Unveiling the Impact of Statin Drugs on Liver Enzyme Variation in COVID-19 Patients in Baghdad, Iraq

Osamah Alkilidar[1], Hayder Albaghdadi[2], Samaa kh.alhashimi[3]

[1,2,3]The Iraqi Ministry of Higher Education, Scientific Research Authority, Center of Environment and Water and Renewable Energy, Iraq

KEYWORDS
Statin Drugs, AST, ALT, ALP, COVID-19.

ABSTRACT
Recent studies have examined the safety of using statin drugs in COVID-19 patients and have suggested that their anti-inflammatory properties may help lessen the severity of the infection and speed up recovery. However, some case reports have indicated that COVID-19 patients taking statins may experience liver injury, a serious adverse effect of the medication. To investigate this further, a study was conducted on 140 patients who were divided into four groups: those infected with SARS-CoV2 while taking statins, those infected without taking statins, those not infected but taking statins, and healthy individuals serving as a control. The results indicate that statins have a significant effect on AST and ALP levels but not on ALT levels, suggesting that the medication does not have a statistically significant impact on liver function..

1. Introduction

With the World Health Organization (WHO) declaring COVID-19 a pandemic that poses a threat to the entire world[1], it has become necessary to study the virus's impact on the body's biochemistry in order to better understand the reasons behind disease exacerbation. Statins are a class of drugs used to lower cholesterol levels for the prevention of cardiac disease[2]. Although rare, liver injury is considered one of the advanced adverse effects of statins[3,2]. However research indicates that statins could potentially play a role, in reducing mortality rates by safeguarding against issues associated with COVID 19 and bolstering the body's immune response, to specific viruses[4]. Statins work by inhibiting an enzyme named HMG-COA reductase, which converts to mevalonate and ultimately leads to the synthesis of cholesterol and several proteins and compounds like co- enzyme Q10[5]. Elevated liver enzymes caused by statins are common[2], and liver injury induced by statins is rare[6]. While clinical studies have shown the safety of statins in patients with cirrhosis and precirrhosis[7], there is concern about the use of these drugs in patients with impaired liver function[8]. This study aims to examine how statins impact liver enzymes, in individuals diagnosed with COVID 19 and their in-hospital outcomes, with a focus on Iraqi patients who have been infected or recovered from COVID-19. Liver enzymes such as Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), and Alkaline Phosphatase (ALP) are essential indicators of liver health, and elevated levels of these enzymes can be a sign of severe COVID-19. Emerging research has put forth the proposition that the administration of statins among individuals affected by C0VID-19 may potentiate the upregulation of ACE2.

ACE2, a multifunctional enzyme, assumes the pivotal responsibility of facilitating the entry of SARS-CoV-2 into human cells, while concurrently playing a vital role in mitigating the initiation of the renin-angiotensin- angiotensinogen system,[9] which could be beneficial for patients. Additionally, elevated levels of plasma interleukin-18 have been sepsis- induced acute respiratory distress syndrome has been found to be linked to increased mortality rates and has also been linked to increased mortality in individuals treated with statins.[10]

In addition to liver enzyme variation, COVID-19 infection also leads to other complications such as acute respiratory distress syndrome (ARDS), sepsis, and multi-organ failure.[11] Therefore, it is important to investigate the potential impact of statin therapy on in-hospital outcomes of COVID- 19 patients.

Recent studies have shown that statin therapy may reduce the severity of COVID-19 and improve clinical outcomes, possibly due to its anti-inflammatory effects. Inflammation plays a crucial role in

the pathogenesis of COVID-19, and statins have been shown to reduce pro-inflammatory cytokines and increase anti-inflammatory cytokines, thereby modulating the inflammatory response in COVID-19 patients.[4]

Moreover, statins have been found to upregulate angiotensin-converting enzyme 2 (ACE2), the receptor used by SARS-CoV-2 for cell entry[12], in experimental models. This finding has generated some concern about whether statin therapy could increase susceptibility to SARS-CoV-2 infection. However, there is currently no evidence to support this hypothesis[13], furthermore. Contradictory outcomes have been documented in multiple empirical studies and clinical trials, signifying an exacerbation in the intensity of symptoms alongside the presence of comorbidities.[14]

In summary, while there are concerns about the potential adverse effects of statin therapy on liver function, recent studies have shown that statins may have a beneficial effect on COVID-19 patients by reducing inflammation and improving clinical outcomes. However, further research is needed to fully understand the impact of statin therapy on liver function and the clinical outcomes of COVID-19 patients.

2. Material and Methods

From March 16 to May 10,2022, samples were collected from Al-Shifa specialized Crisis Center in Baghdad, a facility that has been treating and isolating COVID-19 patients with moderate to advanced cases since the start of the pandemic. To select patients for this study, the medical records of 244 cases were studied and reviewed to answer questions about various factors such, as age the presence of diseases the use of statins, exercise, smoking habits and alcohol consumption. Cases that did not align with the goals of the study were excluded, resulting in 104 individuals being excluded based on comorbidities, medications used, drug allergies, all hepatic diseases, metabolic syndrome, or statin-related allergies. The remaining cohort was divided into four groups: There were 35 COVID 19 patients who were taking statins another group of 35 COVID 19 patients who were not taking statins a group of 35 individuals who were not infected but taking statins and finally a group of 35 individuals who neither had the infection nor were using statins.

To measure the levels of AST, ALT, and ALP in the collected samples, a kit from Roche company made in Germany was used. The serial number for the AST kit was 04657543190, for the ALT kit was 04718569190, and for the ALP kit was 04657373190. All 140 samples were transferred from plain tubes to the instrument's vials and the software was set to measure absorbance and calculate kinetics. This study aims to compare the levels of liver enzymes in COVID-19 patients with and without statin use and in uninfected individuals with and without statin use to determine if there is a correlation between statin use and liver enzyme elevation in COVID-19 patients.

Data analysis was done using SPSS @, version 23.0. The level of significance was set at a P-value <0.05. One-way ANOVA test was carried out for comparison of differences in means of the variables between and within the groups. Tests of multiple comparisons across the p-value were done using a t-test to determine the level of significance and the probability. The median and Q1 and Q3 were calculated for each group and each variable. Statistical analysis results were tabulated and plotted to present the variance between groups. The significant difference between groups was further analyzed through a post-hoc analysis. The findings of this study have shown that statin therapy among COVID-19_ patients is associated with changes in liver enzyme activities; therefore, these may have implications for the clinical management of COVID-19 patients. However, further studies are necessary to confirm these findings and further investigate the benefits and risks of statin therapy in COVID-19 patients.

3. Results and Discussion

Affer the rigorous screening process, 70 COVID-19-positive patients were selected forthe study with informed consent. The age included was from 40 to 83 years The clinical presentation of COVID-19 positive patients was relatively homogenous which included cough, chest pain, myalgia, back pain, diarrhea, fatigue, and headache, The Group A consisted of 35 COVID-19 patients, including those patients who were already receiving

statin therapy for at least three months prior to the viral infection, Interestingly, most of them did not exercise on a regular basis and the use of statins for these patients was based on different comorbidities such as diabetes, CAD, hypercholesterolemia, hypertension, and obesity. By contrast, Group B was made up of 35 COVID-19 patients who were not on statin therapy but shared the same medical conditions with Group A. In addition, Group C consisted of 35 uninfected patients by COVID-19 who had vaccination against the virus but had been subjected to statin therapy for at least three months prior to their inclusion in the study. Finally, Group D represented the control group and consisted of 35 participants who were in perfect health and had never been infected with COVID-19, nor had they ever received any statin drugs.

The demographic characteristics and the distribution of respondents into the four categories are fully represented in Table 1 below. For statistical analysis, the software SPSS R version 23.0 was used, with a priori $p < 0.05$ level of significance. Comparison of means of the variables in both intra- and intergroups was done using the one-way ANOVA test. Multiple comparison tests by t-tests were also carried out for clarification of the significance and probability of the findings observed. Descriptive statistics such as median, Q1, and Q3 were obtained for each variable in each group. Detailed description of participants' characteristics and categorization can be seen in Table 1. below.

Table 1 Characteristics and classification of the admitted cohort into fourgroups

	GROUP A N=35	**GROUP B N=35**	**GROUP CN=35**	**GROUP D N=35**
REANG OF AGE	40 – 83	43 - 82	5 – 75	41 – 68
MALE	54% (n=19)	54% (n=19)	48% (n=17)	57% (N=20)
FEMALE	46% (n=16)	46% (n=16)	51% (n=18)	43% (N=15)
ATORVASTATİN (ATV) 20MG	39% (n=14)	Non	57% (n=20)	NON
ATORVASTATIN (ATV) 40MG	20% (n=7)	Non	3% (n=1)	NON
ROSUVASTATİN (RTV) 20 MG	34% (n=12)	Non	31% (n=11)	NON
ROSUVASTATIN (RTV) 40 MG	9% (n=3)	Non	9% (n=3)	NON
SIMVASTATIN (SVT) 80 MG.	3% (n=1)	Non	No n	NON
DIABETES	26% (n=9)	17% (n=6)	60% (n=21)	NON
CORONARY ARTERY DISEASE (CAD)	14% (n=5)	Non	26% (n=9)	NON
HYPERCHOLESTEROLEMIA	63% (n=22)	35% (n=7)	83% (n=29)	NON

HYPERTENSION	77% (n=27)	91% (n=32)	69% (n=24)	NON
OBESITY	83% (N=29)	29% (N=10)	51% (N=18)	37% (N=13)

Aspartate Aminotransferase (AST)

The outcomes derived from our investigation demonstrate marked distinctions across the four groups under consideration. The null hypothesis is unequivocally discarded, as evidenced by the remarkably low p-value ($p < 0.0001$) in conjunction with an F statistic that surpasses the critical F value (F_crit). Employing the sum of squares (SS) as a metric to gauge within-group and between-group deviations, we can ascertain the extent of variability within and across the groups of interest. These statistical indicators serve as indispensable tools in comprehending the notable dissimilarities observed among the groups, thereby enabling us to derive substantive conclusions based on the amassed data. The observed variability within our study can be attributed to several influential factors, encompassing age demographics, underlying comorbidities, medication utilization, and lifestyle practices. Further comprehensive analysis is warranted to explore the potential impact of these factors on the observed variability, as elucidated in Table 2.

Table 2 AST-ANOVA test results

SOURCE OF VARIATION	SS	DF	MS	F	P-VALUE	F CRIT
BETWEEN GROUPS	59042.624	3	19680.874	5.953	0.00076	**2.671**
WITHIN GROUPS	449565.325	136	3305.627			
TOTAL	**508607.949**	**139**				

Table 3 exhibits the variance, which elucidates the average of the squared differences from the mean. Notably, Group A demonstrates a higher variance, indicating a greater dispersion of values from the group's mean. In contrast, Group B manifests higher average and sum values, suggesting a greater overall magnitude of the variable under consideration within the group.

Table 3 AST-NOVA test summary

GROUPS	COUNT	SUM	AVERAGE	VARIANCE
A	35	2237.6	63.931	7086.876
B	35	2385.6	68.16	5967.736
C	35	928.4	26.525	97.873
D	35	830.7	23.734	70.024

The analysis of median values among the groups reveals significant disparities. Notably, Group B exhibits the highest median value of 39.3. Multiple comparison tests demonstrate high levels of

significance in the A vs. D and B vs. D comparisons, with p-values of 0.001. The A vs. C comparison also exhibits a highly significant p-value of 0.007, while the B vs. C comparison indicates a significant p-value of 0.005. However, the A vs. B and C vs. D comparisons do not exhibit statistical significance, as indicated in Table 4. Among the patients in Group A, 37% (n=13) exhibited elevated levels of AST, with 23% (n=3) among them reaching levels up to nine times the upper limit of normal (ULN). Similarly, in Group B, 35% (n=11) showed elevated serum AST levels, with one patient reaching a level up to eight times the ULN. The extent of elevation was found to be proportional to the statin dosage and the severity of the infection. Further comprehensive information regarding the results of the multiple comparisons test and the proportion of patients with elevated AST levels within each group can be found in Table 4 provided below. The graphical representation of the intergroup differences is depicted in Figure 1.

Table 4 Comparative ASTresults in all cohort

AST	**A**	**B**	**C**	**D**
MEDIAN	37	39.3	24	22
25% PERCENTILE	26	26	20	16.93
75% PERCENTILE	60.7	88	28	31
MULTIPLE COMPARISONS TEST		**P-VALUE**		
A VS. B		> 0.999		
A VS. C		0.007		
A VS. D		0.001		
B VS. C		0.005		
B VS. D		0.001		
C VS. D		> 0.999		

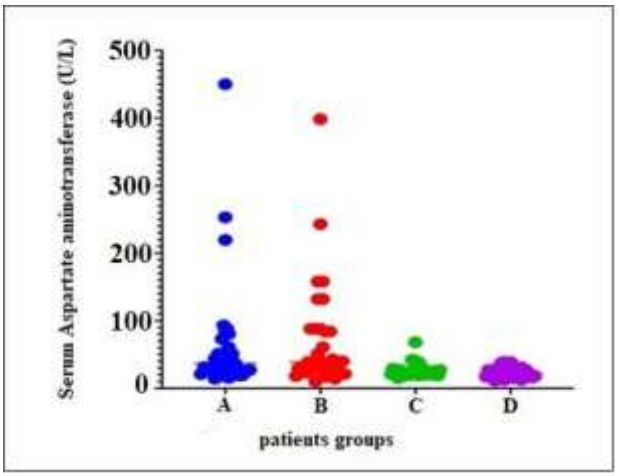

Figure 1 Distribution of patient groups according to AST results

Alanine Aminotransferase (ALT)

The examination of ALT levels across the various groups involved rigorous statistical analysis, which yielded a significant disparity in the p-value among the groups, as indicated by the ANOVA test results. The obtained p-value of 0.0082 was determined to be lower than the predetermined significance level of 0.05, leading to the rejection of the null hypothesis in favor of the alternative hypothesis. Moreover, the F statistic derived from the ANOVA test exceeded the critical F value, further bolstering the acceptance of the alternative hypothesis. The calculated sum of squares for both between-group and within-group variations provided valuable insights into the extent of variability within and across the groups of interest. For comprehensive reference, Table 5 furnishes a detailed account of the results obtained from the ALT-ANOVA test. Collectively, these findings underscore the presence of noteworthy disparities in ALT levels among the diverse groups analyzed in this study. Further investigations are warranted to elucidate the underlying factors contributing to these observed differences and to explore potential treatment modalities for individuals exhibiting elevated ALT levels.

Table 5 ALT-ANOVA test results

SOURCE OF VARIATION	SS	DF	MS	F	P-VALUE	F CRIT
BETWEEN GROUPS	82848.291	3	27616.097	4.08	0.0082	**2.67**
WITHIN GROUPS	920204.357	136	6766.208			
TOTAL	1003052.649	139				

The variance shown in Table 6 explains the average of the squared differences from the mean, which is greater in group B and the average and sum greater in group B.

Table 6 ALT-NOVA test summary

GROUPS	COUNT	SUM	AVERAGE	VARIANCE
A	35	2530.3	72.294	12468.436
B	35	2660.8	76.022	14442.532
C	35	961.4	27.468	57.849
D	35	833.8	23.822	96.015

While examining the median values, it is noteworthy that Group A exhibited a higher median of 34.7. However, the results of the multiple comparisons test indicate non-significant p-values between groups. Despite this, Group A displayed an elevation ratio of 22.8% (n=8), with the highest recorded value reaching 438.6 U/l, equivalent to eight times the upper limit of normal (ULN). In Group B, the elevation ratio was 25.7% (n=9), with the highest recorded value reaching 624 U/l, corresponding to eleven times the ULN. No instances of elevation were observed in Group C, as indicated in Table 7. Out of the total COVID-19 patients, 17 out of 70 (24%) exhibited elevated ALT levels. These findings align closely with a previous study conducted by Smith et al, which reported elevated ALT levels in 16.2% of 105 patients,[15] as depicted in Figure 2.

Table 7 ComparativeALT results in all cohort

ALT	A	B	C	D
MEDIAN	34.7	33.75	28	21.5
25% PERCENTILE	18.5	16.95	22	15.75
75% PERCENTILE	55.8	104.8	31	33.25
MULTIPLE COMPARISONS TEST	P-VALUE			
A VS. B	>0.999			
A VS. C	>0.999			
A VS. D	0.055			
B VS. C	>0.999			
B VS. D	0.058			
C VS. D	>0.999			

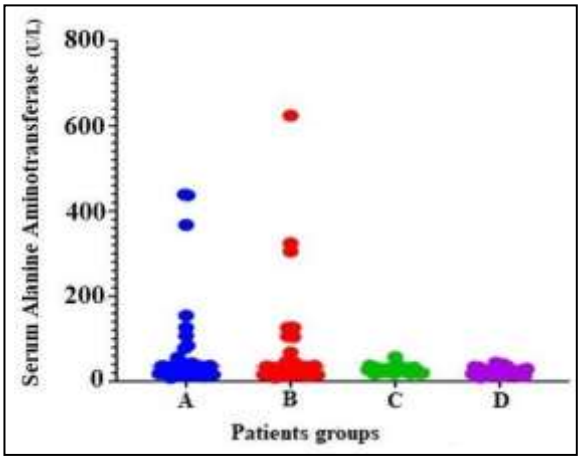

Fig 2 Distribution ofpatient groups according to ALT result

Alkaline Phosphatase (ALP)

The findings derived from the one-way analysis of variance (ANOVA) test provide compelling evidence of a substantial variance discrepancy among the various groups. The exceptionally low p-value, less than 0.0001, coupled with an F statistic surpassing the critical F value (F_crit), supports the acceptance of the alternative hypothesis. The calculated sum of squares (SS), both between and within groups, aids in quantifying the extent of variability within and across the groups of interest. Furthermore, a closer examination of the ALP levels within the groups reveals a higher degree of variability within the groups themselves. Detailed results of the one-way ANOVA test, along with a comprehensive depiction of the variability within the groups, can be found in Table 8 for reference. It is important to acknowledge that the elevated variability within groups has the potential to impact the accuracy and precision of statistical analyses, as well as the interpretation of the obtained results. Consequently, further studies and analyses are warranted to validate and corroborate the findings

presented in this study.

Table 8 ANOVA test results

SOURCE OF VARIATION	SS	*DF*	MS	F	P-VALUE	F CRIT
BETWEEN GROUPS	105320.7	3	35106.89	22.759	5.31E-12	2.6711
WITHIN GROUPS	209780.4	136	1542.503			
TOTAL	315101	139				

As detailed in Table 9 the variance shows the average squared differences from the mean, and it is greater in group A. The average and sum are greater in group A.

Table 9 ALP-NOVA testsummary

GROUPS	COUNT	SUM	AVERAGE	VARIANCE
A	35	4570	130.5714	3404.076
B	35	4277	122.2	2099.871
C	35	2266.9	64.76857	43.3981
D	35	2854	81.54286	622.6672

The study findings reveal differential impacts on ALP levels across the groups, accompanied by noteworthy variations in patient distribution among these groups, as illustrated in Figure 3. To identify the groups exhibiting the most significant differences, a multiple comparisons test was conducted. The results demonstrated that both Group A and Group B exhibited significantly higher ALP levels compared to Group C (p-value < 0.001). Notably, Group A displayed a median value of 116, accompanied by a wider range. Furthermore, the calculated p-values indicated a substantially elevated risk for correlation between Group A and Group D, with a highly significant p-value of 0.002. Group B also exhibited a significant p-value of 0.007 compared to Group D, while Group C demonstrated a significant p-value of 0.46 in comparison to Group D. These findings suggest that the use of statins may contribute to an increase in ALP levels, and the impact of COVID-19 infection on ALP levels aligns with the findings reported by Kumar et al. (2020). The corroborating evidence presented in Table 10 confirms the influence of COVID-19 infection on ALP levels.

Table 10 ComparativeALP results in all cohort

ALP	A	B	C	D
MEDIAN	116	109.5	65	85.5
25% PERCENTILE	84	89.5	59	62.75

75% PERCENTILE	168	158	70	106.5
MULTIPLE COMPARISONS TEST		**P-VALUE**		
A VS. B		>0.999		
A VS. C		<0.001		
A VS. D		0.002		
B VS. C		<0.001		
B VS. D		0.007		
C VS. D		0.046		

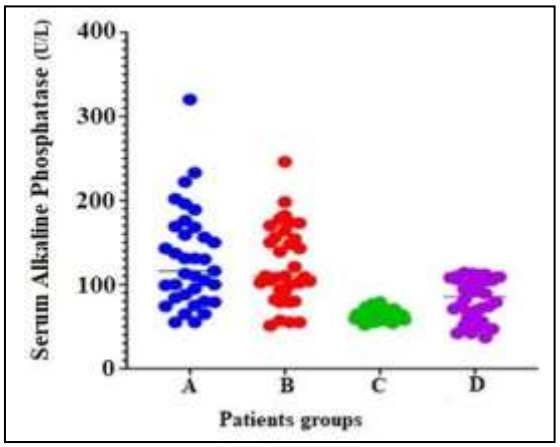

Figure 3 Distribution of patient groups according to ALP results

To summarize the results regarding liver enzymes, it was found that the p-value for AST was highly significant and similar in groups A and B, both registering 0.01. Furthermore, the comparison between group A and group C was also significant, with a p-value of 0.007. However, there was no significant difference in ALT levels among all groups. The mean value of AST in group A was slightly higher than that in group B, with a difference of only 0.95. On the other hand, the comparison between group A and group D regarding ALP levels gave a highly significant probability, with a p-value of 0.001. These results suggest that there are differences in liver enzyme levels among the different groups, with AST and ALP being particularly important indicators of liver injury. These findings are in line with previous studies that have highlighted the role of these enzymes in predicting COVID-19 complications and mortality. Therefore, monitoring these enzymes could be crucial in managing COVID-19 patients and preventing further liver damage.

The statistical analysis revealed that the impact of statins on liver enzymes was not significant, although there was a slight increase in transaminase levels in some patients who were administered with statins, and liver injury was observed to be high in group A. It is important to note that this observation was made specifically for patients who were taking high doses of statins and were also suffering from severe COVID-19 infection. Despite this, the overall effect of statins on liver enzymes was found to be mild. It is also worth noting that further research is needed to fully understand the relationship between statins and liver

function, especially in patients with severe COVID-19 infection.

Three patients who were prescribed statins, two taking ATV 40 mg and one taking SVT 80 mg experienced an increase in their liver enzyme levels. The ALT levels were elevated to 438,367 and 437 U/L respectively while the AST levels were elevated to 219, 253 and 450 U/L. Additionally the ALP levels were increased to 130, 137 and 320 U/L. These: elevated transaminase levels combined with ALP indicate liver injury. All three patients required hospital admission due, to varying severity of COVID 19 infection. Needed ventilation support. They received treatment with Favipiravir, acetaminophen and vitamin C.

In another group of patients (group B) two cases of liver injury were observed. These patients had increased levels of AST (243 and 398 U/L) ALT (324 and 624 U/L) and ALP (143 and 178 U/L). They received the treatment as group A except for statins. Although group A had cases overall the results regarding liver injury were similar between both groups with and without statins. It remains unclear whether statins contributed to hepatotoxicity or not. However it is worth noting that both groups received Favipiravir as part of their treatment regimen which aligns with reports published by Kumar et al., 2021 [16] and Yamazaki et al.,(2021)[17] linking this medication to liver injury, in COVID 19 patients. These results indicate that moderate doses of statins do not cause liver damage, which's, in line with the findings of Bloom et al. (2020)[18] despite the differences in the study population. However, these results are consistent with the idea that statins have no impact on liver enzymes, in COVID 19 patients who are taking statins. They differ from (Castiglione *et al.*, 2020)[19], There was a hypothesis that using statins, in COVID 19 patients who are hospitalized could have an impact on improving symptoms and reducing recovery time. This hypothesis was based on the belief that statins can reduce inflammation by increasing the activity of angiotensin converting enzyme, which's a pathway for the virus. The intention behind this hypothesis was to make statins available as an affordable treatment option, in low-income countries. However, our findings actually showed the effect especially when high doses were used, which resulted in kidney damage. In group A, it was clear that there was a significant association between the increase in AST and the use of statins, as evidenced by a P-value of 0.001. This finding implies that the elevation in AST may not be solely due to liver damage, but may be influenced by other factors as well. Out of the 35 patients in group A, 9 (25.7%) showed an increase in AST levels, with 7 of them also exhibiting elevated ALP and ALT levels, and 2 of them being diagnosed with liver infection. These results underscore the importance of closely monitoring liver enzymes, particularly AST and ALP, as the concurrent elevation of these enzymes could be a predictor of COVID-19 complications and may even reduce mortality rates. Therefore, healthcare providers should be vigilant in monitoring these enzymes to ensure timely intervention and management of any potential liver injury.

In group B, it was observed that 20% (n=7) of the patients had an elevation in AST levels. Out of these 7 patients, 2 also experienced an increase in transaminase with ALP, and one of them developed a liver infection. Nonetheless, it was evident that the severity of infection with COVID-19 had a significant impact on the increase in liver enzymes. The elevation in AST and ALP levels appeared to be associated with the severity of the infection and could potentially serve as indicators to predict the severity of the disease. Therefore, it is crucial to monitor these enzymes closely in COVID-19 patients to detect any potential complications and take timely measures to reduce mortality rates. Hence these findings align with the conclusions drawn by Kumar et al., 2020 in their study of liver enzymes and COVID 19.[20]

The incidence and severity of liver infection and myopathy were more frequent in group B than in group A, indicating that these complications are associated with COVID-19 and may be exacerbated by the presence of statins, particularly at high doses. There is a possibility that when viral infection

depletes energy in muscles the use of statins may cause dysfunction leading to impaired energy transfer and accelerated muscle breakdown. Additionally taking drugs that inhibit CYP pathways and increase levels, in the bloodstream could worsen the situation. Therefore, it is recommended to limit the use of statins in COVID 19 patients to those who have a risk of heart attack, atherosclerotic cardiovascular disease or diabetes. Close monitoring of liver enzymes and avoiding doses of statins is crucial. It's important to weigh the benefits of using statins against the possible risks of liver injury and myopathy for each individual patient. In conclusion a personalized approach based on characteristics and risks should be taken into consideration when deciding whether or not to use statins, in COVID 19 patients.

Reference

[1] Platto S, Xue T, Carafoli E. COVID19: an announced pandemic. Cell Death Dis 2020 119. 2020;11(9):1-13. doi:10.1038/s41419-020-02995-9

[2] Jose J, Al-Tamimi FAA, Helal MM, Jimmy B, Riyami Q Al. Statin associated hepatic adverse effects: A retrospective review from a regional hospital in sultanate of Oman. Oman Med J. 2014;29(5):351-357. doi:10.5001/omj.2014.93

[3] Beltowski J, Wojcicka G, Jamroz-Wisniewska A. Adverse Effects of Statins - Mechanisms and Consequences. Curr Drug Saf. 2009;4(3):209-228. doi:10.2174/157488609789006949

[4] Dashti-Khavidaki S, Khalili H. Considerations for Statin Therapy in Patients with COVID-19. Pharmacotherapy. 2020;40(5):484-486. doi:10.1002/PHAR.2397

[5] Istvan ES, Deisenhofer J. Structural Mechanism for Statin Inhibition of HMG-CoA Reductase. Vol 292.; 2001.

[6] Charles EC, Olson KL, Sandhoff BG, McClure DL, Merenich JA. Evaluation of cases of severe statin-related transaminitis within a large health maintenance organization. Am J Med. 2005;118(6):618-624. doi:10.1016/j.amjmed.2005.02.008

[7] Pose E, Trebicka J, Mookerjee RP, Angeli P, Ginès P. Statins: Old drugs as new therapy for liver diseases? J Hepatol. 2019;70(1):194-202. doi:10.1016/j.jhep.2018.07.019

[8] Karahalil B, Hare E, Koç G, Uslu İ, Şentürk K, Özkan Y. Hepatotoxicity associated with statins. Arh Hig Rada Toksikol. 2017;68(4):254-260. doi:10.1515/aiht-2017-68-2994

[9] Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020;181(2):271-280.e8. doi:10.1016/j.cell.2020.02.052

[10] Rogers AJ, Guan J, Trtchounian A, et al. Association of Elevated Plasma Interleukin-18 Level With Increased Mortality in a Clinical Trial of Statin Treatment for Acute Respiratory Distress Syndrome∗. Crit Care Med. 2019;47(8):1089-1096. doi:10.1097/CCM.0000000000003816

[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;180(7):934-943. doi:10.1001/jamainternmed.2020.0994

[12] Daniels LB, Sitapati AM, Zhang J, et al. Relation of Statin Use Prior to Admission to Severity and Recovery Among COVID-19 Inpatients. Am J Cardiol. 2020;136:149-155. doi:10.1016/J.AMJCARD.2020.09.012

[13] Hariyanto TI, Kurniawan A. Statin therapy did not improve the in-hospital outcome of coronavirus disease 2019 (COVID-19) infection. Diabetes Metab Syndr Clin Res Rev. 2020;14(6):1613-1615. doi:10.1016/j.dsx.2020.08.023

[14] Mitacchione G, Schiavone M, Curnis A, et al. Impact of prior statin use on clinical outcomes in COVID-19 patients: data from tertiary referral hospitals during COVID-19 pandemic in Italy. J Clin Lipidol. 2021;15(1):68-78. doi:10.1016/j.jacl.2020.12.008

[15] Smith PF, Dodds M, Bentley D, Yeo K, Rayner C. Dosing will be a key success factor in repurposing antivirals for COVID-19. Br J Clin Pharmacol. 2021;87(9):3451-3454. doi:10.1111/bcp.14314

[16] Kumar P, Kulkarni A, Sharma M, Nagaraja Rao P, Nageshwar Reddy D. Favipiravir-induced liver injury in patients with

coronavirus disease 2019. J Clin Transl Hepatol. 2021;9(2):276-278. doi:10.14218/JCTH.2021.00011

[17] Yamazaki S, Suzuki T, Sayama M, Nakada T aki, Igari H, Ishii I. Suspected cholestatic liver injury induced by favipiravir in a patient with COVID-19. J Infect Chemother. 2021;27(2):390-392. doi:10.1016/j.jiac.2020.12.021

[18] Bloom PP, Meyerowitz EA, Reinus Z, et al. Liver Biochemistries in Hospitalized Patients With COVID-19. Hepatology. 2020;73(3):2021. doi:10.1002/hep.31326/suppinfo

[19] Castiglione V, Chiriacò M, Emdin M, Taddei S, Vergaro G. Statin therapy in COVID-19 infection. Eur Hear J - Cardiovasc Pharmacother. 2020;6(4):258-259. doi:10.1093/EHJCVP/PVAA042

[20] Kumar A, Kumar P, Dungdung A, Kumar Gupta A, Anurag A, Kumar A. Pattern of liver function and clinical profile in COVID-19: A cross-sectional study of 91 patients. Diabetes Metab Syndr Clin Res Rev. 2020;14(6):1951-1954. doi:10.1016/j.dsx.2020.10.001