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Hepatic dysfunction in COVID-19: A useful prognostic marker of severe disease?

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Abstract
Background: COVID-19 has disrupted many countries worldwide; its high mortality and spread has overwhelmed the healthcare systems. Hence it has become important to identify reliable predictors of disease severity and morbidity which would streamline healthcare resources into improving efficiency of management and thus improving the clinical burden and overall outcome. An increase in LFT parameters has showed an association with severity of the disease and ICU admissions seen by various studies. But none of the studies reviewed the LFT parameters with respect to the outcome. So, this can be done by monitoring LFT parameters and drawing a comparison.
Aim: To correlate serum liver function parameters levels in COVID-19 patients, admitted in an Indian setting, with clinical outcome.
Methods: A single-center, observational cross-sectional study was conducted in COVID-19 positive patients admitted from April1st, 2021 to May 1st, 2021. The diagnosis was confirmed by Real-Time Polymerase Chain Reaction (RT-PCR). Liver function test parameters were compared to clinical outcomes and checked for statistical association.
Results: A total of 157 COVID-19 patients were studied. Mann-Whitney test was used to find the medians of Total Bilirubin (TB) was 1.65 in the population that succumbed to death and 0.3 for the group that got discharged ($p<0.05$). Direct Bilirubin (DB) also showed a significant increase in non survivors 2.4 vs 0.2 ($p<0.05$). Total protein and albumin showed a decrease in levels in the patients that succumbed, median values of TP and Albumin in the non survivors and survivors are 6 and 3.1 and 6.8 and 3.8 respectively (p=0.005 and p=0.001). All enzyme levels were higher in the group that succumbed to death. The median Alkaline Phosphatase (ALP) 273 vs 84 in non-survivor group as compared to the group that got discharged ($p<0.05$). The aspartate aminotransferase (AST) and alanine aminotransferase (ALT) median levels were 144 and 123.5 in non-survivor group and 27 and 23 in the survivor group respectively. ($p<0.05$ for both)
Conclusion: Our study showed an association with increased liver enzyme levels, TB and DB and decreased total protein levels and albumin levels with adverse clinical outcomes. This important association would require additional studies to bring in new criteria and guidelines that would substantiate this finding as this could serve as a cost-effective triaging tool to assess patients according to need foreseeing the prognosis.

Keywords: COVID-19, Liver, LFT, AST, ALT, ALP, albumin, bilirubin

Introduction

Coronavirus disease 2019 (COVID-19) is a highly contagious infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It has rapidly grown into a pandemic after the first cases of this predominantly respiratory viral illness were first reported in Wuhan, Hubei Province, China. In late December 2019, SARS-CoV-2 rapidly disseminated across the world in a short span of time.[1] As per the WHO report on 14th June, 2021, the total number of cases have amounted to 175,306,598 and the number of confirmed deaths to 3,792,777.[2] With the advent of the second wave, India has been burdened with increasing cases, which have now crossed the 30 million mark and the Health Ministry has confirmed 377,031 deaths according to the data published on June 16th, 2021.[3]

COVID-19 has disrupted many countries worldwide, overwhelming their healthcare systems. It has been associated with a death rate higher than any other respiratory viral infection. Hence it has become important to identify reliable predictors of disease severity and morbidity which would streamline healthcare resources into improving efficiency of management and thus improving the clinical burden and overall outcome.

Various biomarkers are being investigated for their role in the determination of outcome and

prognosis of COVID-19. The disease has several laboratory abnormalities such as elevated lactate dehydrogenase (LDH), D-dimer, cardiac troponin I, procalcitonin, ferritin, transaminases, bilirubin, and lower lymphocyte count. [4] Evidence suggests that an impaired immune function and hyper-inflammatory responses are characteristics of COVID-19 severity and mortality. The incidence of liver injury has been reported in the range of 16-53% by several retrospective studies [5]. The prevalence of abnormal liver function tests (LFT) in COVID-19 patients has been reported as high as 76.3%, and an association with higher odds of progressing to severe disease was found with hepatocellular or mixed type of liver injury. Therefore, abnormal liver chemistries have been associated with worser clinical courses. [6, 7] However, not many studies definitely associate abnormal Liver function with mortality.

In this study, we aimed to assess the correlation between different liver function parameters with the clinical outcome of COVID-19 positive patients.

Methods

This was an observational cross-sectional study conducted among patients admitted between April 1st, 2021 and May 1st, 2021 under the Internal Medicine Department in Victoria Hospital, Bangalore Medical College and Research Institute, Bangalore, Karnataka, India. Approval and clearance were obtained from the institutional Ethics Committee (BMCRI/PS/02/2020-21). The patients included in the study were aged ≥18 years of both genders, diagnosed with COVID-19 infection by RT-PCR technique using ABI/Thermo fischer-Taqpath technique. The study excluded patients <18 years of age and those not willing to provide signed informed consent prior to the study.

Case record forms with follow up charts were used to record demographic data, duration, clinical features and incidence of comorbidities like hypertension, diabetes, renal, cardiac and respiratory disorders were noted. All participants were followed up to the outcome. Laboratory results at admission, including routine blood tests, liver function, kidney function, coagulation function, and C-reactive protein, were collected and evaluated. Venous blood samples were collected from each subject evaluation of liver function parameters. A Beckman Coulter DXH 800 was used for routine blood parameter analysis. The blood biochemistry indexes, and liver function tests were measured using the Cobas 6000 c-501. All laboratory data were tested in the same laboratory with standardization and certification procedures.

The Guidelines for Management of COVID-19 - A point of Care Approach (version 4.0) April 2021, given by the Government of Karnataka was used for the management and to discharge patients. According to the guidelines, asymptomatic patients who remained asymptomatic during their stay in the hospital were discharged 10 days after the positive RT-PCR test. There was no requirement of a negative test before discharge of the patient. The patients were advised to follow home isolation for further 7 days and were followed up through tele counseling.

The symptomatic, mild to moderate cases were discharged after 10 days of onset of symptoms only if they exhibited no symptoms for the last 3 consecutive days before discharge and would maintain saturation (>95%) for the last 4 consecutive days without oxygen support and if there was resolution of breathlessness and other clinical signs / symptoms and the repeat inflammatory markers at the time of discharge were either of normal range or showed a decreasing trend. Failing this criterion, the patients were kept in-patient till they achieved a 3 consecutive symptom free period before discharge. Again, there was no requirement of a negative test report before discharge and patient was advised home isolation for further 7 days. For severe cases, a three consecutive day complete symptom-free period post maintenance of saturation without oxygen and a negative RT-PCR report were considered for discharge and advised a 7-day home isolation and tele counselled follow up.

Statistical analysis was carried out using SPSS (Statistical Package for Social Sciences) version 20. [IBM SPASS statistics 9IBM corp. Armonk, NY, USA released 2011)]. Continuous variables were expressed as mean and standard deviation and categorical variables were presented as counts and percentages. Patients were categorized based on outcome, group A being the patients that survived and were discharged and group B containing the patients who succumbed to death, different parameters were compared between these groups using Chi-square test for categorical variables and a non-parametric test, Mann-Whitney test was applied to non-normal distributed data. P value of <0.05 was considered statistically significant.

Results

The study was conducted with 157 patients, who were admitted into Victoria Hospital, Bangalore, under the Internal Medicine department and were diagnosed to be COVID-19 positive. The study population was divided into two groups based on outcome, Group A were discharged from the hospital and Group B succumbed to death. A total of 133(84.7%) were discharged from the hospital and twenty-four (15.3%) patients died during hospitalization, with maximum deaths seen among the middle age groups, 46 years to 65 years who contributed 6.4% of the total 15.3% of deaths. When plotted with a Chi-square test, it was seen that there was no statistical association of age with outcome (χ^2 =7.48 and p value =0.27) (Table 1)

65.0% (n=120) of the patients were men and the male to female ratio of 1.85. Sex of the patient also showed no association with the outcome (χ^2 = 0.067 and p value =0.78). (Table 2 and Figure 1)

Out of 157 subjects 19.1% (n=30) of them were asymptomatic, and of which only 1.3% (n=2) of them succumbed to death. (TABLE 3) The rest 127 of them were symptomatic, with fever, cough and breathlessness being the most common symptoms overall as well as in the mortality group. (Table 4)

Out of the 157 subjects, 27.4 % (n=43) of them had no pre-existing comorbidities at admission. In the rest, the most common comorbidity was Type 2 Diabetes Mellitus, which 48.40 % (n=76) patients had. Other common comorbidities were hypertension (38.9%) and ischemic heart disease (8.9%). (TABLE 5) The patients with chronic kidney disease showed the highest mortality rates. (79%) (Figure 2)

Table 1: Distribution of the subjects based on age

Age		Outcome		Total
		Death	Discharge	
26 to 35 yrs.	Count	3	25	28
	%	1.9%	15.9%	17.8%
36 to 45 yrs.	Count	4	36	40
	%	2.5%	22.9%	25.5%
46 to 55 yrs.	Count	5	20	25
	%	3.2%	12.7%	15.9%
56 to 65 yrs.	Count	5	22	27
	%	3.2%	14.0%	17.2%
66 to 75 yrs.	Count	3	11	14
	%	1.9%	7.0%	8.9%
Above 75 yrs.	Count	3	4	7
	%	1.9%	2.5%	4.5%
Less than 25 yrs.	Count	1	15	16
	%	.6%	9.6%	10.2%
Total	Count	24	133	157
	%	15.3%	84.7%	100.0%
Chi-square value- 7.48				
p value- 0.27				

Table 2: Distribution of the subjects based on gender

Gender		Outcome		Total
		Death	Discharge	
Female	Count	9	46	55
	%	5.7%	29.3%	35.0%
Male	Count	15	87	102
	%	9.6%	55.4%	65.0%
Total	Count	24	133	157
	%	15.3%	84.7%	100.0%
Chi-square value- 0.076				
p value- 0.78				

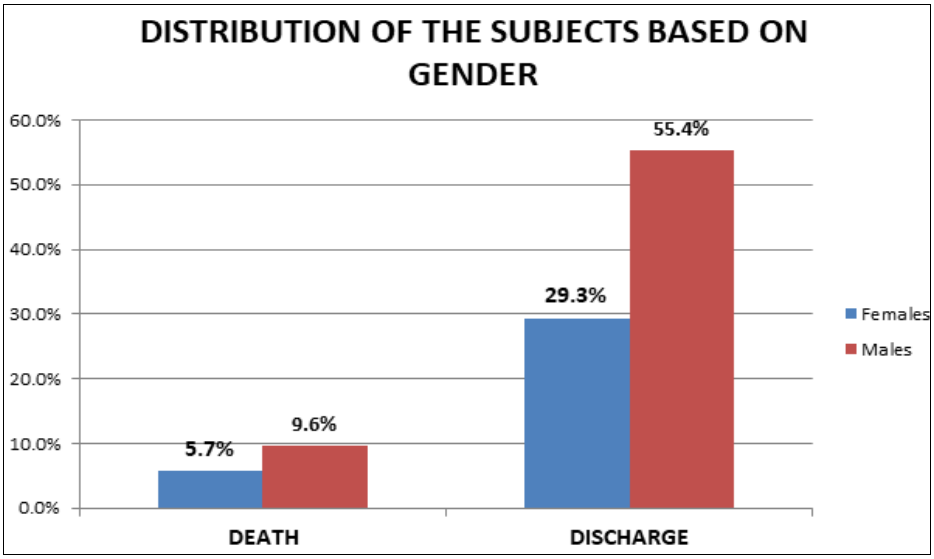

Fig 1: Gender of the patient and clinical outcome

Table 3: Distribution of the subjects based on presence or absence of symptoms

Symptoms		Outcome		Total
		Death	Discharge	
Symptomatic	Count	22	105	127
	%	14.0%	66.9%	80.9%
Asymptomatic	Count	2	28	30
	%	1.3%	17.8%	19.1%
Total	Count	24	133	157
	%	15.3%	84.7%	100.0%
Chi-square value- 2.12				
p value- 0.14				

Table 4: Distribution of the subjects based on presenting complaints

Presenting complaints		Outcome		Total	Chi-square value	p value
		Death	Discharge			
Fever	Count	14	62	76	1.11	0.29
	%	8.9%	39.5%	48.4%		
Cough	Count	10	57	67	0.012	0.91
	%	6.4%	36.3%	42.7%		
Breathlessness	Count	8	29	37	1.5	0.22
	%	5.1%	18.5%	23.6%		
Myalgia	Count	5	18	23	0.86	0.35
	%	3.2%	11.5%	14.6%		
Fatigue	Count	2	21	23	0.9	0.34
	%	1.3%	13.4%	14.6%		
Diarrhea	Count	0	1	1	0.18	0.67
	%	0.0%	0.6%	0.6%		
ANOSMIA	Count	0	16	16	3.21	0.07
	%	0.0%	10.2%	10.2%		

Table 5: Distribution of the subjects based on co-morbidities

CO -MORBIDITIES		OUTCOME		Total	Chi-square value	p value
		Death	Discharge			
Diabetes Mellitus	Count	13	63	76	0.37	0.54
	%	8.30%	40.10%	48.40%		
Hypertension	Count	13	48	61	2.79	0.09
	%	8.30%	30.60%	38.90%		
IHD	Count	2	12	14	0.012	0.91
	%	1.30%	7.60%	8.90%		
CKD	Count	3	9	12	0.94	0.33
	%	1.90%	5.70%	7.60%		
Hypothyroidism	Count	2	11	13	0	0.99
	%	1.3%	7.0%	8.3%		
NIL	Count	6	37	43	0.08	0.77
	%	3.8%	23.6%	27.4%		

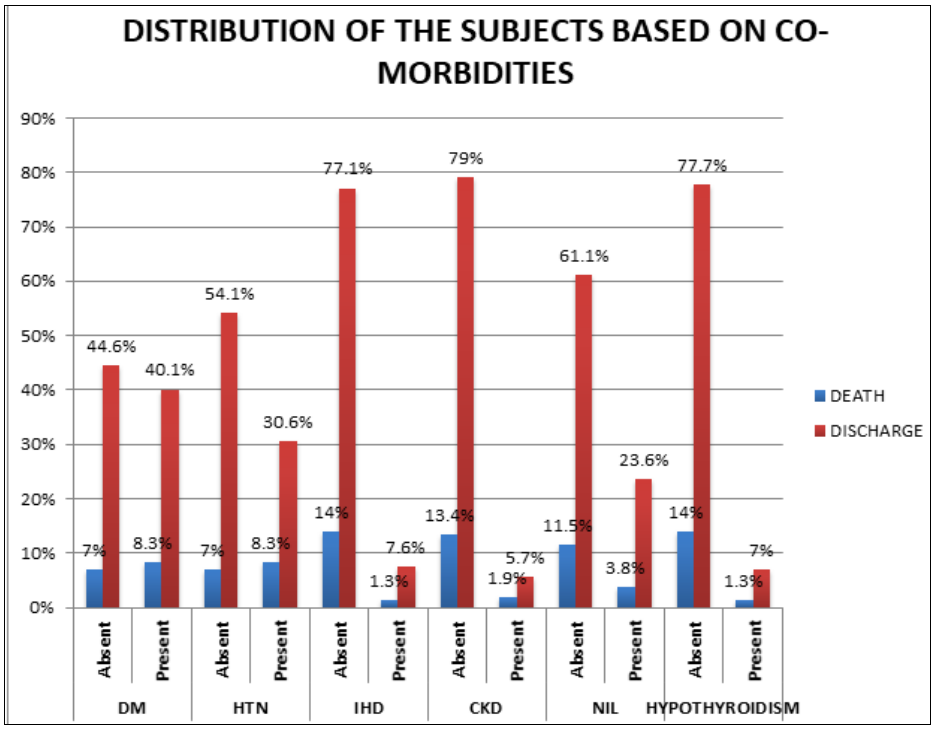

Fig 2: Comorbidities and clinical outcome

The liver function parameters were compared with the clinical outcomes using the Mann-Whitney Test. (Table 6) This rank-based test calculated medians which were used for determining statistical significance based on the p values. The median of Total Bilirubin (TB) was 1.65 in the population that succumbed to death and 0.3 for the group that got discharged, this increase of TB in the group of non-survivors showed statistical significance with $p < 0.05$.

Direct Bilirubin (DB) also showed a significant increase in the patients that did not survive, the median value for whom was 2.4, and 0.2 in the group that survived (p<0.05).
Total protein and albumin, on the other hand showed a decrease in levels in the patients that succumbed, median values of TP in the non survivors and survivors are 6 and 6.8 respectively (p=0.005), median albumin values were 3.1 and 3.8 in the non-survivor vs survivor groups (p=0.001).
Another important finding included the liver enzyme values. The median Alkaline Phosphatase (ALP) values were almost three times in the non-survivor group (237) as compared to the group that got discharged (84) (p<0.05). The amino transferees also were shown to be significantly increased in the patients that did not survive, the aspartate aminotransferase (AST) and alanine aminotransferase (ALT) median levels were 144 and 123.5 in non-survivor group and 27 and 23 in the survivor group. (p<0.05 for both)
The levels of Indirect Bilirubin, Globulin and Albumin/Globulin ratios showed no statistical association with the clinical outcomes.

Table 6: Comparison of the Liver Function Tests Based On Outcome Using Mann-Whitney Test

LFT	Outcome	N	Minimum	Maximum	Median	IQR	p value
TB	Death	24	0	3.4	1.65	0.67	0.00*
	Discharge	133	0	4.7	0.4	0.3	
DB	Death	24	0	3.1	1.2	0.4	0.00*
	Discharge	133	0	3.1	0.2	0.1	
IB	Death	24	0	1.5	0.2	0.2	0.63
	Discharge	133	0	1.6	0.2	0.2	
TP	Death	24	4.8	8.9	6	1.4	0.005*
	Discharge	133	2.3	8.4	6.8	1.1	
ALB	Death	24	1.9	4.1	3.1	0.77	0.001*
	Discharge	133	2.3	5	3.8	0.9	
GLB	Death	24	2.2	5.3	2.95	0.3	0.26
	Discharge	133	1.5	4.8	3	0.4	
A/G RATIO	Death	24	0.7	3.1	1.1	0.3	0.28
	Discharge	133	0.5	2.9	1.2	0.5	
ALP	Death	24	59	512	237	192	0.00*
	Discharge	133	37	281	84	43	
AST	Death	24	27	319	144	117	0.00*
	Discharge	133	6	319	27	19	
ALT	Death	24	19	298	123.5	89	0.00*
	Discharge	133	5	206	23	26	

*Significant

Discussion

Our study showed that ALP, AST, ALT, TB and DB levels were significantly higher in the group that succumbed to death than the group that was discharged. This is in par with studies such as the one by Yan Deng, on clinical characteristics of fatal and recovered cases of coronavirus disease 2019 in Wuhan, China which also showed similar findings in non-survivor to survivor groups, ALT (22.00 [15.00, 34.00] *vs.* 18.70 [13.00, 30.38], *P*=0.010), AST (34.00 [27.00, 47.00] *vs.* 22.00 [17.65, 31.75] *P*<0.001), [8]
Similarly, a study done by Cai Q *et al*., showed that 41% of patients had abnormal liver tests and 5% had a liver injury. During the entire period of hospitalization, 76.3% of patients developed abnormal liver tests, and 21.5% developed a liver injury. Ten patients suffered from multiorgan failure, and three patients died. About 90% patients with abnormal liver test results were mild at admission (*I.e.*, with <2× ULN), and more than 10% of them had increased levels of ALT and GGT (more than 3× ULN) during hospitalization. The increases in AST and TBIL to more than 3× ULN were moderate (about 6% and 3%, respectively), and no increase in ALP was found in this study as compared to ours.[6] Another multicenter analysis of clinical characteristics and outcomes in patients with COVID-19 done by Xiaolong Qi, showed elevated ALT (n = 15 [21.43%], 42.00–72.70 U/L), AST (n = 5 [7.14%]; 42.90–61.00 U/L), and total bilirubin (n = 25 [35.71%], 18.00–148.00 μmol/L) increasing the severity and affecting the outcome of the disease. [9]
Number of studies have suggested that COVID-19 associated acute liver injury is common and mild. And only a few develop a serious liver injury. [10] All of the studies showed that there could be a baseline increase in LFT parameters and with a significant increase in the enzymes there was an association with severity of the disease and ICU admissions. [11,12,13] None of the studies reviewed the LFT parameters with the outcome and have not defined any statistical significance of reviewing outcome with individual parameter as such which our study has aimed to show.
Our study has also showed a decrease in total protein and albumin in patients that succumbed to death. This is consistent with other studies like the one by Wei Huang, which sowed that marked hypoalbuminemia occurred in 38.2%, 71.2%, and 82.4% patients in non-critically ill, critically ill, and death groups, respectively. [14]
There are multiple theories that have been proposed to explain the mechanism of liver injury and deranged LFTs in COVID-19. The SARS-CoV-2 virus has been shown to use the angiotensin-2 converting enzyme (ACE2) as a means for cell entry. In healthy liver tissue, ACE2 is expressed mainly on cholangiocytes [15]. This form of direct viral entry could possibly lead to the liver enzyme derangement seen in COVID-19 patients. In addition, immune-mediated inflammation, such as a cytokine storm, might be a critical factor associated with disease severity and mortality. [16] Immune dysfunction, including lymphopenia or immune system overreaction, which accompanies disease

progression, can also independently lead to liver derangement.

Pneumonia-associated hypoxia and hypotension might also contribute to liver injury [17] or even develop into liver failure in patients with COVID-19 who are critically ill.

Lastly, many of these patients are critically ill and in ICU and maybe on a variety of medications or even parenteral nutrition.

Our study is one of the few studies to plot clinical outcomes with the LFT parameters and statically show their association. More studies are required to completely elucidate the relationship between liver disease and COVID-19 regarding clinical outcomes, as abnormal LFTs serves to be a common transient finding, and due to multifactorial theories explaining the reason for it in patients infected with SARS-CoV-2. Our study is important as it shows the statistical association of clinical outcomes with a common baseline investigation, which could further prove to be a powerful triaging tool, if guidelines for each parameter are laid down with more evidence of further studies.

Conclusion

Our study showed an association with increased liver enzyme levels, TB and DB and decreased total protein and albumin levels with adverse clinical outcomes. This important association would further require additional studies to bring in new criteria and guidelines that would substantiate the finding, this is important as this could serve as a cost-effective triaging tool to assess patients according to need, foreseeing the prognosis.

Declarations

Ethical Approval-
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None.

Conflict of interest-
None.

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