

LABORATORY CHARACTERISTICS AND PRESENTATION OF MULTI-ORGAN AFFECTION AMONG HOSPITALIZED PATIENTS WITH COVID 19 INFECTION IN PUBLIC HOSPITAL IN BITOLA

Ilkovska Biljana ¹, Kotevska B ², Hristovska S ¹, Kostovska I ³, Tosheska-Trajkovska K ³,
Kanazirev B ⁴

¹ Department of medical biochemistry, PHO Clinical Hospital Dr. Trifun Panovski, Bitola, R. of
North Macedonia

²Department of dermato-venerology, Tokuda Hospital, Sofia, Bulgaria

³Institute of Medical and Experimental Biochemistry, Medical Faculty, Ss Cyril and Methodius
University, Skopje, R. of North Macedonia

⁴Propedeutics of Internal Medicine, Varna Medical University, Varna, Bulgaria

Abstract

In December 2019, a highly infectious disease, ie, pneumonia caused by the coronavirus disease SARS-CoV-2, occurred in Wuhan, China, and the World Health Organization has declared its ongoing outbreak a pandemic. The clinical laboratory plays a key role in supporting the monitoring and management of Covid 19 disease.

Our study describes the laboratory characteristics of 103, Covid 19 positive patients hospitalized in the public hospital Trifun Panovski in the period April - June 2020. Only two patients died as a result of the Covid 19. The most common laboratory abnormalities were: elevated lactate dehydrogenase (LDH) and C-reactive protein (CRP).

Leukocytosis was found in 23,3%, and leucopenia in 3% of patients with Covid 19. Covid 19 infection can be associated with myocardial injury, heart failure, vascular inflammation, myocarditis, cardiac arrhythmias, and hypoxic encephalopathy. We found increased values of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and γ -glutamyltransferase (γ -GT) in 35 – 50% of patients. We detected affected renal function in 10% of our patients with Covid 19.

We identified potential biomarkers of disease severity. Our results provide guidance in risk assessment, clinical monitoring and therapy decision-making processes

Keywords: Covid 19, laboratory findings, multi organ failure.

Introduction

In December 2019, a highly infectious disease, ie, pneumonia caused by the coronavirus disease SARS-CoV-2, occurred in Wuhan, China, and the World Health Organization has declared its ongoing outbreak a pandemic [1]. The geographical distribution of Covid 19 covers all continents except Antarctica. Epidemiologists in Wuhan believed the Huanan Seafood Wholesale Market in Wuhan is the point of origin of SARS-CoV-2, due to its connection to the trading of live wild animals [2]. At the time of writing, over 21,732,472 million confirmed Covid 19 cases and over 770,866 Covid 19 related deaths have been reported [3].

Covid 19 is highly contagious disease, with a basic reproduction number of between 1.4 and 6.5, and can be easily spread through coughs and sneezes, talking to infected persons, and touching the eyes, nose, or mouth after touching a contaminated surface [4].

The novel coronavirus belongs to lineage B of the genus betacoronavirus of the Coronavirus family, which includes SARS-CoV and MERS-CoV [5]. The SARS-CoV-2 is the seventh member of the coronavirus family that infects humans [6].

A recent study reported that fever, cough, myalgia or fatigue were common symptoms, and sputum production, headache, haemoptysis, and diarrhea were less common symptoms [7].

All patients had pneumonia and about half developed dyspnea [8]. Incubation duration of Covid 19 infection ranges from 2 to 14 days, and various studies demonstrate that symptoms are seen within an average of 4 to 7 days [9].

The Covid 19 clinical presentation can be: mild- the clinical symptoms were mild, and there was no or mild sign of pneumonia on imaging; moderate - showing fever and respiratory symptoms with radiological findings of pneumonia; severe- in accordance with any of the following: shortness of breath (RR \geq 30 breaths/min); in resting state, oxygen saturation \leq 93%; arterial partial pressure of oxygen/fraction of inspired oxygen \leq 300 mmHg, cases with chest imaging showed obvious lesion progression more than 50% within 24–48 h; critical - one of the following: respiratory failure, requiring mechanical ventilation; septic shock; multiple organ failure.

The Clinical Laboratory plays a key supportive role in management of Covid 19 disease. Routine hematological and biochemical tests are essential in assessing disease severity and monitoring of the disease.

The aim of our study was to identify most laboratory biomarkers of disease severity.

Methods

This study was carried out from April to July 2020 at the Department of Medical Biochemistry and Department of infective diseases of Public Health Organization Clinical Hospital “D-r Trifun Panovski” in Bitola. Our study describes the laboratory characteristics of 103 Covid 19 infected patients hospitalized in Department of infective diseases with moderate stage of the diseases at the age of 17 to 86.

Ethics Committee of Health Organization Clinical hospital “D-r Trifun Panovski” approved the study, and all of the procedures were performed in accordance with ethical approval institutional guidelines. The study protocol followed the ethical guidelines of the most recent Declaration of Helsinki. Written consent was obtained from the participants prior to the start of the study.

Clinical and laboratory measurements - Patient respiratory samples, including nasopharyngeal swabs were collected and real-time polymerase chain reaction (RT-PCR) was used to confirm Covid 19 infection. Data includes: medical history, a physical examination, questionnaire information and laboratory findings of each patient. A confirmed case was defined by a positive result to RT-PCR of nasopharyngeal swab specimens. Blood samples were collected after 12 hours fasting.

Complete blood count (CBC) - CBC was determined in ethylenediaminetetraacetic acid (K-EDTA) blood samples -using Sysmex XP 300/ Sysmex XS 1000 (Sysmex Co, Kobe, Japan) according to the manufacturer's instructions. The obtained indicators were as follows: white blood cell count (WBC $\times 10^9/L$), neutrophil percentage (NEUT%), neutrophil count (NEUT($\times 10^9/L$)), lymphocyte percentage (LYMPH%), lymphocyte count (LYMPH($\times 10^9/L$)), red blood cell count (RBC $\times 10^{12}/L$), hemoglobin (HGB (g/l)), platelets (PLT($\times 10^9/L$)).

Biochemical analyses - Biochemical analyses were performed on Abbot Architect CI 4100 according to the manufacturer's instructions. We determined: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBILI), direct bilirubin (DBILI), creatinine (CREA), urea (UR), γ -glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), creatin kinase (CK), creatin kinase MB fraction (CK-MB), glucose (GLUK), hypersensitive C-reactive protein (hsCRP) and iron.

The data are presented as mean \pm standard deviation (SD). The results were done with the SPSS version 13.

Results

A total of 103 patients confirmed with Covid 19 infection were included in this study, of whom 61 (59.22%) were males and 42 (40.78%) were females. The median age was 53 years, the youngest patient was 17 years old and the oldest was 86 years of age. Study patients were divided in seven age groups presented in Table 1.

Table 1. Age groups of study patients

Age group (years)	Males	Females	Total
10-20	/	1	1
20-30	7	1	8
30-40	9	5	14
40-50	9	5	14
50-60	16	16	32
60-70	14	6	20
70-80	4	4	8
80-90	2	4	6
Total	61	42	103

Hematological and biochemical features of COVID-19 patients are presented in Table 2 and Table 3.

Table 2. Hematological characteristics of COVID-19 patients

	Referent values	Total	Male	Female	p
		N = 103	N = 61 (59.22%)	N = 42 (40.78%)	0.0083
Variables		Mean	Mean	Mean	
WBC ($\times 10^9/L$)	3,5 -10	6.9	8.2	6.3	0.0092
NEUT % (%)	43 - 76	66.49	68.05	64.13	0.1647
NEUT ($\times 10^9/L$)	1.2 - 6.8	4.8	5.6	4.2	0.0021
LYMPH% (%)	17 – 48	22	20	25.9	0.0628
RBC ($\times 10^{12}/L$)	3.8 – 5.8	4.72	4.84	4.6	0.0035
HGB (g/L)	120 - 165	132.6	137.54	125.43	0.001
PLT ($\times 10^9/L$)	150 - 390	281	273	298	0.1029

The results are presented as: N (number), % (percent), Mean (min - max); WBC, white blood cells; Neut, neutrophils; Lymp, lymphocyte; RBC, red blood cells; HGB, hemoglobin; PLT, platelets.

Table 3. Biochemical characteristics of COVID-19 patients

	Referent values	Total	Male	Female	P
		N = 103	N = 61 (59.22%)	N = 42 (40.78%)	
Variables		Mean	Mean	Mean	
ALT (U/L)	0-55	33.5	39	31	0.1988
AST (U/L)	3-34	42.16	36.27	34	0.1423
CK (U/L)	Male 30-200 Female 29-168	220.6	322.7	64.4	0.0582
CK-MB (U/L)	<25	22.1	25.73	20.83	0.0124
LDH (U/L)	125-220	279.9	256.9	252.5	0.0754
GGT (U/L)	Male 12-64 Female 9-36	131.13	72.76	59	0.2001
Urea (mmol/L)	Male 3-92 Female 3,5-7,2	5.46	3.7	4.75	0.2962
Creatinine (µmol/L)	Male 63,6-110 Female 50-98	80.6	63.5	79.5	0.0392
TBILI (µmol/L)	3,4- 20,5	8.75	8.80	8.8	0.0989
DBILI (µmol/L)	<8,6	5.61	4.13	4.1	0.0970
Glucose (mmol/L)	3,8-5,8	5.97	5	5.89	0.0737
hs-CRP (mg/L)	<5	48.89	28.2	15.7	0.2761
Iron (µmol/L)	Male 11,6-31,3 Female 9-30,4	12.09	13.15	8	0.1763

The results are presented as: N (number), % (percent), Mean (standard deviation) (min - max); Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Total bilirubin (TBILI), Direct bilirubin (DBILI), Creatinine (CREA), Urea (UR), γ -glutamyl transpeptidase (GGT), Lactate dehydrogenase (LDH), Creatin kinase (CK), Creatin kinase MB fraction (CK-MB), hypersensitive C-reactive protein (hsCRP)

Haematological parameters

Compared with the reference range our results showed that 24 Covid 19 infection positive patients (23.3%) had increased WBC levels (6 females and 18 males), 3 Covid 19 infection positive patients (2.9%) had decreased WBC count (2 females, 1 male) and 76 other patients had normal WBC count.

Compared with the reference range, 25 Covid 19 infection positive patients (24.27%) had increased neutrophil levels (4 females and 21 males), 4 Covid 19 infection positive patients (3.8%) had decreased neutrophil levels (2 female, 2 males) and normal neutrophil levels were found in the 69 other patients.

Additionally, investigations revealed 19 patients with Covid 19 infection (18.4%) had increased lymphocytes (1 female and 18 males), 31 Covid 19 infection positive patients (30.1%) had lymphopenia (13 females and 18 males) and 53 other patients had normal lymphocyte levels.

Compared with the reference range, 25 Covid 19 infection positive patients (24.27%) had increased neutrophil levels, 4 Covid 19 infection positive patients (3.8%) had decreased neutrophil levels and 69 other patients had normal neutrophil levels.

Compared with the reference range, 3 Covid 19 infection positive patients (2.9%) had increased red blood cell count levels (3 males), 4 Covid 19 infection positive patients (3.8%) had decreased red blood cell count (1 female, 3 males) and normal red blood cell count levels were found in the 96 other patients.

Seven Covid 19 infection positive patients (6.8%) had increased hemoglobin levels (7 males), 19 Covid 19 infection positive patients (18.4%) had decreased hemoglobin concentration (11 females, 8 males) and normal hemoglobin levels were found in 77 other patients. Increased platelets levels were found in 25 Covid 19 infection positive patients (24.27%) (12 females and 13 males), 9 Covid 19 infection positive patients (8.7%) had decreased platelets (1 female, 8 males) and normal platelets count was found in the 69 other patients.

Biochemical tests:

Liver enzymes

Activity of ALT was increased in 34 patients (10 females and 24 males), of AST in 46 patients (17 females and 29 males) and 26 patients (52%) had increased γ -glutamyl transpeptidase activity (10 females and 16 males). Over 66 patients had normal activity of ALT, 55 patients had normal values of AST and 28 patients had normal γ -glutamyl transpeptidase values.

Cardiac markers:

CK activity was increased in 13 patients (1 female and 12 males), 39 patients (11 females and 28 males) had increased activity for CK- MB fraction, 73 patients had normal CK values, and 48 patients had normal CK- MB fraction values.

Other biomarkers:

LDH

The most common laboratory abnormalities were elevated activity of LDH and CRP. LDH activity was slightly elevated in 64 patients (26 females and 38 males), which represents 70% of examinee patients with Covid 19 infection. Only 27 Covid 19 positive patients had normal LDH values.

CRP

CRP was increased in 74 % of Covid 19 infection positive patients (27 females and 47 males). Twenty six patients had normal values.

Kidney biomarkers

Ten patients (4 women and 6 males) had increased values of urea and creatinine.

Iron

About iron homeostasis, 60% of examinee patients had decreased iron levels (11 females and 33 males) and 32 patients had normal values of iron.

Discussion

The laboratory medicine is of crucial importance in diagnosis and treatment of COVID-19 patients. Routine hematological and biochemical tests are critical in process of diagnosis and management of COVID -19 patients. Inflammatory, hematological, cardiac, renal, hepatic and hematological markers can be used in process of assessment of severity status. Serum, plasma or whole blood specimens could be used for performance of different biochemical tests.

Our study was performed on small number of patients (103) who were hospitalized in our hospital in the period of April-June 2020.

Of total of 103 admitted patients, only two patients died as a result of the Covid 19 infection. One patient was 47 years old male, hospitalized with chest pain, and increased cardiac markers. After initial treatment, all laboratory results were normalized, but on the 20th day of hospitalization, he died as a result

of kidney damage. Second patient was 66 years old male, with previous liver damage, and after 10 days of proper medical treatment there was no improvement in his medical condition and he passed away.

Although respiratory symptoms dominate in the clinical picture in Covid 19, it is clear that virus can cause multiorgan affection.

Hematological findings implicate that lymphopaenia is a distinguishing characteristic of Covid 19 infection. The count of limfocythes correlates with severity of disease. Lymphopenia was frequently detected on the hemogram (3%–83.2%) in studies of Lin [10] and Lippi [11].

In our study leukocytosis was found in 23,3%, and leukopenia 3% of patients with Covid 19, lymphopenia was confirmed in 30% of patients with Covid 19. High neutrophil count is associated with poor outcomes and it may be result of secondary bacterial infection, On the other hand, low eosinophil count is commonly seen in patients with Covid 19 infection [12].

There was no significant change in hemoglobin levels of Covid 19 infection positive. Previous studies reported that patients with severe disease have significantly lower hemoglobin values compared with patients with mild conditions [13].

The liver appears to be the second organ involved, after the lungs. The cause of liver damage induced by Covid 19 is not fully understood, and the elevation of liver enzymes may result from cytokine storm or drug-induced liver damage. The Covid 19 infection is considered to be capable of infecting endothelial cells in the bile duct of the liver and causing inflammatory damage to the liver; the cellular damage in the liver may be the direct consequence of viral infection. Additionally, the virus may result in liver damage in varying levels [14].

Covid 19 infection is associated with mild elevation in ALT, AST and bilirubin. Elevated levels of AST, ALT and LDH has been firstly reported this year in 43% of the 99 Covid 19 cases from Wuhan [15].

We found increased values of ALT in 34%, AST in 46% and γ -glutamyltransferase in 52% of patients which is in agreement with study of Henry BM et al [16].

In addition, patients with abnormal liver tests had higher risks of progressing to severe disease [17].

Abnormal liver tests (AST, ALT, total bilirubin and γ -glutamyltransferase) were present in 76.3% of patients and 21.5% of respondents showed liver injury during hospitalization, in particular during the first two weeks after admittance [18].

Liver damage increases upon the prolongation of hospitalization, which could be associated with therapy protocols [19]. Patients on potential hepatotoxic therapies or previous liver damage should be monitored at least twice a week.

Recommendations of the IFCC task group is that monitoring of liver functional tests should be considered in hospital in patients with Covid 19.

Bilirubin increased by 5% associated with hepatocellular damage and cholestatic liver diseases could be seen Covid 19 patients. Hyperbilirubinemia was observed in studies of Guan, Lippi and Santoso [20-22].

LDH is a nonspecific marker of tissue damage. Many studies have shown elevated LDH activity, ranging from 27% to 76% [21, 22].

In our study, LDH was slightly elevated in 70% of examinee patients with Covid 19 infection. Only 27 Covid 19 positive patients had normal LDH values.

In the study of Chen et al. it was observed that advanced age, hypertension and high LDH levels at admission in the hospital were associated with the elevation in hospital mortality rates. LDH activity was higher in severe cases than in mild and moderate cases [23].

Covid 19 infection affects cardiovascular system, too. Covid 19 could be associated with myocardial injury, heart failure, vascular inflammation, myocarditis, cardiac arrhythmias, and hypoxic encephalopathy [17]. Underlying pathophysiology is not well understood but it can be a result of direct viral effect on a myocardium, immune-mediated effect or as a result of respiratory failure or hypoxemia [24].

Authors suggested close monitoring of the cardiac functioning of all patients, especially the severe and critical ones, and to seek possible interventions for patients evincing features of abnormal cardiac injury.

Hence, it was concluded that heart injury signs arise in Covid 19, especially in older patients, hypertensives, and male patients with current smoking habits. Elevated levels of heart injury indicators are associated with higher mortality and shorter survival days [25].

Additionally, the discovery that Covid 19 patients had a simultaneous increase in α -hydroxybutyrate dehydrogenase, myoglobin, CK, or CK-MB fraction suggested that we should pay attention to patients with different degrees of skeletal muscle injuries.

The muscle-induced creatine kinase provides an insight, especially into the assessment of myocardial damage. Creatin kinase MB fraction was found to be high at 45%; higher rates were noted in patients with severe disease course [26].

We detected that renal function was affected in 10% of our patients with Covid 19. The kidneys are one of the most frequently affected extra-pulmonary organs in patients infected with Covid 19; especially, in those patients who are severely ill [8, 23, 27].

There are inconsistent results regarding the association of Covid 19 infection and acute kidney injury. Acute kidney injuries are reported to vary from 1% to 42% [28]. Main causes of AKI can be: direct viral infection, haemodynamic changes, thrombotic vascular processes, glomerular pathology or hypovolaemia of kidneys.

Previous studies of patients affected by the 2013 SARS outbreak have shown that kidney damage is mainly characterized by tubular injury (as reflected by abnormal urine test results) and increased serum creatinine and urea nitrogen concentrations.

Although the underlying virologic mechanisms are not completely understood, it is plausible to speculate that there is binding of the virus to the ACE2 receptor, which is highly expressed in kidney tubules, causing glomerulopathy, acute tubular necrosis and protein leakage in the Bowman's capsule [26].

Kennet found serum creatinine levels higher than 133 $\mu\text{mol/L}$ amongst patients with severe Covid 19 [26], that is in a correlation with our results.

In our study 60% of the patients had a decreased value of serum iron. Seventy four percents had an increased value of C-reactive protein. The high percentage of these indicators indicates the involvement of the immune response in patients, which correlates with previously published studies [29].

High levels of C-reactive protein were noted in the vast majority of Covid 19 patients (3%–91%) and shown to be associated with disease severity [21, 22].

C-reactive protein levels give an idea for disease severity and prognosis. Additionally, it is considered to be a potential early marker for sepsis and mortality. It is suggested that C-reactive protein level, especially at admission, may be critical for grading disease severity [30].

Conclusions

The prevention and control of the Covid 19 outbreak is well underway around the world and efforts must continue to target this virus.

This viral infection appears to adversely affect not only the respiratory system but also several other organ systems, including the urinary, liver, cardiovascular, gastrointestinal and neurological systems.

The Clinical Laboratory plays a key role in supporting the monitoring and management of Covid 19 disease.

In the meantime, we believe that the front-line multidisciplinary team should carefully monitor multi-organ functions, which may also be the key to the survival of infected patients. We suggest an improved knowledge of Covid 19 related extra-pulmonary complications will help to develop better medical management strategies for these patients.

We suggest that CBC should be performed in each patient with Covid 19 infection, because lymphopenia is a hallmark in symptomatic patients and elevated neutrophil to lymphocyte ratio is associated with bad clinical outcomes. We recommend CRP or erythrocyte sedimentation rate (ERS) to be monitored in Covid 19 patient because their increased levels are associated with worse clinical outcomes.

Increased levels of AST, ALT and bilirubin, LDH, urea and creatinine are associated with poor prognosis. Albumin levels should be monitored because they reflect an acute inflammatory state or synthetic liver dysfunctions.

Biochemical and hematological tests are not specific enough to diagnose or to exclude infection itself but they are crucial in severity assessment, clinical monitoring and therapy decision-making processes.

References

1. Huan W, Hongmin Z, Chunhui Y, Cong Y, Wei L, Xin S, et al. Clinical and Immune Features of Hospitalized Pediatric Patients With Coronavirus Disease 2019 (COVID-19) in Wuhan, China. *JAMA Netw Open* 2020; 3(6):e2010895.
2. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; 395:1054-62.
3. WHO
https://covid19.who.int/?gclid=CjwKCAjw97P5BRBQEiwAGflV6ZrV8Ca2ibmnsbtPQJSJ6Tpyzc3ShU0Cu6WAXXczevfV-GO63iYFN1xoCcbEQAvD_BwE
4. Liu Y, Gayle AA, Wilder-Smith A, Rocklöv J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. *J Trav Med* 2020; 27(2):taaa021
5. Zhu N, Zhang D, Wang W, Li, X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China. *N Engl J Med* 2020; 20,382(8):727-733.
6. Chan JFW, Yuan S, Kok KH, To KKW, Chu H, Yang JX, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet* 2020; 395:514–23.
7. Fang J, Liehua D, Liangqing Z, Yin C, Chi W, Cheung, Zhengyuan X. Review of the clinical characteristics of coronavirus disease 2019 (COVID-19). *J Gen Intern Med* 2020; 35(5):1545–1549.
8. Huang C, Wang Y, Li X., Ren L, Zhao J, Hu Y et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395:497–506.
9. Jiang F, Deng L, Zhang L, Cai Y, Cheung CW, et al. Review of the clinical characteristics of coronavirus disease 2019 (COVID-19). *J of General Internal Medicine* 2020; 35(5):1545-1549.
10. Lin JW, Han TW, Woodward M, Anderson CS, Zhou H, et al. The impact of 2019 novel coronavirus on heart injury: a systematic review and meta-analysis. *Prog Cardiovasc Dis*. 2020; YPCAD-01081.
11. Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. *Clinical Chemistry and Laboratory Medicine* 2020; 58 (7).
12. Tanni F, Akker E, Zaman MM, Figueroa N, Tharian B, Hupart KH. Eosinopenia and COVID-19. *J Am Osteopath Assoc* 2020; 120, 504-508.
13. Henry BM, De Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in corona virus disease 2019 (COVID-19): a meta-analysis. *Clin Chem Lab Med* 2020; 58(7): 1021–1028.
14. Recep O, Yeşim T, Akif A. COVID-19: pathogenesis, genetic polymorphism, clinical features and laboratory findings. *Turk J Med Sci* 2020; 50:638-657.
15. Jie L, Jian-Gao F. Characteristics and mechanism of liver injury in 2019 coronavirus. *Disease J Clin Transl Hepatol* 2020; 28; 8(1): 13–17.
16. Henry BM, Vikse J. Clinical characteristics of Covid-19 in China. *N Engl J Med* 2020; 382(19):1860-1861.
17. Piero P, Marcin K, Antonia M, Frank L, Agostino DC. Hepatic consequences of COVID-19 infection. Lapping or biting? *Eur JH Intern Med* 2020; 77: 18-24.

18. Qingxian C, Deliang H, Hong Y, Zhibin Z, Zhang X, Yinan Su, et al. COVID-19: Abnormal liver function tests. *J Hepatol* 2020; 73(3):566–574.
19. Cai Q, Huang D, Yu H, Zhu Z, Xia Z et al. COVID-19: abnormal liver function tests. *J of Hepat* 2020;73(3):566-574.
20. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; 382:1708-1720.
21. Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. *Clin Chem Lab Med* 2020; 58 (7).
22. Santoso A, Pranata R, Wibowo A, Al-Farabi MJ, Huang I et al. Cardiac injury is associated with mortality and critically ill pneumonia in COVID-19: a meta-analysis. *Am J Emerg Med* 2020; S0735-6757(20)30280-1.
23. Chen G, Wu D, Guo W, Cao Y, Huang D et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest* 2020; 130(5):2620-2629.
24. Akhmerov A, Marbán E. COVID-19 and the Heart. *Circ Res* 2020; 126(10):1443-1455.
25. Tahir F, Bin Arif T, Ahmed J, et al. Cardiac manifestations of coronavirus disease 2019(COVID-19), a comprehensive review. *Cureus* 2020; 12(5): e8021.
26. Kenneth IZ, Gong F, Wen Yue L, Giovanni T, Christopher DB, Ming Hua Z. Extra-pulmonary complications of COVID-19: a multi-system disease? *J Med Vir* 2020;1-13.
27. 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; 323(11):1061-1069.
28. Yang X, Jin Y, Li R, Zhang Z, Sun R, Chen D. Prevalence and impact of acute renal impairment on COVID-19: a systematic review and meta-analysis. *Crit Care* 2020; 24(1):356.
29. Paces J, Strizova Z, Smrz D, Cerny J. COVID-19 and the immune system. *Physiol Res* 2020; 16;69(3):379-388.
30. Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY et al. Epidemiologic features and clinical course of patients infected with Covid 19 in Singapore. *JAMA* 2020; 323 (15): 1488-1494.