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Variations in Liver Function Tests among Covid 19 Positive Children Under 12 Years of Age

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Abstract
Background*: Abnormal hepatic profile is prominent among Covid 19 positive adults however limited knowledge is available among children.****Objective*** *:- To study the hepatic profile among hospitalized Pediatric Covid 19 Positive patients.* ***Methods*** *:- A retrospective analysis of 90 Covid 19 positive patients under 12 years of age admitted to a dedicated Covid 19 tertiary care center from April 2020 to March 2021 was done. Liver Function Tests were compared with demographic , laboratory parameters and inflammatory markers.Outcome was measured as recovered , death and prolonged hospital stay.****Results*** *:- Abnormal LFTS with and without liver injury were seen in 12% (n=11) and 60% (n=54) cases respectively. Elevated SGPT (n=19,21%), hypoproteinemia (n=15,17%) and hypoalbuminemia (n=8,9%) was associated with poor outcome.Deranged LFTS was higher in infants (n=19, 79%) and malnourished children (n=2, 50%). Children with comorbidities significantly had abnormal LFTS (n=7,58%) and liver injury (n=4,34%). Anemia was a predominant risk factor for abnormal LFTS (n=15,43%) and liver injury (n=7,20%). Children with deranged LFTS (n=4,57%) and liver injury (n=3,43%) had prolonged hospital stay. All 54 cases (100%) of abnormal LFTS recovered. Four among the 11 cases of liver injury (36.36%) died.* ***Conclusion****: Abnormal LFTS were predominantly seen among Covid 19 positive infants. Malnutrition and Anemia were significant risk factors for abnormal LFTs. Prolonged hospital stay and higher mortality were seen in cases with liver injury.*

Keywords: *Covid 19 , Paediatric , Liver function tests*

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I. Introduction

Novel Coronavirus (SARS- CoV2) responsible for the outbreak of pneumonia in the Wuhan city of Hubei province in the month of December 2019 , are enveloped positive stranded RNA viruses. SARS-CoV2 is a beta virus which acts via the angiotensin converting enzyme 2 (ACE 2) receptor to gain entry into the target cell(1,2). As of June 2021 , there are a total of 179,587,566 cases across the globe spread over 220 countries with 164,282,670 recovered cases (98%) and 3,889,824 expired cases (2%). Among them , 11,415,072 cases are actively infected of which 99.3% have mild disease while the rest 0.7% are critical and require ICU management (3) . Pediatric cases accounted for only 2.7 to 7.8% of all the confirmed Covid 19 cases (4). SARS-Cov2 virus was known to cause predominantly respiratory symptoms such as fever, cough, cold and breathlessness, however apart from pulmonary damage , it also affects gastrointestinal, cardiac and nervous system resulting in multiorgan damage and death (5). Nausea, vomiting, diarrhoea, anorexia, loss of taste and smell are newer extrapulmonary symptoms of Covid 19 and is due to the presence of ACE 2 receptors of SARS-Cov2 virus in the gastrointestinal tract , liver and pancreas (6). Liver dysfunction on admission among Covid positive patients was reported to be 24.1% among adults and 17.8% in the pediatric age group (7). Though the exact nature of liver injury in Covid 19 disease is uncertain , various mechanisms have been postulated such as direct hepatocyte or biliary epithelium injury , drug induced hepatotoxicity , liver injury secondary to exaggerated immune response and cytokine storm and aggravation of preexisting liver injury secondary to Covid 19 disease (6).Several hospital based studies reported liver injury in terms of elevated liver enzymes , total bilirubin and hypoalbuminemia (8,9).However these studies reflect the variation in liver function tests among adults rather than pediatric patients. Limited data is available regarding the extent of liver damage and its outcome in Covid 19 positive children. This study aims to describe the derangement in liver function tests among hospitalized pediatric Covid 19 positive patients.

II. Methodology

This is a hospital based retrospective study conducted from April 2020 to March 2021 in a dedicated Covid 19 tertiary care center admitting both adult and pediatric patients tested positive for Covid 19 disease. Children in the age group of 1 month to 12 years who had symptoms or signs of Covid 19 disease or those who were tested positive through routine contact surveillance were included in this study. Exclusion criteria included Neonates , hospital stay of less than 5 days and children with pre existing chronic liver disease. Children diagnosed positive by either Real Time Polymerase Chain Reaction (RT-PCR) or Rapid Covid Antigen test were isolated. Complete Blood count , Renal function tests , Liver function tests , Coagulation profile , Acute Inflammatory markers like C reactive protein (CRP) , Procalcitonin, IL6 and ferritin , markers of myocardial injury like CK MB and LDH , markers of pancreatic injury like amylase were sent. ECG and Chest X ray was done for all patients. Reports were analysed and compared to the clinical condition of the patient. Abnormal liver function tests were defined as serum total bilirubin more than 1 mg/dl , serum direct bilirubin more than 0.4mg/dl , total protein less than 6.1 gm/dl , serum albumin less than 3.4gm/dl, alanine aminotransferase more than 45 IU/L , aspartate aminotransferase more than 40 IU/L and Alkaline phosphatase more than 420 IU/L (15). Liver injury was defined as elevation in aspartate or alanine transaminase 5 times above the upper limit of normal value or elevation in alkaline phosphatase three times above upper limit of normal value or direct bilirubin more than 1mg/dl or prolonged prothrombin time more than 15 seconds or INR >1.5 in the presence of bleeding manifestation or hepatic encephalopathy or prothrombin time more than 20 seconds or INR > 2 without bleeding manifestations or hepatic encephalopathy (15).Abnormal liver tests were also compared with Anemia and inflammatory markers CRP and ferritin. Anemia was defined as hemoglobin less than 11gm/dl (15). A positive CRP or raised ferritin more than 95 ng/ml was considered as a raised inflammatory marker (15).The children were isolated for a period of 10 days during which they received treatment and outcome was measured as recovered , prolonged stay or death.Data was tabulated in Microsoft Excel sheet 2013 and categorical data was represented as frequency and percentage while continuous data was represented as frequency , percentage , mean , median and standard deviation. Statistical analysis was done using Fisher's exact test and p value < 0.05 was considered significant. Clearance from the Institutional Ethics committee was obtained.

III. Results

Of the 120 Covid 19 positive patients admitted , 30 cases were excluded according to the exclusion criteria. Among the 90 cases enrolled in the study , the majority belonged to the age group of 5-12 years (n=43,47%) with a mean age of presentation being 4.7 years (TABLE 1) . Fever was the predominant symptom (n=48,53%). Loose stools and vomiting were seen in 7 (8%) and 9 (10%) cases respectively. Majority belonged to MKS class III (n=30,33%) and MKS class IV (n=39,44%). Four (5%) and 3 cases (3%) out of 90 had moderate and severe malnutrition respectively and was found to be significantly associated with poor outcome (TABLE 2).

In this study ,25 cases (28%) had normal liver function tests on admission, 54 cases (60%) had abnormal liver function tests without liver injury and 11 cases (12%) had liver injury (TABLE 3). Alanine transaminase was elevated in 19 cases (21%) and was significantly associated with poor outcome (TABLE 4). Hypoproteinemia and hypoalbuminemia was seen in 15 cases (17%) and 8 cases (9%) respectively and had a significant association with poor outcome. Though aspartate transaminase was elevated in 40 (44%) cases , it was not associated with a poor outcome.

While majority of the cases belonged to 5-12 years of age , abnormal liver function tests and liver injury was significantly higher among infants (n=19,79% ; n=3,13%) and children between 1 to 3 years of age (n=9,56% ; n=4,25%) (TABLE 5). Children with malnutrition had a significantly higher risk of deranged LFTS on admission; i.e, 50% (n=2) of children with moderate malnutrition had liver injury while all 3 cases (100%) of severe malnutrition had abnormal LFTS. Also abnormal LFTS (n=7,58%) and liver injury (n=4,34%) was higher among children with comorbidities. Children with anemia had significantly higher risk of abnormal LFTS (n=15,43%) and liver injury (n=7,20%). Of the 11 cases with a positive C reactive protein , 4 cases (36%) had deranged LFTs and liver injury however there was no significant association. Though more cases of abnormal LFTS (n=13,61%) and liver injury (n=5,24%) were seen with elevated ferritin , it was not found to be of any significance. Children with deranged LFTS (n=4, 57%) and liver injury (n=3,43%) had a prolonged stay of more than 10 days.Among the 54 cases with abnormal liver function tests , all of them recovered (n=54, 100%) while all 4 children who died had liver injury.

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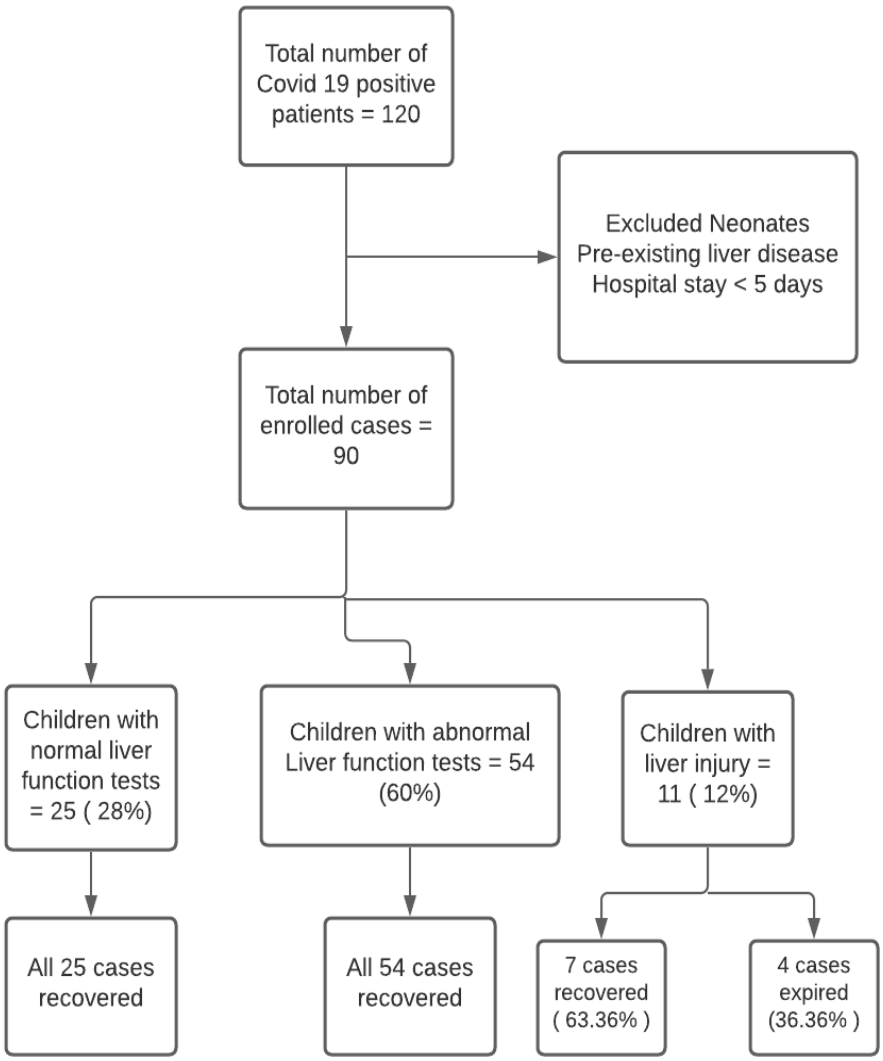

Table 1: Distribution of cases based on sociodemographic characteristics

Parameter	Type	Frequency (%)
Age Group	1 month - 1 Year	24 (27)
	1 - 3 Years	16 (18)
	3 - 5 Years	7 (8)
	5 - 12 Years	43 (47)
Gender	FEMALE	45 (50)
	MALE	45 (50)
Socioeconomic status (MKS - Modified Kuppuswamy classification)	upper (MKS class I)	3 (3)
	upper middle (MKS class II)	18 (20)
	lower middle (MKS class III)	30 (33)
	upper lower (MKS class IV)	39 (44)

Immunisation	incomplete	11 (12)
	complete	79 (88)
Nutrition	Normal	83 (92)
	Moderate Malnutrition	4 (5)
	Severe Malnutrition	3 (3)
Comorbidities	Congenital Heart disease	5 (6)
	Chronic Kidney disease	1 (1)
	ASTHMA	1 (1)
	IMMUNOCOMPROMISED	0 (0)
	THALASSEMIA	0 (0)
	NEPHROTIC SYNDROME	1 (1)
	SICKLE CELL ANAEMIA	2 (2)
	BURNS	2 (2)
	No Comorbidities	78 (87)
Symptoms	Fever	48 (53)
	Cough	26 (29)
	Cold	26 (29)
	Throat pain	3 (3)
	Vomiting	9 (10)
	Loose stools	7 (8)
	Breathlessness	10 (11)
Duration of Symptoms	<5 days	59 (66)
	>5 days	4 (4)
	Asymptomatic	27 (30)

Table 2 : Association of sociodemographic characteristics with outcome

Characteristics	**Recovery**	**Death**	**Total**	**p value**
1. Age Group				
1 month - 1 Year	23 (96)	1 (4)	24 (100)	1
1 - 3 Years	15 (94)	1 (6)	16 (100)	
3 - 5 Years	7 (100)	0 (0)	7 (100)	
5 - 12 Years	41 (95)	2 (5)	43 (100)	
Total	86 (96)	4 (4)	90 (100)	
2. Gender				
Male	44 (98)	1 (2)	45 (100)	0.62

Female	42 (93)	3 (7)	45 (100)	
Total	86 (96)	4 (4)	90 (100)	
3. Socioeconomic status				
MKS Class I (upper)	3 (100)	0 (0)	3 (100)	1
MKS CLass II (upper middle)	17 (94)	1 (6)	18 (100)	
MKS Class III (lower middle	30 (100)	0 (0)	30 (100)	
MKS Class IV (upper lower)	36 (92)	3 (8)	39 (100)	
Total	86 (96)	4 (4)	90 (100)	
4. Immunisation				
Complete	75 (95)	4 (5)	79 (100)	1
Incomplete	11 (100)	0 (0)	11 (100)	
Total	86 (96)	4 (4)	90 (100)	
5. Nutrition				
Normal	81 (98)	2 (2)	83 (100)	0.01
Moderate Malnutrition (MAM)	2 (50)	2 (50)	4 (100)	
Severe Malnutrition (SAM)	3 (100)	0 (0)	3 (100)	
Total	86 (96)	4 (4)	90 (100)	
6. Comorbidities				
Absent	76 (97)	2 (3)	78 (100)	0.08
Present	10 (83)	2 (17)	12 (100)	
Total	86 (96)	4 (4)	90 (100)	
7. Symptoms				
Absent	27 (100)	0 (0)	27 (100)	0.31
Present	59 (94)	4 (6)	63 (100)	
Total	86 (96)	4 (4)	90 (100)	
8. Duration of symptoms				
< 5 days	55 (93)	4 (7)	59 (100)	1
> 5 days	4 (100)	0 (100)	4 (100)	
Total	59 (94)	4 (6)	63 (100)	

Table 3 : Distribution of cases based on abnormal liver function tests on admission (d1)

Liver enzyme levels	Frequency (%)
Normal	25 (28)

Abnormal liver enzymes without liver injury	54 (60)
Abnormal liver enzymes with liver injury	11 (12)

Table 4 : Association of abnormal liver function tests on admission (d1) with outcome

Liver function tests (D1)	Recovery	Death	Total	p value
1. Total bilirubin				
Normal	73 (97)	2 (3)	75 (100)	0.05
Raised	13 (87)	2 (13)	15 (100)	
Total	86 (96)	4 (4)	90 (100)	
2. Direct Bilirubin				
Normal	67 (97)	2 (3)	69 (100)	0.23
Raised	19 (90)	2 (10)	21 (100)	
Total	86 (96)	4 (4)	90 (100)	
3. Alkaline phosphatase				
Normal	61 (97)	2 (3)	63 (100)	0.58
Raised	25 (93)	2 (7)	27 (100)	
Total	86 (96)	4 (4)	90 (100)	
4. Aspartate Aminotransferase				
Normal	49 (98)	2 (2)	50 (100)	0.31
Raised	37 (92)	3 (8)	40 (100)	
Total	86 (96)	4 (4)	90 (100)	
5. Alanine aminotransferase				
Normal	70 (99)	1 (1)	71 (100)	0.02
Raised	16 (84)	3 (16)	19 (100)	
Total	86 (96)	4 (4)	90 (100)	
6. Serum total protein				
Normal	74 (99)	1 (1)	75 (100)	0.01
Low	12 (80)	3 (20)	15 (100)	
Total	86 (96)	4 (4)	90 (100)	
7. Serum Albumin				
Normal	81 (99)	1 (1)	82 (100)	0.002
Low	5 (63)	3 (37)	8 (100)	
Total	86 (96)	4 (4)	90 (100)	

Table 5 : Association of abnormal liver function tests and liver injury with sociodemographic , laboratory parameters and outcome

Characteristics	Normal	Abnormal LFTS without Liver Injury	Liver injury	Total	p value
1. Age group					
1 month - 1 year	2 (8)	19 (79)	3 (13)	24 (100)	0.01
1 - 3 year	3 (19)	9 (56)	4 (25)	16 (100)	
3 - 5 year	1 (14)	6 (86)	0 (0)	7 (100)	
5 - 12 years	19 (44)	20 (47)	4 (9)	43 (100)	
Total	25 (28)	54 (60)	11 (12)	90 (100)	
2. Gender					
Male	16 (36)	26 (57)	3 (7)	45 (100)	0.13
Female	9 (20)	28 (62)	8 (18)	45 (100)	
Total	25 (28)	54 (60)	11 (12)	90 (100)	
3. Socioeconomic Status					
MKS class I (upper)	2 (67)	0 (0)	1 (33)	3 (100)	0.14
MKS Class II (upper middle)	4 (22)	11 (61)	3 (17)	18 (100)	
MKS class III (lower middle)	10 (33)	19 (63)	1 (4)	30 (100)	
MKS class IV (upper lower)	9 (23)	24 (61)	6 (16)	39 (100)	
Total	25 (28)	54 (60)	11 (12)	90 (100)	
4. Immunisation					
Complete	22 (28)	47 (60)	10 (12)	79 (100)	1
Incomplete	3 (27)	7 (63)	1 (10)	11 (100)	
Total	25 (28)	54 (60)	11 (12)	90 (100)	
5.Nutrition					
Normal	23 (28)	51 (61)	9 (11)	83 (100)	0.03
Moderate Malnutrition (MAM)	2 (50)	0 (0)	2 (50)	4 (100)	
Severe Malnutrition (SAM)	0 (0)	3 (100)	0 (0)	3 (100)	
Total	25 (28)	54 (60)	11 (12)	90 (100)	
6. Comorbidities					
Absent	24 (31)	47 (60)	7 (9)	78 (100)	0.04
Present	1 (8)	7 (58)	4 (34)	12 (100)	
Total	25 (28)	54 (60)	11 (12)	90 (100)	
7.Symptoms					
Absent	8 (30)	17 (63)	2 (7)	27 (100)	0.71
Present	17 (27)	37 (59)	9 (14)	63 (100)	

Total	25 (28)	54 (60)	11 (12)	90 (100)	
8. Duration of Symptoms					
< 5 days	19 (31)	31 (53)	9 (16)	59 (100)	0.34
> 5 days	0 (0)	4 (100)	0 (0)	4 (100)	
Total	19 (29)	35 (56)	9 (15)	63 (100)	
9. Anemia					
Absent	12 (22)	39 (71)	4 (7)	55 (100)	0.02
Present	13 (37)	15 (43)	7 (20)	35 (100)	
Total	25 (28)	54 (60)	11(12)	90 (100)	
10. Ferritin					
Normal	18 (31)	35 (59)	6 (10)	59 (100)	0.17
Raised	3 (14)	13 (61)	5 (24)	21 (100)	
Total	21 (26)	48 (60)	11 (14)	80 (100)	
11. C Reactive Protein					
Negative	19 (27)	44 (63)	7 (10)	70 (100)	0.06
Positive	3 (28)	4 (36)	4 (36)	11 (100)	
Total	22 (27)	48 (59)	11 (14)	81 (100)	
12. Duration of stay					
<10 days	25 (30)	50 (60)	8 (10)	83 (100)	0.02
>10 days	0 (0)	4 (57)	3 (43)	7 (100)	
Total	25 (28)	54 (60)	11 (12)	90 (100)	
13.Outcome					
Recovery	25 (29)	54 (63)	7 (8)	86 (100)	0.0001
Death	0 (0)	0 (0)	4 (100)	4 (100)	
Total	25 (28)	54 (60)	11 (12)	90 (100)	

IV. Discussion

In this study , Majority of the cases belonged to the age group between 5-12 years of age with mean age of presentation being 4.7 years and an equal distribution of males and females.(n=45,50%). Though malnutrition was seen in only 7(8%) of the cases , it was significantly associated with poor outcome. This was similar to a study by Saha J et al where malnutrition was associated with higher deaths due to Covid 19 disease (11).Malnutrition increases the incidence and severity of infection by causing growth failure , impairing the immunity , repair and regeneration capability and decreasing humoral and cell mediated immunity.

Out of the 90 cases enrolled , 54 (60%) cases had abnormal liver function tests without liver injury and 11 (12%) cases had liver injury on admission. A study by Alqahtani, Saleh A. indicated that the SARS-Cov2 target receptor , ACE2 , is expressed in the cholangiocytes and hepatocytes apart from the lungs. The virus binds to this receptor and multiples within these cells and causes cytopathic and hepatocyte damage resulting in hepatobiliary dysfunction i.e elevated transaminase and deranged synthetic function among Covid positive patients (12). This was supported by autopsy studies done that detected SARS-Cov2 virus in 41% of the liver tissue with a maximum viral load of 1x106 copies per gram of liver tissue. Classical histopathological findings found included hepatocellular necrosis , cellular infiltration and steatosis (13,14). Elevated alanine transaminase was the most common abnormality seen in children (n=19,21%) and also had a significant association with poor outcome. Also Hypoproteinemia (n=15,17%) and Hypoalbuminemia (n=8,9%) were associated with higher

mortality. This was similar to a study by Tiruneh FT. which reported that aspartate transaminases are predominantly elevated in adults while in children both in mild and severe illness alanine transaminase was more commonly elevated (15). Apart from elevated alanine transaminase, raised aspartate aminotransferase (n=40,44%) , raised alkaline phosphatase (n=27,30%) and raised direct or conjugated bilirubin (n=21,23%) were also seen but had no association with poor outcome. This was in contrast to previous studies done by Di Giorgio, Angelo et al , Qiu, Haiyan et al. and Wang D et al. which suggested that elevated liver enzymes and serum bilirubin were the main indicators of liver damage and severity in Covid positive patients (16,17,18).

Notably , the younger age group was found to have a significantly higher risk of deranged LFTS and liver injury due to Covid 19 disease. 79% (n=19) of the infants and 56% (n=9) of the children between 1-3 years of age had abnormal LFTs.Immature liver during infancy and younger age group can predispose to deranged liver tests in this age group(19,20). Covid 19 positive children with moderate and severe malnutrition had a higher risk of abnormal LFTS and liver injury. Malnutrition affects cellular metabolism and causes mitochondrial dysfunction leading to hepatic dysfunction and raised liver enzymes and hypoalbuminemia (21,22). Abnormal LFTS and liver injury were higher in Covid 19 children with other comorbidities such as congenital heart disease , chronic kidney disease , asthma and burns. Comorbid conditions increase the severity of the infection by upregulating the expression of ACE2 receptors , by impairing the immune system and by delaying the innate antiviral response and secretion of IFN gamma, all of which can increase the organ damage caused by the virus (23). Anemia was found to be a significant risk factor for abnormal LFTs (n=15,43%) and liver injury (n=7,20%). Anemia results in decreased oxygen carrying capacity which in turn causes failure to meet the tissue demands during the hypermetabolic state of infection causing hypoxic injury to the liver. This hypoxic injury is further worsened in critically ill patients with pneumonia(24,25). Most cases with deranged LFTS and liver injury were found to have a negative CRP and normal ferritin level on admission. Though 36% of the cases with a positive CRP had deranged LFTS and liver injury respectively , no significant association was found between CRP and deranged LFTS. This was in contrast to various studies conducted among the adult population that reported a positive correlation between inflammatory markers - CRP and ferritin and abnormal LFTS (26). This difference between adults and children is because of the difference in the immune system and varied response of the immune system to the viral infection. Recent evidence suggests adults have an ineffective cellular response with an overstimulated innate response and uncontrolled cytokine production while children have preserved effector and immunosuppressive components of the adaptive immune system and also trained immunity from other common respiratory viral pathogens that offer cross protection . Lower levels of proinflammatory cytokines and CRP noted among children support this theory (26,27,28).

Children with deranged LFTS and liver injury had a significantly higher risk of prolonged hospital stay. Though children with deranged liver function tests without the presence of liver injury had good recovery , 36% of the children with liver injury had a poor outcome and a significant association was found between abnormal LFTS and poor outcome. This was similar to a study by Boregowda, Umesha, et al. and Yip et al which suggested that hepatic injury among covid positive patients were associated with adverse outcomes (29,30).

Limitations of this study include - a) findings cannot be generalised to all communities of varying epidemiological characteristics , b)Medication history prior to developing covid was not available and c) as mortality was low (4%) , the influence of liver damage on mortality could not be assessed properly.

V. Conclusion

Abnormal liver profile was seen in the majority of the pediatric covid positive patients with infants and children between ages of 1-3 years at a higher risk of developing serious liver injury. Malnutrition independently was associated with a poor outcome and also was a significant risk factor for liver injury apart from presence of comorbidities and Anemia. Children with elevated alanine transaminase , hypoproteinemia and hypoalbuminemia had a poorer outcome. Elevated inflammatory markers were not seen in cases with abnormal LFTS. Children with abnormal liver function tests without liver injury had good recovery when compared to children with liver injury who had prolonged hospital stay and higher mortality.

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