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Comparative Evaluation of Liver Function with Different Grades of Lung Involvement in COVID 19 Patients

Running title : Liver function with lung involvement in covid19

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Abstract:

Background: The coronavirus disease 2019 (COVID-19) outbreak is the global pandemic causes severe acute respiratory syndrome, affects the liver in the earlier stages[5] . In our biochemistry laboratory we observed most of the covid-19 patients have deranged liver function tests commonly mixed type. Thus the main aim of our study was to analyse the association of LFT with lung involvement in symptomatic covid-19 patients with or without comorbidities.

Method: This study is a retrospective cross sectional study, where we collected 1000 biochemical data of RT-PCR confirmed COVID-19 cases with positive CT-chest reports at the time of admission, before starting the treatment and analyzed the biochemistry data in 2 different forms. One is comparing the data of covid-19 positive cases with comorbidity to no comorbidity. Another form, the cases were classified into 4 grades based on the CT-chest, and analyzed the relationship between CT-Chest and liver function parameters.

Results: The data of 1000 cases were compared statistically. It showed a significant number of patients with COVID-19, had abnormal liver function at the earlier state on infection. 90% of the cases have at least one abnormal liver function tests.Patients

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having >50% lung involvement have increased enzyme levels and decreased total protein and albumin levels, when compared with those having <50% lung involvement

Conclusion: In COVID-19 patients, apart from the lung involvement, extra pulmonary manifestations are also common. Liver is the most commonly affected along with lung at earlier stages.

Keywords: COVID-19, Liver Function Tests, At Admission, Comorbidity, and CT-Chest Grades

Introduction

At first an undefined pneumonia was found in Wuhan, Hubei Province, China from December 2019, was caused by a new previously unknown virus and later named as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), and the disease named as Coronavirus Disease 2019 (COVID-19). World Health Organization (WHO) declared COVID-19 disease as a pandemic on March 12th, 2020.[1]

Coronaviruses are 65–125 nm in diameter with single stranded RNA. The family has 4 subgroups; alpha (α), beta (β), gamma (γ) and delta (δ) coronavirus. These viruses cause Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS) culminating in pulmonary failure with high mortality. Although originated in animals, it has transmitted to humans and swiftly spreads globally. This speedy transmission may be due to genetic recombination with boosted transmission capability of virus[2]. In the current pandemic situation, it is obvious that the covid-19 disease can involve multiple organs apart from severe ARDS[3]. Apart from ARDS, the liver is commonly involved and depending upon the disease severity, the patients may present with range of liver involvement from simple elevations of liver enzymes to fulminant hepatitis.

The study of Ezequiel Ridruejo and Cai Q have reported that, the liver injury is mostly mild and transient at admission but had higher risk of developing severe disease during hospitalization in a recent study [4,5]. In their study Qingxian Cai et al have observed a high prevalence of liver test abnormalities and liver injury in COVID-19 admitted in their referral centre and the prevalence considerably increased during hospital stay and this prevalence of abnormal liver tests and liver injury were associated with the progression to severe pneumonia[6] . Salvatore Piano et al., stated in their study, LFTs abnormality is common at the time of admission COVID-19 patients, is related to systemic inflammation, organ dysfunction and is an independent predictor of transfer to ICU or death [7]. With these studies, we believed that abnormal liver parameters can act as a prognostic factor for COVID-19 and planned to study the characteristics of liver parameters in different ways.

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Methodology

This cross-sectional retrospective study was conducted in Institute of Biochemistry, Rajiv Gandhi Government General Hospital, Chennai, Tamilnadu, after obtaining ethical clearance. The laboratory and radiological data of 1000 RT-PCR confirmed covid positive patients on admission were collected. The duration of the study period was from July 10 to August 10, 2020. Laboratory tests included Total Bilirubin, Direct Bilirubin, Total Protein, Albumin, Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST) And Alkaline Phosphatase (ALP).All the biochemical test parameters were analysed in Cobas 6000 fully automated analyser.

The inclusion criteria includes patients confirmed with a SARS-CoV-2 infection by real-time reverse transcription polymerase chain reaction (rRT-PCR), presence of lung involvement confirmed by CT-CHEST findings. All age groups and both the genders were included .The exclusion criteria were rRT-PCR confirmed Covid-19 Patients, without lung involvement, Pregnant and lactating mothers, Patients already under treatment for SARS COV-2 were excluded

There were two groups in the study, the groups were classified based on the presence of comorbid conditions like Type 2 diabetes mellitus(T2DM), Hypertension(HT) ,Coronary artery disease, Chronic obstructive pulmonary disease(COPD), Cerebro vascular accident(CVA)

Group 1: No comorbidity (n=500)
Group 2: Presence of comorbidity (n=500)

The 4 grades were based on CT chest findings as followed in our hospital

Grade 1: < 25 % lung involvement
Grade 2: 26-50% lung involvement
Grade 3: 51-75% lung involvement
Grade 4: >76 % lung involvement.

Results

Data were collected from 1000 rRT-PCR confirmed COVID-19 cases, with CT chest findings. In these 1000 patients, the mean age was 54±20.Five patients were under the age of 20 while one patient was more than 90years, with the peak of 51-60 years.

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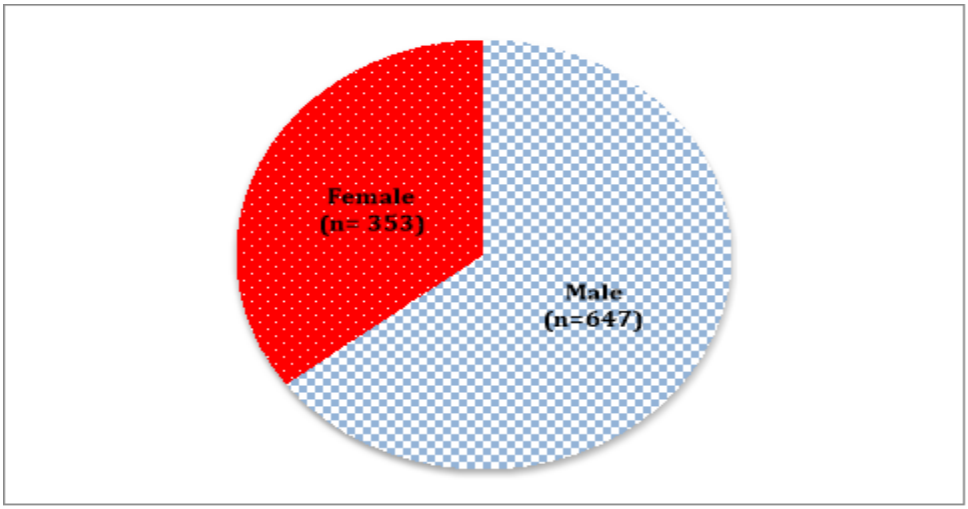

Fig:1 Sex wise distribution of study population

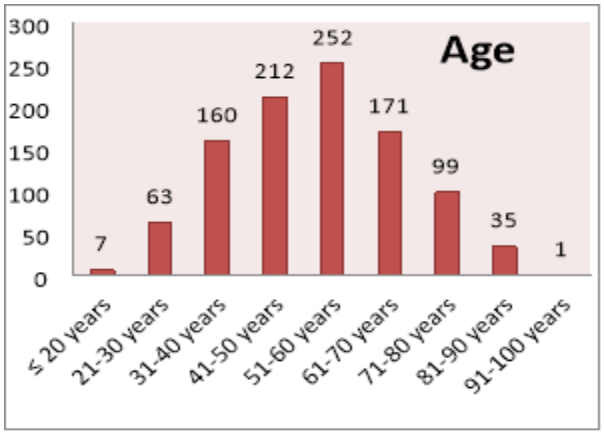

Fig 2: Age wise distribution of study population

Variables	N=1000
Males	647
Females	353
Diabetes	317
Hypertension	219
cardiac cases	73
Renal disorders	38
Respiratory disorders	32
Hypothyroidism	26
various malignancies	17
CNS disorders	16
Others	6

Table 1: Demography of total population

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The frequency of comorbidity in our study group was Diabetes (n=317) and followed by Hypertension (n=219), Cardiac (n=73), Renal (n=38) and Respiratory disorders (n=32), Hypothyroidism (n=26), Various malignancies (n=17), CNS disorders (n=16), and others (n=6). Other disorders includes dilated cardiomyopathy (n=1), myasthenia gravis (n=2), multiple myeloma (n=1), Obesity (n=1) and Osteoarthritis (n=1).Patients without any comorbidity (n=500), one comorbidity (n=265) and affected by more than one comorbidity (n=235).

3.2. Comparison between Patients without Comorbidities versus with Comorbidities:

Among the 1000 patients, 900 patients presented with abnormality in LFT at the time of admission. Among these patients 458 did not have any comorbidity, while 442 has one or more associated comorbidity. The LFT tests were observed, where decrease in total protein and albumin, increase in AST&ALT, while the total bilirubin was normal in 95% of the patients.

	No Comorbidity (500)	No Comorbidity (500) in**%**	Comorbidity (500)	Comorbidity (500) in **%**
ABNORMAL LFT	458	91.6	442	88.4
T.PRO	169	33.8	184	36.8
ALB	158	31.6	200	40
AST	233	46.6	217	43.4
ALT	237	47.4	215	43
ALP	133	26.6	149	29.8
T.BILI	33	6.6	38	7.6
D.BILI	192	38.4	191	38.2

Table 2: Distribution of liver function abnormalities in patients without and with comorbidities

The comparison of each parameter between no comorbid and comorbid group shows there is increased number of cases has abnormal Total Protein, Albumin, Total Bilirubin, Direct Bilirubin and ALP in comorbid groups. But for ALT and AST the number of cases increased in no comorbid groups.

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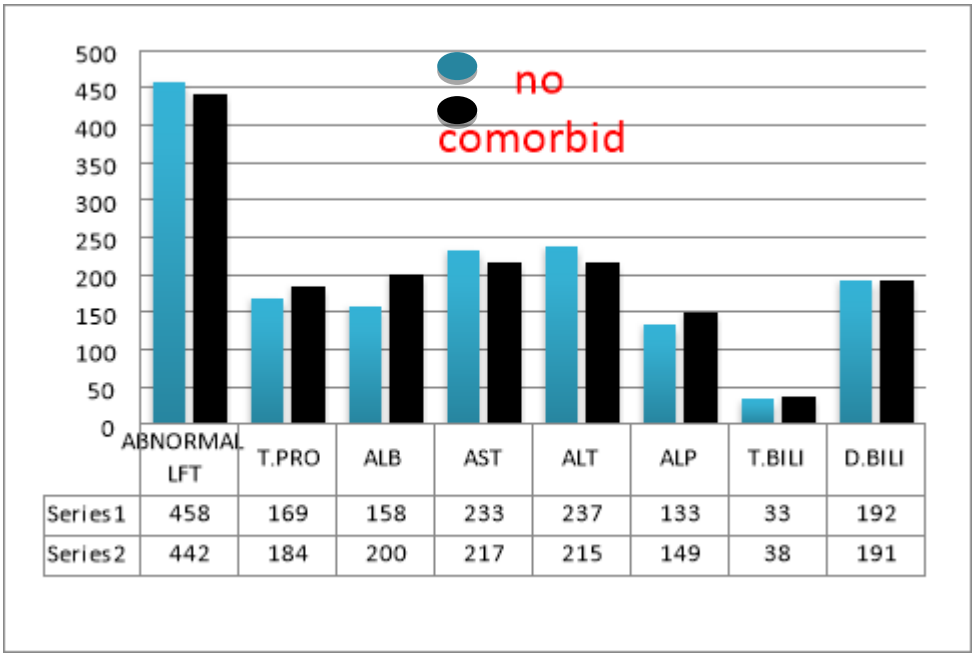

Fig 3 Distribution of liver function abnormalities in patients without and with comorbidities

Liver Function Test Distribution in Patients with no Comorbidities versus with Comorbidities	Presence of Comorbidities		Absence of Comorbidities		P value unpaired t Test
	Mean	SD	Mean	SD	
T.Protein (g/dl)	6.10	0.59	5.98	0.68	0.0035
S. Albumin (g/dl)	3.17	0.50	3.0	0.32	0.0027
T.Bilirubin (mg/dl)	1.16	0.70	1.63	1.61	0.124
D.Bilirubin (mg/dl)	0.41	0.23	0.46	0.34	0.0925
SGOT (IU/L)	62.18	0.23	63.23	37.11	0.666
SGPT (IU/L)	64.00	23.91	66.29	63.26	0.604
ALP (IU/L)	128.79	47.55	128.8	35.33	0.99

Table 3: Comparison of abnormal liver function parameters presence and absence of comorbidities

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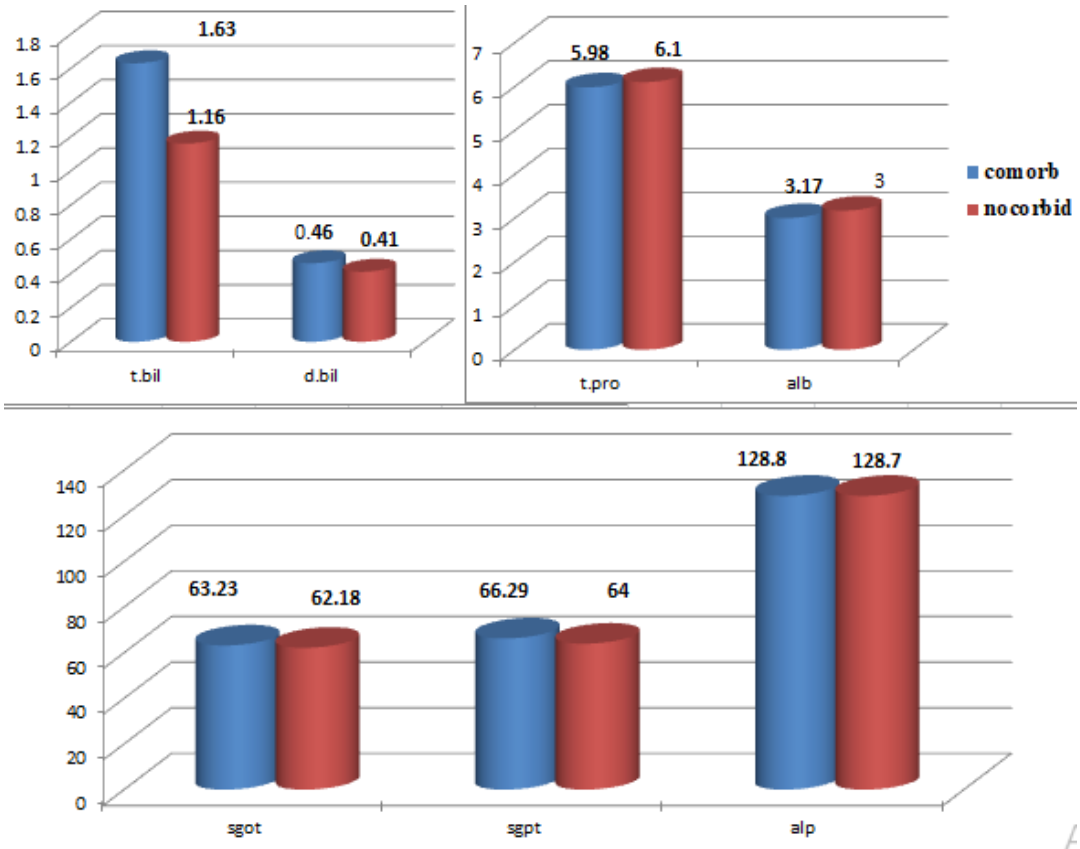

Fig 4: Comparison of abnormal liver function parameters without and with comorbidities

These seven analytes -Total Bilirubin, Direct Bilirubin, Total Protein, Albumin, Alanine Amino transferase (ALT), Aspartate Amino transferase (AST) And Alkaline Phosphatase (ALP) were compared between 2 groups. AST, ALT mean values were elevated irrespective of the presence or absence comorbidities, while all other parameters are within normal range. However the Total Protein and Albumin showed significant decrease (p=<0.001) among the patients with comorbid.

3.3 Liver Function Test Distribution in patients with different Grading of lung involvement

The 1000 cases are classified into no comorbid and comorbid group. The no comorbid and comorbid group is divided into 4 grades based on CT-Chest grading.

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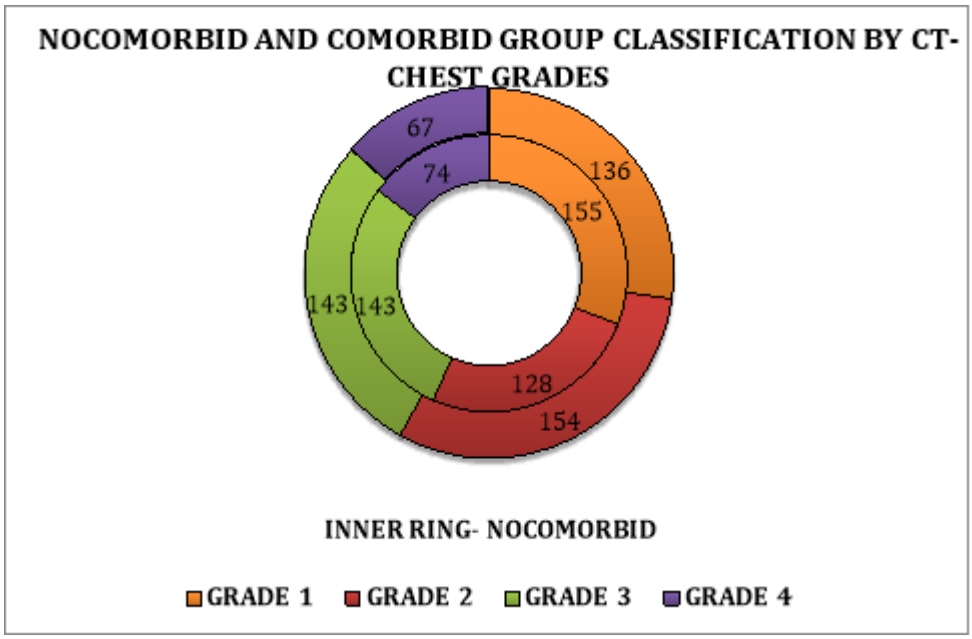

Fig 5: Distribution of nocomorbid and comorbid cases based on CT-LUNG involvement.

For a statistical view the 4 grades of lung involvement are broadly divided into 2 groups (A&B)

Group A: <50% lung involvement (grade 1& 2)

Group B: >50% lung involvement (grade 3& 4)

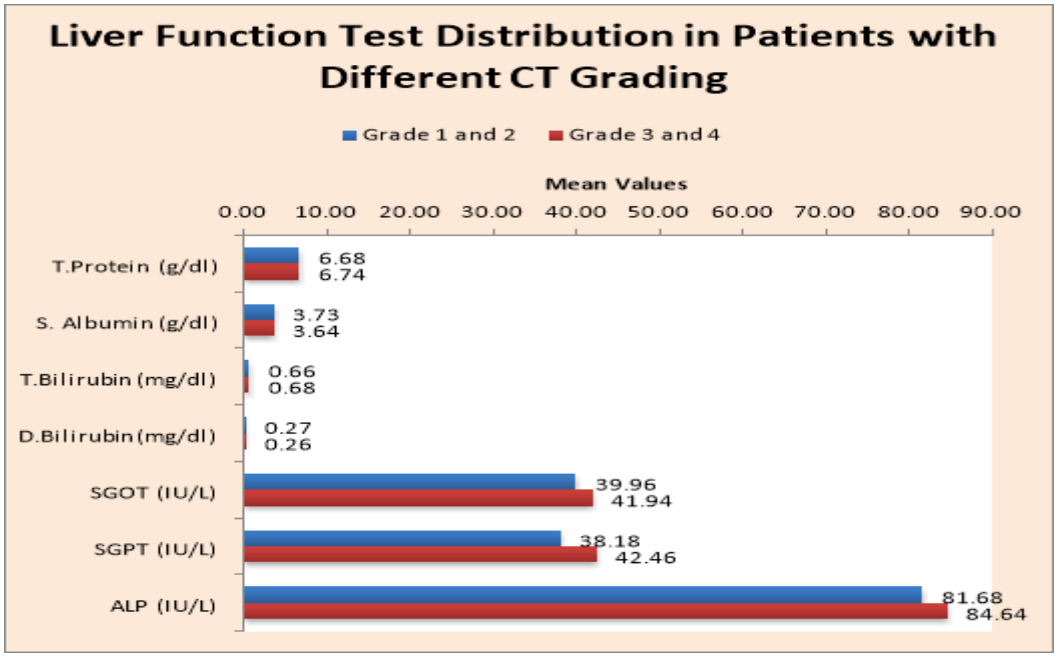

Fig 6: The comparison of liver function tests in group A(grade1&2) and group B(grade3&4)

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 3040 - 3055
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Variable	Groups	Normal LFT	Abnormal LFT	P value Chi Squared Test
T.Protein	Grade 1 and 2	391	181	0.005
	Grade 3 and 4	256	172	
S. Albumin	Grade 1 and 2	397	175	0.001
	Grade 3 and 4	248	180	
T.Bilirubin	Grade 1 and 2	529	43	0.297
	Grade 3 and 4	403	25	
D.Bilirubin	Grade 1 and 2	375	197	0.005
	Grade 3 and 4	243	185	
SGOT	Grade 1 and 2	333	239	0.008
	Grade 3 and 4	213	215	
SGPT	Grade 1 and 2	329	243	0.004
	Grade 3 and 4	207	221	
ALP	Grade 1 and 2	398	174	0.824
	Grade 3 and 4	295	133	

Table 4: the comparison of liver function tests in group A (grade1&2) and group B (grade3&4)

In this chi-square analysis as shown in table 4 there is a strong association between liver function abnormalities & lung injury irrespective of presence of comorbidity. There is increase in AST, ALT, D. Bilirubin and fall in T.protein, albumin with increasing grades of lung involvement i.e: patients having >50% lung involvement (Gr3 &4) having significant liver function abnormalities when compared with those having <50% lung involvement (Gr1&2).

Discussion:

Although the lung is the major organ involved in covid-19 infection involvement of the liver is closely associated with the course of the disease right from the initial stages. Altered liver function was observed in majority of the patients at the time of admission, before starting of treatment [8] .

In the study by Muhammad Sohaib Asghar deranged liver function enzymes levels are the prominent extra-pulmonary clinical manifestation detected in coronavirus disease 19 (SARS Covid-19), approximately reported in at least one-half of the patients [9] ., Anna Bertolini et al reported 46% of study population patients had elevated liver function analytes [10] . In our study we have observed 90% of our patients presented with abnormality in liver function at the time of admission.

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Liver involvement seems to be as equally important as lung involvement in covid-19 infection. The reason for liver dysfunction is the SARS-CoV-2 virus directly binds to ACE2 receptor on cholangiocytes leads to cytopathic effect.

THE PATHOPHYSIOLOGICAL BASIS OF LIVER INJURY:

The liver is the second-largest organ in our body and its weighs around 1.5 to 2.5% of the body weight. It performs various functions like metabolic, secretory and excretory functions[11].It is the principal organ for detoxification and metabolism, and also has a central role in host defence against microbes. Certain viruses like corona virus exhibit a direct cytopathic effect on hepatocytes and cholangiocytes although, in most cases, the pathogenesis seems multifactorial. In Yang et al. study, it was reported that SARS-CoV-2 could cause direct liver cell injury from low oxygen supplies or cytokines as seen in sepsis, affecting the hepatocytes including the subset of hepatocytes called Cholangiocytes which is the lining epithelial cells in bile ducts.

Cholangiocytes are 3% to 5% of the endogenous liver cell population and they form a network of interconnecting ducts from the duct of Hering to the extra hepatic bile ducts, and then lining the intrahepatic and extra hepatic bile duct system. The functions of Cholangiocytes are to determine the final bile composition and secretion of 40% of basal bile flow is produced by the ductal epithelium and this is maintained by cholangiocytes, followed by regulated passage of water through the intercellular tight junctions [12]. These cholangiocytes are morphologically and functionally heterogeneous. The Small cholangiocytes has proliferative abilities and show functional plasticity in disease, while large cholangiocytes has role in hormone regulated bile secretion[13]. Qingxian Cai denoted in his study that, the SARS-CoV-2 virus may bind to angiotensin-converting enzyme 2 (ACE2) on cholangiocytes, leading to cholangiocyte dysfunction and inducing a systemic inflammatory response leading to liver injury [14] .

The angiotensin-converting enzyme 2 (ACE2) receptors expressed in both liver cells and cholangiocytes and these act as host receptors for entry of SARS-CoV-2 group. There are several binding motifs between the SARS-CoV spike protein receptor-binding domain and human ACE2 on cholangiocytes. Constant exposure to virus followed by inflammatory response, direct cytotoxicity due to active viral replication in hepatic cells are more related to liver injury in COVID-19 patients [15] ,this leads to mild symptoms, should be detected early, and the liver function tests play an important role here.

The meta-analysis done by Mohammad Zahedi et al concluded that abnormality in liver functions was higher in patients with severe COVID-19 infection and assumed that abnormal liver markers could act as a prognostic factor for a better

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survey of COVID-19. So detecting and diagnosing liver dysfunction as well as and assessing severity and prognosis, the liver function tests will be very useful[16].

Liver function tests: The useful tests include measurement of Total Bilirubin, Direct Bilirubin, Total Protein, Albumin, Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST) And Alkaline Phosphatase (ALP).

The distribution of liver function abnormalities presented in fig.7. Least affected parameter is total bilirubin (7.1%), while AST and ALT has high percentage of abnormality (44.9% & 45.5%).

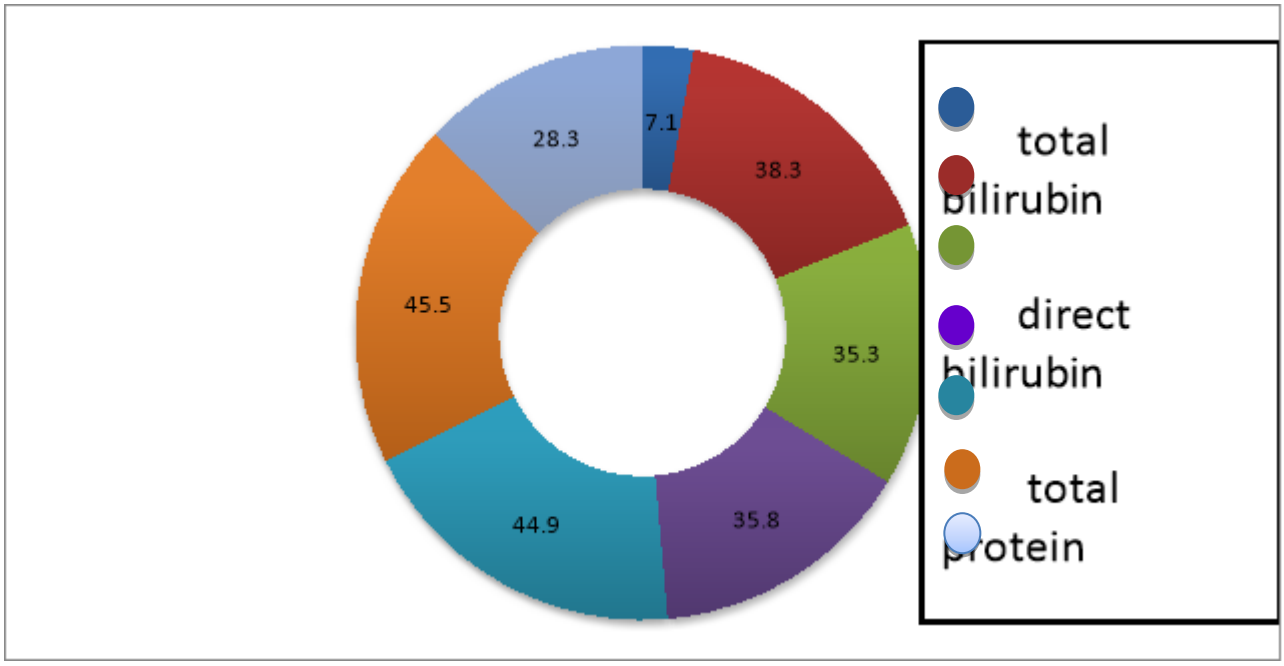

Fig 7: percentage of abnormal liver function parameters

Synthetic functions of liver: Most plasma proteins except immunoglobulins are synthesised is Liver. Synthesis occurs in rough endoplasmic reticulum of hepatocytes and release into the hepatic sinusoids. Albumin is solely synthesised by liver and it implies the extent of working liver cell mass. In our study, 353 patients have decreased total protein (<6.5 gm/dL), 355 patients have decreased in albumin level (<3.5 gm/dL) while 235 (23.5%) patients have low in both total protein and albumin. Seventy percentage (70%) of our study population has present with LFT abnormality mainly involve in the synthetic function of liver. The study by Saleh A Alqahtani and J€orn M Schattenberg showed abnormal levels of albumin (98%) was reported in SARS-CoV-2 infection [17].

Excretory function of liver involves detoxification and disposal of exogenous and endogenous substances. Bilirubin is the excretory product formed by the catabolism of heme. It gets conjugated in the liver to bilirubin diglucuronide and excreted through bile. In our study shows minimal number of patients (n=71) had elevated total bilirubin (> 1.3 mg/dL) while the direct bilirubin was elevated in 383 patients (>0.3 mg/dL), and 43 patients had elevated levels in total and direct bilirubin levels. This is only 4.3% of total study population but 38.3% of 1000 patients have only high direct

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bilirubin levels. The elevated direct bilirubin signifies the impaired excretory function of hepatocytes.

The studies by Lihui Qin et al and Domenico Alvaro have reported that the cholangiocytes regulate the 40% of basal bile flow and bile composition which is produced by ductal epithelium[6] . Another study suggested that unconjugated bilirubin enters the liver via the blood stream and is rapidly absorbed by hepatocytes after dissociating from albumin, followed by a sequential biochemical reaction unconjugated bilirubin is converted to conjugated bilirubin and is excreted into the bile ducts. Hence elevated CB level can be an important marker of liver injury[16] . Chai et al., demonstrated that the expression of ACE2 receptors in bile duct epithelial cells was relatively high and even equivalent to that in alveolar type II cells[17]. Based on above mentioned studies, we report that these mechanisms may be the reason for elevated direct bilirubin in 38.2% of study population.

Liver enzymes: When both aminotransferases are elevated, then consider it is most likely to be related to hepatocellular injury. In Ezequiel Ridruejo study, mentioned that Liver dysfunction may be common in patients with COVID-19 and elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were reported in 16–53% of patients[4] . In Qingxian Cai, Deliang Huang and et al study, they commented 90% patients (both comorbid and no comorbid) shows abnormal liver function test on admission[6] .

In our study, about 45% of the cases had elevated AST and ALT while 28% had elevation of ALP. The increase in AST (73 cases more than 2x UNL and 38 cases more than 3xULN), ALT (135 cases more than 2xULN and 52 cases more than 3xULN) and ALP (12 cases more than 2xULN) in total population. Nearly 45% of the patients show increase in AST and ALT and 28.3% of patients shows increase in ALP values.

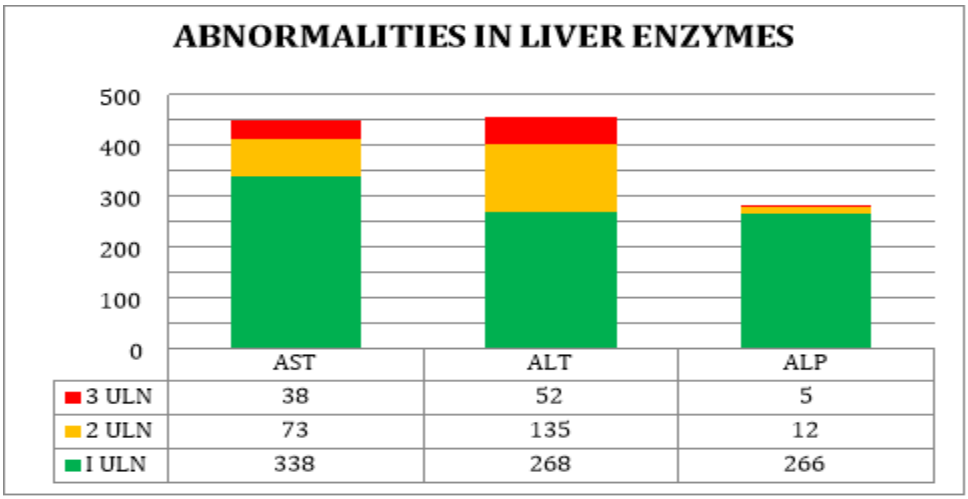

Fig 8: Abnormality in liver enzymes

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As per Li J, Fan JG study, deviations of liver function enzymes are characterised into three classes: hepatic, cholestatic and mixed. That is deranged levels of AST and ALT greater than 3 times the upper ranges are grouped as hepatic, raised levels of ALP twice the upper ranges are categorized as cholestatic, while high levels of a combination of both ALT/AST thrice the upper ranges were categorized as mixed type[18] . Panagiotis Paliogiannis et al observed that the main alterations in liver functions of COVID19 patients included increase in ALT, AST, bilirubin and decrease total protein and albumin concentrations[19]. This shows that our study population has mostly mixed type of liver injury commonly involved hepatic and cholestatic types.

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Comparison of LFT with CT-Chest grades:

Based on CT-chest findings the 4 grades of lung involvement were grouped group A (< 50% lung involvement i.e grade 1&2) and group B (50>% lung involvement i.e grade 3&4). As shown in table 4, the total protein (p=0.005) and albumin (p=0.001) significantly decreased with increasing lung involvement. The direct bilirubin (p= 0.005) and enzymes AST&ALT (p= 0.008 & 0.005) are significantly increased with increasing lung involvement. Accordingly patients in group B case have significant live injury when compared with group A. It shows the hepatic synthetic and excretory functions are affected and the severity correlates with the lung involvement.

Conclusion:

From our study, we understand that 90% of cases have at least one liver parameter involved and it clearly explains that the liver injury is as common as lung injury in covid-19 disease. From our study we observe that the mixed type liver injury is predominant at admission and can progress to severe disease in susceptible patients. Hence with prior liver dysfunction like fatty liver, chronic hepatitis and cirrhosis is highly susceptible to accelerated liver injury. And also it alarms us to observe the medications related to hepatocellular toxicity warranting continuous monitoring of such patients during hospitalization .There is very strong association between LFT abnormalities and lung damage irrespective of presence of comorbidity. This could be useful in the management of covid-19 patients when CT- chest in not available.

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