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THE ROLE OF ANTICOAGULATION IN PREVENTING MYOCARDIAL INFARCTION AND IMPROVING THE OUTCOMES AMONG COVID-19 PATIENTS

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Abstract

COVID-19 has been associated with various cardiovascular complications including acute myocardial injury, myocarditis, arrhythmias, and venous thromboembolism. The infection is severe in patients with pre-existing cardiovascular disease, and in these cases the systemic inflammatory response due to a cytokine storm can lead to acute myocardial infarction. Hypercoagulation in COVID-19 can also predispose patients to fatal vascular events. Furthermore, these patients also have high hematocrit and platelet values, which, in their turn, contribute to the high risk of vascular events.

We hypothesize that the use of anticoagulants and antiplatelets is decisive for prevention of acute coronary syndromes, especially in patients with pre-existing cardiovascular diseases. Prospective cohort study was conducted in patients with confirmed diagnosis of COVID-19 admitted to National Center for Infectious Diseases Ministry of Health of the Republic of Armenia. Clinical, laboratory data, total and cardiovascular mortality, the incidence of a myocardial infarction and treatment regimens were compared in two groups according to the time of the hospitalization: 40-day period in April-May (I Group) and October-November (II Group).

Totally195 patients were enrolled in the study, which were divided into two groups. In I Group there were 93 patients with 36,5% of pre-existing cardiovascular diseases, in II Group 102 patients with 38,2% of pre-existing cardiovascular diseases. There was also drastic difference in laboratory test results between two groups.

I Group was managed with minimal infusion therapy and only 10,7% received anticoagulation. In contrast, II Group was receiving preventive doses of anticoagulants and antiplatelet, and proper infusion therapy was administered. In I Group 7 cases of myocardial infarction were recorded, while patients in II Group, only 3 cases (1 of them with previous 1 of them with previous myocardial infarction).

Statistical analysis revealed no significant difference in overall mortality (4.3% vs 6.86%, p = 0.441) and myocardial infarction incidence (7.5% vs 2.9%, p = 0.149) between two groups. In contrast there was significant difference in the incidence of severe and critically ill cases between two groups (69.9% and 7.5% vs 75.5% and 20.6%, p < .001).

Keywords: *Acute myocardial infarction, COVID-19, emergency medical system, percutaneous coronary intervention, ST-elevation myocardial infarction, acute coronary syndromes*

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Introduction

People of all ages can be infected by the coronavirus disease 2019 (COVID19). People aged 60 years and older, and those with underlying medical problems like high blood pressure, heart and lung diseases, diabetes, obesity or cancer, are at higher

risk of developing serious illness [*CDC-2021.01.22*]. Involvement of the cardiovascular system is common in COVID-19 [*Smeeth L et al., 2004; Chen T et al., 2020; Guo T et al., 2020; Huang C et al. 2020; Shi S et al., 2020; Zhou F et al., 2020*]. Myocardial injury is a common condition among patients hospitalized with COVID-19, and it is associated with higher risk of in-hospital mortality [*Guo T. et al., 2020; Shi S. et al., 2020;*]. COVID-19 has been associated with various cardiovascular complications including acute myocardial injury, myocarditis, arrhythmias, and venous thromboembolism [*Tang N et al., 2020*]. The infection is severe in patients with pre-existing cardiovascular disease, and in these cases the systemic inflammatory response due to a cytokine storm can lead to acute myocardial infarction (MI) [*Prabhu SD., 2004*]. Myocardial infarction caused by the rupture of atherosclerotic plaque resulting in intraluminal thrombus is defined as type 1 MI [*Thygesen K et al.,2018*]. Several potential mechanisms can contribute to the high risk of plaque destabilization and consequently to acute coronary ischemic syndromes in patients with systemic viral infection [*Libby P et al., 2018*]. Viral products known as pathogen-associated molecular patterns entering the systemic circulation activate immune receptors on cells in existing atherosclerotic plaques and predispose to plaque rupture [*Gennaro G et al., 2020*]. It is also believed that such pathogen-associated molecular structures activate inflammasomes and lead to the conversion of emerging pro-cytokines into biologically active cytokines [*Van de Veerdonk F.L. et al., 2011*]. Infection and inflammation can also lead to coronary vascular endothelial dysfunction and cause vasoconstriction and thrombosis [*Vallance P. et al., 1997*]. In these cases patients usually present with dyspnea, which is attributed to pneumonia, therefore MI can be easily overlooked.

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

With COVID-19 infection, the majority of MIs is type 2 and is related to the primary infection, hemodynamic, and respiratory derangement. However, hypercoagulation in COVID-19 can also predispose patients to fatal vascular events [*Shi W et al., 2020*].

Furthermore, these patients also have high hematocrit and platelets values, which, in their turn, contribute to the high risk of vascular events.

We hypothesize that the use of anticoagulants and antiplatelets is vital for prevention of acute coronary syndromes, especially in patients with pre-existing cardiovascular diseases.

MATERIAL AND METHODS

Prospective cohort study was conducted in patients with confirmed diagnosis of COVID-19 admitted to Nork National Center of Infectious Diseases (Yerevan, Armenia). 193 patients were divided into two groups according to the time of the hospitalization: a 40-day period in April-May (group 1) and October-November (group 2). Severity of COVID-19 was defined according to the World Health Organization (WHO) scale criteria [*Son K-B, 2021*]. Clinical, laboratory data, total and cardiovascular mortality, the incidence of an MI and treatment regimens were compared in two groups.

In group 1, 21 (22.6%) moderate, 65 (69.9%) severe and 7 (7.5%) critically ill patients were enrolled with mean age of 49 (28-79), of which 45.2% were male. 90 patients had pneumonia, in 11 cases lesions involved more than 50% of the lung parenchyma, SpO2 fluctuated between 64-97%, acute respiratory distress syndrome was reported in 8 cases. Mortality rate in group 1 was 4.3%. 36.5% of patients had pre-existing cardiovascular diseases (Table 1). 19 patients were regularly receiving aspirin with the dose of 75-150*mg* daily, 16 patients were receiving angiotensin converting enzyme inhibitors and 12 patients were taking statins. During hospitalization group 1 received minimal infusion therapy, 23 of the patients received aspirin 75-150*mg/day*, 10 (10.7%) of the patients received anticoagulants and 9 patients received corticosteroids. Mean hospitalization was 14.3 days.

Group 2 included 4 (3.9%) moderate, 77 (75.5%) severe and 21 (20.6%) critically ill patients with mean age of 53 (27-82) and 47.1% were male, mortality-6.8%. 38.2% of the patients from group 2 had pre-existing cardiovascular diseases (arterial hypertension-21, arrhythmia-4, chronic heart failure- 10,

coronary artery disease – 14 (Table 1)). All of the patients in group 2 had pneumonia confirmed by chest computed tomography, and 41 of them with involvement of more than 50% of lung parenchyma, in 58 cases it was complicated with acute respiratory distress syndrome, SpO2 fluctuated from 45 to 93%. Prior to hospitalization 27 patients were receiving anticoagulants (Xarelto 10-30 *mg* – 14, enoxaparin 4000 *U* – 8, aspirin 75-100 *mg* – 34). All patients in group 2 received enoxaparin 4000*U* od subcutaneous. After laboratory tests and reevaluation of the risk of thrombosis, doses of anticoagulants were changed. In 41 patients D-dimer was 0.4-1.5 *FEU/ml*, 1,6-3 *FEU/ml* in 45, 3.1-10 in 11 and ≥10 in 5 ┌13 patients experienced adverse events (bleeding) from the anticoagulation, therefore doses for these patients were adjusted or anticoagulation was ceased. 96 of the patients received corticosteroids as a part of the treatment during hospitalization. Mean hospitalization for this group was 14.1 days.

Table 1.

Clinical cardiovascular characteristics of patients in the study groups.

	Group 1 n (%)	Group 2 n (%)
Age		
≤ 49y	32 (34.4%)	25 (24.5%)
50-69y	47 (50.5%)	64 (62.75%)
≥70y	14 (15.1%)	13 (12.75%)
Sex, male	42 (45.2%)	48 (47.1%)
Body mass index ≥30	45 (48.4%)	53 (51.9%)
Arterial hypertension	28 (30.1)	38 (37.2%)
Supraventricular tachycardia	7 (7.5%)	10 (9.8%)
Ventricular tachycardia / ventricular fibrillation	2 (2.15%)	1 (0.98%)
Chronic heart failure	6 (6.5%)	10 (9.8%)
Coronary artery disease	10 (10.7%)	14 (13.7%)
Previous myocardial infarction	5 (5.35%)	6 (5.9%)
Percutaneous coronary intervention	6 (6.45%)	9 (8.8) %
Diabetes mellitus	19 (20.4%)	22 (21.6%)
Other comorbidities	14 (13.6%)	12 (11.8%)
Total number pacients	96 (100%)	102 (100%)

Table 2.

Treatment comparison between Group 1 and Group 2

Treatment	Group 1 n(%)	Group 2 n(%)
Aspirin 75-150 *mg/day*,	23 (24.7%)	31 (30.4%)
Anticoagulation,	10 (10.75%)	102 (100%)
Nadroparin,		
4000 *U/day*	8(8.6%)	22 (21.56%)
8000 *U/day*	0	44 (43.13%)
16000 *U/day*	0	8 (7.8%)
Heparin 3500-5000 *U/8h*,	0	23 (22.5%)
Xarelto 10-20 *mg/day*	2 (2.15%)	5 (4.9%)

Study data revealed that group 1 was managed with minimal infusion therapy and only 10.7% received anticoagulation. In contrast, group 2 was receiving preventive doses of anticoagulants and antiplatelet, and proper infusion therapy was administered (Table 2). In group 1, 7 cases of MI were recorded in 15-18th day of disease (3 of them with MI anamnesis). In 6 cases MI developed during hospitalization, and in one case, on the third day following the hospital discharge (23rd day of the disease). In group 2, only 3 cases of MI were recorded (1 of them with previous MI). Elevation of platelets level was recorded on the 3rd week of disease. Mean level of platelets in group 1 was 813±473 $x10^9/L$ and 722±383$x10^9/L$ in group 2. There was also a drastic difference in other laboratory test results between two groups (Table 3).

Statistical analysis revealed no significant difference in overall mortality (4.3% vs. 6,86%, p = 0,441) and MI incidence (7.5% vs. 2.9%, p = 0,149) between two groups. In contrast there was a significant difference in incidence of severe and critically ill cases between two groups (69.9% and 7.5% vs. 75.5% and 20.6%, $p < 0,001$).

We present to you two cases of ST-Elevation Myocardial Infarction (STEMI) in patients with COVID-19 from group 2. In both of them patients were receiving lower doses of anticoagulants due to bleeding complications.

Case presentations

Case 1

A 51-year-old woman with anamnesis of uncontrolled high blood pressure was admitted to the hospital on 8th day of COVID-19 disease with following complaints: fever, weakness, shortness of breath and cough, bleeding from hemorrhoids. Chest computed tomography was performed at the

admission, which revealed progressive bilateral nonspecific interstitial pneumonia with Ground-glass opacity covering 70% of lungs. Clinical findings for this patient at the admission are: t - 37.2*C*, SpO2-86% in room air, 92% with oxygenation, HR-113 *bpm*, BP-140/80 *mmHg*., BMI-33. Blood test results are presented in Table 4.

Patients used to take hypotensive drugs once or twice a month, only in critical situations. Before hospitalization the patient was taking only vitamins, aspirin and azithromycin for 6 days. Treatment regimen with combination of steroid therapy (dexamethasone 12 *mg/day*) and preventive anticoagulation (fraxiparine 4000 *U/day* Subcut) was initiated. Patient received a low dose of anticoagulant due to bleeding hemorrhoids. During hospitalization the patient had fever for 2 more days, cough and dyspnea maintained, and on the third day the acute respiratory distress syndrome developed and the patient was transferred to the Intensive care unit.

Table 3.

Laboratory test results in two Groups

Laboratory data	Group 1 mean (range)	Group 2 mean (range)
Platelets (N-150-400x10^9/*L*)	839 (366-1312)	722 (125-1010)
Hematocrit (36-47%)	38.4 (372-51.1)	38.2 (37-49.2)
D-dimer (<0.55 *FEU/ml*)	-	2.3 (0.5-13.8)
International normalized ratio (0.85-1.2)	0.98 (0.64-2.1)	1.02 (0.72-3.1)
Activated partial thromboplastin time (25-43*sec*)	34.6 (27-43.8)	36.2 (25-44.5)
Fibrinogen (200-400 *mg/dl*)	449.7 (225-635)	497.8 (240-675)

Table 4.

Blood test results

	Results	Normal range
white blood cells (*x10^9/L*)	6.17	4-10
lymphocyte (*x10^9/L*)	0.86	1-3.0
neutrophil (*x10^9/L*)	4.91	1.6-7
platelets (*x10^9/L*)	952	150-400
red blood cells (*x10^{12}/μL*)	6.26	3.9-5.6
hemoglobin (*g/l*)	154	110-160
C-reactive protein (*mg/l*)	68	>5
D-dimer (*FEU/ml*)	0.613	<0.55
Procalcitonin (*g/ml*)	0.01	<0.05n
Ferritin (*ng/ml*)	790	13-350
international normalized ratio	1.12	0.85-1.2
activated partial thromboplastin time (*sec*)	40.6	25-43
Fibrinogen (*mg/dl*)	548	200-400
Glucose (*mmol/l*)	25	<6

Blood tests were repeated and the results are presented in Table 5. 18 hours after the admission to the Intensive care unit, the patient experienced discomfort in the right shoulder.

Electrocardiogram (ECG) was performed, which revealed ST elevation in V1-V3 leads. Troponin T level was also elevated (395 *ng/L*) and had further increase to – 948 *ng/L*. Because of acute respiratory distress syndrome and low SpO2-81% even with oxygenation percutaneous coronary intervention was not possible and patient passed away soon after the diagnosis of STEMI.

Case 2

A 62-year-old man with cardiovascular risk factors including coronary artery disease, hypertension, previous MI and percutaneous coronary intervention, was admitted with COVID-19-induced pneumonia on the 8th day of the disease. Patient had fever, weakness and shortness of breath. COVID-19 was confirmed by real-time reverse transcription-polymerase chain reaction testing

Table 5.

Intensive care unit bood test results

	Results	Normal range
white blood cells (*x10^9/L*)	10.76	4-10
lymphocyte (*x10^9/L*)	0.45	1-3.0
neutrophil (*x10^9/L*)	10.01	1.6-7
platelets (*x10^9/L*)	1345	150-400
C-reactive protein (*mg/l*)	19	>5
D-dimer (*FEU/ml*)	1.23	<0.55
Ferritin (*ng/ml*)	821	13-350
international normalized ratio	1.17	0.85-1.2
activated partial thromboplastin time (*sec*)	41.8	25-43
Fibrinogen (*mg/dl*)	556	200-400

from a nasopharyngeal swab. Clinical findings after physical examination are: t-38.1*C*, SpO2-83-84% in room air and 90% with oxygenation, HR-92 *bpm*, BP-140/80 *mmHg*. ECG was without abnormalities. He was treated with antibiotics and corticosteroids before hospitalization. ECG was performed at the admission, which revealed no significant abnormalities. Laboratory results are presented in Table 6.

This patient also received a low dose of anticoagulant (nadroparin 4000*U/day* Subcut) due to severe nasal bleeding.

During day 1 of the hospitalization patient had a drop of SpO2 to 78% with oxygenation during minimal physical activity. There were signs of encephalopathy. The 12 lead ECG performed before symptoms showed an extreme Left axis deviation, T wave inversion in lead III, ascending (no significant) ST elevation in lead I, aVL (Fig. 1A). On the 2nd day of his hospitalization, a patient experienced severe chest pain and discomfort and had BP drop to 70/40 *mmHg*. The 12 lead ECG performed immediately after symptoms showed the ST elevation in leads II, III, a ventricular fibrillation (VF), reciprocal ST depression in leads V3-V6, extreme left axis. (Fig. 1B).

His troponin T levels came back elevated 193.3 *ng/L* (N-20*ng/L*). Patient received Heparin 10000U

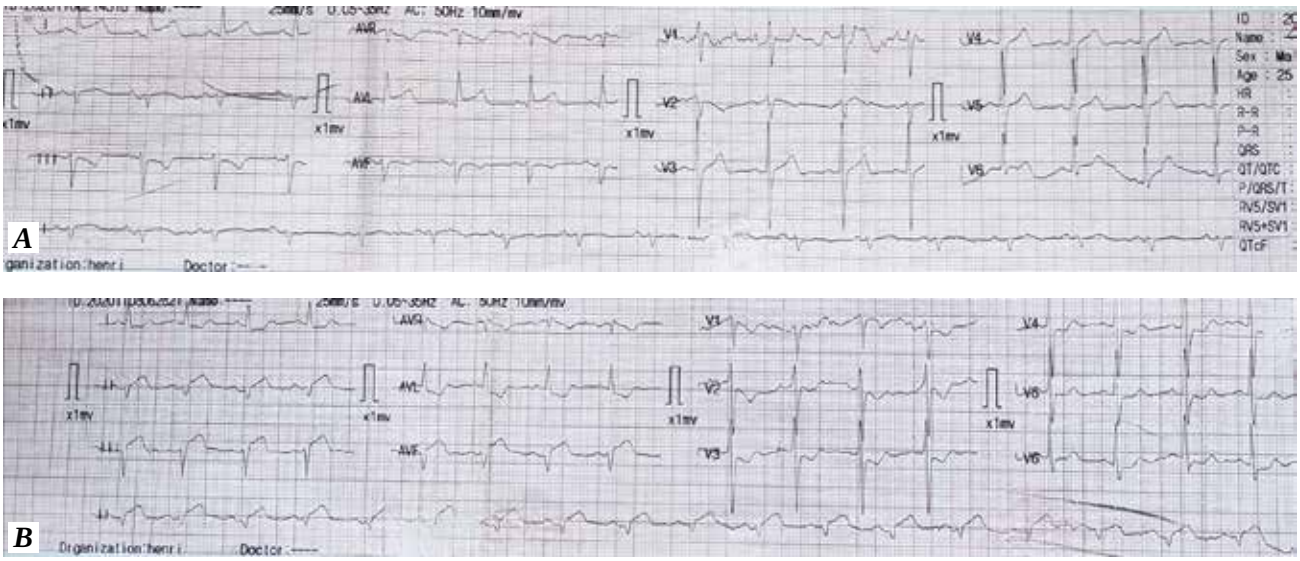

***Figure** 1. Value of the 12 Lead electrocardiogram on the 1st (A) and 2nd (B)days of hospitalization.*

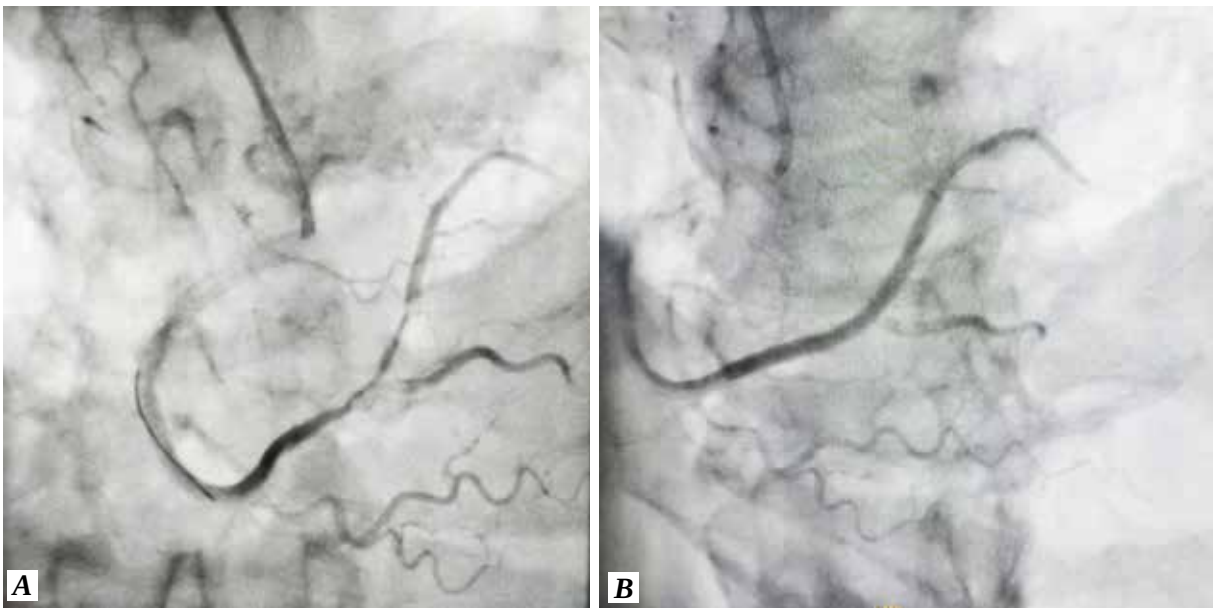

***Figure** 2. Rght coronary artery stenosis on coronary angiogram (A) and after percutaneous coronary intervention. (B)*

TABLE 6.

Blood test results

	Results	Normal range
white blood cells ($x10^9/L$)	11.06	4-10
lymphocyte ($x10^9/L$)	1.03	1-3.0
neutrophil ($x10^9/L$)	8.84	1.6-7
platelets ($x10^9/L$)	1636	150-400
red blood cells ($x10^{12}/L$)	5.72	3.9-5.6
hemoglobin (*g/l*)	165	110-160
C-reactive protein (*mg/l*)	69	>5
D-dimer (*FEU/ml*)	1.73	<0.55
Procalcitonin (*ng/ml*)	0.08	<0.05
international normalized ratio	2.1	0.85-1.2
activated partial thromboplastin time (*sec*)	44.6	25-43
Fibrinogen (*mg/dl*)	621	200-400

TABLE 7.

	Endpoints.		
Hospitalization, mean±SD (days)	14.3±5.2	14.1±4.6	
myocardial infarction n(%)	7(7.5)	3(2.9)	$p = 0.149$
Mortality n(%)	4(4.3)	7(6.86)	$p = 0.441$
CV mortality n(%)	3(3.2)	1(0.98)	

i/v and analgesics. After one hour Troponin T level elevated to 1807.2 *ng/L*. Acute myocardial infarction with ST elevation was diagnosed and patient was transferred to hospital with cath-lab. Coronary angiography revealed proximal lesion in the right coronary artery with 85% stenosis and another lesion in distal right coronary artery (with 90% stenosis) extending to the posterior descending artery, where thrombi were localized (Fig. 1A). Other coronary arteries were affected: 30% stenosis of distal left anterior descending artery, 70% stenosis of proximal left circumflex artery (LCX) and 70% stenosis of the Diagonal 1 artery. Immediate RCA stenting with drug eluting stent was performed (Fig. 2B). On the next day selective percutaneous coronary intervention was performed with stenting of LCX. Dual antiplatelet therapy consisting of oral clopidogrel (75 *mg* od) and aspirin (81 *mg* od) was initiated. After 32 days of prolonged hospitalization, he was discharged under long-term monitoring of cardiologist and hematologist. After 2 weeks, the patient was followed up in an outpatient clinic. He had slightly improved physical strength and nutritional status, and no complications from the dual antiplatelet therapy.

CONCLUSION

A broad range of risk factors and potential cardiovascular complications were assessed and considered in the clinical management tactics.

The poorer outcomes in the early stages of the pandemic were associated with not adequate anticoagulation treatment administration due to a lack of information about a novel virus and clinical management specificities.

Although Group 2 had significantly higher rates of severe cases, there was no significant difference in overall mortality and MI incidence (Table 7). We came to a conclusion that anticoagulants and antiplatelets were crucial for preventing cardiovascular complications especially in patients with comorbidities. Patients with high platelet levels were at higher risk of developing MI, and then of having a worse outcome.

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