Clinical and Research Journal in Internal Medicine
Vol. 3 No. 2, November 2022
e-ISSN: 2723 - 5122, p-ISSN: 2723 - 5130
Available online at https://crjim.ub.ac.id/index.php/crjim/

Original Article

The Association of COVID-19 Degree on Transamination and Bilirubin Levels of COVID-19 Patients in RSUD Dr. Saiful Anwar Malang

Ade Rahmawati[1], Syifa Mustika [2]

[1] *Department of Internal Medicine, Faculty of Medicine Brawijaya University, Dr. Saiful Anwar Regional Hospital Malang, Indonesia*
[2] *Gastro Entero Hepatology Division, Internal Medicine Department of Faculty of Medicine Brawijaya University, Dr. Saiful Anwar Regional Hospital Malang, Indonesia*

ARTICLE INFO

Corresponding Author:
Ade Rahmawati. Department of Internal Medicine, Faculty of Medicine Universitas Brawijaya – RSUD Dr. Saiful Anwar Malang. Jalan Jaksa Agung Suprapto No. 2 Malang, Indonesia. Postal address: 65112.
Email: ade.rahmawati@icloud.com

https://doi.org/10.21776/ub.crjim.2022.003.02.2
Received on July, 22 2022;
Revised on Aug, 30 2022;
Accepted on Sept, 27 2022.

ABSTRACT

Background : Corona virus 2019 (COVID-19) is an infectious viral disease caused by SARS-CoV-2 that has infected the world. COVID-19 can cause abnormalities which are characterized by increased levels of the enzyme transaminase and bilirubin. Research on the association between transaminase enzymes and bilirubin is still limited, further research is needed on the association between the degree of COVID-19 and levels of the transaminases and bilirubin enzymes.
Aim: To determine the association between liver function on the degree of severity and outcome of COVID-19 patients.
Method: This was the cross-sectional study. Sampling method was using consecutive sampling at RSUD Dr. Saiful Anwar Malangwho was treated from June 1st 2021 until November 31st 2021 by the Department of Internal Medicine. Statistical analysis used the Kruskal Walllis and Mann Whitney test with a significance level of p<0.5% and correlation analysis using Spearman.
Result: Among 90 patients included in this study there was a strong positive correlation between the degree of COVID-19 and levels of SGOT (r=0.954, p <0.001) and SGPT (r=0.727, p <0.001) and according to regression test, SGOT has the positive correlation towards degree of COVID-19 severity (p=0.026 CI95%: 0.002-0.028). There was a correlation between the degree of COVID-19 and the total bilirubin level (r=0.586, p=0.011). There was no correlation between levels of transaminase enzymes, total bilirubin, direct and indirect bilirubin on the patient's outcome (p>0.050).
Conclusion: There is a positive correlation between the degree of COVID-19 with levels of the enzyme transaminases, indirect and total bilirubin.

Keywords: COVID-19, transaminases, bilirubin, outcome

INTRODUCTION

Coronavirus 2019 (COVID-19) is an infectious viral disease caused by SARS-CoV-2 and has changed the world's demographics resulting in more than 3.8 million deaths worldwide.[1] In early December 2019, a number of pneumonia patients with unknown etiology

Rahmawati A, Mustika S. *The Association of COVID-19 Degree on Transamination and Bilirubin Levels of COVID-19 Patients in RSUD Dr. Saiful Anwar Malang*. Clinical and Research Journal in Internal Medicine. 2022; 3 (2); 292-300. DOI: https://doi.org/10.21776/ub.crjim.2022.003.02.2

appeared in Wuhan City, Hubei Province, China. Genome sequencing has shown that this pneumonia, named COVID-19 disease, is caused by a new coronavirus (CoV) namely SARS-CoV-2, previously known as 2019-nCoV.[2] In Indonesia, the first case of a COVID-19 patient was identified on March 2, 2020, in Depok. Until now (5 January 2022) the number of positive confirmed cases is more than 4,264,000.[3]

COVID-19 infection is initiated by the binding of the virus to the angiotensin-converting enzyme 2 (ACE2) receptor in the lower respiratory tract, which is the primary human receptor for the Spike (S) glycoprotein MERS-CoV and SARS-CoV.[4] Based on published literature, 14%-53% of patients with COVID-19 may develop liver dysfunction. Liver dysfunction can be characterized by elevated liver enzymes and is significantly higher in severe and critical COVID-19 and is associated with a poor prognosis.[5]

In a meta-analysis of 45 studies, the most common hepatic biochemical abnormality in COVID-19 was hypoalbuminemia (39.8%), followed by elevated gamma-glutamyl transferase (GGT 35.8%), or aminotransferase [aspartate aminotransferase (AST 21.8%) and alanine aminotransferase (ALT 20.4%)].[6] The incidence of elevated liver enzymes was also higher in COVID-19 patients requiring intensive care unit (ICU) treatment (62%) compared to non-ICU patients (23%).[5] This shows that the degree of liver damage is directly proportional to the severity of the COVID-19 disease.[7]

In addition, COVID-19 infection can also cause disorders of the biliary system. Research by Wang et al., (2020) showed a significant increase in total bilirubin in COVID-19 patients with severe symptoms who were admitted to the ICU.[8] This effect occurs due to the presence of ACE2 receptors in the gallbladder and the presence of cytokines that can cause damage to bile structures.[9] However, research on the association between the degree of COVID-19 and levels of the transaminases enzyme and bilirubin levels is still limited, especially in Indonesia. Therefore, there is a need for research on the association between the severity of COVID-19 and levels of transaminases and bilirubin enzymes in COVID-19 patients.

METHODS

This study used a cross-sectional research method. This study aims to determine the association between the degree of COVID-19 and the levels of transaminitis enzymes and bilirubin in patients treated by the Department of Internal Medicine at RSUD dr. Saiful Anwar Malang.

The research was conducted in the inpatient room of RSUD Dr. Saiful Anwar Malang by taking data on COVID-19 patients who were treated by the Department of Internal Medicine from June 1, 2021, to November 31, 2021. The target population in this study was COVID-19 patients while the affordable population of this study was COVID-19 patients at RSUD Dr. Saiful Anwar Malang was treated from June 1, 2021, to November 31, 2021, by the Department of Internal Medicine and underwent hospitalization. Patients' data were obtained from the COVID-19 medical record at the dr. Saiful Anwar Malang. The sampling method used a consecutive sampling method with a total of 90 samples.

The inclusion criteria of the study were, confirmed inpatient with SARS-Cov-2 through a Real-Time Polymerase Chain Reaction examination, age >17 years, have complete medical

records (name, gender, age, and address), and not diagnosed with liver disease (alcoholic). or non-alcoholic fatty liver, hepatitis, cirrhosis, and hepatocellular carcinoma). The exclusion criteria from this study were hospitalized patients who were confirmed to be SARS-CoV-2 through rapid antigen and antibody tests, aged <17 years, did not have a complete medical record and were diagnosed with liver disease (alcoholic or non-alcoholic fatty liver, hepatitis, cirrhosis, and cirrhosis). hepatocellular carcinoma). Research data is presented in descriptive form for the characteristics of the sample. The data of the dependent variable of the study were categorized into numbers. Statistical testing using Statistical Product and Service Solution (SPSS) software.

RESULTS

Most of the respondents were male and the average age was 55.76±14.94 years. The most common symptom found was shortness of breath with a percentage of 88.9%. The least common symptoms were melena and epigastric pain with a percentage of 1.1%. Most of the COVID-19 patients who were treated had a critical grade with a mortality rate of 74.4% Table 1.

The differences in transaminase enzyme levels are based on the degree of covid-19. the increase in the degree of COVID-19 is in line with the increase in levels of the transaminase's enzyme. Based on the Kruskal Wallis statistical test, showed that there was a significant difference between the levels of SGOT and SGPT between groups. Based on the Mann-Whitney test, showed that there was a significant difference in the levels of the transaminase enzyme between mild and moderate degrees in Table 2.

Table 1. Sample Characteristic

Characteristic	n(%)
Sex	
Male	50 (55.5)
Female	40 (44.4)
Age	55 ± 14.9
Symptoms	
Shortness of breath	
Yes	80 (88.9)
No	10 (11.1)
Fever	
Yes	26 (28.9)
No	64 (71.1)
Nausea	
Yes	19 (21.1)
No	71 (78.9)
Vomiting	
Yes	12 (13.3)
No	77 (85.6)
Epigastric Pain	
Yes	1 (1.1)
No	89 (98.9)
Hematemesis	
Yes	2 (2.2)
No	88 (97.8)
Melena	
Yes	1 (1.1)
No	89 (98.9)
Degree of COVID-19	
Mild	4 (4.4)
Moderate	10 (11.1)
Severe	23 (25.6)
Critical	53 (58.9)
Prognosis	
Dead	67 (74.4)
Alive	23 (25.6)

Based on the normality test, it was found that the data were not normally distributed, so it was continued with the Spearman test shown in table 3 and figure 1. Based on table 3 shows that there is a correlation between the degree of COVID-19 on the levels of SGOT

and SGPT (p <0.05). There is a strong positive correlation between the degree of COVID-19 and levels of SGOT and SGPT. These results indicate that the higher the degree of COVID-19 in the patient, the higher the level of SGOT or SGPT will also increase.

Table 2. The difference of transaminase level based on degree of COVID-19

Degree of COVID-19	SGOT	p-value	SGPT	p-value
Mild	38.6 ± 8.3[a]	< 0.001*	49.3±40.6[a]	< 0.001*
Moderate	78.9 ± 5.1[a]		68.3±30.8[a]	
Severe	133.1 ±5.0[b]		107.1±32.5[b]	
Critical	269.3 ± 178.1[c]		152.8 ±57.2[c]	

*. Kruskal Wallis Test; different notations (a,b,c) showed significant differences by Mann Whitney test.
*. SGOT, Serum Glutamic Oxaloacetic Transaminase; SGPT, Serum Glutamic Pyruvic Transaminase

Table 3. The correlation test in transaminase enzyme on degree of COVID-19

Spearman Correlation	SGOT		SGPT	
Degree of COVID-19	r	p	r	p
	0.954	<0.001	0.727	< 0.001

*. Mild correlation r<0.4; Moderate r 0.4-0.6; Strong >0.6. *SGOT, Serum Glutamic Oxaloacetic Transaminase; SGPT, Serum Glutamic Pyruvic Transaminase

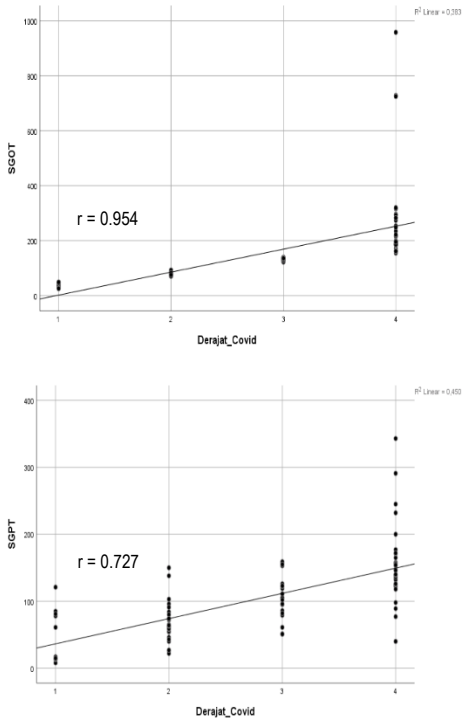

Figure 1. Graph of correlation transaminase enzyme on degree of COVID-19

The difference in bilirubin levels based on the degree of COVID-19, from the normality test that was carried out, it was found that the data were not normally distributed, so it was continued with the Kruskal Wallis and Mann Whitney tests. there are differences in total

bilirubin and indirect bilirubin levels based on the degree of COVID-19 Table 4. The highest total and indirect bilirubin levels are at critical levels. Based on the Kruskal Wallis test, showed that there was a significant difference between total and indirect bilirubin levels based on the degree of COVID-19. Based on the Mann Whitney test, shows that there is a significant difference between mild and severe degrees to moderate and critical degrees.

Table 4. The difference of bilirubin level based on the degree of COVID-19

Degree of COVID-19	Total Bilirubin	p-value	Indirect Bilirubin	p-value
Mild	0.3 ± 0.1[a]	0.010*	0.2 ± 0.1[a]	0.005*
Moderate	1.6 ± 2.0[b]		1.2 ±1.6[b]	
Severe	2.3 ± 0.2[a]		2.2±0.1[a]	
Critical	3.1 ± 3.8[b]		2.7±2.8[b]	

* Kruskal Wallis Test; different notations (a,b,c) showed significant differences by the Mann Whitney test.

The correlation test of bilirubin levels with the degree of COVID-19 is shown in table 5. Based on the normality test, it was found that the data were not normally distributed, so it was continued with the Spearman test.

Table 5. The correlation test in bilirubin level on the degree of COVID-19

Spearman Correlation	Total Bilirubin		Indirect Bilirubin	
Degree of	r	p	r	p
COVID-19	0.586	0.011	0.081	0.750

Mild correlation r<0.4; Moderate r 0.4-0.6; Strong >0.6

Table 5 shows that there is a correlation between the degree of COVID-19 and the levels of total and direct bilirubin (p<0.05). There is a moderate correlation between the degree of COVID-19 and total bilirubin. There is no correlation between the degree of COVID-19 and indirect bilirubin. These results indicate that the higher the degree of COVID-19 in the patient, the higher the total and direct bilirubin.

Differences in transaminase enzyme levels based on patient prognosis are shown in table 6. Based on the normality test, it was found that the data were not normally distributed, so it was continued with the Kruskal Wallis and Mann Whitney test.

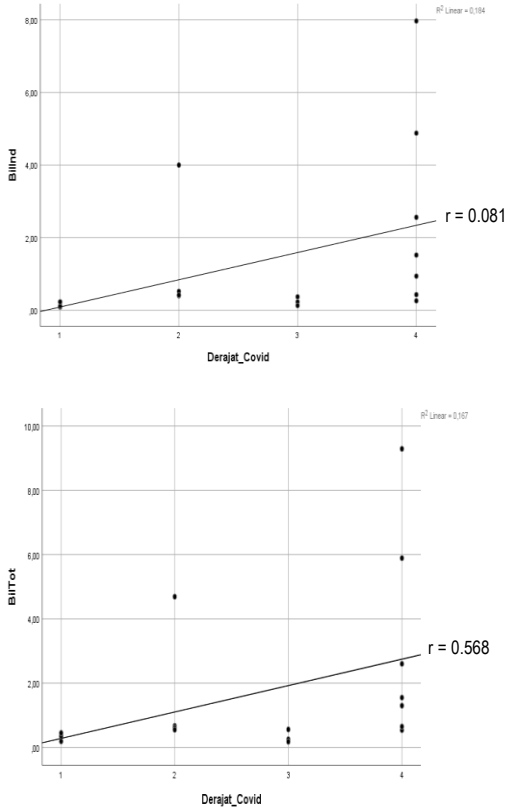

Figure 2. Graph of correlation bilirubin level on the degree of COVID-19

Table 6. The difference of transaminase level based on the prognosis of patients

Prognosis	SGOT	p-value	SGPT	p-value
Dead	163.1 ±141.3	0.253	108.3±61.3	0.774
Alive	147.0±144.4		103.7±52.2	

* Kruskal Wallis Test; different notations (a,b,c) showed significant differences by the Mann Whitney test. SGOT, Serum Glutamic Oxaloacetic Transaminase; SGPT, Serum Glutamic Pyruvic Transaminase.

Based on table 6 shows that transaminase enzyme levels were higher in patients who died than in those who were alive. Based on the Mann-Whitney test showed that there was no

significant difference in transaminase enzyme levels between living and dead patients. The results of the correlation test for transaminase enzyme levels based on the patient's prognosis are shown in table 7. Based on the normality test, it was found that the data were not normally distributed, so it was continued with the Spearman test.

Table 7. The correlation test in transaminase enzyme on prognosis of patients

Spearman correlation	SGOT		SGPT	
Prognosis	r	p	r	p
	-0.121	0.255	-0.030	0.776

* Mild correlation r<0.4; Moderate r 0.4-0.6; Strong >0.6. SGOT, Serum Glutamic Oxaloacetic Transaminase; SGPT, Serum Glutamic Pyruvic Transaminase.

Table 7 shows that there is no correlation between the degree of COVID-19 and levels of SGOT and SGPT (p>0.05). Based on Figure 7 shows that the higher the levels of SGOT and SGPT will not increase mortality rate.

Table 8. The regression test in transaminase enzyme and bilirubin level on degree of COVID-19

Variable	Beta	Cl95%	p-value
SGPT	0.004	0.000-0.008	0.058
SGOT	0.015	0.002-0.028	0.026
Tota Bilirubin l	0.153	-2.406-2.712	0.899
Indirect Bilirubin	-0.367	-3.262-2.529	0.789

*SGOT, Serum Glutamic Oxaloacetic Transaminase; SGPT, Serum Glutamic Pyruvic Transaminase

Table 8 shows the analysis of the variable levels of transaminases and bilirubin levels on the degree of COVID-19. Based on the table above, shows that SGOT has a significant effect on the degree of COVID-19 (p<0.05). The difference in bilirubin levels based on the patient's prognosis is shown in table 8. Based on the normality test, it was found that the data were not normally distributed, so it was continued with the Kruskal Wallis and Mann Whitney tests.

Table 9. The difference of bilirubin level based on the prognosis of patients

Prognosis	Total Bilirubin	p-value	Indirect Bilirubin	p-value
Dead	1.49±1.82	0.882	1.18±1.53	0.546
Alive	2.24±3.94		1.81±3.44	

Table 9 shows that total and indirect bilirubin levels tend to increase in living patients. Based on the Mann-Whitney test, showed that there was no significant difference between total and indirect bilirubin levels between the prognoses of death and living. The differences and correlation of bilirubin levels based on the patient's prognosis are shown in Table 9 and Table 10. Based on the normality test, it was found that the data were not normally distributed, so it was continued with the Spearman test.

Table 10. The correlation test in bilirubin level on the prognosis of patients

Spearman correlation	Total Bilirubin		Indirect Bilirubin	
Prognosis	r	P	R	p
	-0.036	0.888	-0.142	0.562

*Mild correlation r<0.4; Moderate r 0.4-0.6; Strong >0.6

Based on table 10 shows that there was no correlation between the patient's prognosis of total bilirubin and indirect bilirubin (p> 0.05). Elevated total and indirect bilirubin levels tend to improve the patient's prognosis.

DISCUSSIONS

This study shows significant differences in transaminase enzyme levels based on the degree of COVID-19. In addition, there is a positive correlation indicating an increase in

transaminase enzyme levels and an increase in the degree of COVID-19. However, there were no differences and correlations between transami-nase enzyme levels and patient prognosis. COVID-19 can cause symptoms in the respiratory system, but COVID-19 can also cause some extra pulmonary symptoms such as liver damage. In some COVID-19 patients, an increase in liver function markers such as SGOT and SGPT was found.[10]

A study conducted by Cai et al (2020) at the Shenzhen Hospital from January 2020 to February 2020, it showed that in 417 positive COVID-19 patients 76.3% had abnormal liver function examination results and 21.8% had a liver injury in the hospital.[11] Another study stated that there were abnormal liver enzymes in COVID-19 patients with poor and low grades.[10] Abnormal liver function in COVID-19 patients can be caused by several things, such as the presence of immune cell-mediated inflammation such as the presence of cytokine storms, and the presence of pneumonia that causes hypoxia. The presence of cytokines in the liver indicates infection or viral replication in liver cells. The use of drugs can also cause liver damage such as the use of lopovipar/ritonavir, and chloroquine which has the potential to be hepatotoxic. There is a reactivation of previous chronic liver disease and the last is the reactivation of hepatitis B virus.[12]

Research conducted by Wang et al., (2020) showed that an increase in aminotransferase and alanine aminotransferase indicated the course of disease severity.[8] Ultrastructural observations showed the presence of viral particles which were characterized by the presence of nail-like formations in the cytoplasm of hepatocytes. SARS-CoV 2 infects hepatocytes by causing swelling of the mitochondria, dilatation of the endoplasmic reticulum, and depletion of glycogen granules. Immunohistochemical examination showed that there were few CD4+ and CD8+, then there was also no eosinophil infiltration, cholestasis, fibrin deposits, granulomas, or a lot of central necrosis.[8] The presence of systemic inflammation occurs due to the response to pulmonary damage. Can cause damage to many organs, one of which is the liver. As a result of an increase in inflammatory mediators causing liver damage which is also associated with hypoxia-reoxygenation, Kupffer cells are over-activated and oxidative stress, as well as increased activity of the nervous system and adenocorticoid glands, cause an increase in hepatic biochemistry abnormalities.[14]

In patients with severe COVID-19 conditions, changes in oxygenation caused by lung damage cause a rapid increase in aminotransferases which is a response to respiratory failure, shock, and heart failure. The condition of heart failure that occurs in patients with severe COVID-19 causes a rapid decrease in arterial pressure which can then lead to hepatocellular hypoxia. In addition, an increase in the central venous system causes congestion in the hepatic veins which also causes hypoxia in liver cells.[13,15]

Research conducted by Wang et al., (2020) was conducted on 156 COVID-19 patients with 54 severe symptoms and 102 mild symptoms, 41.0% showed ALT abnormalities.[8] The results are different from studies conducted in Austria and Northern Italy showed an increase in SGOT in patients with SARS-Cov2 infection, this is different from a study conducted in the provinces of Zhejiang and Rome which only found 16% and 20% of patients who experienced an increase in SGOT.16 in a study

conducted by Ubieto et al., (2021) showed that there was a significant increase in both SGOT and SGPT in 75% of COVID-19 patients. 17 This increase could be due to a decrease in the clearance of SGOT by hepatic sinusoids.[19]

In this study, it was found that there was a strong positive correlation between the degree of COVID-19 and bilirubin levels. However, there was no difference and no correlation to the patient's prognosis. In another study, in addition to an increase in SGOT and SGPT in COVID-19 patients, an increase in the total bilirubin value was found in 35% of cases.[19] A study conducted by Liu et al., (2020) showed that an increase in total bilirubin can lead to an increase in risk factors for death in COVID-19 patients. ACE-2 receptors are more commonly found in the gallbladder epithelium compared to the liver, which can be a factor in the increase in bilirubin.[18] The presence of an increase in total bilirubin is associated with a cholestatic condition that can be caused by bile duct proliferation, inflammation, or can be due to obstruction. Conditions caused by SARS-Cov-2 cause an increase in cytokines that can lead to the induction of hepatocellular cholestasis by downregulation of the bilirubin excretory system.[19] A study conducted by Wang et al., (2020) showed a significant increase in total bilirubin in COVID-19 patients with severe symptoms who were treated in the ICU.8 Another study by Poligiannis and Angelo (2020) showed that there were high bilirubin levels in severe COVID-19 patients compared to moderate COVID-19 patients. This shows that total bilirubin increases significantly in severe COVID-19 patients.[20] Research conducted by Zhao et al (2020) showed that infection with SARS-Cov-2 would interfere with the function of defense and transport of bilirubin in cholangiocytes through dysregulation of genes for tight junction formation and bile acid transport.[21] This could be due to the effect of infection. cytopathogenic caused by the presence of SARS-Cov-2 which binds to ACE-2. The presence of disturbances in the bile duct will cause disturbances in the liver thereby increasing the indirect bilirubin.[9]

In this study, the number of patients who had bilirubin levels checked was still small, so further research using a larger sample is needed. In addition, in this study, liver damage and bilirubin were only detected based on the levels of transaminases and bilirubin enzymes, so further research is needed to determine structural damage to these two organs.

CONCLUSION

There is a significant association between levels of transaminase enzymes, total bilirubin, and the indirect degree of COVID-19. There is a strong positive correlation between the degree of COVID-19 and levels of SGOT and SGPT, where according to the regression test SGOT has the strongest correlation with the severity of COVID-19. There was a correlation between the degree of COVID-19 and the total bilirubin level. There was no correlation between the levels of transaminase enzymes, total bilirubin, and indirect bilirubin on patient outcomes, it can be concluded that SGOT, SGPT, Bilirubin have a strong correlation with the severity of COVID-19.

Reference

1. Cascella, Marco, Michael Rajnik, Abdul Aleem, Scott C, Dulebohn, Raffaela di Napoli. Features, Evaluation and Treatment of Coronavirus (COVID-19). 2021
2. Xu, X., Chen, P., Wang, J., Feng, J., Zhou, H., Li, X., Zhong, W., & Hao, P. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human

transmission. Science China. Life sciences, 63(3), 457–460. 2020.

3. Kemenkes. Peta sebaran COVID-19. cited on 5 Januari 2022. Available from: https://covid19.go.id/peta-sebaran. 2021
4. Kuba, K., Imai, Y., Rao, S., Gao, H., Guo, F., Guan, B., Huan, Y., Yang, P., Zhang, Y., Deng, W., Bao, L., Zhang, B., Liu, G., Wang, Z., Chappell, M., Liu, Y., Zheng, D., Leibbrandt, A., Wada, T., Slutsky, A. S., … Penninger, J. . A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nature medicine, (2005). 11(8), 875–879.
5. Zhang, C., Shi, L., & Wang, F. S. Liver injury in COVID-19: management and challenges. The lancet. Gastroenterology & hepatology. (2020). 5(5), 428–430.
6. Wu, Y., Li, H., Guo, X., Yoshida, E. M., Mendez-Sanchez, N., Levi Sandri, G. B., Teschke, R., Romeiro, F. G., Shukla, A., & Qi, X. Incidence, risk factors, and prognosis of abnormal liver biochemical tests in COVID-19 patients: a systematic review and meta-analysis. Hepatology international, (2020). 14(5), 621–637.
7. Kumar-M, P., Mishra, S., Jha, D. K., Shukla, J., Choudhury, A., Mohindra, R., Mandavdhare, H. S., Dutta, U., & Sharma, V. (2020). Coronavirus disease (COVID-19) and the liver: a comprehensive systematic review and meta-analysis. Hepatology international, (2020). 14(5), 711–722.
8. Wang, F., Yang, Y., Dong, K., Yan, Y., Zhang, S., Ren, H., Yu, X., & Shi, X. CLINICAL CHARACTERISTICS OF 28 PATIENTS WITH DIABETES AND COVID-19 IN WUHAN, CHINA. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists, (2020). 26(6), 668–674.
9. Liu, Z., Li, J., Long, W., Zeng, W., Gao, R., Zeng, G., Chen, D., Wang, S., Li, Q., Hu, D., Guo, L., Li, Z., & Wu, X. Bilirubin Levels as Potential Indicators of Disease Severity in Coronavirus Disease Patients: A Retrospective Cohort Study. Frontiers in medicine. 2020. 7.
10. Xu, W., Huang, C., Fei, L., Li, Q., & Chen, L. Dynamic Changes in Liver Function Tests and Their Correlation with Illness Severity and Mortality in Patients with COVID-19: A Retrospective Cohort Study. Clinical interventions in aging, (2021). 16, 675–685.
11. Cai, Q., Huang, D., Yu, H., Zhu, Z., Xia, Z., Su, Y., et al. COVID-19: Abnormal Liver Function Tests. J. Hepatol. (2020).73 (3),
12. Ali N. Association Between COVID-19 Infection and Liver Injury: A Review of Recent Data. Frontiers in medicine, 7, (2020). 458.
13. Bertolini, A., van de Peppel, I. P., Bodewes, F., Moshage, H., Fantin, A., Farinati, F., Fiorotto, R., Jonker, J. W., Strazzabosco, M., Verkade, H. J., & Peserico, G. Abnormal Liver Function Tests in Patients With COVID-19: Relevance and Potential Pathogenesis. Hepatology (Baltimore, Md.), 72(5), (2020). 1864–1872
14. Li, J., & Fan, J. G. Characteristics and Mechanism of Liver Injury in 2019 Coronavirus Disease. Journal of clinical and translational hepatology, (2020). 8(1), 13–17.
15. Kavoliuniene, A., Vaitiekiene, A., & Cesnaite, G. Congestive hepatopathy and hypoxic hepatitis in heart failure: a cardiologist's point of view. International journal of cardiology, (2013) 166(3), 554–558.
16. Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., Xiao, Y., … Cao, B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet (London, England). (2020). 395(10223), 497–506.
17. Benedé-Ubieto, R., Estévez-Vázquez, O., Flores-Perojo, V., Macías-Rodríguez, R. U., Ruiz-Margáin, A., Martínez-Naves, E., Regueiro, J. R., Ávila, M. A., Trautwein, C., Bañares, R., Bosch, J., Cubero, F. J., & Nevzorova, Y. A. Abnormal Liver Function Test in Patients Infected with Coronavirus (SARS-CoV-2): A Retrospective Single-Center Study from Spain. Journal of clinical medicine, (2021).10(5), 1039.
18. Cai, Q., Huang, D., Yu, H., Zhu, Z., Xia, Z., Su, Y., Li, Z., Zhou, G., Gou, J., Qu, J., Sun, Y., Liu, Y., He, Q., Chen, J., Liu, L., & Xu, L. COVID-19: Abnormal liver function tests. Journal of hepatology, (2020). 73(3), 566–574.
19. Nardo, A. D., Schneeweiss-Gleixner, M., Bakail, M., Dixon, E. D., Lax, S. F., & Trauner, M. Pathophysiological mechanisms of liver injury in COVID-19. Liver international : official journal of the International Association for the Study of the Liver, (2021). 41(1), 20–32.
20. Paliogiannis, P., & Zinellu, A. Bilirubin levels in patients with mild and severe Covid-19: A pooled analysis. Liver international : official journal of the International Association for the Study of the Liver, (2020). 40(7)
21. Zhao YM, Shang YM, Song WB, et Al. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. EClinicalMedicine. (2020). 25:100463