Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.63, No.2(2023). p.88-95; DOI: https://doi.org/10.14238/pi63.2.2023.88-95

Original Article

Association of CD4 cell counts and viral load with cystatin C level in children with human immunodeficiency virus (HIV) infection

Wita Rostania, Anggraini Alam, Dany Hilmanto

Abstract

Background The ease of access to antiretroviral therapy (ART) has improved both survival rate and comorbidities in patients with human immunodeficiency virus (HIV) infection. Impaired kidney function is one of the most common comorbidities of HIV. CD4 and viral load can be used to monitor HIV progression and to determine the effectiveness of ART. The most commonly used estimated-glomerular filtration rate (e-GFR) technique is to use serum creatinine but often causes late detection of kidney dysfunction while serum cystatin increases at the beginning of the GFR decrease. This supports cystatin C serum as an early diagnostic tool to detect kidney function or biomarker early kidney disorders.

Objective To evaluate a possible association between serum cystatin C as a marker of kidney function and HIV progression through CD4 levels and viral load.

Methods This cross-sectional study was conducted through evaluation of secondary data from medical and laboratory records of pediatric patients who had routine visits to the HIV Clinic at Dr. Hasan Sadikin General Hospital, Bandung, West Java, in January-February 2020.

Results Sixty subjects were reviewed in the study. Median cystatin C-based eGFR was 28.1mL/minute/1.73m^2. Subjects were categorized by viral load result into <40 and ≥40 copies/mL. The median serum cystatin C was significantly higher [3.7 (range 2.61-6.55) mg/L] in the >40 copies/mL viral load group than the <40 copies/mL group [2.4 (range 0.26-13.61) mg/L]. The median absolute CD4 count, CD4 percentage, and cystatin C were 776 (range 7-1644) cells/mm^3, 27.5 (range 1.6-57.4) %, and 3 (range 0.26-13.61) mg/L, respectively. There were no significant correlations (r=-0.2; P=0.1) between CD4 and serum cystatin C

Conclusion Higher viral load associates with higher cystatin C level, while CD4 shows no correlation to cystatin C. However, patients with low CD4 tend to have increased cystatin C level. **[Paediatr Indones. 2023;63:88-95; DOI: https://doi.org/10.14238/pi63.2.2023.88-95].**

Keywords: *CD4 cell counts; cystatin C; glomerular filtration rate; HIV; viral load*

The HIV infection prevalence has reportedly increased globally in recent years due to the ease of access to antiretroviral therapy (ART).[1] The consequence is that longer patient life leads to higher risk of impaired multi-organ function, including the kidney, due to HIV infection or side effects of life-long medication use.[2-5]

Pediatric HIV patients with kidney dysfunction are at high risk of rapid progression of kidney disease to a terminal stage, thus, appropriate management plans are urgently needed to prevent irreversible damage and kidney dysfunction.[6-10] The estimated glomerular filtration rate (eGFR) is the recommended method to detect early change of kidney function.[10] The use of creatinine-based eGFR examination is less sensitive compared to cystatin C due to several confounding factors.[11-16] However, the analysis of serum cystatin C levels in Indonesia are still limited and only performed based on certain clear indications according to the clinical manifestations and chosen antiretroviral

From the Department of Child Health, Universitas Padjadjaran Medical School/Dr. Hasan Sadikin General Hospital, Bandung, West Java, Indonesia.

Corresponding author: Wita Rostania. Department of Child Health, Universitas Padjadjaran Medical School/Dr. Hasan Sadikin General Hospital. Jl. Pasteur no. 38 Bandung 40161, West Java, Indonesia. Email: wita.rostania@gmail.com.

Submitted December 23, 2021. Accepted April 11, 2023.

medication.[11-14, 17-21]

Five percent of HIV patients develop AIDS within 3 years, while 12% took 20 years to develop AIDS. Clinical and laboratory measurements are used to determine the prognosis of HIV infection. Since HIV infection has become an epidemic worldwide, routine T-CD4 lymphocyte counts are performed to monitor the course of infection and as an indicator of decline in the immune system. Since the mid-1990s when technology was discovered to quantitatively measure HIV RNA in plasma, also known as HIV viral load, the test began to be routinely carried out by clinicians as a better predictor of HIV infection progression than T-CD4 lymphocytes. Viral load testing is also frequently used to determine the relative effectiveness of ART in several clinical trials.[22-23]

Studies in pediatric HIV patients have been limited. Most studies were conducted in African countries, which populations have different genetic predisposition from the Indonesian. Therefore, we aimed to evaluate for possible associations between CD4 cell count, HIV viral load, and serum cystatin C level as a kidney function marker in determining disease progression in pediatric HIV patients compared to creatinine-based eGFR.

Methods

This cross-sectional study was conducted from medical and laboratory records of patients who routinely visited Teratai HIV clinic at Dr. Hasan Sadikin General Hospital, Bandung, West Java, in January-February 2020. The inclusion criteria were: children aged 5 to 18 years and known diagnosis of HIV infection according to *World Health Organization* (WHO) criteria. Positive virological test results in children aged less than 18 months and positive serological test results in children over 18 months old.[24] Exclusion criteria were previous history of kidney or thyroid disorders, ongoing use of high-dose steroid therapy, and obesity.

Characteristics of subjects collected from medical records were age, sex, age at diagnosis, time since diagnosis, duration of ART treatment, type of ART medication, transmission route, clinical stage at diagnosis, CD4 cell counts, viral load, and creatinine level. Archived biological specimens from previous study[25] were used to measure serum cystatin C by utilizing *Human Cys-C (Cystatin C) ELISA KIT* (*Elabscience Biotechnology Inc*., Catalog No: E-EL-H0055). The Filler formula was used to calculate eGFR based on serum cystatin C.[18]

Subjects' characteristics are presented in median and range since the data were not normally distributed by Shapiro-Wilk test normality test. Correlation analysis was performed using Spearman rank test. All data analyses were performed using StataCorp Stata MP ver. 15 software. Statistically significant results were evidenced by 95% confidence interval with P values <0.05. This study was approved by the Research Ethics Committee of Dr. Hasan Sadikin General Hospital, Bandung.

Results

There were 60 patient medical records and archived biological specimens from the study period (January-February 2020). Subjects were comprised of 33 (55%) males and 27 (45%) females, with an age range of 5 to 18 years. The median age at diagnosis was 3 years and mean duration of ART was 7.5 years. All subjects had experienced vertical HIV transmission from their mother. Lamivudin was the most preferred ART, while stavudine was the least prescribed medication. Tenofovir was initially given to 4 subjects but had been discontinued for one year prior to the study period. Fifty-six (93.3%) subjects had eGFR 60 mL/min/1.73m^2. Forty-three (71.7%) subjects were in advanced stages (CKD clinical stage III or IV) at the time of diagnosis. The characteristics of subjects are listed in **Table 1**.

The absolute CD4 count, percentage CD4, HIV viral load, serum cystatin C level, and cystatin C-based eGFR results are shown in **Table 2**. Ten subjects (16.7%) were immunocompetent based on their CD4 count, 6 (10%) had mild immunodeficiency, and 4 (6.7%) had severe immunodeficiency, by WHO criteria.[21] The HIV viral load detected in the ten subjects with high viral load ranged from 99 to 316,214 copies/mL. Fifty-six (93.3%) subjects experienced kidney disorders as the most frequent comorbidity, with 28 (50%) subjects having severely decreased GFR. There are 53 subjects (88.3%) with an increase in serum cystatin levels (>1mg/L).

Table 3 shows there was no significant correlation between serum cystatin C and CD4, in either absolute count or percentage (P>0.05 for both). However, viral load and serum cystatin C level had a statistically significant association (P=0.05) (**Table 4**).

Median serum cystatin C was significantly higher in the >40 copies/mL viral load group than the <40 copies/mL group, as shown in the box plot in **Figure 1**.

Table 1. General characteristics of subjects

Characteristics	(N=60)
Sex, n (%)	
Male	33 (55.0)
Female	27 (45.0)
Median age (range), years	11.5 (5-18)
Median age at diagnosis (range), years	3 (0.3-10)
Median duration of ART (range), years	7.5 (1-15)
Type of ART used	
Tenofovir	4 (6.7)
Stavudin	1 (1.7)
Lamivudin	60 (100)
Zidovudin	53 (88.3)
Abacavir	2 (3.3)
Nevirapine	33 (55.0)
Evafirenz	22(36)
Lopinavir/ritonavir	4 (6.7)
Nutritional status, n (%)	
Normal	41 (68.3)
Wasted	9 (15.0)
Severely wasted	7 (11.7)
Overweight	3 (5.0)
Clinical stage of HIV at diagnosis, n (%)	
I	4 (6.7)
II	13 (21.6)
III	25 (41.7)
IV	18 (30)

ART=antiretroviral therapy

Discussion

Renal complications secondary to HIV infection and treatment with antiretroviral drugs are concerns that have emerged due to the increased survival of HIV patients. The risk of death due to end-stage kidney disease has increased from <1 to 5 %, and renal failure has become an important cause of mortality in HIV infected children.[26]

Two previous studies identified several risk factors for kidney disorders among pediatric HIV patients, which included sex, age, nutritional status, body height percentile, clinical and immunological HIV classification, type of ART, HIV viral load, and CD4 count.[27-28] In addition, another study mentioned that HIV-associated nephropathy (HIVAN), Afro-American ethnicity, family history of terminal stage of kidney disease, proteinuria, and severe immunodeficiency were risk factors associated with terminal kidney disorders.[29]

Our subjects had high mean serum cystatin C level of [3.3 (SD 2.3) mg/L]. This result was higher compared to that in studies in pediatric HIV patients conducted in Lagos, Nigeria [0.77 (SD 0.29) mg/L],[30] Benin City [1.01 (SD 0.44) mg/L],[31] as well as in 250 adult HIV patients who participated in the Nutrition for Healthy Living (NHFL) study [1.03 (SD 0.02mg)/L].[32] The difference might have been due to higher proportion of subjects with increased serum cystatin C in our study compared to subjects in Lagos and Benin City (88.3%, 16.7%, and 23.4%, respectively) as well as different ethnicities of subjects. The increased serum cystatin C may also have been

Table 2. Laboratory results

Examination	Value	P value*
Median CD4 count (range), cells/mm^3	776 (7-1644)	0.35
Median percentage CD4+ (range), %	27.5 (1.6-57.4)	0.00
Viral load, n (%)		
<40 copies/mL	50 (83.3)	0.00
≥40 copies/mL	10 (16.7)	0.10
Median cystatin C (range), mg/L	3 (0.26-13.61)	
Median cystatin C-based eGFR (range), mL/min/1.73m^2	28.1 (8.7-88.6)	
Median creatinine based eGFR (range), mL/min/1.73m^2	148.3 (87.8-278.2)	
Mean cystatin (SD) C, mg/L	3.3 (2.3)	
Mean cystatin C-based eGFR (SD), mL/min/1.73m^2	39.2 (33.3)	
Mean creatinine based eGFR (SD) , mL/min/1.73m^2	153.4 (37.6)	

*Shapiro-Wilk test

Table 3. Analysis of CD4 and serum cystatin C

Variables	r	P value*
Absolute CD4 count with serum cystatin C	-0.2	0.1
Percentage CD4+ with serum cystatin C	-0.2	0.1

*Spearman's test

Table 4. Analysis of viral load and serum cystatin C

Viral load	Median serum cystatin C (range), mg/L	P value*
<40, copies/mL	2.4 (0.26-13.61)	0.05
≥40, copies/mL	3.7 (2.61-6.55)	

*Mann-Whitney test

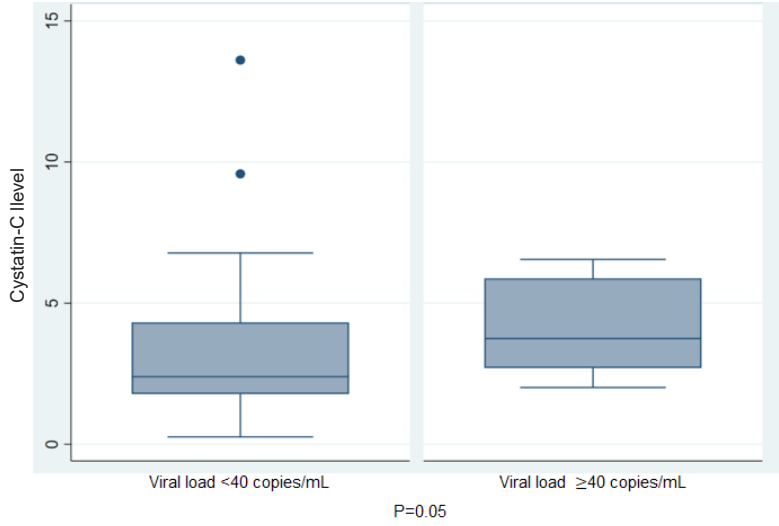

Figure 1. Box-plot of serum cystatin C according to viral load

due to the fact that 71.7% of our subjects were in clinical stage III and IV at the time of HIV diagnosis, with a median age at diagnosis of 3 years.

A previous study reported increased prevalence of kidney disorders among African-American black people with HIV related to apolipoprotein L-1 (APOL1) gene variant, with increased risk of HIV associated nephropathy (HIVAN) up to 29-fold.[33] APOL1 risk alleles were associated with focal and segmental glomerulosclerosis (FSGS), hypertension-attributed end stage kidney disease, proteinuria, impaired renal function, and kidney disease progression, and with more severe histological abnormalities (glomerulosclerosis, interstitial fibrosis, and tubular atrophy) in those with FSGS or proteinuria.[33] Individuals with two APOL1 risk alleles have an estimated 4% lifetime risk for developing FSGS, and untreated HIV- infected individuals have a 50% risk for developing HIVAN. The effect of carrying two APOL1 risk alleles explains 18% of FSGS and 35% of HIVAN; alternatively, eliminating this effect would reduce FSGS and HIVAN by 67%. A survey of world populations indicated that the APOL1 kidney risk alleles are present only on African chromosomes. Zhang *et al.*[34] reported that the African-American, Hispanic, and Asian APOL1 G1 and G2 allele frequencies were 0.22 and 0.13, 0.037 and 0.025, and 0.013 and 0.004, respectively. However, the APOL1 allele has not been well studied in Asia.

This kidney disorder might be also associated with the HIV-1 subtype infecting the patient. HIV-1 subtype C was reported to be the dominant strain in Southern Africa, Eastern Africa, and Southern Asia; while subtype A was common in West Africa, and subtype B was highly prevalent in West Africa, Europe, Australia, and America.[35] Several studies reported that subtypes CRF01_AE, B, C and G were the most common in Indonesia.[36-38] HIV-1 subtype C has been identified as a risk factor for HIVAN,35 whereas subtype CRF01_AE was reported to be associated with the progression of HIV infection.[39]

In our study, there were 4 (7%), 21 (38%), and 31 (55%) subjects with eGFR in the ranges of 60-89, 30-59, and <30 mL/min/1.73m^2, respectively. These percentages of patients with decreased eGFR were much higher than in two other studies.

Dondo *et al.*[40] showed that 34.6% of pediatric HIV patients had mild-moderate renal dysfunction (eGFR 30 to <90 mL/min/1.73m^2). Furthermore, Fredrick *et al.*[28] reported that 15.8%, 59.6%, and 34.6% of pediatric HIV patients aged 1-14 years had eGFR in the ranges of 30-59, 60-89, and >90ml/min/1.73m^2, respectively). Decreased eGFR in our study was similar to studies that showed that the most frequent renal manifestation in pediatric HIV patients receiving ART in India was a reduction in eGFR, which was noted in 44% of subjects.[41]

The elevated cystatin C in our subjects is evidence of subclinical kidney damage, as the kidney can serve as an HIV reservoir leading to continuous increases of serum cystatin C.[42] As such, we propose cystatin C to be a prognostic marker of kidney and cardiovascular functions, as well as a predictor of mortality compared to creatinine-based eGFR.[43] A previous study showed that serum cystatin C levels in a control group of all ages were consistently stable according to the reference value of healthy children.[44]

Serum cystatin C-based eGFR calculation revealed that 93.3% of our subjects had decreased kidney function, indicating detrimental effects of HIV on the kidneys. This finding was also supported by several predisposing factors, including longer duration of HIV, history of nephrotoxic drug consumption, and comorbidities such as tuberculosis, diabetes mellitus, or any other systemic inflammation commonly found in pediatric our HIV patients.

We found no significant correlation between CD4 (both absolute count and percentage) and cystatin C. However, HIV patients with low CD4 cells tended to have high serum cystatin C. These result is consistent with previous Nigerian study that showed no relationship between kidney function and immunological/clinical stage of HIV in pediatric patients,[30] though the lack of association might have been due to the small sample size. However, our findings were contradictory to those of Abiodun *et al.*[31] which showed a weak correlation between CD4 count and serum cystatin C level in pediatric HIV patients older than 5 years of age (r=-0.281; P=0.005). Our study results also demonstrated inconsistencies between clinical and immunological response in HIV, in which kidney disorders were significantly associated with severe immunosuppressive state, but not with several parameters to determine HIV clinical stage. This observation might have been due to factors such as history of co-morbidities like advanced stage of tuberculosis, with or without immunological and kidney dysfunction. Kidney disorders might also be the initial clinical manifestation of HIV in some patients.

The CD4 count and viral load are the most well-established variables to determine the severity of immunodeficiency and disease progression of HIV.[12] CD4 count is also correlated with terminal stage of kidney disease.[11] We found significantly higher median serum cystatin C level in the group with viral load >40 copies/mL. Therefore, we were able to predict serum cystatin C level using viral load, instead of CD4. A study showed that viral load was a better prognostic variable rather than CD4 count, yet the validity of the study was limited due to small sample size and did not take any other established prognostic variables or combinations into consideration.[22]

Creatinine and cystatin C-based eGFR values were significantly different in our study. The median creatinine-based eGFR was 148.3 (range 87.8-278.2) mL/min/1.73m^2, indicating that 93.3% of subjects had normal kidney function. However, the cystatin C-based eGFR calculation was much smaller with median of 28.1 (range 8.7-88.6) mL/min/1.73m^2, which indicated that 56 (93.3%) subjects had decreased kidney function according to the 2014 KDIGO criteria45 for chronic kidney disease. Therefore, our findings provide evidence for the superiority of cystatin C over creatinine as a marker of renal dysfunction. Detecting impaired kidney function will be possible by measuring the Cystatin C levels compared to waiting for the reduced eGFR with creatinine serum results.

A limitation of our study was not analyzing proteinuria as a risk factor of kidney disorders. Furthermore, serum cystatin C measurement by nephelometric test and Filler's formula have not been validated in pediatric HIV patients. Further study is needed with a larger sample size and cohort method with serial cystatin C and eGFR measurements after three months to exclude transient decrease of eGFR due to other factors.

In conclusion, HIV viral load is significantly associated with serum cystatin C level, while CD4 count has no significant correlation with cystatin C.

Conflicts of interest

None declared.

Acknowledgments

The authors would like to thank Hadiyana and Fajar, for their guidance in statistical analysis of the data.

Funding acknowledgments

The authors received no specific grants from any funding agency in the public, commercial, or not-for-profit sectors.

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