SCHOLASTIC:
Journal of Natural and Medical Education
Volume 2 Issue 2, Year 2023 ISSN: 2835-303X
https://univerpubl.com/index.php/scholastic

The Course of Covid-19 in Arterial Hypertension and Evaluate the Effectiveness in Diagnosis

Tadjiev B. M.
Doctor of Medicine, Associate Professor at the Tashkent Pediatric Medical Institute, Uzbekistan

Khusanov A. M
Director of the Republican specialized hospital, Zangiata № 1

Khasanova Sh. A.
Basic doctoral student in the 3st year of the Tashkent Pediatric Medical Institute, Uzbekistan

Nurmatov A. X.
Responsible for science

Xaliqova Sh.
Tashkent Pediatric Medical Institute e infectious diseases of children, phthisiology and pulmonology of infectious diseases assistant

Article Information

Received: December 11, 2022
Accepted: January 12, 2023
Published: February 13, 2023

Keywords: *Covid-19.*

ABSTRACT

Cardiovascular disease (CVD) is considered the leading cause of death worldwide, and none other than these is the leading cause of death each year. An estimated 17.9 million people died of CVD in 2016, accounting for 31% of all deaths worldwide. 85% of these deaths were caused by heart attacks and strokes. More than 75% of deaths occur in low- or middle-income countries. 17 million deaths from noncommunicable diseases were observed under the age of 70, with 82% of cases occurring in low- and middle-income countries, of which 37% were due to CVD. According to the World Health Organization (WHO), the number of deaths from CVD in 2019 increased by almost 2 million compared to 2000. Patients with CVD and the associated risk factor, hypertension, are reported to be at greater risk of developing COVID-19 and adverse outcomes due to COVID-19. To reduce the negative impact on the health and economy of the European Region, effective control of CVD is recommended.

Due to the newly identified coronavirus infection, a faster increase in mortality rates has been noted during the pandemic. Taking into account the peculiarities of a large number of deaths due to CVD, scientific research is being carried out all over the world to develop modern methods for diagnosing and treating the disease, in particular, studying the pathogenetic relationship between COVID-19 and CVD; changes in the blood coagulation system in both diseases. Important are the recommendations for individual antiplatelet and anticoagulant therapy for both diseases, depending on changes in the blood coagulation system in each patient.

In order to prevent the wide spread of coronavirus infection, ensure the sanitary and epidemiological well-being of the population and use the capabilities of non-governmental medical organizations in restoring the health of patients, a number of measures were planned. “...

in order to reduce the consequences of the spread of coronavirus infection and organize the provision of effective medical services to patients, the Ministry of Health of the Republic of Uzbekistan has created a reserve of over 5 thousand beds in state medical institutions .. " [1]. Therefore, it becomes necessary to develop an individual approach to the treatment of patients with coronavirus infection, especially patients with CVD, taking into account risk factors for the disease and changes in the hemostasis system.

This dissertation research to a certain extent serves to fulfill the tasks set in the Decree of the President of the Republic of Uzbekistan dated March 26, 2020 No. PP-4649 "On additional measures to prevent the spread of coronavirus infection in the Republic of Uzbekistan", Decree of the President of the Republic of Uzbekistan dated July 25, 2020 No. UP-6035 "On measures to mitigate the consequences of the coronavirus pandemic, fundamentally improve the system of sanitary and epidemiological welfare and public health" [2], Decree No. UP-5969 dated March 19, 2020 "On priority measures to mitigate the negative impact of the coronavirus pandemic and the global crisis on industries economy", temporary recommendations for the treatment of patients with coronavirus infection COVID-19 [3], as well as in other legal documents related to this activity.

The degree of knowledge of the problem. All over the world, the PAI-1 gene and its plasma protein have been studied and are still being studied in various fields of medicine and in various diseases, as well as in people of different nationalities and nationalities. PAI-1 provides a complex and difficult to define biological example of how a single enzyme can act on different tissues and organs. The results of a study in a healthy Turkish population showed that the 4G/4G polymorphism of the PAI-1 gene was associated with high levels of low-density lipoprotein and triglycerides. Evaluation of the PAI-1 gene in a population with hyperlipidemia can determine the prognosis and etiology of the disease (Nurkay Katrancioglu , 2011).

According to a Thai meta-analysis and other published data, homozygous 4G polymorphism is a risk factor for ischemic stroke in Asians, but this is not the case in the Caucasoid population (Anunchai Assawamakin , Narin Sriratanaviriyakul , 2012).

Furthermore, ACE/DD genotype and elevated plasma PAI-1 may be two independent risk factors for myocardial infarction in Chinese hypertensive patients (Jing-Ren Jeng , Horng-Jyh Harn , 1998). In the study on insulin resistance in atherosclerosis (IRAS), differences in CVD rates in 3 ethnic groups were noted. However, low PAI-1 levels in Blacks and high PAI-1 levels in Hispanics compared with previously published data indicate higher rates of CVD in Blacks and lower or similar levels of CVD in Americans than in Hispanics. Another study showed that chronic activation of the renin-angiotensin- aldosterone system, aldosterone levels and insulin resistance was associated with a high degree of PAI-1. In addition, the above data support the hypothesis that aldosterone may be the main mediator of PAI-1 levels in hypertensive patients (Nadarajah Srikumar , 2002).

In our country, this study was conducted in patients with a history of various thromboembolic complications, and in the studied groups, the presence of high 5G/4G heterozygosity was considered polymorphic. A study of patients with coronary heart disease, stable exertional angina and practically healthy individuals, conducted on this issue, revealed the presence of the 4G / 5G genotype of the PAI-1 gene, which increased the risk of developing coronary artery

1Decree of the President of the Republic of Uzbekistan dated March 26, 2020 No. PP-4649 "On additional measures to prevent the widespread spread of coronavirus infection in the Republic of Uzbekistan "

[2]Decree of the President of the Republic of Uzbekistan dated July 25, 2020 No. UP- 6035 " On measures to mitigate the consequences of the coronavirus pandemic, fundamentally improve the system of sanitary and epidemiological welfare and public health"

[3]Temporary recommendations for the management of patients infected with COVID-19 dated 06/30/2020

disease by 1.5 times, and the 4G / 4G genotype by 2.7 times (Khasanova Sh.A., Tajievyu.B.M ., 2017). However, the amount of PAI-1 in plasma in patients with coronary artery disease and COVID-19 has not been studied.

Based on the above data, in modern cardiology, in the field of early diagnosis of this disease and the development of possible thromboembolic complications, an urgent task is to optimize antiplatelet and anticoagulant therapy for patients and develop new treatment algorithms.

Compliance of the dissertation research with the research plans of the higher educational institution where the dissertation was completed. This study was conducted by the "1st Zangiata" hospital in accordance with the research plan on the topic "Study of the relationship between biochemical parameters of blood hemostasis in major diseases of the cardiovascular system and risk factors and the development of preventive measures to reduce morbidity and their correction"

The aim of the study was to evaluate the diagnostic value of the plasminogen activator inhibitor protein (PAI-1) and improve the effectiveness of treatment of patients with and without COVID-19 against the background of coronary artery disease.

Research objectives:

To identify risk factors leading to changes in the plasmin system in patients with IHD and stable exertional angina with/without COVID-19;

to evaluate changes in the plasmin hemostasis system in patients with coronary artery disease, stable exertional angina and with/without COVID-19;

to determine the quantitative content of tissue plasminogen activator inhibitor type 1 (PAI-1) and to determine the leading potentially sensitive markers of thrombus formation in patients with/without COVID-19;

to develop, based on the results of clinical and laboratory studies, a cascade model for the management of patients with stable exertional angina with/without COVID-19 in primary care and hospital settings;

to develop, based on changes in the plasmin system, a differentiated approach to the treatment of patients with IHD, stable exertional angina and with/without COVID-19;

The object of the study was 130 patients who were hospitalized in the cardiology department of the Multidisciplinary Hospital "1st Zangiata Hospital" with a diagnosis of coronary artery disease: stable exertional angina with/without COVID-19.

The subject of the study is venous blood , including the lipid spectrum, coagulogram, indicators of the biochemical, hormonal and fibrinolytic systems.

Research methods The studies were carried out using clinical, functional, instrumental, biochemical, enzyme immunoassays, questionnaires and statistical analysis.

The novelty of the study lies in the following:

for the first time, the marker protein of the plasmin system PAI-1 was evaluated in patients with/without COVID-19 against the background of stable exertional angina, while this protein was significantly increased in patients with COVID-19;

in patients with/without COVID-19 against the background of stable exertional angina, the association between the marker of the plasmin system PAI-1 and the leading risk factors for coronary artery disease was assessed, and the relationship of the PAI-1 protein with anxiety-depressive syndrome, smoking, obesity, and hypercholesterolemia was revealed;

for the first time, changes in the vascular-platelet and renin-angiotensin- aldosterone system were revealed in patients with the PAI-1 plasmin system marker and existing risk factors, as well as a correlation with endothelin , a marker of endothelial dysfunction;

a cascade model for recommending anticoagulant drugs to COVID-19 patients with risk factors for developing coronary artery disease is proposed, taking into account the correlation with indicators of the plasmin system, coagulogram, changes in the renin-angiotensin- aldosterone system and the amount of endothelin .

The practical results of the study consists of the following:

proved the practical significance of determining the PAI-1 protein in plasma in patients with IHD and stable exertional angina for predicting the progression of the disease and the development of thromboembolic complications;

the practical significance of identifying the leading risk factors for coronary artery disease, coagulogram parameters, endothelin , PAI-1 protein was shown in order to prevent a more severe course of coronary artery disease and prevent thrombogenic complications in patients with/without COVID-19;

expediency of introducing a cascade model of recommendations for anicoagulant therapy in patients with coronary artery disease with/without COVID-19 based on coagulogram, endothelin , and PAI-1 protein was proved.

The reliability of the study results is confirmed by modern clinical, laboratory, instrumental and statistical methods used in the work, a sufficient number of patients, the correspondence of the results obtained to theoretical and practical calculations, comparison of the study results with data from foreign and 33 domestic studies, conclusion, confirmation of the results obtained by authorized structures.

The practical significance of the study.

The scientific significance of the study lies in the study of the pathogenetic features of the fibrinolytic system in patients with leading risk factors for coronary artery disease with/without COVID-19, markers of the plasmin system, as well as the development of recommendations for individual antiplatelet and anticoagulant therapy for these patients.

The practical value of the work lies in the fact that the implementation of practical recommendations formulated on the basis of the results obtained will allow timely identification of the risk of thrombogenic complications, especially in patients with coronary artery disease with COVID-19.

Implementation of the research results. According to the results of a study evaluating factors of the fibrinolytic system, plasminogen activator inhibitor factor and renin-angiotensin-aldosterone system in patients with/without COVID-19 suffering from CAD:

the methodological recommendation "Assessment of the risk of development and progression of coronary heart disease using factors of the fibrinolytic system" was approved (Conclusion of the Ministry of Health of the Republic of Uzbekistan No. 8p-7/117 dated 03.03.2022). These guidelines allow for early diagnosis of thrombotic complications, at a time when it is impossible to conduct molecular genetic analysis;

The obtained scientific results of the study are implemented in the practice of health care, in particular, in the cardiology department of the Multidisciplinary Clinic of the Tashkent Medical Academy and the Family Polyclinic No. 16 of the Zangiata district of the Tashkent region (Conclusion of the Ministry of Health of the Republic of Uzbekistan dated March 3, 2022, No. 8p-7 / 117). The implementation of the results of the study makes it possible to diagnose at an

early stage the aggravation of the course of the disease and the appearance of thromboembolic complications in patients with coronary artery disease with/without COVID-19.

Approbation of the research results. The results of this study were discussed at 4 international and 2 republican scientific and practical conferences.

Publication of research results. A total of 15 scientific papers were published on the topic of the dissertation, of which 6 articles were in scientific publications, including 4 in republican and 2 in foreign journals recommended by the Higher Attestation Commission of the Republic of Uzbekistan for publication of the main scientific results of dissertations.

MAIN CONTENT

The introduction of the dissertation substantiates the relevance and significance of the study, the requirements for this work, the purpose, tasks, object and subject of the study, the compliance of this study with the priorities of science and technology of the republic, the scientific novelty and practical results of the study are presented, the scientific and practical significance of the results obtained, implementation in practice of research results, information about published works and the structure of the dissertation.

In the first chapter of the dissertation **"Modern approach to fibrinolytic factors in coronary artery disease"** an analysis of international studies is consecrated, an analysis of foreign and domestic sources is presented. The literature review consists of 3 subsections, which provide information on the clinical and etiopathogenetic significance of the fibrinolytic system in patients with coronary artery disease, the role of type 1 plasminogen activator inhibitor in patients with COVID-19, markers of endothelial dysfunction. The results of studies of the role of fibrinolytic factors in the development and course of coronary artery disease, the occurrence of thromboembolic complications are described.

Chapter II of the dissertation **"Materials and Methods of Research"** presents data containing a general description of the clinical material, laboratory and instrumental research methods and statistical processing of the results. Clinical material for the study was collected in the period from 2020 to 2021 in the cardiology departments of the multidisciplinary "1st Zangiota Hospital". To fulfill the tasks set, 130 patients were involved in scientific work. They were divided into two groups depending on whether they were infected with SARS-CoV-2 infection. The 1st group included 67 patients hospitalized in the 1st cardiology department of the Multidisciplinary Clinic of the Tashkent Medical Academy without COVID-19. Of these, 36 (53.7%) men and 31 (46.3%) women. Patients with coronary artery disease, stable angina pectoris II-IV functional class and hypertension (I-II degree), whose average age was 60.2 ± 0.76;

The 2nd group included 63 patients diagnosed with COVID-19 (code HKK-10 U 07.1), who had confirmed hospitalization in the dispensary "1st Zangiata hospital ." At the time of obtaining the biomaterial for the study, the average duration of inpatient treatment of patients was 2 ± 0.6 days. At the time of diagnosis of COVID-19, patients were diagnosed with a history of coronary artery disease: stable angina pectoris FS II-IV and AH (I-II degree). The number of men in this group was 29 (60.0%), and women 34 (61.9%). There were no significant differences in the number of men and women in the groups (p> 0.01).

The following cases were excluded from the study: patients with chronic obstructive pulmonary disease (COPD), tumors, acute and severe chronic heart failure, severe chronic renal and hepatic insufficiency, life-threatening arrhythmias and bleeding, as well as patients in the intensive care unit. care unit did not turn on.

Patients of both groups included in the study suffered from stable exertional angina (SEA), the

diagnosis was established according to the classification of SEA according to its functional classes (FC).

According to the study data, patients included in group 1 without COVID-19 CHF FC II was detected in 28 (41.8%) patients, FC III in 36 (53.7%) and FC IV in 3 (4.5%) patients . In the 2nd group of patients with COVID-19

26 (41.2%) were diagnosed with stable angina II FC, 29 (46.0%) - III FC and 8 (12.7%) - IV FC.

As shown in Table 1, the mean age of patients without COVID-19 in group 1 was 60.2 ± 0.76 years compared with 63.1 ± 2.0 years for patients with COVID-19 in group 2.

In the 1st group, there were 36 men (53.7%), women - 31 (46.3%), and in the 2nd group - 34 men (54.0%), 31 women (46.3%), where no differences were found (p≥0.01). In the 1st group, 43 patients (64.2%), in the 2nd group, 39 (61.9%) patients had a hereditary predisposition to coronary artery disease. The average duration of CHD was 5.5 ± 0.34 years in group 1 and 5.6 ± 1.2 years in group 2. No significant statistical difference between these indicators was found (p≥0.01).

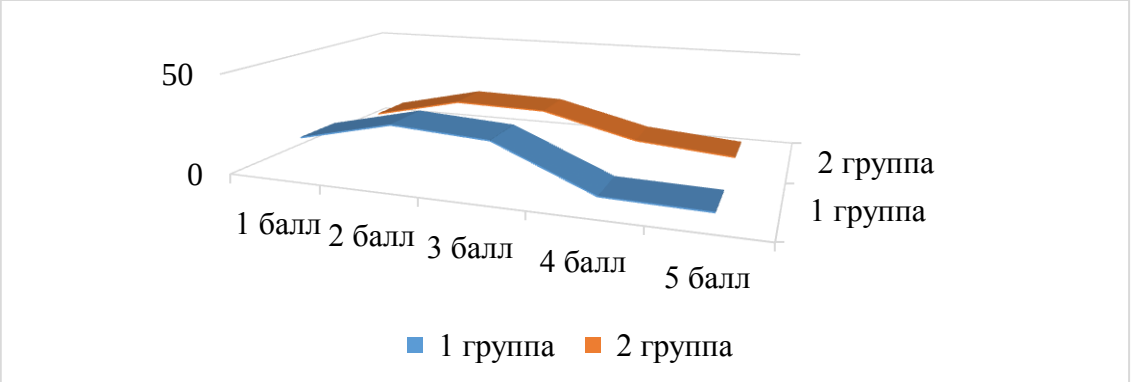
Table 1. Clinical characteristics of patients

Indicators	IHD patients not infected with COVID- 19 **(n=67)**	Patients with CAD infected with COVID-19, **(n=63)**
Age, years	60.2±0.76	63.1±2.0
IHD duration, in years:	5.5±0.34	5.6 ± 1.2
Men	36 (53.7%)	29 (46.0)
Women	31 (46.3%)	34 (54.0%)
hereditary predisposition	43 (64.2%)	39 (61.9%)

The analysis of patient data revealed the following: 1 comorbid condition was diagnosed in 42 (66.7%) patients with COVID-19, 2 and 3 comorbidities in 26 (41.3%) patients. The most frequent comorbidities and their complications were noted: obesity in 41 (65.1%), diabetes mellitus in 16 (25.4%), hypertension in 37 (58.7%), CHF in 23 (36.6%) and chronic acalculous cholecystitis in 8 (12.6%) patients.

The fourth subchapter of the dissertation "Results research » dissertation consists of 4 subsections. Our study included patients with coronary artery disease, i.e. SSN, where, when collecting patient complaints, clinical symptoms were also assessed and the following results were obtained. Patients in both groups were interviewed using the Verbal Pain Scale (VPS) to assess heart pain prior to treatment. According to these data, the average pain score in group 1 was 2.2±0.16, and in group 2 it was 2.6±0.10 (diagram 1).

Diagram 1. Pain scores on the verbal assessment scale (VBS) between groups



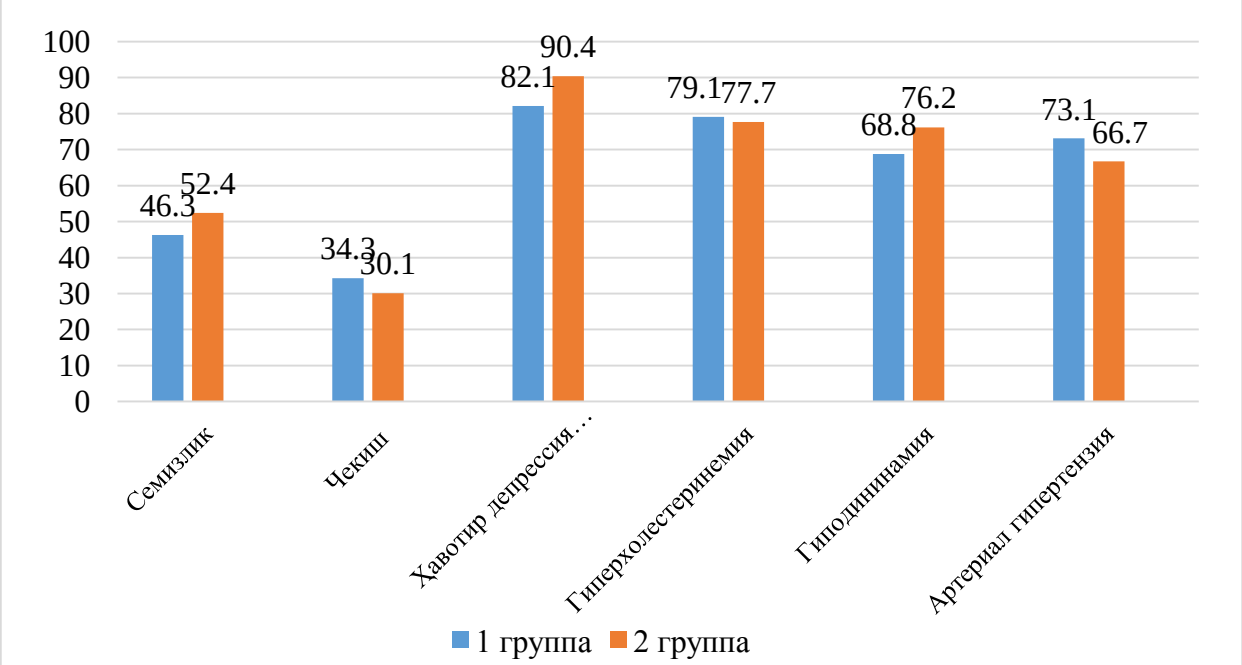
With HSP, pain intensity was assessed from 1 to 5 points, while 15 (22.3%) patients of the 1st group had symptoms of discomfort (1 point), 26 (38.8%) had mild compressive pain (2 points) , and 23 (34.3%), were observed in 3 (4.5%) patients with compressive pain of moderate intensity (3 points), severe compressive (4 points) and severe pain (5 points). In the 2nd group of patients, 1 point - 10 (15.9%), 2 points - 21 (33.3%), 3 points - 20 (31.7%), more often than in the 1st group, there were patients with compressive pain and severe pain syndrome, 8 (12.7%) patients scored 4 points and 4 (6.3%) patients - 5 points.

The concept of risk factors (RF) originated in the 20th century, and today, given the importance of RF in the development and progression of all diseases, their timely detection and control are among the most pressing issues. In modern recommendations, risk factors for diseases, guidelines for their detection and control are constantly updated, and new types of risk factors appear that are identified over time.

Based on the tasks set in our study, in patients with coronary artery disease in both groups, the occurrence of risk factors with a high probability of a direct effect on the activity of the plasmin system was studied, these risk factors are presented below in the form of a table (diagram 2).

Hereditary predisposition, one of the uncontrollable risk factors, was observed in 43 (64.2%) patients in the 1st group and in 39 (61.9%) in the 2nd group (p>0.01). Controlled risk factor hypercholesterolemia was detected in 53 (79.1%) patients in group 1 and in 49 (77.7%) patients in group 2. A high degree of physical inactivity was revealed in 46 patients (68.8%) in the 1st group, in 48 patients (76.2%) in the 2nd group (p>0.01).

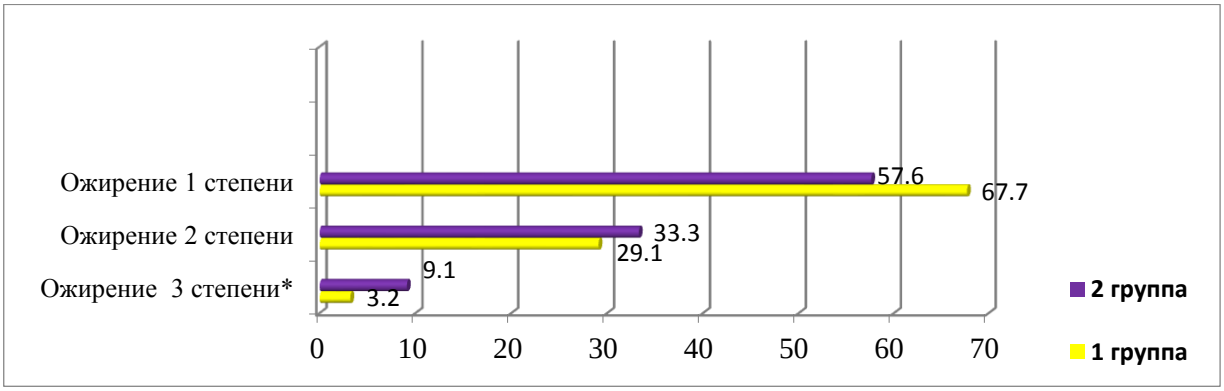
Diagram 2. Prevalence of uncontrolled risk factors for coronary artery disease among patient groups with/without COVID-19



Next, the prevalence of the most common risk factors for coronary artery disease such as obesity, nicotine addiction, anxiety-depressive syndrome and their high probability of influencing the activity of the plasmin system will be consecrated in detail.

Obesity, hypercholesterolemia and arterial hypertension. The degree of obesity in patients was calculated and evaluated using the Quetelet formula. Chart 3 shows the distribution of obesity levels in the main group.

Diagram 3. Distribution of obesity levels among CAD patients with/without COVID-19



According to the results of our study, obesity of the 1st degree was detected in 21 patients (67.7%) in the 1st group and in 19 patients (57.6%) in the 2nd group ($p < 0.05$). The prevalence of grade 2 obesity was not statistically different between the groups. According to the data, 9 people (29.%) in the 1st group and 11 (33.3%) patients in the 2nd group were diagnosed with obesity of the 2nd degree. Obesity grade 3 prevailed in group 2 compared to group 1, i.e. the frequency of occurrence was 1 (3.2%) and 3 (9.1%), respectively ($p < 0.05$).

Arterial hypertension did not significantly differ in the frequency of occurrence in both groups. AH was diagnosed in 49/67 (73.1%) patients without COVID-19, of which 1st degree AH - 16/67 (23.9%), 2nd degree AH - 22/67 (33%), 3rd degree AH - 11/67 (16.4%) patients (Table 2).

Table 2. The prevalence of arterial hypertension among patients included in the study

Number of patients	**Arterial pressure (mm. see set .)**				R
	high normal 130-139/85-89	1 st. AG 140-159/ 90-99	2st. AG 160-179/ 100-109	3 art. AG ≥180/110	
1 group (n=67)	18/67 (26.8%)	16/67 (23.9%)	22/67 (33 %)	11/67 (16.4%)	p< 0.03
group 2 (n=63)	19/63 (30.2%)	11/63 (17.4%)	18/63 (28.6%)	15/63 (23.8%)	

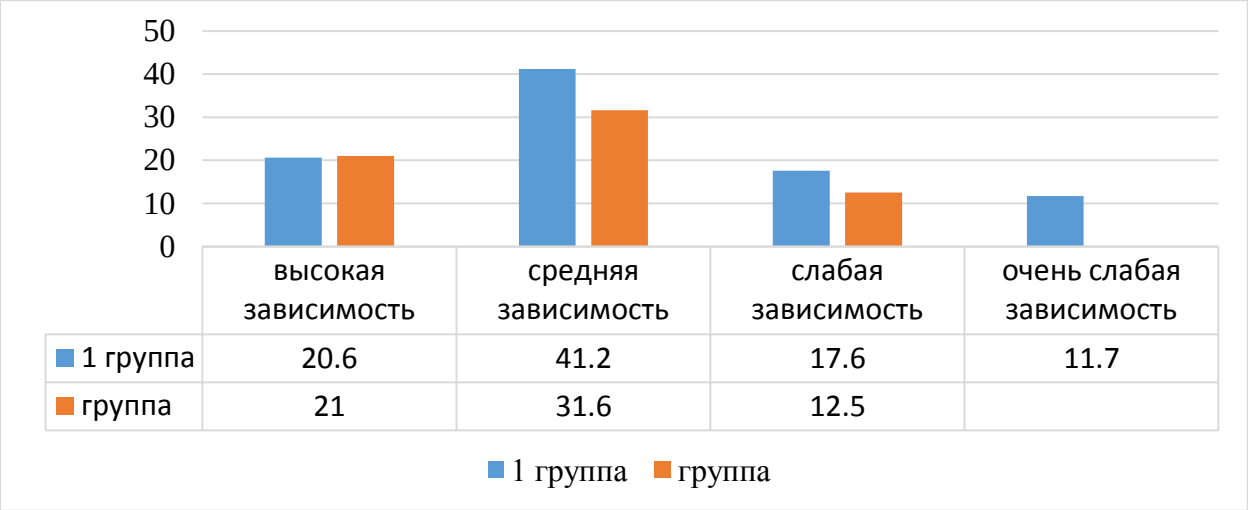
Hypertension was also detected in patients with COVID -19, so 44/63 (69.7%) had different levels of hypertension, i.e. AH 1 - in 11/63 (17.4%), AH 2 - in 18/63 (28.6%), and AH 3 degree was detected in 15/63 (23.8%) patients. AH was not detected in 20 (29.8%) patients without COVID-19 and in 11 (17.5%) patients with COVID-19 ($p < 0.03$).

One of the important risk factors for coronary artery disease and hypertension is smoking. The assessment of the severity of smoking in patients included in the study was carried out according to the Fagerström scale, the results of which are presented in the 4th diagram. According to the results of the survey, a significant statistical difference in the groups was observed between very high and moderate nicotine addiction. A very high nicotine dependence was found in 3 patients (8.8%), in the 1st group with very high and medium nicotine dependence in 14 (41.2%) patients, and in the 2nd group in 9 people (36.8%). %) with very high nicotine dependence and moderate dependence in 7 (31.6%) patients ($p<0.01$). There was no significant statistical difference between groups with high nicotine addiction, this indicator was found in 7 patients (20.6%) in group 1 and in 5 patients (21.0%) in group 2 ($p>0.05$).

A significant statistical difference in relation to low nicotine dependence was not found in 6 (17.6%) patients in the 1st group and in 3 (12.5%) in the 2nd group. Very low dependence was found in 4 (11.7%) patients of group 1. In the 2nd group, patients with very low dependence

were not identified.

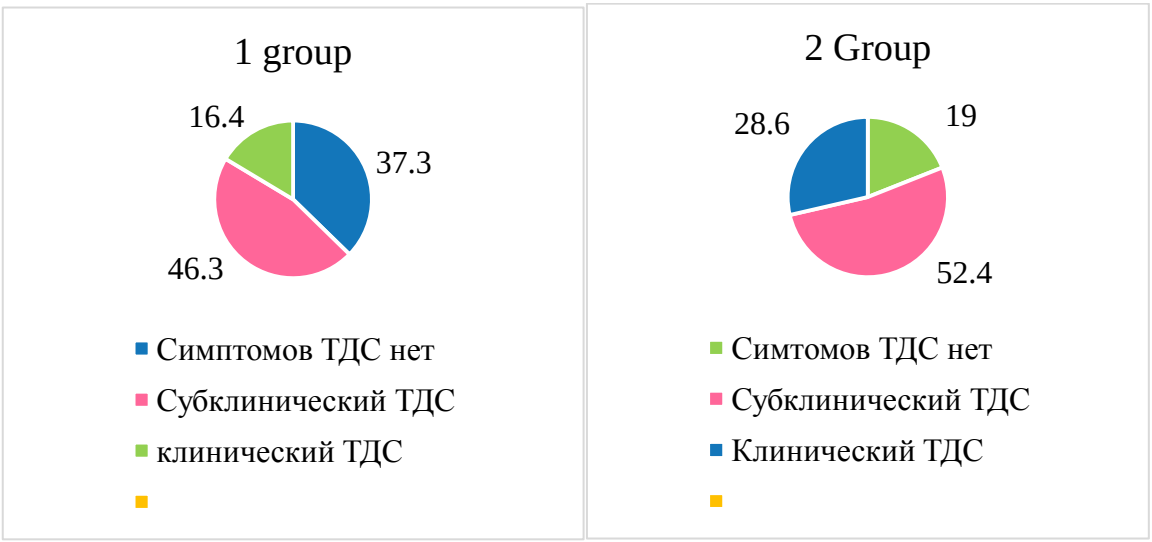
Diagram 4. Levels of nicotine dependence in CAD patients with/without COVID-19



Anxiety-depressive syndrome. The presence of anxiety-depressive syndrome in patients was assessed using the HADS scale, the results of which are presented in the 5th diagram.

According to the results of the study, TDS symptoms were absent in 37.3% (25/67) of patients in the 1st group and in 28.6% (18/63) of patients in the 2nd group.

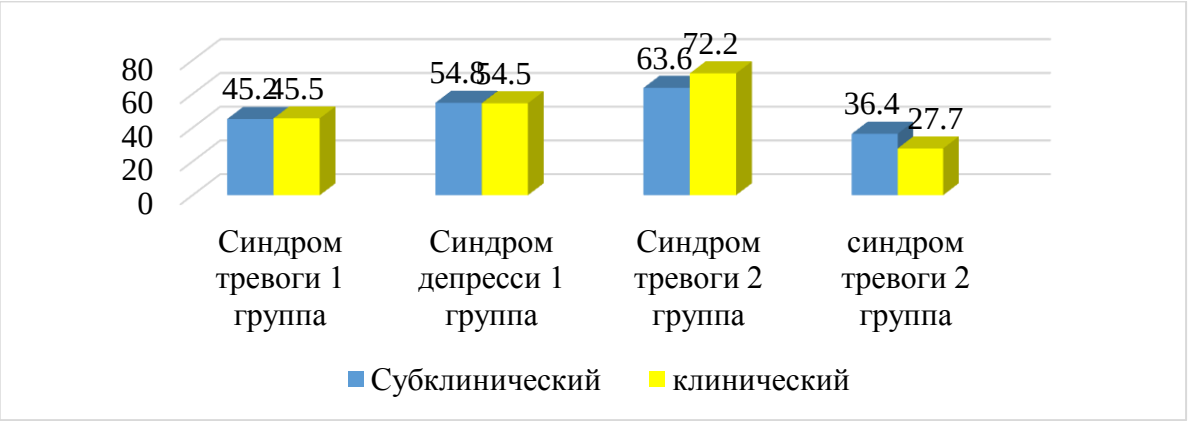
Diagram 5. TDS prevalence among CAD patients with/without COVID-19



The subclinical level of TDS did not statistically significantly differ in both groups, so in patients of the 1st group this figure was 46.3% (31/67), and in the 2nd group 52.4% (33/63) (p>0 .05). Clinically pronounced TDS was detected in 16.4% (11/67) of patients in group 1 and in 19.0% (12/63) of patients in group 2.

According to the data obtained, in group 1, 14 (45.1%) of 31 patients with subclinical TDS were diagnosed with anxiety syndrome and 17 (54.8%) with depression syndrome (diagram 6).

Diagram 6. TDS prevalence among CAD patients with/without COVID-19



In the 2nd group of 33 patients with subclinical TDS, 21 (63.6%) had an anxiety syndrome and 12 (36.4%) had a depressive syndrome. Of the 11 patients, 5 had a clinical course of anxiety syndrome (45.5%), 6 had a depressive syndrome (54.5%). Anxiety syndrome with clinical manifestations was detected in the 2nd group and occurred in 13 patients (72.2%), depressive syndrome - in 5 patients (27.7%). The results showed that the clinical manifestations of TDS prevailed in the 1st group with more depressive symptoms and in the 2nd group with anxiety.

Fibrinolytic system, clinical picture of coagulogram data. In our study, there was an increase in the level of PAI-1 in both studied groups. However, its number was 1.3 times higher in the 2nd group than in the 1st. This indicator confirms the presence of a high risk of thrombogenic complications in patients with COVID-19.

Table 3. Indicators of the PAI -1 level in patients with coronary artery disease with / without COVID-19

Indicators	Control group (n=25)	Patients		
		1 group (n=67)	2 group (n=63)	R
PAI-1(ng /ml)	33.3±2.07	54.8±3.47	72.0±7.6	p< 0.01

The results showed a significant increase in plasma PAI-1 in the main group of patients. Compared with practically healthy people, the amount of this biomarker was 1.6 times higher in patients with coronary artery disease without COVID-19 and 2.2 times higher in patients with COVID-19.

A significant increase in the amount of PAI-1 indicates an increased risk of endothelial and hemostatic disorders in patients with and without COVID-19, which, in turn, increases the risk of thrombogenic complications in both groups.

The parameters of the coagulogram were also studied in apparently healthy controls and patients with coronary artery disease, where the following results were obtained (table 4).

Table 4. Coagulogram parameters in healthy individuals of the control group and patients with COVID-19

Indicators	Healthy, n=25	Patients without COVID-19, n=67	Patients with COVID-19, n=63
Platelets, ($10^{9/l}$)	188±15.2	216±10.3*	371±20.3*
Platelet aggregation	65±5.1	78±6.1 **±15.2**	82±5.2 **±5.2**
clotting time start (min):	3 ^{3} ±0.1 4 ^{5} ±0.1	3 ^{1} ±0.1	2 ^{2} ±0.1 2 ^{9} ±0.1

end (min):		3^{6} ±0.1	
PTI (%)	70.8±3.1	91.7±4.2	140.9±5.3*
APTT **(sec.)	30.8±0.2	25.4±0.9	22.1±0.9
INR***	1.01±0.05	0.90±0.02	0.86±0.03
Fibrinogen (mg/l)	2.9±0.2	3.7±0.1	5.3±0.1*
Hematocrit (%)	32.3±1.2	37.1±1.2	40.1±1.2

* p< 0.05; **APTT-partially active thromboplastin time;*** INR-international normalized ratio

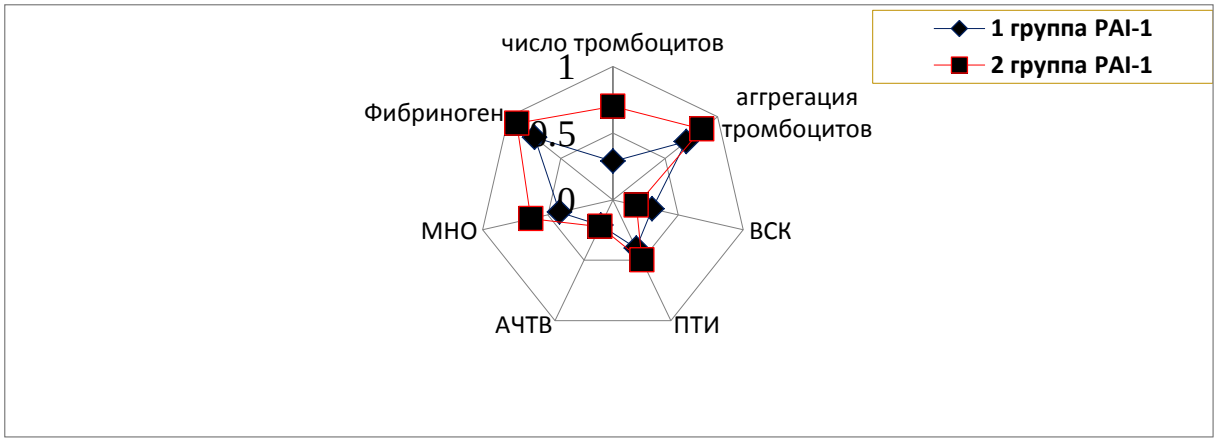
According to the data presented in the table, there were no deviations in the values of the coagulogram in the group of practically healthy individuals. Comparison of indicators of groups 1 and 2 showed the following results. So, in patients of the 2nd group, the number of platelets was 1.4 times higher, and PTI and fibrinogen 1.5 times higher.

The mean values of platelet aggregation and hematocrit were above the upper limit of normal. Differences were observed between patients with COVID-19 and healthy individuals in the following parameters. The number of platelets differed in patients with COVID-19 with a difference of 183±6.1x109/l and the PTI index with a difference of 21.1% in the direction of their increase.

Based on the above data, according to diagram 7, the correlation relationship between the amount of PAI-1 and the coagulogram values in both main study groups is shown.

So, in the 1st group, i.e. in patients with CAD without COVID-19, a strong correlation was found between the PAI-1 protein, platelet aggregation, and fibrinogen (r= 0.75; 0.7); a moderately strong correlation was found with clotting time, IPT, and INR (r = 0.3; 0.4; 0.41); weak correlation with platelet count and APTT (r = 0.29; 0.21). In group 2, IHD patients with COVID-19 had a strong correlation between PAI-1 and platelet count, their aggregation, and fibrinogen (r = 0.7; 0.85; 0.92); a moderately strong correlation with PTI and INR (r = 0.5; 0.63), a weak correlation was also found with blood clotting time and APTT (r = 0.18; 0.22).

Diagram 7. Correlation relationship between PAI-1 and coagulogram parameters



Based on the data obtained, it can be concluded that there is a higher risk of developing thrombotic complications in patients with coronavirus infection. The close relationship between COVID-19 and thrombosis is of great clinical importance. This conclusion can be substantiated by the fact that plasma levels of PAI-1 in patients with COVID-19 were 33.3 ng / ml higher than in healthy people, and the following post-COVID complications were observed in these same patients within 1 month after the disease : acute coronary syndrome in 9 (14.2%) patients out of 63 patients, acute myocardial infarction in 5 (7.9%) patients.

Previous studies have shown that endothelin (ET) is a sign of impaired cardiovascular function

in myocardial infarction. ET is also a sign of coronary atherosclerosis and coronary endothelial dysfunction, as well as impaired liver and kidney function.

High plasma ET can be detected in different conditions: during ischemia, after hemodialysis, at high levels of arterial hypertension, and can also be observed after transplantation of the heart, liver, kidneys and bone marrow. Based on the local impact of ET, it is natural to assume that its high production will lead to a deepening of the pathological process in IHD. In our study, a significant increase in the level of ET was not observed. An increase in the number of ET was noted in 21/67 (31.3%) patients of the 1st group and in 32/63 (50.8%) patients of the 2nd group. The mean value of ET was 203.6±14.9 ng /ml in the 1st group and 229.7±26.5 ng /ml in the 2nd group. Thus, the average level of ET in the 2nd group was 1.1 times higher than in the 1st group.

A lot of literature data speaks of the relationship of stress factors and the system of blood coagulation, coagulation and fibrinolysis , which increase simultaneously with acute stress, although in this case, procoagulant factors are more powerful than fibrinolytic factors, leading to a prothrombotic state. In chronic stress, only the procoagulant pathway is more activated. A number of scientific studies have also been carried out, showing that an increase in the number of platelets, platelet aggregation and fibrinogen under the influence of various stressors, in turn, leads to bleeding. It is known that the amount of cortisol in the body increases in response to any stressor. Based on the above data, we determined the level of cortisol in the blood of patients included in the study under chronic stress conditions (table 5).

The results of the study of practically healthy individuals included in the control group of the study did not reveal any negative shifts in this indicator. An increase in cortisol levels was observed in 23/67 (34.3%) patients without COVID-19 and in 27/63 (40.3%) patients with COVID-19 in the main study groups.

There was no significant difference in mean cortisol levels between the main groups (p>0.01). Compared with the control group, this figure was 1.5 times higher in patients of groups 1 and 2.

The role of the renin-angiotensin- aldosterone system in the development of hypertension and coronary artery disease has been studied in many scientific studies. A number of studies have shown that this system is also important in a new coronavirus infection. In our scientific research, the level of renin and aldosterone included in the RAAS system was also studied, where the following results were obtained (Table 5).

Table 5. Parameters of the renin-angiotensin- aldosterone system in patients with coronary artery disease with/without COVID-19

Indicators	Control group (n=25)	Patients		
		1 group (n=67)	2 group (n=63)	R
Renin, µIU / ml	40.1±2.07	60.7±3.05	66.5±5.4	p< 0.05
Cortisol mmol/l	168.4±21.05	242.1±20.93	244.4±44.3	p>0.05
Aldosterone, ng /ml	115.5±13.33	207.6±16.37	209.7±35.9	p>0.05

As shown in Table 5, we can see that the renin content in both groups of patients was above normal values. This indicator was higher in 39/67 (58.2%) patients without COVID-19 and averaged 60.7±3.05 µIU /ml. In 41/63 (65.1%) patients with COVID-19, the average level was 66.5±5.4 µIU /ml.

Intergroup comparative values showed that in patients with COVID-19, the content of renin was 1.1 times higher (p < 0.01) than in group 1, i.e. in patients with COVID-19. These same patients have high blood pressure, which is difficult to control, and a relatively severe course of COVID-19.

One of the reasons we evaluate aldosterone levels in our study is that an increase in blood levels of aldosterone is one of the factors that increase PAI-1 expression. Aldosterone leads to the development and progression of endothelial dysfunction by increasing the formation of PAI-1 in endothelial cells and vascular smooth cells.

In our study, there was no significant increase in aldosterone levels between the main groups (p>0.01). In patients of the 1st and 2nd groups, this indicator was 1.8 times higher than in the control group. A high level of aldosterone was detected in 26 (38.8%) of 67 patients in group 1 and in 25 (39.6%) of 63 patients in group 2.

To understand how these indicators contribute to the development of coronary artery disease without coronavirus infection against the background of arterial hypertension, we analyzed the relationship between the studied indicators.

Table 6. Correlation of PAI-1 parameters with endothelin, cortisol, renin-angiotensin-aldosterone system

Indicators	PAI-1	
	r	P
Endothelin	0.68	<0.01
cortisol	-0.11	<0.05
Renin	0.9	<0.05
Aldosterone	0.75	<0.05

According to Table 7, the amount of PAI-1 in plasma has a moderate correlation with the amount of endothelin (r = 0.68; r = 0.01). A strong correlation relationship was observed between PAI-1 and renin (r = 0.9; r = 0.05), PAI-1 and aldosterone (r = 0.78; r = 0.01). It was found that there is a weak inverse correlation between PAI-1 and cortisol is r = -011; p = 0.05).

The table below shows the correlation relationship between the indicators of the renin-angiotensin- aldosterone system, endothelin and CHD RF.

Thus, in our study, a strong direct correlation of TDS with endothelin (r = 0.71), cortisol (r = 0.9), renin (r = 0.88) and a moderate correlation with aldosterone (r = 0.66) was revealed.

Table 7. Co-correlation of indicators of the renin-angiotensin- aldosterone system, endothelin and risk factors for coronary artery disease

Risk factors	endothelin		cortisol		renin		aldosterone	
	r	p	r	p	r	p	R	P
TDS	**0.71**	<0.05	**0.9**	<0.05	**0.88**	<0.05	**0.6**	<0.05
Obesity	**0.8**	<0.05	**0.86**	<0.05	**0.7**	<0.05	**0.75**	<0.05
Smoking	**0.89**	<0.05	**0.81**	<0.05	**0.46**	<0.05	**0.39**	<0.05
Hypodynamia	**0.73**	<0.05	**0.67**	<0.05	**0.62**	<0.05	**0.4**	<0.05

Obesity as one of the main risk factors leading to the development of CHD has a strong direct correlation with all parameters, i.e. the highest values of r were noted with cortisol (r = 0.86) and endothelin (r = 0.8). This figure was 0.7 and 0.75 for renin and aldosterone, respectively. A strong direct correlation was found between smoking and endothelin with cortisol, while a moderately strong relationship was observed between smoking and renin with aldosterone. A strong direct association was observed between physical inactivity, a major CVD risk factor, and endothelin, a moderately strong association was observed between cortisol and renin , and a weak direct association was observed between aldosterone.

Table 8. Coagulogram and ET-1 parameters in patients with COVID-19 before starting anticoagulant therapy

Indicators	2 group (n=63)
Platelets, ($10^{9/l}$)	371±20.3
PTI (%)	140.9±5.3
APTT (sec.)	22.1±0.9
INR	0.86±0.03
Fibrinogen (mg/l)	5.3±0.1
Hematocrit (%)	40.1±1.2
D -Dimer mgFEU /ml	2.6±0.17
PAI-1(ng /ml)	72.0±7.6
ET-1 (ng /ml)	229.7±26.5

Thus, it can be assumed that elevated levels of PAI-1 in patients are directly related to high levels of renin, aldosterone, and cortisol in the blood. Exceeding these values from the norm may be associated with the presence of manageable risk factors for coronary artery disease, such as TDS, obesity, smoking, and physical inactivity. An increase in these indicators leads to a more severe course of the disease in patients.

It is known that there are no direct indications for the appointment of anticoagulants in CHF. However, the conditions of the pandemic have led to some modification of this state, i.e. patients with CHF were prescribed anticoagulant therapy depending on the course of the disease against the background of COVID-19. Table 8 shows coagulogram parameters and mean ET-1 values in patients before anticoagulant treatment.

Analyzing the indicators presented in the table, it was noted that the number of platelets was higher by 1.03 times, and fibrinogen by 1.5 times. PTI and hematocrit values corresponded to the upper limit of normal, and APTT and INR were shortened. D - dimer and PAI-1 levels were higher in patients with COVID-19, which was 2.2 times higher than normal. ET levels did not exceed the overall averages.

Patients with coronary artery disease, included in the main group 1 of our study, infected with COVID-19, received antiplatelet drugs as recommended, but did not receive anticoagulant therapy.

Patients of the main 2 groups, i.e. IHD with COVID-19, received anticoagulants in combination with antiplatelet agents: 34 of them received heparin (5000 IU x 4 max.) and 29 received fractionated heparin (Clexane). The dose of clexane averaged 0.6-0.8 ml, depending on the patient's body mass index. Patients were observed for 3 days and the above parameters were re-evaluated against the background of anticoagulant therapy (Table 9). The results showed that in patients treated with heparin, the amount of PAI-1 did not change, and the amount of ET-1 increased during treatment. In contrast, patients treated with clexane experienced a relative decrease in PAI-1 and ET-1 levels.

Table 9. Coagulogram and ET-1 against the background of anticoagulants in patients with COVID-19

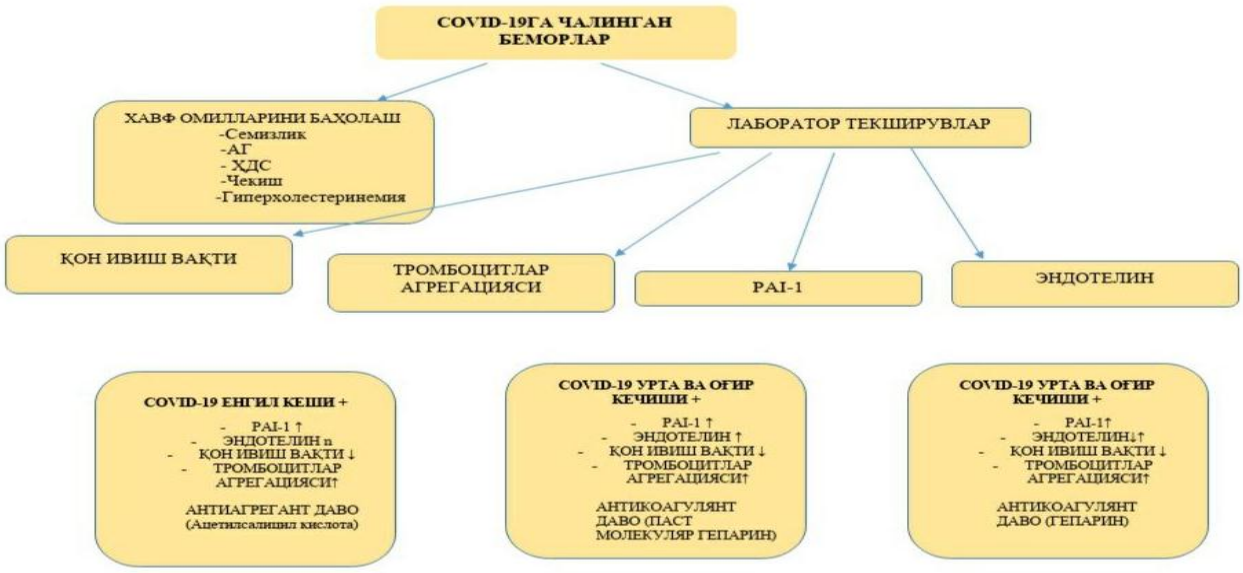
Options	Patients receiving heparin (n=34)	Patients receiving Clexane (n=29)
Platelets, ($10^{9/l}$)	359±20.3	365±20.3
PTI (%)	126.7±5.3	130.9±5.3
APTT (sec.)	28.6±0.9	23.1±0.9

INR	0.91±0.03	0.90±0.03
Fibrinogen (mg/l)	4.7±0.1	4.6±0.1
Hematocrit (%)	39.7±1.2	39.5±1.2
D -Dimer mgFEU /ml	2.2±0.17	2.2±0.17
PAI-1(ng /ml)	71.7±7.6	65.6±7.6
ET-1 (ng /ml)	309.9±26.5	227.3±26.5

Based on these results, it can be concluded that clexane is more effective than heparin in patients with COVID-19 and that heparin may slightly increase endothelial damage, which, in turn, requires further research in this area.

Based on our results, we developed the following algorithm for selecting anticoagulant drugs in patients with COVID-19 (Diagram 8).

Diagram 8. Cascade model of selection of anticoagulant drugs in patients with coronary artery disease with COVID-19



According to this algorithm, in addition to coagulogram parameters, before prescribing anticoagulant therapy in patients with COVID-19, it is recommended to determine the amount of PAI-1 and ET-1 in the blood, as well as to assess the risk factor for coronary artery disease.

When high levels of PAI-1 and ET-1 are detected in the blood, regardless of the severity of the disease, according to the results of our study, low molecular weight heparin is recommended for patients. If the amount of PAI-1 and ET-1 in the blood does not change or increases, heparin can be prescribed to the patient.

CONCLUSION

Based on research on the dissertation of the Doctor of Philosophy (PhD) on the topic “Clinical diagnostic criteria and features of the manifestations of COVID-19 in patients at risk”, the following conclusions can be drawn:

1. In our study, an association of plasma PAI-1 protein with TDS, smoking, hypertension, obesity and hypercholesterolemia was revealed , according to which PAI-1 protein is associated with moderate and low smoking and hyperlipidemia (r=0.3; r=0.1) . TDS, AH, has a positive correlation with obesity (r = 0; 0.01; 0.06).

2. A significant increase in the amount of PAI-1 indicates an increased risk of endothelial and hemostatic disorders in patients with and without COVID-19, which, in turn, increases the risk of thrombogenic complications in both groups. According to the results, the amount of PAI-1 in patients of the 1st group was 1.6 times higher than in healthy people, and in patients with COVID-19 of the 2nd group, this figure was 1.2 times higher than in the 1st group. th group.
3. Indications for the leading markers potentially sensitive to thrombosis in patients with COVID-19 against the background of an increase in the PAI-1 protein: platelet aggregation and blood clotting time, a positive correlation of these indicators with the PAI-1 protein was found. In both groups of patients, the level of renin was above the norm, in the 1st group it was 1.3 times higher than the norm, and in the 2nd — 1.4 times. The level of endothelium was higher in 13.4% of patients of the 1st group and in 44.4% of patients of the 2nd group.
4. As a result of the study, it was concluded that for the prevention of early macro- and microthrombosis and the prevention of thrombogenic complications, according to the algorithm of primary / systemic and inpatient management of patients with stable exertional angina and COVID-19 protein PAI-1, blood coagulation, time, platelet aggregation, coagulogram parameters, determination of the amount of endothelin .
5. Acetylsalicylic acid in patients with mild COVID-19 with an increase in PAI-1 and platelet aggregation and a decrease in blood clotting time; Low molecular weight heparin in combination with acetylsalicylic acid in patients with COVID-19, in patients with moderate to severe disease with high levels of PAI-1 protein and endothelin ; Direct-acting anticoagulants in combination with acetylsalicylic acid are recommended for patients with elevated levels of PAI-1 protein and endothelin in the blood.

References:

1. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected (2020)
2. COVID-19: investigation and initial clinical management of possible cases (2020)
3. Report of the WHO-China Joint Mission on Coronavirus DIsease 2019 (COVID-2019) February 16-24, (2020)
4. Ai T., Yang Z., Hou H., Zhan C., Chen C., Lv W., Tao Q., Sun Z., Xia L. Correlation of Chest CT and RT-PCR Testing in Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases // Radiology. -- (2020). -- Feb 26. -- C. 200642.
5. Bajema KL, Oster AM, McGovern OL, Lindstrom S., Stenger MR, Anderson TC, Isenhour C., Clarke KR, Evans ME, Chu VT, Biggs HM, Kirking HL, Gerber SI, Hall AJ, Fry AM, Oliver SE Persons Evaluated for 2019 Novel Coronavirus - United States, January 2020 // MMWR Morb Mortal Wkly Rep. -- (2020). -- Feb. 14. -- V. 69, **No. 6** . -- C. 166-170.
6. Chan JF, Yuan S., Kok KH, To KK, Chu H., Yang J., Xing F., Liu J., Yip CC, Poon RW, Tsoi HW, Lo SK, Chan KH, Poon VK, Chan WM, Ip JD, Cai JP, Cheng VC, Chen H., Hui CK, Yuen KY A familial cluster of pneumonia associated with the 2019 novel coronavirus

indicating person-to-person transmission: a study of a family cluster // Lancet. -- (2020). -- Feb. 15. -- T. 395, no. 10223. -- C. 514-523.

7. Kanatzhan Kemelbekov , Elmira Ospanova , Bakhtygul Baimakhanova , Zharylkap Zhumabekov et al. "epidemiologicalcharacteristics-of-new-coronavirus-diseasescovid-19-features-of-risk-factors-and-clinicalfeatures-of-the-child-population", Electronic Journal of General Medicine (2020)
8. Chen H., Guo J ., Wang C., Luo F., Yu X., Zhang W., Li J., Zhao D., Xu D., Gong Q., Liao J., Yang H., Hou W., Zhang Y. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records // Lancet. -- (2020). -- Mar 7. -- T. 395, No. 10226. -- C. 809-815.
9. Amitabh B. Suthar, Sara Schubert, Julie Garon , Alexia Couture, Amy M. Brown, Sana Charania . "COVID-19 case definitions, diagnostic testing criteria, and surveillance across the pandemic's 25 highest burden countries", Cold Spring Harbor Laboratory, (2021)
10. Chen N., Zhou M., Dong X., Qu J., Gong F., Han Y., Qiu Y., Wang J., Liu Y., Wei Y., Xia J., Yu T., Zhang X., Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study // Lancet. -- (2020). -- Feb 15. -- T. 395, no. 10223. -- C. 507-513.
11. Li Y., Xia L. Coronavirus Disease 2019 (COVID-19): Role of Chest CT in Diagnosis and Management // AJR Am J Roentgenol . -- 2020. -- Mar 4. -- C. 1-7.
12. Liu D., Li L., Wu X., Zheng D., Wang J., Yang L., Zheng C. Pregnancy and Perinatal Outcomes of Women With Coronavirus Disease (COVID-19) Pneumonia: A Preliminary Analysis // AJR Am J Roentgenol . -- (2020). -- Mar 18. -- C. 1-6.
13. Liu K., Fang YY, Deng Y., Liu W., Wang MF, Ma JP, Xiao W., Wang YN, Zhong MH, Li CH, Li GC, Liu HG Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province // Chin Med J (Engl). -- (2020). -- Feb 7.
14. Organization WH Director-General's remarks at the media briefing on 2019- nCoV on 11 February (2020)
15. National COVID-19 Guidelines MoH RUZ, 2020 http://www.minzdrav.uz/documentation/detail.php?ID=58045
16. Wang D., Hu B., Hu C., Zhu F., Liu X., Zhang J., Wang B., Xiang H., Cheng Z., Xiong Y., Zhao Y., Li Y., Wang X., Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China // Jama. -- (2020) -- Feb 7.
17. Wei M., Yuan J., Liu Y., Fu T., Yu X., Zhang ZJ Novel Coronavirus Infection in Hospitalized Infants Under 1 Year of Age in China // Jama. -- (2020). -- Feb 14.
18. Wu Z., McGoogan JM Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention // Jama. -- (2020). -- Feb 24.
19. Yang X., Yu Y., Xu J., Shu H., Xia J., Liu H., Wu Y., Zhang L., Yu Z., Fang M., Yu T., Wang Y., Pan S., Zou X., Yuan S., Shang Y. Clinical course and outcomes of critically ill

patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study // Lancet Respir Med. -- (2020) -- Feb 24.

20. Zhao W., Zhong Z., Xie X., Yu Q., Liu J. Relation Between Chest CT Findings and Clinical Conditions of Coronavirus Disease (COVID-19) Pneumonia: A Multicenter Study // AJR Am J Roentgenol . -- (2020). -- Mar 3. -- C. 1-6.
21. Coronavirus (COVID-19) infection and pregnancy (RCOG). https://www.rcog.org.uk/globalassets/documents/guidelines/2020-03-28-covid19-pregnancy-guidance.pdf
22. Queensland Clinical Guidelines Perinatal care of suspected or confirmed COVID-19 pregnant women. guideline no. MN20.63-V1-R25. Queensland 40 Health. (2020). Available from: http://www.health.qld.gov.au/qcg
23. Poon LC, Yang H., Kapur A., Melamed N., Dao B., Divakar H., David McIntyre H., Kihara AB, Ayres-de-Campos D., Ferrazzi EM, Carlo Di Renzo G., Hod M. Global interim guidance on coronavirus disease 2019 (COVID-19) during pregnancy and puerperium from FIGO and allied partners: Information for healthcare professionals // Int J Gynaecol Obstet. -- (2020). -- Apr 4
24. Hui, David S.; Azhar , Esam E.I .; Madani , Tariq A.; Ntoumi , Francine; Cock, Richard; Dar, Osman; Ippolito, Giuseppe; Mchugh , Timothy D.; Memish , Ziad A. The continuing epidemic threat of novel coronaviruses to global health – the latest novel coronavirus outbreak in Wuhan, China (English) // International Journal of Infectious Diseases: journal. — (2020). - January 14 (vol. 91). - P. 264-266. — ISSN 1201-9712. — DOI:10.1016/ j.ijid.2020.01.009.
25. Guidance COVID-19: investigation and initial clinical management of possible cases/ https://www.gov.uk/government/publications/ Updated 27 April (2020).
26. Jonas F Ludvigsson. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. actapediatrica. First published:23 March (2020) https://doi.org/10.1111/apa.15270.