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The impact of the severity of HIV infection on the prevalence of liver fibrosis in children

Ida Bagus Gde Suwibawa Putra,* Ketut Dewi Kumara Wati, I Putu Gede Karyana, I Gusti Ngurah Sanjaya Putra, Ni Nyoman Metriani Nesa

ABSTRACT

Background: The fibrotic process in liver fibrosis is faster when there is coinfection with HIV than in Hepatitis B or Hepatitis C mono-infection.
Objectives: We sought to compare the presence of liver fibrosis based on Aspartate Aminotransferase to Platelet Ratio Index (APRI) in HIV clinical stage I-II and III-IV. We also sought to identify factors associated with liver fibrosis in HIV-infected children.
Methods: The population was HIV-infected children who were registered in 2006-2014 Sanglah hospital's TApHOd (Treat Asia Pediatric HIV Observational Database) cohort. The cutoff point for fibrosis was APRI > 0.5. The sample was grouped into two outcomes: liver fibrosis and without fibrosis. The associations of liver fibrosis to the severity of HIV clinical stage and other variables were analyzed using Fisher-Exact test.
Results: From 81 HIV-infected subjects, 46 were in stage III-IV and 35 in stage I-II. The range of APRI was 0.11 to 12.01. There were 27 subjects with liver fibrosis. There were 21 subjects with liver fibrosis in stage III-IV HIV infection and 6 in stage I-II. The analysis showed in a group of liver fibrosis patients; there are more patients with the severe clinical stage of HIV (p-value = 0.009).
Conclusion: Liver fibrosis is more common in the more severe clinical stage of HIV infection in children than in the milder clinical stage. Advanced clinical stage significantly increases the risk for liver fibrosis.

Keywords: APRI, liver fibrosis, HIV, children
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Department of Child Health, School of Medicine, Udayana University/ Sanglah General Hospital, Bali, Indonesia

INTRODUCTION

The survival rate of patients infected with human immunodeficiency virus (HIV) has increased over the last decade because of the availability of highly active antiretroviral therapy (HAART). Meanwhile, other comorbidities, such as chronic liver disease, have become the leading cause of morbidity and mortality in this population.[1] Previous studies with adult population have demonstrated that 20 to 75% of HIV-monoinfected individuals have elevated liver enzymes.[2]

Chronic liver disease is the most common non-AIDS-related cause of death among individuals with HIV infection. A coinfection of HIV and hepatitis C virus (HCV) or hepatitis B virus (HBV) is responsible for a significant proportion of liver disease among HIV-infected individuals. However, HIV-monoinfected individuals are also at risk for liver disease from a variety of other factors including opportunistic infections, AIDS-related neoplasms, alcohol and other substance abuse, non-alcoholic fatty liver disease, and medication-related hepatotoxicity.[2]

An opportunistic infection may cause liver disease as a comorbid in HIV infected patient. AIDS-related liver disease such as AIDS cholangiopathy, acalculous cholecystitis, vanishing bile duct syndrome sometimes occur. Bacterial opportunistic infection associated with hepatic involvement such as *Mycobacterium complex* and *Mycobacterium tuberculosis*, fungal infection including *Cryptococcus neoformans*, *Histoplasma capsulatum*, and *Coccidiodes immitis*. Several virus infections also found in HIV infected patient with liver involvement. One of the most common opportunistic infection involving the liver detected in the autopsy of patients with advanced AIDS is *Cytomegalovirus* (CMV), but rarely results in clinical hepatitis.[3]

Elevated serum activity of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) involved in the breakdown of amino acids reflects liver cell injury.[4] Interpreting whether an abnormal liver chemistry value is related to medications, comorbidities, or HIV infection itself can be difficult, and symptomatic children receive no further evaluation.[5]

The gold standard for determining the severity of advanced liver disease is a liver biopsy. However, liver biopsy is an invasive procedure. It is associated with complications, concerns of sampling error, and inter-observer and intra-observer interpretation variation. Consequently, there has been much interest in the use of non-invasive markers to accurately assess the extent of the hepatic injury and fibrosis.[6]

*Corresponding to:
Ida Bagus Gde Suwibawa Putra, Department of Child Health, Faculty of Medicine, Udayana University, Sanglah General Hospital, Bali, Indonesia
suwibawa@gmail.com

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Aminotransferase to platelet ratio index (APRI) is a simple calculation of two laboratory variables: AST and platelet count. APRI can be used as a simple, user-friendly, and reliable algorithm to predict fibrosis. It may avoid liver biopsies in patients with no or minimal fibrosis. This score can be easily used at the bedside or in an outpatient setting.[7]

Hepatic fibrosis is a dynamic process initiated by a liver injury which results in an increased deposition of extracellular matrix between the hepatocytes and the liver sinusoids (space of Disse), which is mainly inhabited by hepatic stellate cells (HSCs). HIV directly infects HSCs so that it promotes HSC collagen I expression and secretion of the proinflammatory chemokine monocyte chemoattractant protein-1 (MCP-1). The HIV gp120 protein also induces activation of tissue-inhibitor metalloproteinases (TIMP). The two proteins, MCP-1 and TIMP, are essential for chemotaxis of leukocytes and these mediators promote liver inflammation and fibrogenesis. HIV also renders hepatocytes sensitive to the TNF-related apoptosis-inducing ligand receptor (TRAIL), which can lead to hepatocyte death and subsequent liver fibrosis. HIV can also infect liver macrophages, known as the Kupffer cells. These cells play a crucial role in hepatocyte apoptosis and are involved in the induction of steatosis. HIV-infected macrophages/monocytic cells secrete high levels of tumor growth factors-β (TGF-β) which activates HSC that promote fibrosis.[8]

The more severe stages of HIV are associated with bacterial translocation of the gastrointestinal tract and the presence of *E. coli* in the liver.[9,10] Intestinal mucosal damage in HIV patients leads to a disruption of the gut epithelial barrier, facilitating leakage of microbial products from the gastrointestinal tract. Thus, promoting bacterial translocation into the portal and systemic circulation. When bacterial translocation occurs, the bacterial lactation receptor (TLR) 4 and other pathogen recognition receptors acting as the first line of defense by clearing bacteria from the liver through phagocytosis. In this process, cytokines, such as tumor necrosis factor (TNF), interleukin (IL)-1 and IL-6, which are pro-inflammatory mediators that promote liver fibrosis by directly activating HSCs or by priming and recruiting other leukocyte populations.

Determining the presence of liver disease is very important in the care of HIV infected individuals. The identification of HIV infected patients with advanced liver fibrosis is important because certain antiretrovirals should be avoided. However, there is a limited study that evaluated liver fibrosis among HIV infected children. This study aimed to determine the different stages of liver fibrosis based on the HIV clinical infection stage in children.

METHODS

Our study is a retrospective study. The subjects were patients recorded during 2006-2014 in Sanglah hospital's Treat Asia Pediatric HIV Observational Database (TApHOd). In 2016, we mined the demographic data and the laboratory results performed when the patients were diagnosed with HIV infection for the very first time.

The inclusion criteria were children aged 18 months to 12 years old at the time of the initial diagnosis. The subjects were excluded if there were incomplete demographic and or laboratory data. The data collected include the patient's sex, age, hemoglobin level, platelet count, AST level, CD4 T-cell count, HIV staging according to the World Health Organization (WHO) classification.[11,12]

The platelet count and the AST level were used to calculate the APRI score, where > 0.5 is considered as present liver fibrosis.[13,14] APRI score = (AST/upper limit of normal) x 100 / platelet (10^9/L). The sample was categorized into two groups of outcome: with and without liver fibrosis based on the APRI score.

The age of the patient at the initial diagnosis was categorized into under or equal to 5 years old and above five years old. The hemoglobin level was categorized into normal and anemia (<12 mg/dL). CD4 T-cell percentages were categorized from total CD4 <25% and >25%. The stages of HIV infection was categorized into stage I-II and stage III-IV.

The demographic data and the laboratory results were presented descriptively. Age, hemoglobin concentration, CD4 percentages, and HIV clinical stages were compared with the state of the liver based on APRI score using Fisher-exact tests in IBM SPSS statistics software 23.

RESULTS

The data of eighty-one patients were analyzed. The subject characteristics are presented in Table 1. Our sample consisted of 41 males and 40 females. There were more patients under 5 years old (76.5%). The age median was 3.47, the youngest was 0.34 years old, and the oldest was 8.29 years old. There were more patients with anemia (81.5%). The hemoglobin median was 10.4 mg/dL, the lowest was 5.4 m/dL, and the highest was 14.2 mg/dL. Patients with CD4 under or equal to 25% were more than the ones with CD4 over than 25% (92.6% vs. 7.4%). Based on the clinical stages of HIV infection, 13 patients were in stage 1, 22 in stage 2, 33 in

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Table 1 Demographic characteristics

Variables	f	%	Median	Min	Max	IQR
Sex						
Male	41	50.6%				
Female	40	49.4%				
Age			3.47	0.34	8.29	2.87
<5	62	76.5%				
≥5	19	23.5%				
Hemoglobin			10.40	5.40	14.20	2.60
≤12	66	81.5%				
>12	15	18.5%				
CD4			11.00	0.00	38.50	13.00
≤25%	75	92.6%				
>25%	6	7.4%				
Clinical Stage			3			
1	13	16.0%				
2	22	27.2%				
3	33	40.7%				
4	13	16.0%				
APRI			0.41	0.11	12.01	0.32
<0.5	54	66.7%				
≥0.5	27	33.3%				

Table 2 Fisher's Exact Test results

	Fibrosis (n=27)		Normal (n=54)		
Variables	f	%	f	%	p value
Age					
< 5 year	23	85.2%	39	72.2%	0.269
> 5 year	4	14.8%	15	27.8%	
Hemoglobin					
< 12	22	81.5%	44	81.5%	1
> 12	5	18.5%	10	18.5%	
CD 4					
< 25 %	24	88.9%	51	94.4%	0.395
> 25 %	3	11.1%	3	5.6%	
Clinical Stage					
I-II	6	22.2%	29	53.7%	0.009
III-IV	21	77.8%	25	46.3%	

stage 2, 13 in stage 4. Based on APRI score, there was 33.3% with fibrosis.

A Fisher's Exact Test was used to analyze the relationship between APRI and age, hemoglobin, CD4, and clinical stage (Table 2). The results showed that the only variable showing a significant relationship with APRI was the clinical stage of HIV infection. There were more patients in clinical stage III and IV of HIV infection with liver fibrosis, compared to those in clinical stage I and II ($p<0.05$)

DISCUSSION

Ourstudy explored the potential risk factors promoting liver fibrosis in HIV-infected children. Our data were collected prior to HAART because the therapy may interfere with the results due to its potential hepatotoxicity. Based on APRI score, 33% of our sample has liver fibrosis. Compared to the results of research in children in the United States (6.5%) or Latin America (3.2%), our frequency of liver fibrosis is quite high.[15] However, both studies used a different cutoff point for APRI score.

The proportion of children over or equal to 5 years in our study was less than children under 5 years old. It may be related to a lower state of immunity in younger age so that opportunistic infection symptoms will manifest clinically. Therefore, a patient is suspected of HIV infection and diagnosed at a younger age.

The analysis showed no association between CD4 and liver fibrosis in patients with HIV infection, confirming the result of a study by Dallapiazza et al..[15] However, Castellares et al. showed low CD4 levels correlates significantly with liver fibrosis in patients with other liver infection coinfected with HIV.[1]

Our study showed that patients with severe HIV clinical stages (stage III and IV) have significantly higher APRI score compared with milder clinical stages (stage I and II) ($p=0.004$). The result confirms that the more severe the HIV clinical stages, the more pro-inflammatory factors available to promote liver fibrosis.[9,10]

CONCLUSION

Liver fibrosis is more common in the severe clinical stage of HIV infection in children than in the mild clinical stage. Advanced clinical stage of HIV infection significantly increases the risk for liver fibrosis.

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