

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Covid-19 and cardiovascular diseases: statistics

According to the available data, the incidence of cardiovascular risk factors and cardiovascular diseases (CVDs) is high in patients with COVID-19.The most common concomitant CVD is arterial hypertension (AH) (Table 1). However, it is obvious that the results of the studies highly depend on the region, selection approaches of patients for hospitalization, as well as their average age. Obtained data requires further systematization, and, therefore, current findings on the frequency of various cardiovascular risk factors and CVDs in patients with COVID-19 will be refined and adjusted in future.

COVID-19 and cardiovascular diseases: interaction features

Many studies claim that COVID-19 in patients with CVD is characterized by more severe course and has worse prognosis.

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Table 1. **The frequency of cardiovascular risk factors and CVDs in patients diagnosed with COVID-19 and admitted to the hospital**

	Inciardi R.M. et al. [1]	Goyal P. et al. [2]	Cummings M.J. et al. [3]	Myers L.C. et al. [4]	Guo T. etal. [5]	Shi S. et al. [6]	Guan W. et al. [7]
Number of patients	99	393	257 with acute hypoxemic respiratory failure	377	187	671 with severe COVID-19	1099
Patient's selection procedure	Consecutive admissions with pneumonia, retrospective analysis	Consecutive admissions, retrospective analysis	Prospective cohort study	Retrospective cohort study	Retrospective analysis of electronic records	Retrospective analysis of electronic records	Retrospective analysis of electronic records
Hospitals	1 hospital inBrescia (Italy)	1 hospital in New York (USA)	2 hospitals in New York (USA)	47 hospitals in California	1 hospital in Yuhan (China)	1 hospital in Yuhan (China)	552 hospitals in 30 regions of China
Period of data collection	4–25 of March, 2020	3–27 of March, 2020	March 2nd — April 1st, 2020	1–31 of March, 2020	January 23 — February 23d, 2020	January 1st— February 23, 2020	December 11th — January 29th, 2020
Cardiovascular risk factors (according to the anamnesis)							
Age (years)	Mean 67,0	Median 62,2	Median 62,0	Mean 61,0	Mean 58,5	Median 63	Median 47,0
Smokers	20%	5.1%	13% (including patients who quitted smoking)		9.6%		12.6%
Dyslipidemia	30%						
Diabetes mellitus (DM)	31%	25.2%	36%	31.3%	15.0%	14.5%	7.4%
Obesity	23%	35.8%					
Chronickidneydisease (CKD)	15%		14%	12.7%	3.2%	4.2%	0.7%
AH	64%	50.1%	63%	43.5%	32.6%	29.7%	15%
Chronic heart failure (CHF)	21%		19%	5.8%		3.3%	
Coronary artery disease (CAD)	16%	13.7%			11.2%	8.9%	2.5%
Atrial fibrillation (AF)	19%					1.0%	

Retrospective analysis of the data collected from 99 consecutively admitted patients with COVID-19 and pneumonia with known outcomes during the first 14 days after admission to one of the hospitals in Brescia (Northern Italy) showed that 53 patients with CVDs (CHF, AF or CAD) had higher levels of creatinine, NT-proBNP, high-sensitive cardiac troponin, and procalcitonin [1]. At the same time,these patients initially much more often received blockers of the renin-angiotensin-aldosterone system (RAAS), anticoagulants and statins. As a result, patients with concomitant CVDs had higher rates of mortality and septic shock (36% versus 15%, p=0.02 and 11% versus 0, p=0.02, respectively), and also showed tendency for more frequent occurrence of respiratory distress syndrome, as well as venous and arterial thrombosis. Mortality increased with age and also was significantly higher in patients with CHF, CAD, DM, CKD and with higher level of NT-proBNP, but not with the history of RAAS blockers and anticoagulants treatment.

Retrospective analysis of the data from 187 patients at the University Hospital of Wuhan (China) showed13.3% hospital mortality rate in patients without CVD and normal cardiac troponin level and 37.5% — in patients with CVD and normal cardiac troponin level, 69.4% — in patients with combination of CVD and increased cardiac troponin level [5]. At the same time, the level of cardiac troponin more often increased in the elderly patients and patients with CVDs (54.5% versus 13.2%) and correlated with the level of C-reactive protein (CRP) and NT-proBNP. Patients with elevated cardiac troponin levels more frequently had malignant ventricular arrhythmias and required mechanical ventilation (MV)

According to the retrospective analysis of the data from 671 patients admitted with severe COVID-19 to the University Hospital in Wuhan (China), increased level of cardiac troponin I was independently associated with: age, the presence of AH, CAD, CHF and increased level of CRP [6]. At the same time, increased cardiac troponin I, as well as increased level of the MB fraction of creatine phosphokinase and NT-proBNP, were independent predictors of hospital mortality. In addition, CAD and chronic heart

diseases were independent predictors of mortality according to multivariable regression analysis.

The analysis of the data from 5257 patients with acute hypoxemic respiratory failure in New York, revealed the following independent predictors of hospital mortality: age, CAD or CHF [3].

The results of all these researches indicate that more severe course of the disease, including myocardial damage and dysfunction in patients with COVID-19 and CVDs, can be explained by combination of reasons.

1. Cardiovascular system damage in patients with COVID-19.

It was found that endotheliocytes of lungs, small intestine, kidneys, heart, liver is frequently damaged in patients with COVID-19 due to direct exposure to the virus, systemic immune / inflammatory response and so-called "cytokine storm", as well as due to general infectious pathological changes [8–13]. Since endothelial dysfunction plays important role in the pathogenesis of CVDs, we can expect aggravation of its clinical manifestations and / or the occurrence of complications in such patients. COVID-19 is also characterized by inflammatory changes in the myocardium with corresponding complications (heart failure, cardiac arrhythmias and conduction disorders) [14]. In addition, cardiovascular system can be damaged due to the progression of existing CVDs, as well as severe dysfunction of other organs (lungs, kidneys, liver).

Thrombus formation is activated during COVID-19 that in most severe cases can lead to consumptive coagulopathy and consumptive thrombohemorrhagic disorder. [15–18]. These processes contribute to the appearance of thrombotic / thromboembolic complications (mainly venous) [19]. In addition, microangiopathy with inflammation and thrombosis without thromboembolism has been described in patients with COVID-19that may be associated not only with the activation of thrombus formation processes, but also with the possible direct endothelium damage by SARS-CoV-2 virus, as well as severe immune inflammation that triggers "immunothrombosis" [8–10]. It is believed that such changes contribute to progressive lung damage during COVID-19. These data also confirm the hypothesis of atherosclerotic plaques destabilization and increased risk of "typical" atherothrombotic complications in patients with COVID-19.

The data on incidence of thrombotic / thrombo-embolic complications in admitted patients with COVID-19 are presented in Table 2. The true incidence

Table 2. **Thrombotic / thromboembolic complications in admitted patients with COVID-19**

Patient contingent	Thrombosis prevention, heparin dose	Total number of thrombotic/ thromboembolic complications	Deep vein thrombosis (DVT) in the lower extremities / pulmonary embolism (PE)	Other thrombosis
388 (362closed cases), 16 % Transferred to intensive care unit (ICU). Doppler ultrasound (DU)/ Computer tomography (CT) due to clinical manifestations [20]	In 75 % not from ICU In 100 % of patients from ICU (intermediate doses 21 %, therapeutic doses 23 %)	7.7 %: in 6.6 %, not from ICU, in 27.6 % from ICU. Half during the first 24 hours after admission.	DVT 4.4 % PE 2.8 %	Ischemic stroke 2.5 % Acute coronary syndrome (ACS) 1.1 %
184 patients with pneumonia in ICU. DU/CT due to clinical manifestations [21]	In all patients (doses were elevated from preventive to intermediate during treatment)	16.8 %	DVT 1.6 % PE 13.6 %	Ischemic stroke, Myocardial infarction (MI) or arterial thromboembolism 1.6 %
198 patients, 37 % in ICUrequiring MV. DU/CT due to clinical manifestations [22]	In all patients (doses close to intermediate)	17 %: 3.2 % in patients not from ICU; 39 % in patients from ICU	DVT11 %: 1.6 % not in ICU, 27 % in ICU PE 5.6 %: 1.6 % not in ICU, 12 % in ICU	
81 patients with severe pneumonia in ICU. DU in all patients [23]	No		25 %	
143 patients, 74.2 % with severe disease course DU in all patients [24]	37.1 %		DVT 46.1 % (34.8 % proximal) — 34.0 % with prevention, 63.3 % without prevention	
452 patients, CT due to clinical manifestations [25]	Not known; 79.3 % of patients with confirmed pulmonary embolism received preventive doses of low-molecular-weight heparin		PE 6.4 %	

of such complications, as well as the effectiveness of different approaches for its prevention, is currently difficult to assess due to significant differences between conducted studies — mainly retrospective studies (databases, medical records analysis), different disease severity in included patients, different approaches for preventionand diagnosis of thrombosis / thromboembolism (usually studies include only patients with clinical manifestations). However, it is obvious that the risk of venous thromboembolic complications increases with disease severity and additional risk factors accumulation.

2. Modification of CVD treatment in patients with COVID-19.

Discontinuation or significant reduction in doses of CVD treatment in patients with COVID-19 has potentially adverse consequences and increases the risk of CVD complications. Such medications include: RAAS inhibitors and beta-blockers in patients with CHF with reduced left ventricular ejection fraction, myocardial ischemia control agents, including antiarrhythmic therapy to prevent life-threatening or severe heart rhythm disturbances in patients with the history of myocardial infarction, antihypertensive treatment in patients with arterial hypertension.

3. Cardiotoxicity of medications used for COVID-19 prevention and treatment.

4. The impact of COVID-19 on health services and lack of resources for timely CVD treatment.

In addition to the lack of resources for the treatment of non-communicable diseases during COVID-19 pandemic, modern (especially invasive) methods for CVD diagnosis and treatment are limited, that is associated with anti-epidemic measures, reduction of contacts with potentially infected patients and limited examinations due to increased risk of contamination. For example, experts from the European Society of Cardiology proposed to increase the amount of time before primary percutaneous coronary intervention in patients with ACS with persistent ST-segment elevation to 60 minutes that will potentially increase mortality, especially in the first hours after the MI onset [14].

5. Psychological consequences of the COVID-19 pandemic associated with quarantine, increased stress level and the fear of hospitals due to possible COVID-19 contamination (including patients with acute CVD manifestations).

The number of hospitalizations for MI significantly decreased in Northern California from January 1 to April 14, 2019 compared with 2020 and correlated with the number of COVID-19 cases [26]. A similar pattern of MI hospitalizations was noted in northern Italy [27]. In one of the regions of Italy the number of percutaneous coronary interventions for acute coronary syndromes (per 100,000 inhabitants) decreased by 32 % during the COVID-19 outbreak compared with 4 weeks before the beginning of the epidemic and decreased by 50 % in the last 2 weeks of the observation period (when the number of diagnosed COVID-19 cases increased) [28]. This decrease was especially pronounced in patients aged over 55 years old.

According to multicenter national registry of patients who were admitted to intensive care units in Italy, from March 12 to 19 during the COVID-19 pandemic the number of hospitalizations for MI significantly decreased by 48 % compared with the same week in 2019 (MI with ST segment elevation on the electrocardiography (ECG) — by 26.5 %, MI without ST segment elevation on the ECG — by 65.1 %), and this pattern was observed in all regions of the country (northern, central and southern) [29]. At the same time mortality rate (relative risk (RR) 3.3; p <0.001) and the frequency of most severe complications — cardiogenic shock, life-threatening arrhythmias, myocardial rupture and severe mitral regurgitation, significantly increased (RR 1.8; p=0.009). However, mortality rate in patients with MI with ST segment elevation on ECG did not increase, when severe complications occurred more frequently (RR 2.1; p=0.037). The frequency of coronary angiography did not decrease (94.9 and 94.5 %, respectively). The number of hospitalizations for heart failure (by — 46.8 %) and AF (by — 53.4 %) significantly decreased.

The reasons for this phenomenon are being analyzed and include both lack of health care system resources and the fear of patients to stay at the hospital and, therefore, the admission of patients with worst prognosis. The rate of hospitalization refusal and their outcomes are worth further investigation.

6. Possible prehospital sudden death rate increase.

The analysis showed that the frequency of cardiac death increased by 52 % outside the hospital in 4 provinces of Italy in the Lombardy region from February 21 to April 20, 2020 compared with the same period in 2019 [30]. At the same time, emergency medical teams arrived later in 2020 (15 minutes versus 12 minutes in 2019; p <0.001) and less often restored spontaneous circulation (8.6 versus 19.8 % in 2019; p <0.001). Proven or possible COVID-19 disease was reported in 74 % of prehospital circulatory arrest cas-

es. During the COVID-19 epidemic the frequency of visits for medical care increased by 94.1 %, while the number of visits due to MI with ST segment elevation decreased by 40.2 %. This may be the consequence of COVID-19 severe clinical manifestations (including in combination with CVD).

Features of cardiovascular diseases diagnosis during COVID-19 pandemic

The approaches to CVD diagnosis during COVID-19 pandemic remain the same. At the same time, scheduled diagnostic procedures may be postponed until pandemic's end in order to reduce the risk of infection transmission and protect healthcare workers.

Patients with severe course of COVID-19 may need additional differentiation of infectious disease progression from the onset of CVD or its complications. For example, D-dimer blood concentration increases in patients with COVID-19 that indicates disease progression and poor prognosis, but not always thrombotic / thromboembolic complications [31,32].

Differential diagnosis of increased cardiac troponin blood level that indicates cardiomyocytes damage is another issue of special concern [11,12]. It can be explained by the occurrence of ischemic myocardial necrosis due to atherothrombosis that lead to myocardial infarction, or myocardium oxygenation imbalance due to hypoxia, hypotension, tachyarrhythmia, etc. (that lead to type 2 MI). In addition, patients with COVID-19 showed other, non-ischemic causes of myocardial damage (necrosis) — myocarditis, microangiopathy with inflammation and thrombosis, takotsubo /stress cardiomyopathy, general infectious process consequences (for example, myocardial damage in patients with sepsis), massive pulmonary embolism. The detection of the cause is essential for the choice of patient treatment strategy (for example, the dual antiplatelet therapy in patients with acute coronary syndrome and additional anticoagulant in patients without type 1 myocardial infarction may be excessive). Obviously, myocardial damage with various manifestations / complications is associated with more severe course of COVID-19.

Features of CVD prevention and treatment during the COVID-19 pandemic

Patients with COVID-19 need to follow standard (recommended) approaches for prevention and treatment of CVD. This is especially important during the COVID-19 pandemic, since an infectious disease contributes to additional cardiovascular system damage and aggravates the course of existing CVDs. However, it was recommended to limit instrumental investigations (especially invasive) and treatment of CVD in patients with less severe cases, when it will not lead to clinical course and prognosis deterioration, in order to reduce the spread of infection and to protect healthcare workers [14]. At the same time, hospitals should attempt to distinguish patients with suspicious or diagnosed COVID-19 and documented absence of the disease [14]. However, the data revealed that existing COVID-19diagnostic methods are limited, especially on early stages. As a result, all admitted patients should be considered potential carriers of the SARS-CoV-2 virus until proven otherwise. Unfortunately, this can be time-consuming, while the treatment of the CVDs cannot be postponed.

When treating patients with CVD and COVID-19, drug interactions should be considered. Such information is published by the group on drug interactions of the University of Liverpool [33], as well as presented in documents prepared by other expert groups [14,16].

It is not clear yet if CVD treatment can affect the incidence and severity of COVID-19. Thus, a wide discussion on the possible role of ACE inhibitors/ angiotensin receptor blockers did not reveal any unambiguous answer: on the one hand, according to pathophysiology, patients who receive ACE inhibitors/ angiotensin receptor blockers should have more severe course of COVID-19, on the other hand, there are clinical evidences of neutral and even positive effect of this group of medications on the course of the disease [1, 5, 29, 34–42]. Some studies also showed lower hospital mortality rate in patients with COVID-19 who received statins [29, 43]. At the same time, it should be noted that these data were obtained from retrospective analysis and are not reliable enough from the perspective of evidence-based medicine.

According to available data on the COVID-19 pathogenesis, it is recommended to use heparin (preferably low molecular weight) in all admitted patients for deep vein thrombosis prevention, with the possibility intermediate dose titration (aboveusual preventive, but below therapeutic) or even therapeutic, in patients with low risk of bleeding [16, 44–46]. There is no consensus on the optimal dose of anticoagulants in patients with COVID-19, but many specialists recommend higher (at least intermediate) doses in patients with severe disease course, when expected frequency of thrombosis / thromboembolism is high, and microvascular thrombosis can be suspected.

However, high doses of anticoagulants can cause hemorrhage into the lung tissue with hemorrhagic pneumonitis in patients on mechanical ventilation [47, 48]. Verified thrombotic / thromboembolic complication is an indication for therapeutic doses of anticoagulants, however, in clinical practice, they can be used in patients with suspicious clinical symptoms when instrumental examination is not available or is postponed [16, 44–46]. One of the arguments for heparin administration in patients with COVID-19 is its pleiotropic and anti-inflammatory effect [49].

Antithrombotic treatment discontinuation due to drug interactions or thrombohemorrhagic syndrome development with consumption coagulopathy can lead to adverse consequences. In particular, is not recommended to use antiplatelet agents in patients with low platelet count [15, 16]. Due to significant change of antithrombotic activity of clopidogrel (decrease) and ticagrelor (increase), they are not recommended to be prescribed together with lopinavir / ritonavir [16].

Some medications that are used to treat COVID-19 can have adverse cardiovascular effects, especially in patients with CVD. For example, chloroquine / hydroxychloroquine can prolong the QT interval and contribute to the occurrence of ventricular arrhythmias, as well as, heart blocks [14]. The length of QT can increase even more when chloroquine / hydroxychloroquine is used together with azithromycin [50].

Before administration of medications that prolong QT interval, experts of the European Society of Cardiology recommend to assess the presence of other risk factors (congenital long QT syndrome, other medications that prolong the QT interval, female gender, age over 65 years, the presence of structural heart disease — reduced left ventricular contractility and myocardial hypertrophy, bradycardia with heart rate below 50 beats per minute, the presence of chronic renal failure, hepatic failure, as well as electrolyte disorders — hypokalemia, hypomagnesemia, hypocalcemia) [14]. All reversible risk of QT interval prolongation and ventricular arrhythmias should be eliminated before the beginning of the treatment. It is also necessary to monitor the ECG with the assessment of the corrected QT interval that should not exceed 500 m/s (or ⩾550 m/s with QRS complex width over 120 m/s) and should not lengthen by over 60 m/s during treatment [14]. It is also recommended to pay particular attention to patients with clinical manifestations of the arrhythmia's onset, as well as patients with vomiting, diarrhea, signs of heart or respiratory failure, and other organs dysfunction.

It is essential to timely suspect the occurrence of CVD aggravation and adjust treatment strategy in patients with COVID-19. After the recovery from COVID-19, it is important to assess its consequences for the cardiovascular system and adjust the treatment, focusing on existing approaches for the management and prevention of various CVDs (there are no specific interventions for patients with COVID-19).

Conclusion

Thus, the COVID-19 adversely affects the course of CVD and vice versa. Therefore, on the one hand, it is essential to maintain effective approaches for the prevention and treatment of cardiovascular complications, on the other hand, to be prepared for more severe course of COVID-19 in such patients. It is necessary to involve the most experienced healthcare professionals for their treatment, who can prevent, recognize and treat not only the new infectious disease and its complications, but also cardiovascular pathology.

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