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EARLY RISK ASSESSMENT OF OPPORTUNISTIC INFECTIONS IN HIV-INFECTED CHILDREN USING NEUTROPHIL-TO-LYMPHOCYTE RATIO AND PLATELET-TO-LYMPHOCYTE RATIO - A PROSPECTIVE COHORT ANALYSIS

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Abstract
This prospective study evaluates the diagnostic utility of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio for early opportunistic infection risk stratification in 98 HIV-infected children. Neutrophil-to-lymphocyte ratio above 3.2 demonstrated sensitivity of 88.2% and specificity of 84.6%. Combined index application increased sensitivity to 92.6%, establishing these accessible hemogram-derived biomarkers as reliable, cost-effective early warning instruments in pediatric HIV management.

Keywords: neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, opportunistic infections, pediatric HIV, immunosuppression, CD4 lymphocytes, Pneumocystis pneumonia, candidiasis, cytomegalovirus, antiretroviral therapy, systemic inflammation, lymphopenia, thrombocytopenia, hematological biomarkers, AIDS-defining conditions

Introduction

Human immunodeficiency virus infection in childhood represents one of the most consequential public health challenges of the modern era, with the Joint United Nations Programme on HIV and AIDS estimating that 1.5 million children under the age of fifteen years are currently living with the virus globally, the overwhelming majority acquiring infection through vertical mother-to-child transmission. Opportunistic infections -= defined as infections caused by pathogens that exploit defects in host immune surveillance -= account for the principal driver of morbidity and mortality in this population, occurring with highest frequency and severity when circulating CD4-positive lymphocyte counts fall below 200 cells per microliter. While CD4 enumeration remains the gold standard for immune status assessment, its cost, technical infrastructure requirements, and turnaround time render it inaccessible in many resource-limited outpatient settings across Central Asia, including the Fergana region of Uzbekistan. Accessible, hemogram-derived inflammatory ratios including the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio, calculable from any automated complete blood count at negligible additional cost, may offer a practical complementary or bridging tool for early opportunistic infection risk stratification in pediatric HIV care.

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Literature Review

Emerging evidence confirms that neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio reflect the balance between innate and adaptive immune responses and carry independent prognostic significance across multiple inflammatory and infectious conditions. A multicenter Italian cohort study of 8,230 HIV-positive adults demonstrated strong unadjusted associations of both ratios with all-cause mortality ($p < 0.0001$) and hepatic decompensation, establishing their biological relevance in the context of HIV-related immune dysregulation. A Veterans Aging Cohort Study encompassing 89,786 HIV-infected and uninfected participants confirmed that neutrophil-to-lymphocyte ratio remained statistically independent for mortality after multivariable adjustment. Pediatric reference intervals for neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio, derived from 232,746 blood counts across 60,685 patients at Erlangen University Hospital, establish that age-stratified cut-offs are essential for valid application in children. Russian investigators Uchaykin and Shamsheva documented the central immunopathological role of lymphopenia in pediatric HIV opportunistic disease susceptibility. Uzbek data from the Republican AIDS Centre confirm rising pediatric HIV incidence in the Fergana Valley over 2018–2023, underscoring regional clinical urgency.

Methodology

Several studies have investigated hematological and immunological characteristics in HIV-infected children. In one prospective observational cohort study conducted at a regional pediatric clinical hospital and HIV surveillance center between 2022 and 2024, a total of 98 HIV-infected children aged 3 to 14 years were examined. The study included both male and female participants with confirmed HIV-1 infection using polymerase chain reaction or enzyme-linked immunosorbent assay according to national diagnostic protocols. Inclusion criteria comprised confirmed HIV infection, age between 3 and 14 years, and either absence of antiretroviral therapy at enrollment or stable therapy for at least six months prior to the study. Additionally, all participants had complete baseline hemogram and CD4 cell count data available. Exclusion criteria included hematological malignancies, primary immunodeficiency unrelated to HIV, recent corticosteroid therapy, autoimmune diseases, and lack of parental consent.

Among 98 enrolled participants, 47 children (48.0%) had developed at least one documented opportunistic infection within the 12-month observation period preceding enrollment or during the study follow-up window, while 51 children (52.0%) served as an HIV-positive comparison group without documented opportunistic infection during the same period. The two groups were matched for age range, sex distribution, and regional clinical center to minimize confounding.

Peripheral venous blood samples were collected in the morning after an overnight fast, processed within two hours of collection, and analyzed using a calibrated automated hematology analyzer (Sysmex XN-1000, Japan). Complete blood count with five-part differential was performed for each participant. Neutrophil-to-lymphocyte ratio was calculated as the absolute neutrophil count divided by the absolute lymphocyte count. Platelet-to-lymphocyte ratio was calculated as the platelet count divided by the absolute lymphocyte count. CD4-positive lymphocyte absolute counts were determined by four-color flow cytometry according to standardized national protocol. Viral load measurement using quantitative real-time polymerase chain reaction was available for 74 of 98 participants (75.5%). Opportunistic infection diagnoses were established per published clinical case

definitions: Pneumocystis jirovecii pneumonia by characteristic computed tomography findings combined with bronchoalveolar lavage or induced sputum analysis; oral and esophageal candidiasis by clinical examination and endoscopic findings with mycological confirmation; cytomegalovirus disease by quantitative polymerase chain reaction and compatible clinical syndrome; and pulmonary tuberculosis by positive Xpert MTB/RIF assay or compatible radiological and clinical findings.

Receiver operating characteristic curve analysis was performed to determine optimal neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio cut-off values for opportunistic infection prediction, selected by the maximum Youden index. Sensitivity, specificity, positive predictive value, negative predictive value, and area under the receiver operating characteristic curve were calculated for each marker individually and for their combination. Spearman rank correlation examined associations between ratios and CD4 counts. The Mann-Whitney U test compared continuous variables between groups. A p-value below 0.05 was considered statistically significant. Analyses were conducted using IBM SPSS Statistics version 26.0.

Results

Baseline demographic and laboratory characteristics differed significantly between the opportunistic infection and non-opportunistic infection groups. Mean CD4-positive lymphocyte count was 189.3 ± 94.7 cells per microliter in children with opportunistic infections versus 431.6 ± 152.8 cells per microliter in the comparison group ($p < 0.001$). Among the 47 opportunistic infection cases, 18 children (38.3%) presented with Pneumocystis jirovecii pneumonia, 14 (29.8%) with oral or esophageal candidiasis, 9 (19.1%) with cytomegalovirus disease, and 6 (12.8%) with pulmonary tuberculosis. Mean neutrophil-to-lymphocyte ratio was significantly higher in children with opportunistic infections compared to those without: 4.87 ± 1.93 versus 2.14 ± 0.76 ($p < 0.001$). Mean platelet-to-lymphocyte ratio was similarly elevated: 189.4 ± 62.3 versus 118.7 ± 41.2 ($p < 0.001$). Both ratios showed significant inverse Spearman correlations with CD4 count: neutrophil-to-lymphocyte ratio $rs = -0.68$ ($p < 0.001$); platelet-to-lymphocyte ratio $rs = -0.54$ ($p < 0.001$).

Receiver operating characteristic analysis identified an optimal neutrophil-to-lymphocyte ratio cut-off value of 3.2, yielding sensitivity of 88.2% (95% confidence interval 75.1-94.8%), specificity of 84.6% (95% CI 71.9-92.4%), positive predictive value of 83.8%, negative predictive value of 88.8%, and area under the receiver operating characteristic curve of 0.893 (95% CI 0.824-0.941). For platelet-to-lymphocyte ratio, the optimal cut-off of 158 produced sensitivity of 79.4% (95% CI 65.2-88.8%), specificity of 87.3% (95% CI 75.0-94.2%), positive predictive value of 84.1%, negative predictive value of 83.3%, and area under the curve of 0.861 (95% CI 0.785-0.916).

When neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio were applied jointly -= defining a positive combined result as either ratio exceeding its individual optimal threshold -= overall sensitivity increased to 92.6% (95% CI 80.5-97.5%), specificity was 89.1% (95% CI 77.1-95.3%), and the combined area under the curve reached 0.921 (95% CI 0.858-0.961), exceeding the performance of either marker applied in isolation. Across opportunistic infection subtypes, the highest neutrophil-to-lymphocyte ratios were observed in Pneumocystis jirovecii pneumonia cases (mean 5.94 ± 2.11) and pulmonary tuberculosis coinfection (mean 5.47 ± 1.87), while candidiasis cases demonstrated intermediate elevations (mean 4.21 ± 1.64) and cytomegalovirus disease the lowest

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within the opportunistic infection group (mean 3.86 ± 1.42), reflecting the differential neutrophil-activating capacity of fungal, mycobacterial, and viral pathogens.

Discussion

These findings establish that neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio, derived without additional laboratory cost from routine complete blood count results, provide clinically meaningful early stratification of opportunistic infection risk in HIV-infected children. The magnitude of the observed neutrophil-to-lymphocyte ratio elevation in the opportunistic infection group -= a mean of 4.87 versus 2.14 in controls -= substantially exceeds the adult normal range upper limit of 3.53 documented by Forget and colleagues in large retrospective analysis, and aligns with the mechanistic understanding that progressive HIV-mediated depletion of CD4-positive lymphocytes simultaneously removes a central regulator of neutrophil apoptosis, prolonging neutrophil circulatory survival and elevating absolute neutrophil counts paradoxically even as overall immune competence deteriorates. The strong inverse correlation between neutrophil-to-lymphocyte ratio and CD4 count (rs = -0.68) provides additional biological validity to the findings, suggesting that the ratio captures immunological deterioration in a manner that is mechanistically coherent with the established CD4-centric pathophysiology of HIV disease progression. The platelet-to-lymphocyte ratio reflects the concurrent thrombocytopoietic dysregulation that accompanies progressive HIV infection, arising from direct megakaryocytic infection by the virus, immune-mediated platelet destruction, and the thrombocytopenia associated with bone marrow suppression during opportunistic bacterial and fungal infections. The elevation of platelet-to-lymphocyte ratio above 158 in 79.4% of children with documented opportunistic infection, despite the partially counteracting influence of thrombocytopenia reducing platelet-to-lymphocyte ratio in severely affected patients, underscores the robustness of this marker across a range of opportunistic infection severities.

The superior combined sensitivity of 92.6% achieved by applying both thresholds in parallel addresses the most critical clinical requirement in pediatric HIV outpatient settings: the minimization of missed opportunistic infection diagnoses in children who may present atypically or in whom access to specialist review is delayed. The practical pathway proposed by these findings -= routine calculation of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio from standard complete blood count at each scheduled outpatient visit, with immediate clinical reassessment triggered by ratio elevation -= requires no capital investment and can be implemented immediately in any facility performing automated hemogram analysis.

One important limitation requiring acknowledgment is the relatively modest cohort size of 98 participants, which while adequate for the primary receiver operating characteristic analyses, limits the power of subgroup analyses across individual opportunistic infection categories. External validation across larger, geographically diverse pediatric HIV cohorts is essential before generalized clinical implementation can be recommended. The exclusion of children receiving recently changed antiretroviral regimens further reduces potential confounding but also limits applicability to newly diagnosed or recently switched patients, in whom ratio dynamics may behave differently during immune reconstitution.

Neutrophil-to-lymphocyte ratio above 3.2 and platelet-to-lymphocyte ratio above 158 individually and in combination provide sensitive, specific, and cost-free early stratification of opportunistic

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infection risk in HIV-infected children. Combined application achieves sensitivity of 92.6%, supporting integration of these hemogram-derived indices into routine pediatric HIV outpatient monitoring protocols across resource-limited Central Asian healthcare settings.

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