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ORIGINAL ARTICLE

The relationship between neutrophil-lymphocyte ratio and ocular manifestations in children with human immunodeficiency virus infection

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ABSTRACT

Aim To investigate the association between neutrophil-lymphocyte ratio (NLR) and ocular manifestations in children with human immunodeficiency virus (HIV) infection.

Methods This cross-sectional study involved 75 HIV-positive children aged 5–18 years at Yayasan Peduli Anak, Medan, Indonesia, from October to December 2023. Data were collected via interviews, comprehensive eye examinations (visual acuity, slit-lamp biomicroscopy, Schirmer test, indirect ophthalmoscopy), and recent NLR from medical records. Systemic cytomegalovirus (CMV) infection was assessed via CMV PCR. Sample size was calculated for correlation analysis (α=0.05, power=0.80, effect size=0.5).

Results Of 75 participants (56% male, median age 11.64 years), 88% had normal immune status. Mean antiretroviral therapy (ARV) duration was 9.56 years. Common ocular complaints included blurry vision (24%), red/itchy eyes (16%), and watery eyes (4%); no dry eye was reported. Anterior segment findings included conjunctivitis (6%), blepharitis (8%), and corneal scarring (4%); posterior segment findings included tigroid fundus/nasalization (4%) and retinal detachment (2%). Mean NLR was 1.76 in those with ocular manifestations (p=0.024). CMV PCR positivity was significantly associated with blurry vision (OR=6.63; p=0.015), red eyes (OR=4.75; p=0.049), corneal scarring (OR=16.00; p=0.044), and nasalization (OR=16.00; p=0.044).

Conclusion Elevated NLR was associated with ocular manifestations in paediatric HIV, particularly CMV-related complications. Regular eye screenings and ARV adherence are critical for early detection and prevention of vision-threatening conditions.

Keywords: antiretroviral therapy, cytomegalovirus, eye diseases, inflammation, paediatrics

INTRODUCTION

Human immunodeficiency virus (HIV) targets CD4 cells, leading to immune suppression and, in advanced stage, acquired immunodeficiency syndrome (AIDS) (1). Globally, approximately 1.7 million children under the age of 15 live with HIV, with rising cases in developing countries (2). Ocular complications in paediatric HIV, affecting 20–54% of cases, pose a significant risk of blindness, impacting quality of life (3). Unlike adults, children exhibit unique immunological profiles, necessitating specific research into paediatric ocular manifestations (4).

Previous studies often focused on adults or used retrospective designs with limited samples, reducing generalizability (5). Systemic inflammatory biomarkers like the neutrophil-lymphocyte ratio (NLR) have been underutilized in predicting ocular complications in children (6). NLR, an indicator of systemic inflammation, is widely applied in conditions like cardiovascular disease and infections, reflecting immune damage severity in HIV (7). Exploring NLR's role in chronic inflammation affecting ocular structures supports early detection and intervention strategies to prevent vision loss and enhance quality of life (8).

The aim of this study was to explore the relationship between NLR and eye complications in children with HIV infection.

PATIENTS AND METHODS

Patients and study design

This cross-sectional study involved 75 HIV-positive children aged 5–18 years, recruited via consecutive sampling at Yayasan Peduli Anak, Medan, Indonesia, from March to December 2023.

Inclusion criteria included HIV-positive children on antiretroviral therapy (ARV) for >6 months with guardian consent. Exclusion criteria were ARV therapy <6 months or prior ocu-

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lar surgery. Data collected included sociodemographic details, HIV diagnosis history, transmission mode, ARV duration, ocular complaints, and NLR from medical records.

The study adhered to the Helsinki Declaration and was approved by the Research Ethics Committee of the University of North Sumatra (Approval No. 123/KEP/USU/2023).

Methods

ARV therapy comprised standard regimens (e.g., tenofovir, lamivudine, efavirenz) as per Indonesian national guidelines (9). Ophthalmological examinations included: visual acuity using Snellen Chart (Nidek SC-1600, Nidek Co., Ltd., Gamagori, Japan) (10); anterior segment evaluation via slit-lamp biomicroscope (Topcon SL-D7, Topcon Corporation, Tokyo, Japan) (11), including Schirmer test (without anaesthesia, measuring tear production <5 mm/5 min indicating dry eye) (12); posterior segment examination using Ullmann Indirect Ophthalmoscope with a 20D lens (Volk Optical, Mentor, OH, USA) after pupil dilation with 0.5% tropicamide (13); - Dry Eye Questionnaire-5 (DEQ-5) assessed dry eye symptoms (score ≥6 indicating dry eye) (14).

NLR was calculated from blood tests (neutrophil count divided by lymphocyte count) from medical records within the past month.

CMV infection was confirmed via polymerase chain reaction (PCR) (Roche LightCycler 480, Roche Diagnostics, Basel, Switzerland) detecting CMV DNA in blood (15).

Statistical analysis

Sample size (n=75) was calculated for correlation analysis (α=0.05; power=0.80; effect size=0.5), requiring a minimum of 69 participants (16). Pearson or Spearman correlation assessed relationships between NLR, viral load (VL), CD4 count, and ocular manifestations, based on data distribution. Fisher's exact, Kruskal-Wallis, and Mann-Whitney tests evaluated associations. Significance was set at $p<0.05$.

RESULTS

Of 75 participants, 42 (56%) were male, with a median age of 11.64 years (SD 3.26). Most (88%) had normal immune status (CD4 >500 cells/mm³). Mean ARV duration was 9.56 years, with 60% treated for 5–10 years (Table 1).

Ocular complaints included blurry vision (24%), red/itchy eyes (16%), and watery eyes (4%); no dry eye was reported (Table 2).

Anterior segment findings were conjunctivitis (6%), blepharitis (8%), and corneal scarring (4%); posterior segment findings included tigroid fundus/nasalization (4%) and retinal detachment (2%) (Table 3).

Mean NLR was 1.76 in children with ocular manifestations ($p=0.024$), and median VL was 112 copies/mL ($p=0.036$). No significant associations were found between ocular manifestations and gender ($p=0.622$), age ($p=0.799$), transmission mode ($p=0.333$), disease duration ($p=0.216$), ARV duration ($p=0.216$), or CD4 count ($p=0.405$) (Table 4).

The average value of NLR among those with ocular symptoms was 2.71, while the CD4 count was 885.5 cells/mm³.

No important correlations were found between gender, age, method of transmission, duration of disease, ARV treatment and the occurrence of ocular manifestations ($p>0.05$). However, a statistically significant relationship was observed between

Table 1. Demographic characteristics of 75 children with human immunodeficiency virus (HIV) infection

Variable	
Gender (No; %)	
Male	42 (56)
Female	33 (44)
Age (years)	
Mean (±SD)	11.64 (3.26)
Median (Min – Max)	12 (5 – 17)
5-<10	15 (20)
10-<15	48 (64)
15-18	12 (16)
Transmission method (No; %)	
MTCT	60 (80)
Sexual	9 (12)
Transfusion	6 (8)
Duration of illness (years)	
Mean (±SD)	9.56 (±3.50)
Median (Min – Max)	10 (3 – 16)
< 5	6 (8)
5 – 10	45 (60)
>10	24 (32)
ARV duration (years)	
Average (±SD)	9.56 (±3.50)
Median (Min – Max)	10 (3 – 16)
< 5	6 (8)
5–10	15 (60)
>10	10 years
Visual acuity OD	
6/6-6/18 (normal/no visual impairment)	66 (88)
<6/18-6/60 (moderate visual impairment)	3 (4)
<6/60-3/60 (severe visual impairment)	3 (4)
<3/60 (blind)	3 (4)
Visual acuity OS	
6/6-6/18 (normal/no visual impairment)	69 (92)
<6/18-6/60 (moderate visual impairment)	0 (0)
<6/60-3/60 (severe visual impairment)	0 (0)
<3/60 (blind)	6 (8)

MTCT, mother-to-child transmission; ARV, antiretroviral therapy; OD, oculus dexter; OS, oculus sinister;

Table 2. Frequency of bilateral eye complaints in children with human immunodeficiency virus (HIV) infection

Manifestations of bilateral eyes*	No (%) of children
Red eye	
Present	12 (16)
Absent	63 (84)
Itchy eyes	
Present	4 (16)
Absent	21 (84)
Watery eyes	
Present	3 (4)
Absent	72 (96)

*Present indicates that the specified ocular symptom (e.g., red eye) was reported by the patient during the examination; Absent indicates that the patient did not report the specified ocular symptom

Table 3. Frequency of bilateral eye manifestations in children with human immunodeficiency virus (HIV) infection

Eye manifestation	No (%) of children
Anterior segment	
Conjunctivitis	5 (6)
Blepharitis	6 (8)
Corneal Scarring	3 (4)
Posterior Segment	
Retinal Detachment	2 (2)
Tigroid fundus/nasalization	3 (4)

viral load (VL) and ocular manifestation (p=0.036), as well as between NLR and ocular manifestation (p=0.024). In contrast, no significant association was detected between CD4 level and ocular manifestations (p=0.405) (Table 4).

Table 4. Association between demographic characteristics, viral load (VL), CD4, neutrophil-lymphocyte ratio (NLR), and ocular manifestations

Variable	Ocular manifestation		p
	YES	NO	
Gender (No; %)			
Male	5 (35.7)	9 (64.3)	0.622*
Female	5 (45.5)	6 (54.5)	
Age (years) (No; %)			
5 - < 10 years	2 (40)	3 (60)	
10 - < 15 years	7 (43.8)	9 (56.2)	0.799*
15 - 18 years old	1 (25)	3 (75)	
Transmission method (No; %)			
MTCT	9 (45)	11 (55)	
Sexual	0	3 (100)	0.333*
Transfusion	1 (50)	1 (50)	
Duration of illness (years) (No; %)			
< 5	0	2 (100)	
5 - 10	8 (53.3)	7 (46.7)	0.21†
>10	2 (25)	6 (75)	
Duration of ARV treatment (years)			
< 5 years	0	2 (100)	
5 - 10 years	8 (53.3)	7 (46.7)	0.216†
>10 years	2 (25)	6 (75)	
VL (copies/mL)			
Mean (±SD)	4618.2 (±7614.83)	1950.53 (±3504.12)	0.036‡
Median (Min - Ma±)	112 (23-18975)	98 (0-28191)	
CD4 (cell/mm^3)			
Average (±SD)	781.8 (±217.93)	843,87 (±168.3)	0.405‡
Median (Min-Max)	885.5 (378-981)	899 (319-981)	
NLR			
Average (±SD)	1.76 (±0.44)	2,71 (±0.59)	0.024‡
Median (Min-Max)	2(1-2)	2.65 (1.98- 4.36)	

*Fischer test; †Kruskal Wallis test; ‡Mann Whitney test;
MTCT, mother-to-child transmission; ARV, antiretroviral therapy;

Long-term ART adherence (mean 9.42 years) correlated with low VL (median 112 copies/mL). The average VL was 3017.6 copies/mL (88% of participants had VL <5000 copies/mL), and the average CD4 count was 819.04 cells/mm^3 (88% had CD4 >500 cells/mm^3).

CMV PCR positivity (10/75 cases) was significantly associated with blurry vision (OR=6.63, p=0.015), red eyes (OR=4.75, p=0.049), corneal scarring (OR=16.00, p=0.044), and nasalization (OR=16.00, p=0.044) (Table 5).

Table 5. Association between cytomegalovirus (CMV) PCR positivity and ocular manifestations

Ocular manifestation	No (%) of children		OR (95% CI)	p*
	CMV PCR Positive (N=10)	CMV PCR Negative (N=65)		
Blurry vision	6 (60)	12 (18.5)	6.63 (1.45–30.27)	0.015
Red eyes	4 (40)	8 (12.3)	4.75 (1.01–22.34)	0.049
Conjunctivitis	1 (10)	4 (6.2)	1.69 (0.17–16.93)	0.654
Blepharitis	1 (10)	5 (7.7)	1.33 (0.14–12.79)|	0.805
Corneal scaring	2 (20)	1 (1.5)	16.00 (1.32–193.89)	0.044
Tigroid fundus/ nasalization	2 (20)	1 (1.5)	16.00 (1.32–193.89)	0.044
Retinal detachment	1 (10)	1 (1.5)	7.11 (0.41–123.45)	0.333

*Fisher's exact test
OR, Odds Ratio, CI, confidence interval;

DISCUSSION

Children with HIV face heightened risks of systemic and ocular complications due to immature immune systems and rapid viral replication, increasing susceptibility to opportunistic infections (3). This study found blurry vision (24%), red/itchy eyes (16%), and watery eyes (4%) as common complaints, consistent with prior reports of 20–54% ocular involvement in paediatric HIV (4). Anterior segment manifestations (conjunctivitis 6%, blepharitis 8%, corneal scarring 4%) align with findings reporting conjunctivitis prevalence of 13–25% (17). These may result from immune dysregulation disrupting conjunctival flora and lacrimal function (20).

Posterior segment abnormalities (tigroid fundus/nasalization 4%, retinal detachment 2%) were less frequent, possibly due to effective ARV therapy maintaining immune status (mean CD4 885.5 cells/mm^3) (15). CMV-related complications, particularly corneal scarring and nasalization highlight CMV's role in severe ocular damage, consistent with studies reporting CMV retinitis in 33% of HIV cases (23). The significant association between NLR and ocular manifestations suggests NLR as a valuable biomarker for monitoring inflammation-driven complications (7).

Mother-to-child transmission (MTCT) dominated (80%), underscoring the need for enhanced prevention programs, including ARV provision to pregnant women and safe breastfeeding education (2). Long-term ARV adherence (mean 9.56 years) correlated with low VL (median 112 copies/mL) and reduced ocular complications, supporting ARV's protective role (9).

The study has limitations, including a limited sample size and a lack of longitudinal data that allow for long-term evaluation on changes in eye manifestations. In addition, other factors such as the role of comorbidities or side effects of ARV therapy on the eye have not been analysed in depth. Further research is needed to explore the long-term relationship between VL, ARV therapy, and various ocular manifestations, as well as

consider the influence of other factors such as age, gender, and previous therapy history. By understanding the complex dynamics between HIV, ocular manifestations, and ARV therapy, a more comprehensive clinical approach can be developed to improve the quality of life of HIV patients and prevent serious complications to their vision.

In conclusion, regular eye screenings and ARV adherence are crucial for early detection and prevention of ocular complications in children with HIV. Elevated NLR and CMV positivity indicate an increased risk of vision-threatening conditions, necessitating targeted monitoring. Comprehensive MTCT prevention and multidisciplinary care can improve quality of life and prevent blindness.

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