

## Age Dependent Abnormalities of Serum AST Levels Children Hospitalized with COVID-19

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### Abstract

AST levels have been reported to be increased in children and adults with COVID-19 infection. The majority of these cases with an increased AST level have clinically advanced COVID-19 disease. A wide range of possible mechanisms responsible for the increased AST levels have been proposed.

AST levels have been advanced, but no single factor has been identified as being responsible. Laboratory evidence for either a subclinical coagulopathy in children or an overt coagulopathy in adults is frequently present in individuals with increased AST levels, who are infected with COVID-19. Most likely, a combination of factors contributing to the increased AST levels and COVID-19 infected adults. In contrast, no single or combination of factors has been identified as being responsible for the increased AST levels in children. It has been proposed by several groups in Asia that the immaturity of the neonatal liver may be responsible, but no specific factor of the immature liver has been proposed or identified.

Recognizing that the problems of an abnormal AST in children is highest in those less than age 2 and declines progressively thereafter such that rare cases of AST elevations are identified in children age more than 2 and declines through age 5 years. Recognizing this age-dependent prevalence of an elevated AST in children infected with COVID-19, it is proposed to be the failure to develop Kupfer cells with endothelial cell linings resulting in the creation of a subendothelial space variant mononuclear cells consisting of macrophages, functional B cells that selectively secrete IgA as well as a wide array of cytokines that in combination with T cells that protect the liver from viral induced liver cell injury.

**Keywords:** COVID-19; Serum; Children

### Abbreviations

ADD: Acute Diarrheal Disease; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; CRP: C Reactive Protein; LDH: Lactate Dehydrogenase

### Introduction

The spectrum of COVID-19 presentation is wide, with very mild symptoms consisting of a sore throat and a loss of smell and or

taste [1], to overt illness resulting in progressive disease manifestations to include acute respiratory disease that progress to pneumonia and pulmonary failure, acute renal injury with progression to renal failure, and liver injury manifested as increased levels of transaminases, particularly AST, and the development of a diffuse microvascular endothelial injury manifested by the development of myocarditis, coronary artery disease, cerebrovascular disease and ultimately an overwhelming disseminated intravascular coagulopathy [2,3].

In general pediatric cases of the coronavirus disease and particularly COVID-19 infection in children are either asymptomatic or percent with mild symptoms and are usually acquired as a result of close contact with an adult with a COVID-19 infection, often one of their parents [4,5]. Reports of the unique clinical features of children with acCOVID-19 infection, particularly infants is scarce and poorly understood as compared to children greater than age 5.

**Aim**

To identify the risk ratio (RR) for abnormal transaminase levels, particularly an increased level of AST, and the difference between less than and greater than 2 years of age, the time point recognized at which the majority of children have a normal hepatic structure. The goal of the present investigation was to provide quantitative measures associated with abnormal liver injury tests that differ between infants age 1 day to less than 2 years of age and those age greater than 2 years extending to children less than 5 years of age.

**Methods**

The clinical records and laboratory results for infants less than 1 year to 2 years of age and preschoolers aged 3 to 5 years of age in a cohort of 245 children with laboratory-confirmed COVID-19 infection, admitted from March 13 to September 30, 2020, to Hospital "Victor Babes" in Bucharest, Romania were reviewed. The clinical features of each child and the results of their laboratory tests to include D-dimers obtained at admission were recorded for subsequent analysis. All demographic, laboratory and clinical data were retrieved from the electronic files of the hospital and entered in a EpiInfo 7 data base [6]. Data manipulation began with the separation of the studied cohort into two subgroups: (a) Infants age 0-2 years and (b) preschool children age 3-5 years. The data for each variable of interest was converted into categorical variables segregated as normal versus abnormal values for each age group.

**Results**

The data analysis revealed complete similarity between the 2 subgroups (p > 0.05) in terms of the laboratory data (ALT, CRP, LDH, and Quick time,) and the clinical features of their disease (diarrhea at hospital admission, mean days in hospital, mean hospital cost, and type of newborn delivery). (see Table 1). In contrast, an elevated AST value was noted in 76.9% of the infants (aged 0-2) being 3 times greater than the 29.6% of children aged 3-5 years (RR: 2.59; CI: 1.60 - 3.96); p < 0.0001). In addition, the prevalence's

of fever, neutropenia and an elevated D-dimer levels at hospital admission were significantly greater (p < 0.05) in children aged 0 - 2 years on compared to the preschooler aged 3-5 years.

Issues	Group		Relative Risk	P value
	Infants 0-2 rs	Children 3-5 rs		
Clinical	n:180	n: 65		
Fever before admission %	73.8	56.6	0.0458	
ADD before admission %	19.4	.3	0.2898	NS
Mean Hos Sta da s	8.81	10.06	0.0747	NS
Mean Cost Hospital/Pax RO	3655.72	3850.88	0.5346	NS
Born Cesarean section %	52.3		0.5268	NS
Laboratory				
Abnormal AST %	75.0	20.6	0.0000	
Abnormal ALT %	9.3	3.4	0.2806	NS
Neutropenia %	43.9	0.0	0.0024	
Abnormal CRP %	22.4	30.4	0.3587	NS
Abnormal D-dimer %	40.0		0.0178	
Abnormal LDH %	22.3		0.2374	NS
Abnormal quick time %	7.3		0.9791	NS

**Table 1:** Clinical features found at hospital admission in children hospitalized for Covid 19.

**Discussion**

The proposed pathophysiological mechanisms of liver injury abnormal in COVID-19 infected individuals includes an uncontrolled inflammatory response, drug induced liver injury (particularly ASA and NSAIDs) administered to control fever, hepatocyte and/or choanocytes infection, hypoxic-ischemic injuries, and sinusoidal micro-thrombosis within the liver as a result of endothelial cell injury that initiates a local hyper coagular state [7,8]. In adults, it has reported in China that elevated AST and ALT levels are predictors of severe disease and identify individuals with an likelihood of a fatal outcome [9-14]. This finding has not been reported in

studies in the IJ Aited States represent the differences in hepatitis B and hepatitis C infection in infants and preschoolers but does not occur in western societies [15]. COVID-19 infected children with elevated aminotransferase levels (both ALT and AST) have been reported previously but have not been identified as a predicate of an increased risk of death [16-18]. Zhou and colleagues have speculated [18] that an immaturity of the infant liver may be responsible for high prevalence of an elevated AST levels observed particularly in infants. They suggested that the metallization of liver with advancing age in children explains the normal AST levels in older children (age 2-5 years of age) and adults infected with Covid-19 viruses. This maturation process consists of a progressive reduction of the liver mass without sinusoids and the increasing number of functionally competent hepatic plates associated with sinusoids. This matching of hepatic plates with a sinusoids enables the development of the sub endothelium and its varied sub endothelium mononuclear cell populations consisting of macro phages, immunocytes responsible for immunoglobulin production particularly local IgA and both the B and T cell populations that control viruses that are capable of injuring the hepatocyte population. In addition, the viral induced injury of the sinusoidal endothelium initiates the microvascular injury responsible for the hyper coagulable state that is responsible for the vascular thrombosis not only in the liver but also in the larger vascular system associated with the hypercoagulable state that occurs with advanced disease and often leads to the individuals death [19].

## Conclusion

Recognizing that the problems of an abnormal AST children is highest in those less than age 2 and declines progressively thereafter such that rare cases of AST elevations are identified in children age more than 2 and declines through age 5 years. Recognizing this age-dependent prevalence of an elevated AST in children infected with COVID-19, it is proposed to be the failure to develop hepatic plates with endothelial cell linings resulting in the creation of a subendothelial space variant mononuclear cells consisting of macrophages, functional B cells that selectively secrete IgA as well as a wide array of cytokines that in combination with T cells that protect the liver from viral induced liver cell injury.

- **Sampling:** Was unnecessary as all subjects were included
- **Review:** Research Committee Approval: unnecessary as all of the subjects data were reported and contained in a national surveillance system available to the public.

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