Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages.13111-13119
Received 05 March 2021; Accepted 01 April 2021

ANALYSIS OF HEMOSTASIS INDICATORS IN PATIENTS WITH CORONAVIRUS INFECTION

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ABSTRACT

Objective of the study: To study disorders of hemostasis in patients with COVID-19.

Research materials: 200 patients with COVID-19 treated in departments of the 2nd Zangiata infectious diseases hospital.

Research methods: PT, PTI, INR, APTT, fibrinogen, adhesion, aggregation and retraction of platelets. Research results: with COVID-19, there is an increase in platelet adhesion by 11.2 - 58.0%, aggregation by 21.9 - 60.0%, shortening of retraction by 12.5 - 31.2%, significant mixing of the three phases of coagulation hemostasis towards hypercoagulability.

Conclusion: The displacement of hemostasis towards hypercoagulability was higher in patients with severe and extremely severe coronavirus infection.

Key words: COVID-19, hemostasis, adhesion, aggregation, platelet retraction, PTI, INR, fibrinogen.

INTRODUCTION

COVID-19 is a systemic infection, one of the most common complications of which is hypercoagulability. Blood clotting disorders are quite common among patients with severe course of coronavirus infection [1, 2].

One of the formidable complications of COVID-19 is venous thromboembolism. Prolonged immobilization during illness, dehydration, acute inflammation, risk factors for cardiovascular diseases (hypertension, diabetes, obesity) or cardiovascular diseases (coronary or peripheral artery disease, previous ischemic stroke) and classical genetic thrombophilia (for example, heterozygous Factor V Leiden mutation) - all of these factors are common comorbidities that potentially increase the risk of venous thromboembolism in hospitalized patients with COVID-19. Damage to endothelial cells when the virus binds to ACE-2 also increases the risk of venous thromboembolism. The release of huge amounts of inflammatory mediators, hormones and immunoglobulins in severe or critically ill patients can lead to an increase in blood viscosity.

In addition, mechanical ventilation, central venous catheterization and surgery also damage the vascular endothelium. A combination of all of the above factors can lead to deep vein thrombosis or even pulmonary embolism. Therefore, all patients hospitalized with COVID-19 are advised to assess the risk of developing venous thromboembolism and, if the risk is high, prescribe pharmacological thromboprophylaxis [3].

As a result of a multicenter retrospective study in China, during the first two months of the epidemic, 46.4% of patients showed an increased level of D-dimer (≥0.5 mg / L), among severe cases this increase was significantly more pronounced (59.6% versus 43.2% with a moderate course of the disease) [4]. D-dimer dynamics may reflect the severity of the disease, and elevated levels may predict adverse outcomes [5].

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D-dimer values above 1.5 μg / L were recorded in 36% of patients in a descriptive study with 99 cases of COVID-19 in Wuhan [6]. Other studies also confirmed that D-dimer and prothrombin time levels were higher on admission in patients requiring intensive care [7, 8].

In patients with myocardial injury as a result of COVID-19, blood clotting disorders were more often detected [9]. Among patients with high troponin T levels, there were more cases of increases in prothrombin time, activated partial thromboplastin time, and D-dimer level [10].

Among 201 patients with pneumonia caused by COVID-19, an increase in prothrombin time was associated with a high risk of developing acute respiratory distress syndrome, while an increase in the level of D-dimer was significantly associated with an increased risk of developing acute respiratory distress syndrome and death [11]. The differences between D-dimer levels in surviving and deceased patients were greater than when comparing groups with and without acute respiratory distress syndrome; This observation may indicate that complications associated with DIC syndrome lead to the death of many patients, regardless of the presence of acute respiratory distress syndrome.

On the basis of multivariate analysis in a multicenter retrospective cohort study, it was found that increased levels of D-dimer (more than 1 μg / ml) were significantly associated with death [2]. In another retrospective study by Tang et al. (183 patients with COVID-19) noted that the deceased patients had higher levels of D-dimer, fibrin degradation products (FDP), as well as increased prothrombin time and activated partial thromboplastin time compared to survivors. It is noteworthy that symptoms during the course of the disease in 71.4% of the deceased patients and 0.6% of the survivors met the clinical criteria for DIC. The average time from admission to the onset of disseminated intravascular coagulation was 4 days [12].

In a prospective study evaluating the coagulation profile in patients with COVID-19, the levels of D-dimer, PRP, and fibrinogen were significantly higher than in the control group (healthy subjects). In severe disease, the D-dimer values were higher than in mild disease [13]. All of the above data indicate that increased D-dimer levels and disseminated intravascular coagulation are widespread in patients with severe COVID-19 [14].

It seems that dysregulation of the immune system and endothelial dysfunction are actively involved in the pathophysiology of COVID-19, however, the details of these processes remain to be clarified in future studies.

Purpose of the study was to study disorders of the vascular-platelet and plasma hemostasis links in patients with COVID-19.

MATERIALS AND METHODS

The object of the study was 200 patients with COVID-19 and developed bilateral pneumonia, treated in the departments of the 2nd ZangiataInfectious Diseases Hospital. Of these, group 1 consisted of 48 (24.0%) patients with mild COVID-19, group 2, 57 (28.5%) patients with moderate COVID-19, group 3, 62 (31.0%) patients with COVID-19 severe and group 4 of 33 patients with extremely severe COVID-19. The control group consisted of 20 patients with negative responses to PCR studies for COVID-19 and immunological markers IgM and IgG without a history of respiratory diseases.

The diagnosis was established on the basis of complaints, physical examination of patients and, of particular importance was the study of the anamnesis of the disease, in which contact with a sick person was established, the duration of the appearance of clinical signs and the reasons, with which the patient associates the development of the disease. In addition, a PCR study for coronavirus infection, X-ray examination and MSCT of the chest were mandatory.

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Analysis of the distribution of patients by age showed that among patients with coronavirus infection, persons from 50 to 69 years old prevailed (Table 1).

Table 1. Distribution of patients with coronavirus infection by age

Patient groups	Age								Total	
	18-29		30-49		50-69		≥70			
	Abs	%	Abs	%	Abs	%	Abs	%	Abs	%
Control group,n=20	5	25,0	5	25	5	25	5	25	20	100
1st group,n=48	8	4,0	13	6,5	21	10,5	6	3,0	48	24,0
2nd group,n=57	9	4,5	15	7,5	23	11,5	10	5,0	57	28,5
3rd group,n=62	8	4,0	16	8,0	26	13,0	12	6,0	62	31,0
4th group,n=33	5	2,5	9	4,5	12	6,0	7	3,5	33	16,5
Total	30	15,0	53	26,5	82	41,0	35	17,5	200	100,0

As can be seen from the table, 15% of patients were young people from 18 to 29 years old, 26.5% of patients from 30 to 49 years old, 41% of patients from 50 to 69 years old and 17.5% of patients over 70 years old.

The research methods were coagulogram with determination of prothrombin time, prothrombin indices, international normalized ratio, activated partial thromboplastin time, fibrinogen, determination of adhesive and aggregation function of platelets.

RESULTS

To study the vascular-platelet link of hemostasis, the adhesive and aggregation functions of platelets were studied. Platelets are involved in primary hemostasis and are involved in the first phase of blood coagulation.

The study of platelet function showed that in patients with the main groups of COVID-19, compared with the control group, there is a distinct increase in the adhesive and aggregation properties of platelets. The study of the adhesive ability of platelets revealed a significant increase in this indicator in all four groups with coronavirus infection. According to the study, the adhesive property of platelets in group 1 was 45.3 ± 4.2% ***, in group 2 - 51.2 ± 4.8% ***, in group 3 - 59.4 ± 5.1% * **, in group 4, 63.2 ± 5.5% ***, while the indicator of the adhesive ability of platelets in the control group was 26.7 ± 3.1%. It was found that the adhesive capacity of platelets increased depending on the severity of the disease, i.e. the highest platelet adhesiveness was observed in group 4 of patients with extremely severe COVID-19, which indicated hypercoagulation in the platelet hemostasis (Fig. 1).

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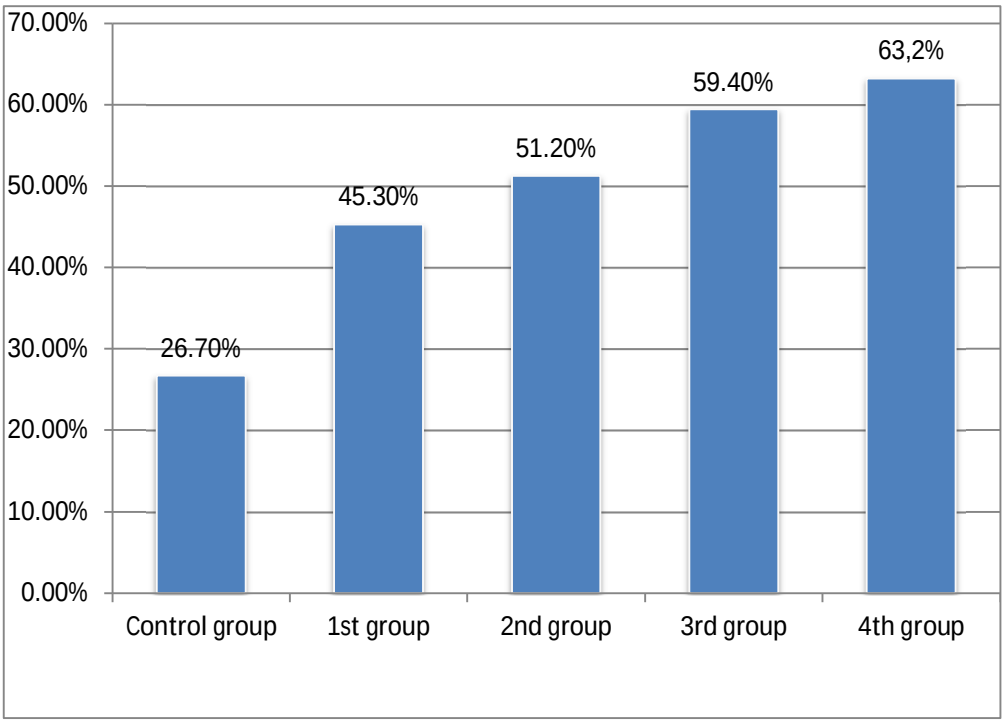
Figure 1. Platelet adhesion in coronavirus infection



Platelet aggregation was studied in two dilutions of the hemolysate-aggregation test: with a dilution of 10-2 (hemolysate-aggregation test 10-2) and 10-6 (hemolysate-aggregation test 10-6). The study of the aggregation properties of platelets showed that in the main groups with COVID-19 there is a significant shortening of the aggregation ability of platelets, which indicated the predominance of hypercoagulation. In group 1, these indicators in the first and second dilutions were 12.1 ± 1.1 * sec and 25.2 ± 1.3 *** sec. respectively. Aggregation properties of group 2 platelets in dilution hemolysate-aggregation test 10-2 was 11.0 ± 1.0 *** sec, hemolysate-aggregation test 10-6 was 20.4 ± 1.6 *** sec. In group 3, there were pronounced changes in the direction of hypercoagulation in these indicators: hemolysate-aggregation test 10-2 8.6 ± 0.9 *** sec, hemolysate-aggregation test 10-6 was 16.3 ± 1.1 *** sec. Group 4 also had hypercoagulation with hemolysate-aggregation test 10-2 6.2 ± 0.8 *** sec, hemolysate-aggregation test 10-6 was 12.5 ± 0.9 *** sec. In the control group, the parameters of the hemolysate-aggregation test were as follows: hemolysate-aggregation test 10-2 15.5 ± 0.8 sec and hemolysate-aggregation test 10-6 32.8 ± 1.4 sec.

The above showed that the adhesive and aggregating ability of platelets in the groups of patients with COVID-19 were significantly increased compared to the control group, which indicated an increase in platelet function and a tendency to hypercoagulability in this category of patients.

In addition, the determination of the retraction of the blood clot also belongs to the parameters of the platelet hemostasis. When studying the platelet retraction time, it was found that the baseline values in patients with the main COVID-19 groups were shortened, which is also characteristic of the hypercoagulable state. A significant increase in the retraction time of platelets in the main groups was found from 0.22 ± 0.02 sec. and up to 0.28 ± 0.02 sec., and in the control group 0.32 ± 0.02 sec. (Table 2).

Table 2. Thrombocytic hemostasis in patients with COVID-19

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Indicators of hemostasis	Hemolysate-aggregation test 10^{-2}, sec	Hemolysate-aggregation test 10^{-6}, sec	Retraction
Control group,n=20	15,5 ± 0,8	32,8 ± 1,4	0,32± 0,02
1st group,n=48	12,1 ± 1,1*	25,2 ± 1,3***	0,28± 0,01
2nd group,n=57	11,0±1,0***	20,4 ± 1,6***	0,26±0,02**
3rd group,n=62	8,6 ± 0,9***	16,3 ± 1,1***	0,24 ± 0,02***
4th group,n=33	6,2 ± 0,8***	12,5 ± 0,9***	0,22 ± 0,02***

*Note: * -P <0.05, ** - P <0.01, *** - P <0.001 significant in relation to the control group.*

Thus, in patients with coronavirus infection, pronounced violations of the functional properties of platelets are observed with an increase in platelet activity, which is characterized by an increase in platelet adhesion by 11.2 - 58.0% and platelet aggregation properties by 21.9 - 60.0%, and a shortening of the retraction time. blood clot by 12.5 - 31.2%.

Coagulation hemostasis consists of a cascade of reactions involving plasma coagulation factors. The plasma link of hemostasis was studied in three phases of blood coagulation. To study the first phase of blood coagulation, the blood clotting time by the Moravitz method and the active partial thromboplastin time were studied.

In patients of the main groups with COVID-19, a pronounced shortening of blood clotting time was observed. So, in group 1, the beginning of coagulation was 94.2 ± 7.5 * s, the end of coagulation was 160.3 ± 10.8 *** s, in group 2, the beginning of coagulation was 73.5 ± 8.2 *** s. , end of coagulation 125.8 ± 11.7 *** s. In groups 3 and 4, significant violations of the blood coagulation time were also observed: in group 3, the beginning of coagulation was 66.7 ± 6.2 *** s, the end of coagulation was 115.7 ± 8.9 *** s, and in group 4 beginning of coagulation at 56.5 ± 5.7 *** s, end of coagulation 107.2 ± 11.8 *** s. In the control group, these indicators were as follows: the beginning of coagulation at 125.3 ± 11.0 s, the end of coagulation 248.0 ± 16.6 s. Shortening of the blood clotting time showed a pronounced hypercoagulation in the plasma hemostasis in patients with COVID-19 compared with the control group (Table 3).

Table 3. Assessment of the first phase of blood coagulation in COVID-19

Groups	Blood clotting time onset, sec	Blood clotting time end, sec	Activated partial thromboplastin time, sec
Control group,n=20	125,3 ± 11,0	248,0 ± 16,6	29,1 ± 3,39
1st group,n=48	94,2 ± 7,5*	160,3± 10,8***	20,8 ± 1,2*
2nd group,n=57	73,5 ± 8,2***	125,8 ± 11,7***	18,0 ± 1,3**
3rd group,n=62	66,7 ± 6,2***	115,7±8,9***	16,8 ± 1,1***
4th group,n=33	56,5 ± 5,7***	107,2±11,8***	15,9 ± 1,5***

*Note: * -P <0.05, ** - P <0.01, *** - P <0.001 significant in relation to the control group.*

As can be seen from the table, the plasma indicator of the activated partial thromboplastin time in patients of the main COVID-19 groups was shortened: in group 1, the activated partial thromboplastin time was 20.8 ± 1.2 * s, in group 2, 18.0 ± 1.3 ** s, in group 3 16.8 ± 1.1 *** and in group 4 15.9 ± 1.5 *** s. In the control group, the activated partial thromboplastin time was 29.1 ±

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3.39 s. Severe violations of blood clotting time and activated partial thromboplastin time showed that patients with COVID-19 had hypercoagulation in the first phase of the plasma hemostasis link.

To study the second phase of the plasma link of hemostasis, the prothrombin time, prothrombin index and international normalized ratio were studied. The study of the indicators of the second phase of blood coagulation showed a significant mixing of blood coagulation towards hypercoagulation in patients with the main groups of COVID-19.

The prothrombin time was significantly shortened in patients from the main COVID-19 groups in relation to the control group. So, in group 1 the prothrombin time was 10.2 ± 0.9 * s, in group 2 - 9.1 ± 0.7 ** s, in group 3 - 8.3 ± 0.8 *** s, and in 4 the group, this indicator was 6.8 ± 0.7 *** s. the prothrombin time of the control group was 13.0 ± 1.1 s.

The prothrombin index was calculated using the formula and was within 127.5 ± 5.1 **%, 142.9 ± 6.1 ***%, 156.6 ± 7.3 ***% and 191.2 ± 9 , 3 ***% in groups 1, 2, 3 and 4 with COVID-19, respectively. This indicated severe hypercoagulability (Table 4).

Table 4. AssessmentofthesecondphaseofbloodcoagulationinCOVID-19

Groups	**Prothrombin time, sec**	**Prothrombin index,%**	**International Normalized Ratio**
Control group,n=20	13,0 ± 1,1	100,0 ± 7,2	1,0 ± 0,09
1st group,n=48	10,2 ± 0,9**	127,5 ± 5,1**	0,78 ± 0,06*
2nd group,n=57	9,1 ± 0,7***	142,9 ± 6,1***	0,70 ± 0,04**
3rd group,n=62	8,3 ± 0,8***	156,6 ± 7,3***	0,64 ± 0,05***
4th group,n=33	6,8 ± 0,7***	191,2 ± 9,3***	0,52 ± 0,07***

*Note: * -P <0.05, ** - P <0.01, *** - P <0.001 significant in relation to the control group.*

As can be seen from the table, the international normalized ratio was shortened in all COVID-19 groups. In group 1, the international normalized ratio was 0.78 ± 0.06 *, in group 2, 0.70 ± 0.04 **, in group 3, 0.64 ± 0.05 ***, and in group 4, 0.52 ± 0.07 ***. In the control group, this indicator was 1.0 ± 0.09.

To characterize the third phase of blood coagulation, the amount of fibrinogen, plasma heparin tolerance, thrombotest and thrombin time were determined.

The study of the amount of fibrinogen showed a significant increase in the concentration of fibrinogen with a tendency to severe hypercoagulability. In group 1, the amount of fibrinogen was 556.0 ± 52.0 ** mg / dl, in group 2 - 638.0 ± 61.1 *** mg / dl, in group 3 - 723.5 ± 66.7 *** mg / dl and in group 4 922.1 ± 75.3 *** mg / dl. In the control group, this indicator was 290.4 ± 60.5 mg / dl.

In the study of the third phase of the plasma - coagulation link of hemostasis, it was revealed that patients of the main groups with COVID-19 have a distinct shortening of thrombin time compared to the control group. Thus, the thrombin time of group 1 was 10.9 ± 1.1 ** s, group 2 was 9.5 ± 1.0 *** s, group 3 was 8.7 ± 0.8 *** and group 4 was 7.9 ± 0.7 ***. The thrombin time of the control group was 15.7 ± 1.0.

A distinct increase in plasma tolerance to heparin was also found in patients in groups 1, 2, 3 and 4 compared with the control group. Tolerance index for 1 group was 217.1 ± 25.9 * s, 2 groups 198.3 ± 25.3 ** s, 3 groups 168.9 ± 23.4 *** and 4 groups 140.5 ± 22.4 ***, while in the control group this indicator was 309.0 ± 52.1 s.

Thrombotest is determined by the intensity of the formation of a fibrin clot. Grade III is characterized by the inferiority of a loose clot, Grade IV the clot is formed and glued to the wall of

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the test tube, Grade V the clot fills the entire volume of the test tube. The main part of thrombotest indicators were 6.0-7.0 degrees in patients of the main group with COVID-19.

Indicators of fibrinogen, thrombin time, plasma tolerance to heparin and thrombotest are shown in Table 5.

Table 5. Indicators of the third phase of plasma hemostasis in COVID-19.

Groups	**Fibrinogen (mg%)**	**Thrombin time (sec)**	**Plasma Tolerance to Heparin (sec)**	**TT**
Control group,n=20	290,4±60,5	15,7±1,0	309,0±52,1	4,8 ± 0,41
1st group,n=48	556,0±52,0**	10,9±1,1**	217,1±25,9*	6,0±0,37*
2nd group,n=57	638,0±61,1***	9,5±1,0***	198,3±25,3**	6,5±0,43**
3rd group,n=62	723,5±66,7***	8,7±0,8***	168,9±23,4***	6,8±0,40***
4th group,n=33	922,1±75,3***	7,9 ± 0,7***	140,5 ± 22,4***	7,0±0,34***

*Note: * -P <0.05, ** - P <0.01 significant in relation to the control group.*

In the study of the third phase of blood coagulation, pronounced hypercoagulability was found in all groups with COVID-19 in relation to the control group.

CONCLUSION

1. Analysis of the distribution of patients by age showed that among patients with coronavirus infection, persons from 50 to 69 years old prevailed.

2. Study of platelet function showed that patients with coronavirus infection have pronounced violations of the functional properties of platelets with an increase in platelet activity, which is characterized by an increase in platelet adhesion by 11.2 - 58.0% and platelet aggregation properties by 21.9 - 60.0 %, shortening the blood clot retraction time by 12.5 - 31.2%.

3. It was found that the adhesive, aggregating ability of platelets and their retraction were higher depending on the severity of the disease, i.e. the highest rate of platelet function was observed in groups 3 and 4 of patients with severe and extremely severe COVID-19.

4. In patients of the main groups with COVID-19, a pronounced shortening of blood coagulation time and activated partial thromboplastin time was observed, which indicated pronounced hypercoagulation in the first phase of the plasma hemostasis link in patients with COVID-19.

5. The study of the indicators of the second phase of blood coagulation showed a significant mixing of blood coagulation towards hypercoagulation in patients with the main groups of COVID-19 with a pronounced shortening of the prothrombin time and the international normalized ratio, an increase in the prothrombin index.

6. In the study of the third phase of blood coagulation, pronounced hypercoagulability was found in all groups with COVID-19 with a significant increase in the concentration of fibrinogen and a shortening of the thrombin time.

7. The shift of plasma hemostasis towards hypercoagulability was higher in groups 3 and 4 of patients with severe and extremely severe coronavirus infection.

REFERENCES

1. Deng Y., Zou J.H., Sun S.S., Liu B.J., Wang L., Shi J.Y., Xiong X.A. and Zhang S.F. Tag-based Analysis at the BESIII Experiment. Journal of Physics: Conference Series 1525 (2020) 012083 IOP Publishing doi:10.1088/1742-6596/1525/1/012083 1 Z Institute of High Energy Physics, Chinese Academy of Sciences, 19B Yuquanlu, Shijingshan District, Beijing, China.
2. Zhou F, Yu T, Du R, et al (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet, online 2020, March 11. DOI: https://doi.org/10.1016/S0140- 6736(20)30566-3.
3. Diane M. Ward‡1, Opal S. Chen§ , Liangtao Li‡ , Jerry Kaplan‡ , Shah Alam Bhuiyan¶ , Selvamuthu K. Natarajan¶ , Martin Bard¶ , and James E. Altered sterol metabolism in budding yeast affects mitochondrial iron–sulfur (Fe-S) cluster synthesis Received for publication, January 5, 2018, and in revised form, May 11, 2018 Published, Papers in Press, May 17, 2018, DOI 10.1074/jbc.RA118.001781 Cox 2018 Ward et al. Published under exclusive license by The American Society for Biochemistry and Molecular Biology, Inc.
4. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. doi: https://doi.org/10.1056/NEJMoa2002032
5. Snijders D, Schoorl M, Schoorl M, Bartels PC, van der Werf TS, Boersma WG: D-dimer levels in assessing severity and clinical outcome in patients with community-acquired pneumonia. A secondary analysis of a randomised clinical trial. EUR J INTERN MED 2012, 23(5):436–441.
6. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The It is made available under a CC-BY-NC-ND 4.0 International license . (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. medRxiv preprint doi: https://doi.org/10.1101/2020.04.02.20051029; this version posted April 6, 2020. The copyright holder for this preprint Lancet. 2020;395(10223):507-513. doi:https://doi.org/10.1016/S0140- 6736(20)30211-7
7. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA. 2020. doi:https://doi.org/10.1001/jama.2020.1585
8. Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., … Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet. https://doi.org/10.1016/S0140-6736(20)30183-5;
9. Shi S, Qin M, Shen B, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China [published online ahead of print, 2020 Mar 25]. *JAMA Cardiol*. 2020;e200950. doi:10.1001/jamacardio.2020.0950
10. Guo T, Fan Y, Chen M, et al. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol.* Published online March 27, 2020. doi:10.1001/jamacardio.2020.1017
11. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020; Mar 13. doi:10.1001/jamainternmed.2020.0994
12. Tang, N., Li, D.J., Wang, X. and Sun, Z.Y. (2020) Abnormal Coagulation Parameters Are Associated with Poor Prognosis in Patients with Novel Coronavirus Pneumonia. Journal of Thrombosis and Haemostasis, 18, 844-847.https://doi.org/10.1111/jth.14768
13. Han H, Xie L, Liu R, et al. Analysis of heart injury laboratory parameters in 273 COVID-19 patients in one hospital in Wuhan, China. J Med Virol 2020; 92: 819-823.

14. Lippi G, Plebani M. Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chim Acta 2020; 505:190–191.