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LIVER IMPAIRMENT AS A PREDICTIVE FACTOR FOR MORTALITY RATE OF COVID-19 PATIENTS

By

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ABSTRACT

Background: In the current COVID-19 pandemic, which is caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV2), disease diagnosis is essential for optimal management, timely isolation of infected cases in order to prevent further spread and is associated with significant morbidity and mortality burden.

Objective: To assess the liver impairment as a predictive factor for mortality rate of COVID -19 patients.

Patients and Methods: The prospective study included 100 patients with Covid-19 infection who were admitted to Al-Hussein and Bab Al-Shaʻaria University Hospitals. The study was during the period from 1st of February 2021 to 31th of May 2021 and divided in to five groups according to liver functions tests. Presenting clinical manifestations, laboratory findings, radiological findings and mortality rate were recorded from electronic medical records. Diagnoses of COVID-19 patient were done according to criteria of ministry of health and population- Egypt.

Results: The results revealed that the mean of platelets reaching to a minimum mean value at group E and the mean of the neutrophil /lymphocyte ratio reaching to a maximum mean value at Group E, while the lymphocyte /monocyte ratio reaching to a minimum mean value at Group E. There were significant difference among all groups regarding ALT, AST, total bilirubin, direct bilirubin and serum Albumin with P value =0.001 in all parameters. Also there were significant decreases of serum albumin in groups C, D and E when compared with group A, and there were significant increases of total bilirubin, direct bilirubin mean values in group E when compared with group A. There were significant increase of prothrombin time (PT) and INR in groups E when compared with group A. The results showed a significant difference (p-value <0.05) between recovered and died cases for each group with higher mortality rate at group D (7 cases with a percent of 30.4%), then at group E (3 cases with a percent of 25%), and there were 88% recovered and 12% died in all studied COVID-19 patients. The results revealed that the higher mortality rates at group D and E between patients having chest CT scoring 4 and 5.

Conclusion: Patients with accompanying chronic liver diseases are predisposed to developing a more severe course of COVID-19 and increase the mortality rate, but on the other hand, a more complicated presentation of SARS-CoV-2 infection increases the risk of liver failure.

Keywords: COVID-19, liver impairment chronic liver diseases, mortality rate.

INTRODUCTION

Accumulated data suggest that more than one-third of patients hospitalized due to SARS-CoV-2 infection might have impaired liver function. An increase in aspartate transaminase (AST) and alanine transaminase (ALT) activity, especially in men, results in a severe course of COVID-19. In general, a higher level of ALT, thrombocytopenia and hypoalbuminemia are indices of increased mortality in COVID-19 patients. Moreover, hypoalbuminemia is recognized as an independent marker of severe SARS-CoV-2 infection, poor prognosis and higher mortality *(Gholizadeh et al., 2020* and *Liu et al., 2020-b)*, but the change in albumin does not parallel the severity of hepatocellular injury in COVID-19 *(Zhang et al., 2020)*. This suggests that there may be mechanisms other than a hepatocellular injury that explains the profound hypoalbuminemia seen in COVID-19. One of the possible mechanisms is the intense systemic inflammation being reported in severe COVID-19 *(Qin et al., 2020)*. Hypoalbuminemia is common in many inflammatory diseases because increased capillary permeability can result in the escape of albumin to the interstitial space *(Soeters et al., 2019)*.

For diagnosis, health specialists use the Reverse Transcription Polymerase Chain Reaction (RT-PCR) test for the detection of the nucleic acid of the SARS-CoV-2 in the respiratory specimens (such as oropharyngeal swabs or nasopharyngeal sampling) *(Liu et al., 2020-c)*. Chest CT imaging may also be helpful for diagnosis in individuals where there is a high suspicion of infection based on symptoms and risk factors; however, guidelines do not recommend using CT imaging for routine screening *(Salehi et al., 2020)*.

Recommended measures to prevent infection include frequent hand washing, maintaining physical distance from others (especially from those with symptoms), quarantine (especially for those with symptoms), covering coughs, and keeping.

The present study aimed to understand the impairment of the liver as a predictive factor for mortality rate of Covid-19 patients.

PATIENTS AND METHODS

This prospective study included 100 patients with Covid-19 infection who were admitted to Al-Hussein and Bab Al-Shaʼaria University Hospitals. The cases were collected during the period from 1st of February 2021 to 31th of May 2020. All procedures followed Al-Azhar University Ethical Committee regulations. Written consents were taken from all patients before collecting any information or starting any procedure. Patients were divided in to five groups according to liver functions tests as follow:

- **Group A** included COVID-19 patients who were medically free and showed normal liver functions tests after affection.
- **Group B** included COVID-19 patients who known to have chronic illness and showed normal liver functions tests after affection.
- **Group C** included COVID-19 patients who were medically free and showed disturbed liver functions tests after affection.

- **Group D** included COVID-19 patients who known to have chronic illness and showed disturbed liver functions tests after affection.
- **Group E** included COVID-19 patients who had compensated liver diseases and showed disturbed liver functions tests after affection.

Inclusion criteria: Patients of all ages, both genders, positive results confirmed by standard SARS-CoV-2 RT-PCR.

Exclusion criteria: – ve SARS-CoV-2 RT-PCR test.

All patients were subjected to the following procedures: 1- Full history including demographic characteristics. 2- General physical and systemic examination. 3- Routine investigations including: -Liver function tests (ALT, AST, total bilirubin, serum albumin, prothrombin time and INR) and renal function tests (serum creatinine and blood urea). -Complete blood count (HGB, RBCs count, platelet count, WBCs count, lymphocyte-monocyte ratio and neutrophil-lymphocyte ratio). 4- Radiological investigations: CT Chest for all patients. On CT chest, each of the 5 lung lobes was visually scored from 0 to 5 as follows: 0, no involvement; 1, < 5% involvement;2, 5%–25% involvement; 3, 26%–50% involvement; 4, 51%–75% involvement; and 5, > 75% involvement **(Pan et al., 2020)**. 5- Diagnosis of COVID-19 patient according to criteria of ministry of health and population-Egypt. 6- All patients received medical treatment according to protocols of ministry of health and population Egypt.

Statistical Analysis:

The data were entered, coded and processed on computer using Statistical Packaged for the Social Science **(IBM SPSS version 22, 2013)**. The level $P \leq 0.05$ was considered the cut-off value for significance. Description of quantitative variables was as mean, SD and range. Description of qualitative variables was as number and percentage. Chi-Square test $\chi 2$ was used to compare qualitative variables between groups. Kruskal–Wallis test was used for abnormally quantitative variables, to comparison among more than two groups. Mann Whitney U test was used for abnormally quantitative variables, to compare between two studied groups. Pearson correlation coefficient was used for measuring the strength and direction of a linear relationship between two variables. Repeated measures ANOVA were used for comparison among more than two means in quantitative data. In case of significance, least significant difference (LSD) test was performed to detect pairs of groups significantly different.

RESULTS

The mean of platelets reaching to a minimum mean value of 183.17 ± 118.45 at group E **(Table 1)**.

Table (1): Means and standard deviations of Age and blood cells and comparison between all groups

Parameters / Variables		Range			Mean	±	S. D	p. value	Post Hock test (LSD)			
Age	Group A	20	–	80	47.80	±	20.05	0.011	P1	0.018	P6	0.774
	Group B	22	–	97	59.79	±	16.78		P2	0.955	P7	0.447
	Group C	20	–	66	48.12	±	14.10		P3	0.015	P8	0.013
	Group D	25	–	87	61.04	±	15.90		P4	0.011	P9	0.010
	Group E	44	–	76	63.92	±	9.61		P5	0.017	P10	0.616
HGB	Group A	9.5	–	16	12.75	±	2.26	0.048	P1	0.148	P6	0.612
	Group B	5.4	–	16.3	11.62	±	2.46		P2	0.449	P7	0.345
	Group C	8.4	–	17.8	13.41	±	2.77		P3	0.343	P8	0.070
	Group D	6.1	–	15.3	11.97	±	2.25		P4	0.048	P9	0.001
	Group E	5.7	–	15.6	10.83	±	2.70		P5	0.017	P10	0.201
Platelets	Group A	109	–	462	279.73	±	97.91	0.201	P1	0.601	P6	0.392
	Group B	58	–	521	260.85	±	113.62		P2	0.813	P7	0.067
	Group C	138	–	584	289.47	±	121.61		P3	0.548	P8	0.376
	Group D	15	–	454	256.57	±	123.26		P4	0.054	P9	0.052
	Group E	45	–	365	183.17	±	118.45		P5	0.410	P10	0.078
WBCs	Group A	3	–	12.4	8.00	±	3.38	0.149	P1	0.874	P6	0.052
	Group B	2.64	–	18.24	8.44	±	4.16		P2	0.124	P7	0.352
	Group C	3.1	–	69	12.85	±	15.03		P3	0.058	P8	0.723
	Group D	2.5	–	49	13.85	±	11.18		P4	0.348	P9	0.625
	Group E	3.5	–	24.2	11.22	±	5.30		P5	0.097	P10	0.404

P1: Group A & Group B. P2: Group A & Group C. P3: Group A & Group D.
P4: Group A & Group E. P5: Group B & Group C. P6: Group B & Group D.
P7: Group B & Group E. P8: Group C & Group D. P9: Group C & Group E.
P10: Group D & Group E. SD: Standard deviation.

The mean of the neutrophil /lymphocyte ratio reaching to a maximum mean value of 12.21 ± 8.71 at group E while the lymphocyte /monocyte ratio reaching to a minimum mean value of 2.13 ± 1.80 at group E **(Table 2)**.

Table (2): Means and standard deviations of some variables of differential leucocytic count and comparison between all groups.

Variables \ Parameters		Range			Mean	±	S. D	p. value
Neutrophil / lymphocyte %	Group A	1.35	–	39.46	7.94	±	9.75	0.629
	Group B	0.71	–	22.75	7.66	±	4.81	
	Group C	1.03	–	26.34	9.23	±	7.13	
	Group D	2.01	–	31	11.37	±	10.04	
	Group E	1.47	–	31	12.21	±	8.71	
Lymphocyte / monocyte %	Group A	0.74	–	10	4.71	±	2.41	0.296
	Group B	0.48	–	23.13	3.15	±	4.02	
	Group C	0.7	–	5.37	3.02	±	1.73	
	Group D	0.75	–	31.21	4.69	±	6.76	
	Group E	0.63	–	6.66	2.13	±	1.80	

SD: Standard deviation.

Kruskal–Wallis test showed significant difference among all groups regarding the serum creatinine and blood urea with P value <0.05 in both serum creatinine and blood urea **(Table 3)**.

Table (3): Means and standard deviations of some variables of kidney functions tests and comparison between all groups

Variables \ Parameters		Range			Mean	±	S. D	p. value	Post Hock test (LSD)			
Serum Creatinine	**Group A**	0.5	–	1.6	0.96	±	0.26	0.006	P1	0.643	P6	0.001
	Group B	0.3	–	5.3	1.18	±	0.93		P2	0.969	P7	0.887
	Group C	0.3	–	1.8	0.98	±	0.38		P3	0.001	P8	0.001
	Group D	0.6	–	11.1	2.81	±	2.86		P4	0.619	P9	0.636
	Group E	0.7	–	1.9	1.25	±	0.40		P5	0.661	P10	0.004
Blood Urea	**Group A**	16	–	88	41.16	±	19.54	0.003	P1	0.177	P6	0.001
	Group B	16	–	232	67.24	±	54.21		P2	1.0	P7	0.764
	Group C	8	–	86	41.16	±	20.45		P3	0.001	P8	0.001
	Group D	24.3	–	451	122.95	±	105.92		P4	0.408	P9	0.395
	Group E	30	–	117	61.00	±	26.69		P5	0.160	P10	0.006

P1: Group A & Group B. P2: Group A & Group C. P3: Group A & Group D.
P4: Group A & Group E. P5: Group B & Group C. P6: Group B & Group D.
P7: Group B & Group E. P8: Group C & Group D. P9: Group C & Group E.
P10: Group D & Group E. SD: Standard deviation.

The mean values of ALT in groups C, D and E were 98.12±68.21 & 69.39±48.49 and 59.33±30.39 respectively. The mean values of AST in groups C, D and E were 78.76±51.97 & 81.93±69.19 and 77.17±51.51 respectively, and the mean values of serum albumin in groups C, D and E were 3.70±0.62 & 3.32±0.68 and 2.47±0.78 respectively. There were significant decreases of serum albumin in groups C, D and E when compared with group A with P value < 0.05. Also, there were significant increases of total bilirubin, direct bilirubin mean values in group E when compared with Group A with P value <0.05. Kruskal–Wallis test showed a significant difference among all groups regarding the ALT, AST, total bilirubin, direct bilirubin and serum albumin with P value =0.001 in all parameters **(Table 4)**.

Table (4): Means and standard deviations of some variables of liver functions tests and comparison between all groups

Parameters / Variables		Range			Mean	±	S. D	p. value	Post Hock test (LSD)			
ALT	Group A	6	–	38	21.33	±	10.86	0.001	P1	0.958	P6	0.001
	Group B	8	–	40	20.70	±	8.49		P2	0.001	P7	0.004
	Group C	24	–	286	98.12	±	68.21		P3	0.001	P8	0.022
	Group D	12	–	227	69.39	±	48.49		P4	0.012	P9	0.009
	Group E	16	–	121	59.33	±	30.39		P5	0.001	P10	0.464
AST	Group A	12	–	41	28.07	±	9.86	0.001	P1	0.756	P6	0.001
	Group B	6	–	40	23.82	±	8.83		P2	0.001	P7	0.001
	Group C	28	–	210	78.76	±	51.97		P3	0.001	P8	0.821
	Group D	8.5	–	337	81.93	±	69.19		P4	0.005	P9	0.923
	Group E	22	–	216	77.17	±	51.51		P5	0.001	P10	0.760
Total Bilirubin	Group A	0.3	–	1.1	0.63	±	0.27	0.001	P1	0.957	P6	0.651
	Group B	0.2	–	1.3	0.61	±	0.30		P2	0.665	P7	0.001
	Group C	0.3	–	1.2	0.75	±	0.29		P3	0.749	P8	0.882
	Group D	0.2	–	1.3	0.71	±	0.31		P4	0.001	P9	0.001
	Group E	0.3	–	8.2	1.83	±	2.11		P5	0.586	P10	0.001
Direct Bilirubin	Group A	0.07	–	0.5	0.19	±	0.13	0.001	P1	0.910	P6	0.905
	Group B	0.1	–	0.9	0.22	±	0.21		P2	0.807	P7	0.001
	Group C	0.1	–	0.8	0.26	±	0.19		P3	0.838	P8	0.953
	Group D	0.09	–	0.8	0.24	±	0.18		P4	0.001	P9	0.001
	Group E	0.1	–	7.85	1.30	±	2.15		P5	0.864	P10	0.001
Serum Albumin	Group A	3.5	–	5.1	4.18	±	0.47	0.001	P1	0.014	P6	0.017
	Group B	2.6	–	4.6	3.72	±	0.48		P2	0.024	P7	0.001
	Group C	2.5	–	4.79	3.70	±	0.62		P3	0.001	P8	0.051
	Group D	1.9	–	4.5	3.32	±	0.68		P4	0.001	P9	0.001
	Group E	0.4	–	3.4	2.47	±	0.78		P1	0.014	P6	0.017

P1: Group A & Group B. P2: Group A & Group C. P3: Group A & Group D.
P4: Group A & Group E. P5: Group B & Group C. P6: Group B & Group D.
P7: Group B & Group E. P8: Group C & Group D. P9: Group C & Group E.
P10: Group D & Group E. SD: Standard deviation.

The mean values of PT and INR in group E were 17.01±5.16 and 1.44±0.45 respectively. There were significant increases of PT and INR in group E when compared with group A with P value <0.05. Kruskal–Wallis test showed significant difference among all groups regarding the PT and INR with P value <0.05 in both PT and INR **(Table 5)**.

Table (5): Means and standard deviations of some variables of bleeding profile and comparison between all groups

Variables \ Parameters		Range			Mean	±	S. D	p. value	Post Hock test (LSD)			
PT	Group A	11.9	–	18.2	13.38	±	1.44	0.013	P1	0.353	P6	0.432
	Group B	10.6	–	32.4	14.38	±	3.81		P2	0.555	P7	0.027
	Group C	11.7	–	19.2	14.11	±	2.21		P3	0.131	P8	0.358
	Group D	11.7	–	28.7	15.13	±	3.51		P4	0.008	P9	0.028
	Group E	13	–	31.8	17.01	±	5.16		P5	0.787	P10	0.129
INR	Group A	0.9	–	1.9	1.16	±	0.23	0.042	P1	0.771	P6	0.308
	Group B	1	–	2.73	1.19	±	0.33		P2	0.872	P7	0.022
	Group C	0.8	–	1.8	1.18	±	0.25		P3	0.269	P8	0.332
	Group D	0.91	–	2.27	1.28	±	0.28		P4	0.026	P9	0.032
	Group E	1	–	2.5	1.44	±	0.45		P5	0.911	P10	0.156

P1: Group A & Group B. P2: Group A & Group C. P3: Group A & Group D.
P4: Group A & Group E. P5: Group B & Group C. P6: Group B & Group D.
P7: Group B & Group E. P8: Group C & Group D. P9: Group C & Group E.
P10: Group D & Group E. SD: Standard deviation.

Mann Whitney U test was conducted to test the significant difference between recovered and died for all cases regarding some variables of liver functions tests. The results revealed no significant differences between recovered and died mean values of the ALT for all cases P-value >0.05. However, there was a significant difference between recovered and died mean values of the AST, total bilirubin, direct bilirubin and serum albumin for all cases with P-value <0.05 for all cases **(Table 6)**.

Table (6): Comparison of some variables of liver functions tests between recovered and died for all cases among COVID 19 patients

Variables \ Parameters		Range			Mean	±	S. D	p. value
ALT	Recovered	6	–	286	46.52	±	45.97	0.053
	Died	15	–	227	73.75	±	59.02	
AST	Recovered	6	–	210	46.46	±	37.26	0.017
	Died	17	–	337	105.67	±	94.74	
Total Bilirubin	Recovered	0.2	–	2.2	0.69	±	0.36	0.004
	Died	0.5	–	8.2	1.66	±	2.13	
Direct Bilirubin	Recovered	0.07	–	1.4	0.25	±	0.23	0.024
	Died	0.1	–	7.85	1.14	±	2.19	
Serum Albumin	Recovered	0.4	–	5.1	3.60	±	0.74	0.032
	Died	1.8	–	4.1	3.11	±	0.75	

SD: Standard deviation

Pearson correlation coefficient was conducted to determine the relationship between ALT and AST. Results revealed a positive correlation between ALT and AST for groups C, D and E (r=0.805, 0.676 and 0.813 respectively and for all cases r=0.766) **(Table 7)**.

Table (7): Correlation between ALT and AST among COVID-19 patients

ALT / AST	*r*	*p*
Group A	0.161	0.568
Group B	0.253	0.155
Group C	0.805	0.001
Group D	0.676	0.001
Group E	0.813	0.001
Total	0.766	0.001

r: Pearson correlation. p: probability value.

The results showed that a significant difference (p-value <0.05) were found between recovered and died cases for each group with higher mortality rate at group D (7 cases with a percent of 30.4%) then at group E (3 cases with a percent of 25%) and there was 88 cases (88%) recovered and 12 cases (12%) died in all studied COVID-19 patients **(Table 8)**.

Table (8): Comparison of mortality rate between recovered and died cases for all cases and each group among COVID-19 patients

Groups / Mortality rate		Group A (n=15)	Group B (n=33)	Group C (n=17)	Group D (n=23)	Group E (n=12)	P-value
Recovered (n=88)	**N**	15	32	16	16	9	0.006
	%	100.0%	97.0%	94.1%	69.6%	75.0%	
Died (n=12)	**N**	0	1	1	7	3	
	%	.0%	3.0%	5.9%	30.4%	25.0%	

N: number of cases.

There were significant differences (p-value <0.05) between recovered patients and died patients as regard to CT chest. There were radiological findings suggesting that COVID-19 in CT chest of all including cases with higher mortality rate at group D (7 cases with a percent of 30.4% and 5 cases of them with score 5 with a percent of 21.7%), then at group E (3 cases with a percent of 25% and 2 cases of them with score 5 with a percentage of 16.6%) and there was 88 cases (88%) recovered and 12 cases (12%) died in all studied COVID-9 patients. The results revealed that the higher mortality rate at group D and E between patients having chest CT scoring 4 and 5 **(Table 9)**.

Table (9): Comparison CT findings between recovered and died cases for all COVID-19 patients.

CT findings \ Score			Score 1	Score 2	Score 3	Score 4	Score 5	P-value
Group A (n=15)	**Recovered (n=15)**	**N**	6	3	3	2	1	-
		%	40.0%	20.0%	20.0%	13.3%	6.6%	
	Died (n=0)	**N**	0	0	0	0	0	
		%	.0%	.0%	.0%	.0%	.0%	
Group B (n=33)	**Recovered (n=32)**	**N**	2	3	8	9	10	0.668
		%	6.0%	9.0%	24.2%	27.2%	30.3%	
	Died (n=1)	**N**	0	0	0	1	0	
		%	.0%	.0%	.0%	3.0%	.0%	
Group C (n=17)	**Recovered (n=16)**	**N**	3	3	4	3	3	0.485
		%	17.6%	17.6%	23.5%	17.6%	17.6%	
	Died (n=1)	**N**	0	0	0	1	0	
		%	.0%	.0%	.0%	5.8%	.0%	
Group D (n=23)	**Recovered (n=16)**	**N**	1	6	2	4	3	0.125
		%	2.3%	26.0%	8.6%	17.3%	13.0%	
	Died (n=7)	**N**	0	0	1	1	5	
		%	.0%	.0%	2.3%	2.3%	21.7%	
Group E (n=12)	**Recovered (n=9)**	**N**	2	1	2	2	2	0.647
		%	16.6%	8.3%	16.6%	16.6%	16.6%	
	Died (n=3)	**N**	0	0	0	1	2	
		%	.0%	.0%	.0%	8.3%	16.6%	
All Cases (n=100)	**Recovered (n=88)**	**N**	14	16	19	20	19	0.027
		%	14.0%	16.0%	19.0%	20.0%	19.0%	
	Died (n=12)	**N**	0	0	1	4	7	
		%	.0%	.0%	1.0%	4.0%	7.0%	

N: number of cases.

DISCUSSION

In the present study, it was found that the mean of the neutrophil /lymphocyte ratio reaching to a maximum mean value at group E and the lymphocyte /monocyte ratio reaching to a minimum mean value of 2.13 ± 1.80 at group E. Our results were in agreement with *Chan and Rout (2020)* who stated that patients with severe COVID-19 disease had higher

NLR value compared to non-severe disease and level of NLR correlated with COVID-19 disease severity. Also in our study, it was found that the lymphocyte /monocyte ratio reaching to a minimum mean value at group E. Our results agreed with *Liu et al. (2020-a)* who reported that T helper cells induce the production of cytokines such as interleukin-17 through the nuclear factor kappa light-chain-enhancer of activated B cells (NF-kB) signaling pathway, leading to increased aggregation of monocytes. SARS-CoV-2 infects circulating immune cells and increases apoptosis of lymphocytes, leading to lymphopenia. A lower ratio of circulating lymphocytes to monocytes (LMR) predicts severe and extremely severe COVID-19 as the clearance of the virus is delayed due to lymphopenia and also a decrease in CD4+ T cells. Either a rise or fall in lymphocyte levels is an extremely crucial prognostic indicator of mortality in COVID-19.

NLR elevation was found to be associated with poor outcomes in myocardial infarction, coronary artery disease, atherosclerosis, chronic obstructive pulmonary disease (COPD) and high nuclear grade renal cell carcinoma (RCC) *(Hu et al., 2015* and *Ye et al., 2019).* LMR level has been correlated with several malignancies that might have complex interplay between immune system and oncogenesis. Their prognostic effectiveness has been investigated in hematological malignancies and solid tumors such as colon, bladder, and lung cancers *(Ye et al., 2019).* Moreover, a study from Italy proved that COVID-19 patients had higher monocyte absolute count values compared to patients with flu, suggesting a potential prognostic role of monocyte - macrophages activation *(Gu et al., 2016* and *Curtoloet al., 2020).*

Patients with sustained elevated NLR had worse results in almost all measured outcomes. An inflammatory response activates the local innate immunity of the body to provide protection against ingress of microorganisms. However, abnormalities can occur in host defense systems in response to infection. A dysregulated or unbalanced inflammatory response escalates and releases an excess of pro-inflammatory mediators such as IL-1, IL-6, IL-8, and TNF a, which can result in systemic inflammatory response syndrome *(Tatum et al., 2020).* Progression of this cascade and hyperinflammation worsens the initial burden. High levels of neutrophil infiltration and systemic circulation result in increased systemic arginase activity, which results in depleted systemic arginine *(Caldwell et al., 2018).* Arginine is the sole substrate for nitric oxide (NO) production, which has known antiviral activity against RNA viruses such as SARS-CoV-2 *(Luiking et al., 2012* and *Caldwell et al., 2018).*

In the present work, our resulted revealed that there was a significant increase of ALT and AST mean values in groups C, D and E when compared with group A. Also, our results showed that there was a significant increase of total bilirubin, direct bilirubin mean values in group E when compared with group A. There were significant decrease of serum albumin mean value in groups C, D and E when compared with group A with a minimum mean value in group E, there was a significant increase of PT and INR

mean values in groups E when compared with group A. These results agreed with *Ghoda & Ghoda (2020)* and *Kullar et al. (2020)* who found that regardless of existing CLD, COVID-19 was associated with mild to moderate liver failure, reflected mainly by hypertransaminasemia, elevation of gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP) levels (less frequently), hypoproteinemia and prolonged prothrombin time.

In our results, no significant difference between recovered and died mean values of the ALT for all cases. However, there were significant difference between recovered and died mean values of the AST, total bilirubin, direct bilirubin and serum albumin for all cases, and were associated with severity and mortality among COVID-19 patients, but there was a positive correlation between ALT and AST for groups C, D and E and for all cases. Our findings were in agreement with *Alqahtani et al. (2020)*, *Chen et al. (2020)* and *Ghweil et al. (2020).*

Some reports have even proved the presence of a correlation between abnormal liver tests and coagulation dysfunction in SARS-CoV-2 pneumonia, highlighting the significant role of the liver in this disease *(Chen et al., 2020)*. However, the data are too scanty to differentiate an exact background of hypertransaminasemia in COVID-19 patients with a pre-existing chronic liver failure or a certain hepatotoxic impact of SARS-CoV-2 infection. The catastrophic emergence of COVID-19 has led to large volumes of research from epicentres of infection, with some focusing on COVID-19-related liver impairment. In this regard, *Wang et al. (2020)* found that very minimal elevations in alanine (ALT) and aspartate aminotransferase (AST; ALT >AST) to disease severity and demonstrate ‘specific’ COVID-19-related cytopathic changes and virus-like particles on post-mortem liver histopathology. Furthermore, they found that severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) caused massive apoptosis and binucleation of hepatocytes, resulting in liver enzyme abnormality and synthetic liver dysfunction, the latter in the form of hypoalbuminemia. Their painstaking work is commendable, but their assessment of clinical and investigational events may not reflect the reality.

Philips et al. (2020) reported that the degree of elevation in AST and ALT can only be considered an ‘altered’ liver test, not akin to acute hepatic injury. In hepatic impairment, there must be very clear evidence for metabolic (hypoglycaemia, hyperammonemia), secretory (hyperbilirubinemia) and synthetic (hypoalbuminemia, raised prothrombin time) dysfunction. Except for a mild rise in ALT and hypoalbuminemia, significant liver dysfunction is elusive in the current study. Importantly, hypoalbuminemia, in the absence of other significant liver test abnormalities, virtually rules out the hepatic origin of this abnormality.

Acute liver injury is best identified by international normalized ratio >2.0 *(Koch et al., 2017)*. The liver biopsy findings of hepatocyte apoptosis, binuclear or occasional multinuclear syncytial hepatocytes, in the absence of viral inclusions and presence of moderate steatosis, with mild focal lobular or portal inflammation are non-specific findings

that may not be related to viral cytopathy. These findings can undoubtfully be seen in sepsis and multi-organ dysfunction associated with critical illness (moderate to severe apoptosis, steatosis, lobular and portal inflammation), aging, drug-induced liver injury and fatty liver disease (binucleation or polyploidy– a feature of liver cell renewal and not injury) *(Hsu and Duncan, 2015).*

The COVID-19 related liver injury is defined as any liver damage occurring during disease progression and treatment of COVID-19 in patients with or without pre-existing liver disease *(Sun et al., 2020).* The impact of COVID-19 virus infection on the liver is still unclear. Several studies have shown that COVID-19 virus infection causes abnormality in liver function proven by elevation of serum liver biochemistries such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin. The incidence of elevated ALT and AST are ranged from 2.5% - 50% to 2.5% - 61.1%, respectively *(Ridruejo and Soza, 2020).* Low of albumin level is also a marker of severe infection and poor prognosis *(Giuliano, 2020).*

In the present work, our results showed that a significant difference were found between recovered and died cases for each group as regard to mortality rate with higher mortality rate was found at group D (30.4%), then at group E (25%) and there was 88% recovered and 12% died in all studied COVID-9 patients. Our results were in a line with *Liu et al. (2020)* and *Gholizadehet al. (2020)* who reported that the accumulated data suggest that more than one-third of patients hospitalized due to SARS-CoV-2 infection might have impaired liver function. An increase in aspartate transaminase (AST) and alanine transaminase (ALT) activity, especially in men, results in a severe course of COVID-19. In general, a higher level of ALT, thrombocytopenia and hypoalbuminemia are indices of increased mortality in COVID-19 patients. Moreover, hypoalbuminemia is recognized as an independent marker of severe SARS-CoV-2 infection, poor prognosis and higher mortality. Also our results were in concomitant with *Sulaiman et al. (2020)* who stated that the mortality rate of COVID-19 virus infection in patients with pre-existing chronic liver disease and cirrhosis found that patients with chronic liver disease and cirrhosis had clinical factors associated with poor outcomes from COVID-19 virus infection.

Recent investigations on complications of COVID-19 have revealed that the occurrence of liver injury ranged from 14.8% to 53%. Also, it is accompanied mainly by abnormal ALT/AST levels followed by slightly elevated bilirubin levels *(Xu et al., 2020).* The proportion of liver injury in death cases and severe COVID-19 patients was significantly higher than that in mild patients *(Huang et al., 2020).*

Concerning CT chest, our results showed that the findings were bilateral peripheral ground glass opacity among all cases who affected by COVID-19 infection, and it was found that there was a significant difference between recovered patients and died patients as regard to CT chest. There were radiological findings suggested COVID-19 in CT chest of all including cases with higher mortality rate was found at group D 30.4% out of them

21.7% with CT chest scoring 5 then at group E 25% out of them 16.6% with CT chest scoring 5 and there was 88% recovered and 12% died in all studied COVID-9 patients. Our results revealed that the higher mortality rate was found in Group D and E between patients having CT chest scoring 4 and 5. The same findings were reported by multiple studies *(Ghweil et al., 2020*; *Majidi & Niksolate, 2020*; *Song et al., 2020* and *Wong et al., 2020)*. So, CT chest findings were predictors in the severity and mortality of COVID-19 infection.

CONCLUSION

Impaired liver diagnostic test results constitute common findings in COVID-19 patients. Deterioration of liver function worsens the prognosis, increases the risk of severe SARS-CoV-2 infection and prolongs the duration of hospitalization. Abnormal liver function test results may be predictors of COVID-19 severity and mortality rate.

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إعتلال الكبد كعامل تنبؤى لمعدل وفيات مرضى الكوفيد-19

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خلفيـــة البحـــث: فـــى ظـــل الوبـــاء الحـــالى لمـــرض فيـــروس كورونـــا-19، النـــاجم عـــن متلازمـــة الجهـــاز التنفســـى الحـــادة الوخيمـــة، ويعـــد تشخيصـــه ضـــروريا لأخـــذ العـــلاج المناســـب والعـــزل المبكـــر للحـــالات المصـــابة منعـــا للمزيـــد مـــن إنتشـــار هـــذا المـــرض، والذى يكون مصحوبا بشكل كبير بحالات من الأعياء والوفيات.

الهـــدف مـــن البحـــث: دراســـة تقيـــيم إعـــتلال الكبـــد كعامـــل تنبـــؤى لمعـــدل وفيـــات مرضـــى الكوفيد-19.

المرضـــى وطـــرق البحـــث: تـــم إجـــراء هـــذه الدراســـة علـــى مائـــة مـــريض يعـــانون مـــن فيـــروس كورونـــا- 19 وكـــانوا محجـــوزين بكـــل مـــن مستشـــفى الحســـين ومستشـــفى بـــاب الشـــعرية الجـــامعيين، وقـــد تـــم تجميـــع حـــالات هـــذا البحـــث مـــن الفتـــرة فـــى أول فبرايـــر ســـنة 2021 إلـــى نهايـــة شـــهر مـــايو لســـنة 2021، وقـــد تـــم تقســـيم الحـــالات إلـــى خمســـة مجموعـــات طبقـــا لنتـــائج وظـــائف الكبـــد بالاضـــافة إلـــى التحاليـــل المعمليـــة الأخـــرى التـــى تـــم اجراؤهـــا فـــى هـــذه الدراســـة مثـــل صـــورة الـــدم ووظـــائف الكلـــى، وكـــذلك عـــن طريـــق اجراء الأشعة المقطعية.

نتـــائج البحـــث: أظهـــرت النتـــائج ان هنـــاك فـــروقاً ذات دلالـــة إحصـــائية بـــين جميـــع المجموعـــات فيمـــا يتعلـــق بـــالأنزيمات الكبديـــة (ALT,AST)، كمـــا كـــان هنـــاك انخفـــاضاً ذو دلالـــة إحصـــائية فـــي مصـــل الألبـــومين فـــي المجموعـــات C و D و E عنـــد المقارنـــة مـــع المجموعـــة A، وكانـــت هنـــاك زيـــادات ذات دلالـــة إحصـــائية بـــين متوســـط قـــيم البيليـــروبين الكلـــى والبيليـــروبين المباشـــر فـــي المجموعـــة E بالمقارنـــة مـــع المجموعـــة A، كمـــا وجـــد أنـــه كانـــت هنـــاك زيـــادة ذات دلالـــة إحصـــائية بـــين متوســـط قـــيم,

وقت البروثرومبين و معدل INR في المجموعات E عند مقارنتها بالمجموعة A. وهناك فروقا ذات دلالة إحصائية بين الحالات المتعافية وحالات الوفاة لكل مجموعة فيما يتعلق بمعدل الوفيات مع ارتفاع معدل الوفيات في المجموعة D بنسبة 30.4٪ ثم في المجموعة E بنسبة 25٪، وتم شفاء 88 حالة بنسبة 88٪ وتوفي 12 حالة بنسبة 12٪ في جميع مرضى الكوفيد-19.

الاستنتاج: يعتبر المرضى الذين يعانون من أمراض الكبد المزمنة أكثر عرضة إلى زيادة خطورة الأعراض عند الاصابة بمرض فيروس كورونا-19 وأيضا زيادة معدل الوفيات، ومن ناحية أخرى فإن زيادة المضاعفات الناجمة عن الاصابة بمتلازمة الجهاز التنفسي الحادة الوخيمة لمرض فيروس كورونا-19 يزيد من نسبة خطورة الإصابة بالفشل الكبدي.

الكلمات الدالة: فيروس كورونا-19، اعتلال الكبد، أمراض الكبد المزمنة، معدل الوفيات.