REVISTA DO INSTITUTO DE MEDICINA TROPICAL DE SÃO PAULO
JOURNAL OF THE SÃO PAULO INSTITUTE OF TROPICAL MEDICINE

ORIGINAL ARTICLE

https://doi.org/10.1590/S1678-9946202466067

Neutrophil/lymphocyte and platelet/lymphocyte ratio in seropositive women for human immunodeficiency virus (HIV) and human papillomavirus (HPV) coinfection

Karina Donato Fook[1,2], Maria José Abigail Mendes Araújo[2], Alessandra Costa de Sales Muniz[2], Mônika Machado de Carvalho[2], Ana Cléa Cutrim Diniz de Morais[1,2], Deborah Rocha de Araújo[2], Sulayne Janayna Araújo Guimarães[2], Camila Penha Abreu Souza[2], Carla Déa Trindade Barbosa[1,2], Maria Fernanda Lima Bertolaccini[2], Ilka Kassandra Pereira Belfort[3,4], Fernanda Ferreira Lopes[1], Sally Cristina Moutinho Monteiro[1]

ABSTRACT

This study aims to investigate the possible association between neutrophil/lymphocyte and platelet/lymphocyte ratio in women with HIV, undergoing antiretroviral treatment, with HPV coinfection. This is a cross-sectional study with HIV positive women; their biological samples were collected for laboratory tests (complete blood count) and oncotic cytology for detection of HPV DNA, by PCR-Nested (PGMY and GP primers). Viral load and CD4 and CD8 T-cells counts were obtained from medical records. The data were analyzed, comparing the two groups: those with coinfection and those without it. From 82 HIV seropositive women, 50% exhibited HPV coinfection and 12.2% of coinfected patients had cervical cell alterations. Quantification of viral load, CD4 and CD8 T-cells count, CD4 / CD8 ratio and neutrophil/lymphocyte (NLR) and platelet/lymphocyte (PLR) ratio presented significant differences between groups ($p<0.05$). The predicting power of NLR and PLR in differentiating HIV/HPV coinfection which demonstrated differences between groups (AUC of 0.882 and 0.776 for NLR and PLR, respectively). There is a relation between the neutrophil/lymphocyte and platelet/lymphocyte ratio with HIV/HPV coinfection in women undergoing antiretroviral treatment, suggesting a state of greater and persistent systemic inflammation, reflecting as a biomarker for screening and monitoring these patients.

KEYWORDS: Human immunodeficiency virus. Human papillomavirus. Oncotic cytology. Biomarkers.

[1]Universidade Federal do Maranhão, Programa de Pós-Graduação em Saúde do Adulto, São Luís, Maranhão, Brazil

[2]Universidade Federal do Maranhão, Hospital Universitário, Laboratório de Análises Clínicas e Histocompatibilidade, São Luís, Maranhão, Brazil

[3]Secretaria Municipal de Saúde de São Luís, São Luís, Maranhão, Brazil

[4]Faculdade Laboro, São Luís, Maranhão, Brazil

Correspondence to: Fernanda Ferreira Lopes
Universidade Federal do Maranhão, Programa de Pós-Graduação em Saúde do Adulto, Av. dos Portugueses, 1966, Vila Bacanga, CEP 65080-805, São Luís, MA, Brazil

E-mail: fernanda.ferreira@ufma.br

Sally Cristina Moutinho Monteiro
Universidade Federal do Maranhão, Programa de Pós-Graduação em Saúde do Adulto, Av. dos Portugueses, 1966, Vila Bacanga, CEP 65080-805, São Luís, MA, Brazil

E-mail: sally.monteiro@ufma.br

Received: 13 May 2024

Accepted: 2 October 2024

INTRODUCTION

Human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) are public health issues, with 37.9 million HIV-positive individuals in the world and 1.7 million new cases per year[1]. HIV positive women are more susceptible to opportunistic infections and neoplasms, such as human papillomavirus (HPV) infection, when compared to HIV-negative women[2-4]. HIV infection facilitates HPV infection and replication, making it more severe and persistent[5-7]. Furthermore, low CD4 T-cell count and high HIV viral load are independent risk factors for HPV. Such findings are consistent with an important role for the immune response and inflammatory markers in the control[8] and prognostic evaluation of HPV infection.

HIV-positive people on antiretroviral treatment have a persistent degree of systemic inflammation and low activation of the immune system[9]. Elevated levels of inflammatory markers can predict adverse events, as well as low CD4 T-cells and plasma replication of HIV[10,11].

Recently, two biomarkers of blood parameters (neutrophil/lymphocyte [NLR] ratio and platelet/lymphocyte [PLR] ratio) have been shown to be indicative of systemic inflammation, as well as predictive biomarkers of morbidity and mortality for cardiovascular (CVD) and non-cardiovascular diseases, such as cancer and chronic kidney disease (CKD)[12-14]. In a cohort of HIV-positive people, NLR and PLR were associated with risk of death in cases of solid tumors or lymphoma[15], while NLR was considered an independent prognostic factor for cancer-free survival in patients with cervical intraepithelial neoplasia (CIN)[16].

The relation between systemic inflammatory process and development of cancer is well established. Moreover, NLR and PLR are biomarkers of poor prognosis in different organic disorders, with such biomarkers also being related to a cell-mediated immune response in HPV infection control[12-14,16]. Therefore, this study aimed to investigate the possible association between NLR and PLR with the presence of the human papillomavirus in women with human immunodeficiency virus undergoing antiretroviral treatment.

MATERIALS AND METHODS

Ethical approval and consent to participate

This research was approved by the Research Ethics Committee of the University Hospital of the Federal University of Maranhao (Hospital Universitario da Universidade Federal do Maranhao - HU-UFMA, Sao Luis, Maranhao State, under Nº 2.776.970 and C.A.A.E Nº 70989617.4.0000.5086). Investigators explained the study objectives and methodology; all participants were adults and provided written informed consent to take part in the study. Consent forms were kept separately from questionnaires and biological samples to guarantee the ethical standards.

Study population

This is a cross-sectional survey with 82 HIV-positive women. All participants were served at two Reference Centers for HIV treatment in the Sao Luis city, Maranhao State, Brazil. Inclusion criteria were a) age ≥18 years; b) more than five years since HIV diagnosis; c) be in treatment with antiretroviral therapy (ART) for the last three years and at the time of sample collection; d) no CD4 nadir <50 cells/mm^3. Furthermore, pregnant women, women with contraindications for Pap smears (for example, current use of vaginal eggs, menstruation, vaginal douches in the last 24 hour and hysterectomies) were not included.

All participants answered a sociodemographic questionnaire (age, educational level, sexarche, marital status, number of sexual partners during lifetime and type of sexual practice, among others), current history of the disease, drug treatment, information about other sexually transmitted infections and habits (use of tobacco and / or illicit drugs, among others).

Laboratorial investigation

Sample collection

Samples of cervical swabs were collected for cytological and molecular biology exams to detect human papillomavirus. Blood samples were subjected to performance evaluation of the complete blood count.

The CD4 and CD8 T-cells count (cells/mm^3), with flow cytometry, and detectable viral load (copies/mL) data were obtained from electronic medical records of the hospital reference service. The CD4 and CD8 T-cells count and viral load results retrieved from patients' electronic records were selected according to their temporal proximity to the time of testing for HPV on patients' blood samples (conducted in up to three months).

Laboratory tests and oncotic cytology

The blood counts were processed by an Advia 2120 analyzer (Siemens Healthcare Diagnostics, Deerfield, IL). The neutrophil/lymphocyte ratio (NLR) was obtained by dividing the absolute neutrophil count by the absolute lymphocyte count. The platelet/lymphocyte ratio (PLR) was obtained by dividing the absolute platelet count by the absolute lymphocyte count. Oncotic cytology assays were performed using cytological smears obtained with Ayre spatula (ectocervical sample) and endocervical brush (endocervical sample), extended on a glass slide, fixed with ethanol and stained using the Pap smear. The 2001 Bethesda System was used for reporting cervical or vaginal cytologic diagnoses.

HPV DNA testing

DNA extraction was performed following the manufacturer's guidelines (Biopur Mini Spin Plus Extraction Kit, Biometrix, PR, Brazil). The Nested Polymerase Chain Reaction (PCR) technique was performed using a GeneAmp PCR System 9700 thermocycler (Applied Biosystems, Thermo Scientific, California, USA), with PGMY 09 and

11 primers (amplifying 450bp sequences from the region L1 of viral DNA) and GP + 5 and GP + 6 (amplifying 190bp sequences of the L1 region of viral DNA). Samples known as HPV-positive were used as a positive control, whereas ultrapure water was the negative control.

For the amplification reaction using the PGMY09/11 primers, the initial denaturation took place in 2 min at 95 °C followed by 40 cycles of denaturation for 40 s at 95 °C, 40 s of annealing at 55 °C, 40 s of extension at 72 °C. The second round of the Nested PCR was carried out with the GP5 + / GP6 + primers with an initial denaturation at 95 °C for 4 min followed by 45 cycles of denaturation at 95 °C for 45 s, annealing at 40 °C for 1 min and extension at 72 °C for 1 min[17]. The amplification products were evaluated by electrophoresis on 1.5% agarose gel in TBE 1X buffer for 30 minutes at 5 V / cm in a horizontal vat (Life Technologies, Carlsbad, CA, USA). The bands were stained with 0.1% Red Gel (Invitrogen) and visualized using an ultraviolet transilluminator (BioRad Laboratories, Hercules, CA, USA).

Data analysis

Data were analyzed with IBM SPSS® Statistics program version 24.0 Windows (SPSS Inc., Chicago, IL) and level of significance was $p<0.05$ (two-tailed). The Chi-square test and Fisher's exact test were used for group comparison for categorical variable, between HPV+ (positive) or HPV− (negative) participants. The normal distribution of numerical variables was verified, and, after that, Student's *t*-test was used to verify the differences between the means of the categorical groups evaluated.

RESULTS

The sample consisted of 82 HIV-positive women undergoing antiretroviral treatment, of which 41 (50%) were positive for DNA-HPV. Table 1 describes the socioeconomic status of HPV-positive and HPV-negative participants, with a total of 68.3% participants having studied for less than 9 years. In the group of HPV-positive women (HIV/HPV coinfection), it was found that 51.2% live with a partner; 70.7% have a family income of up to 1 minimum wage (Brazilian currency); 51.2% had their first sexual intercourse between 12 and 15 years old; 53.7% had up to three sexual partners during their lifetime; 48.8% use condoms during sexual intercourse; 51.8% practice oral/anal intercourse; 19.5% are smokers; 7.6% had more than four children and 43.9% had an abortion episode. There were no statistically significant differences in socioeconomic aspects and health data between the study groups (Table 1).

Oncotic cytology assays indicated atypical cells in 12.2% of HPV-positive participants and 2.4% of HPV-negative participants (Figure 1), with statistical difference between the groups (Fisher's exact test, $p = 0.010$). In the HPV-positive participants, of those Pap smear showing some atypical squamous cells of uncertain significance (ASC-US), 4.9% presented high-grade squamous intra-epithelial lesion (HSIL) and 2.4% presented low grade squamous intraepithelial neoplasia (LSIL). Among HPV-negative participants, a total of 2.4% Pap smear results presented ASC-US.

Although higher values were observed in the group with HIV/HPV coinfection, no statistically significant difference was found for the following variables: total leukocytes; total neutrophils; total platelets; hemoglobin concentration; and hematocrit between HPV-positive and HPV-negative participants. When CD4 T-cell, CD8 T-cell and the CD4/CD8 ratios were evaluated, there were statistically significant differences ($p = 0.02$; $p = 0.02$ and $p = 0.03$ respectively). The elevation neutrophil/lymphocyte ratio ($p = 0.04$), platelet/lymphocyte ratio ($p = 0.01$) and viral load ($p = 0.04$) also showed a statistical difference between groups (Table 2). All these parameters show higher values among coinfected participants.

Receiver-operating characteristic curve models were assembled to evaluate the area under the curve (AUC). The predicting power of NLR and PLR in differentiating HIV/HPV coinfection were analyzed, which demonstrated differences between groups. The NLR presented an AUC of 0.882 (Sensitivity = 54.2%, Specificity = 100%, Cut off >2.014 and $p>0.05$) and the PLR AUC of 0.776 (Sensitivity = 90.5%, Specificity = 54.5, Cut off >107.06 and $p>0.05$), demonstrating that they are possible predictors of HPV coinfection (Figure 2).

DISCUSSION

In this study, CD4 T- and CD8 T-lymphocyte count, CD4/CD8 ratio, viral load, lymphocyte count, the neutrophil/lymphocyte and platelet/lymphocyte ratios in HIV-positive women were associated with HPV coinfection. Inflammation can largely influence several stages of tumorigenesis, from tumor initiation to promotion and metastatic progression. Moreover, inflammatory cells and their mediators are in fact an essential component of the tumors microenvironment (TME), with cancer cells being able to induce inflammatory reactions through various mechanism[18]. HIV infection increases the risk of coinfections, such as HPV[5-7], although some studies show no impact on HPV-associated disease[19,20]. Thus, it is still necessary to study HPV infection and its connection to HIV due to its great importance for public health.

Table 1 - Socioeconomic and health data of women with and without HIV/HPV coinfection, Sao Luis, Maranhao State, Brazil, 2019.

	HPV positive (%) N=41	HPV negative (%) N=41	*p*-value
Age			
18 to 34 years	29.3	22.0	0.691
35 to 49 years	39.0	39.0	
More than 50 years	31.7	39.0	
Education Level			
≤ 9 years	68.3	68.3	0.648
> 9 to 12 years	22.0	26.8	
> 12 years	9.8	4.9	
Marital Status			
With partner	51.2	43.9	0.507
Without partner	48.8	56.1	
Family income *			
Up to a minimum wage	70.7	65.9	0.853
1 to 3 minimum wages	24.4	26.8	
3.1 to 5 minimum wages	4.9	7.3	
Age of first sexual intercourse	0	0	0.825
< 12 years	51.2	48.8	
12 to 15 years	48.8	51.2	
> 15 years			
Number of sexual partners			
≤ 3	53.7	46.3	
4 to 6	29.3	31.7	0.775
≥ 7	17.1	22.0	
Condom use			
Yes	48.8	48.8	1.0
No	51.2	51.2	
Anal/Oral intercourse			
Yes	53.7	39.0	0.184
No	46.6	61.0	
Contraceptive use			
Yes	5.1	2.5	
No	94.9	97.5	0.541
Smoking			
Yes	19.5	7.3	0.125
No	80.5	92.7	
Parity			
Nulliparity	4.9	14.6	0.258
1 to 3	19.5	12.2	
≥4	75.6	73.2	
Abortion			
Yes	43.9	41.5	0.823
No	56.1	58.5	

Data presented in proportion. Tests used: Chi-square and Fisher's exact test. *Minimum wage in Brazil, 2019 = R$ 998.00.

This study has also found that atypical cells on oncotic cytology were more frequent in HPV-positive participants. The data obtained from the analyzed population showed a low proportion of coinfected participants (HIV/HPV) with cytological changes, however, it was more frequent in HIV/HPV coinfection participants, corroborating with literature data that detected a higher prevalence of cytological lesions in the population with HIV/HPV coinfection[21]. There were atypical cells on oncotic cytology in 12.2% of HPV-positive participants (higher proportion of ASCUS and HSIL). Hawes *et al.*[22] found similar results in HIV-seropositive Africans with a rate of 12.3% of LSIL, while Zhang *et al.*[23] found 16% with cellular changes.

Association between the risk of HPV infection and its persistence was observed in HIV-positive women, and cytological changes and progression to intraepithelial neoplasia are facilitated in HIV/HPV coinfection, so

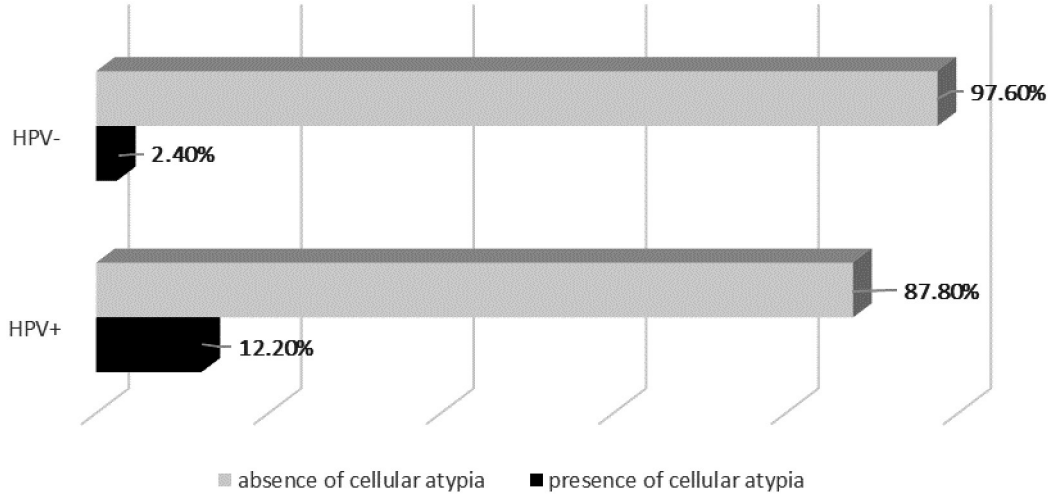

Figure 1 - Frequency of atypical cells (%) detected in oncotic cytology assays of cervical smear in women with HIV. Sao Luis, Maranhao State, Brazil, 2019.

Table 2 - Laboratorial data of women with and without HIV/HPV coinfection. Sao Luis, Maranhao State, Brazil, 2019.

	HPV-positive N= 41	HPV-negative N=41	*p*-value
CD4 T-cell	581.66±270.27	767.51±251.97	**0.02**
CD8 T-cell	945.24±424.24	744.35±326.84	**0.02**
CD4/CD8 ratio	0.81±0.52	1.07±0.60	**0.03**
Leucocytes	5982.78±3453.58	5725.57±1836.14	0.69
Neutrophils	3353.97±3274.31	3048.57±1417.21	0.61
Lymphocytes	2225.42±688.82	1863.58±568.97	**0.03**
Hemoglobin	12.88±1.09	12.72 ±1.60	0.62
Hematocrit	40.10±3.61	39.93±4.11	0.82
Platelets	329666.8 ±538276.6	260029.4±80268.29	0.44
Neutrophil/lymphocyte ratio	3.17±4.60	1.26±0.46	**0.04**
Platelet/lymphocyte ratio	154.34±94.24	111.11±34.23	**0.01**
Viral load	240.22±628.40	44.25±12.60	**0.04**

Data presented in mean ± Standard Deviation. Test used: Student's t-test. CD4 = Cluster of differentiation 4; CD8 = Cluster of differentiation 8.

immunodeficiency is a predictor of cervical injury in this population[24].

Lower CD4 T-cell count in HIV-positive women leads to a greater chance of HPV infection and evolution of cervical injury[25]. The data presented here demonstrated that coinfected participants had lower CD4 T-cell and CD4/CD8 ratios than participants without coinfection, while there was an increase in CD8 T-cell. Notably, due to antiretroviral treatment, the former were not more severely immunodeficient (<200 cells/mL), stressing the importance of medication adherence in this population[26].

The NLR and PLR and viral load showed statistically significant values in HIV/HPV coinfection, even in the presence of antiretroviral treatment and the ROC curve models demonstrating that they are possible predictors for presence of the HPV. There was a reduction in CD4 T-lymphocytes, which in turn increased the number of neutrophils, CD8 T-lymphocytes and viral load, suggesting a state of greater and persistent systemic inflammation in individuals living with HIV/HPV coinfection. NLR and PLR ratios are emerging as new biomarkers of systemic inflammatory response used as noninvasive and low-cost prognostic indicators for solid tumors[18,27]. Furthermore, it is well established in the literature that the inflammatory state has an essential role in carcinogenesis[28-30]. However, few studies addressed this correlation in HIV-seropositive population with HPV coinfection without cancer.

NLR has been an important marker of systemic inflammation with predictive and prognostic value in several types of cancers[28] and is an independent marker

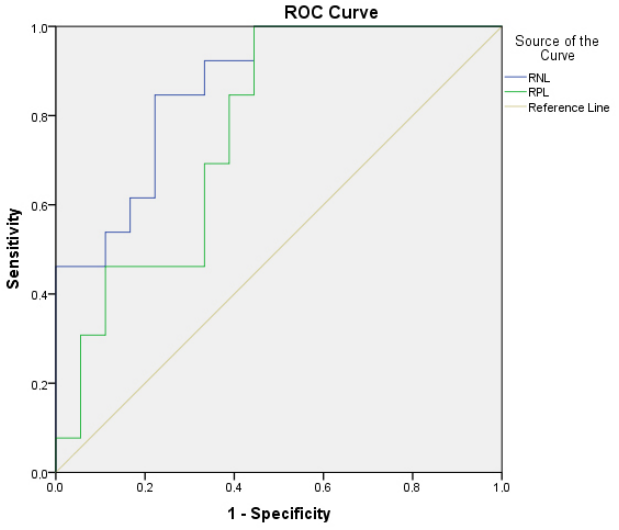

Figure 2 - Receiver-operating characteristic curve for significant markers in the prediction of HPV presence in HIV-infected women. Sao Luis, Maranhao State, Brazil, 2019. NLR = Neutrophil lymphocyte ratio; PLR = Platelet lymphocyte ratio; ROC = Receiver-operating characteristic.

for survival of patients after tumor resection surgery in women with cervical intraepithelial neoplasia[16]. Cervical intraepithelial neoplasia is one of the most common neoplasms, of which HPV is the main causative agent, and the impaired neutrophil migration could be an early event in tumor development[31]. Compared with CIN and early-stage cervical cancer, leukocytosis, neutrophilia, lymphopenia, and NLR ≥ 5 were more frequently observed in advanced stage cervical cancer patients[32].

In this study the results show an increase in NLR in HIV/HPV coinfected women reflecting a systemic inflammation with neutrophilia and lymphopenia. Thus, do our results reflect the contribution of NLR as a biomarker for screening an inflammation and monitoring cellular changes in these patients? This hypothesis needs to be further investigated.

Considering that platelets play a role in inflammation, function as effectors of injury in a variety of pulmonary disorders and syndromes, facilitate tissue repair and act in the growth and development of metastases of various cancers, their immunomodulatory properties have been investigated by many studies[33,34]. Bilir *et al.*[35] found that higher PLR values were significantly correlated with decreased overall survival for patients with cervical cancer group and in the persistent human papilloma virus groups. Palaia *et al.*[36], by treating locally advanced cervical cancer, found that patients with low NLR and PLR showed significantly better responses to concomitant chemoradiation or neoadjuvant chemotherapy (NACT).

During HIV infection, an exaggerated systemic inflammatory response guides platelet dysfunction in which platelets are inappropriately activated, followed by immunological destruction and thrombocytopenia[37]. Platelets derived from HIV-infected individuals under stable antiretroviral therapy show increased mitochondrial dysfunction, activation of the intrinsic pathway of apoptosis and undermined granule secretion in response to thrombin[38].

Two studies[37,38] show that inflammation leads to an imbalance in the maintenance of platelet homeostasis, which supports the use of this hematological component as a possible alternative inflammatory biomarker. Therefore, this imbalance can explain why elevated PLR was associated with HIV/HPV coinfection in women in our study.

In clinical practice, NLR and PLR can estimate organic changes and the inflammatory response, and they can be considered recent biomarkers, which are associated with inflammation and aggregation pathways. However, more studies should be performed to confirm our outcomes. This study holds some limitations, namely: sample size and the lack of determination of serum concentrations of classic inflammatory markers such as interleukins (eg IL6) and ultra-sensitive C-reactive protein (CRPus). However, it is a pioneering study on the neutrophil/lymphocyte ratio and the platelet/lymphocyte ratio in patients living with HIV with and without HPV infection. Additionally, it is a preliminary study, and it could be considered a prototype for future studies of a prospective and randomized design.

CONCLUSION

In women with HIV/HPV coinfection and under antiretroviral treatment, there is association between the neutrophil/lymphocyte and platelet/lymphocyte ratio suggesting a state of greater and persistent systemic inflammation and lower lymphocyte proportions; however, prospective randomized studies should be performed to confirm this hypothesis and to determine the usefulness of NLR and PLR in surrogacy for alternative inflammatory biomarkers.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

FUNDING

This study was financed in part by the Research and Scientific and Technological Development of Maranhao (FAPEMA - Fundacao de Amparo a Pesquisa e ao Desenvolvimento Cientifico e Tecnologico do Maranhao),

UNIVERSAL 01017/2017, and Coordenacao de Aperfeicoamento de Pessoal de Nivel Superior - Brasil (CAPES), Finance Code 001.

REFERENCES

1. Silva Junior JF, Martins Neto C, Cardoso BL, Costa EM, Beserra OL, Carneiro VS. Quality of life of HIV-positive people: relationship between socioeconomic status and viral stage. Rev Bras Promoç Saude. 2020;33:9841.
2. Levi JE, Kleter B, Quint WG, Fink MC, Canto CL, Matsubara R, et al. High prevalence of human papillomavirus (HPV) infections and high frequency of multiple HPV genotypes in human immunodeficiency virus-infected women in Brazil. J Clin Microbiol. 2002;40:3341-5.
3. Mbulawa ZZ, Coetzee D, Marais DJ, Kamupira M, Zwane E, Allan B, et al. Genital human papillomavirus prevalence and human papillomavirus concordance in heterosexual couples are positively associated with human immunodeficiency virus coinfection. J Infect Dis. 2009;199:1514-24.
4. Kojic EM, Kang M, Cespedes MS, Umbleja T, Godfrey C, Allen RT, et al. Immunogenicity and safety of the quadrivalent human papillomavirus vaccine in HIV-1-infected women. Clin Infect Dis. 2014;59:127-35.
5. Beachler DC, Weber KM, Margolick JB, Strickler HD, Cranston RD, Burk RD, et al. Risk factors for oral HPV infection among a high prevalence population of HIV-positive and at-risk HIV-negative adults. Cancer Epidemiol Biomarkers Prev. 2012;21:122-33.
6. Duarte BF, Silva MA, Germano S, Leonart MS. Diagnóstico do câncer anal na coinfecção pelo papiloma vírus humano (HPV) e pelo vírus da imunodeficiência humana (HIV). Rev Inst Adolfo Lutz. 2016;75:1710.
7. Massad L, Keller M, Xie X, Minkoff H, Palefsky J, D'Souza G, et al. Multitype infections with human papillomavirus: impact of human immunodeficiency virus coinfection. Sex Transm Dis. 2016;43:637-41.
8. Palefsky JM, Minkoff H, Kalish LA, Levine A, Sacks HS, Garcia P, et al. Cervicovaginal human papillomavirus infection in human immunodeficiency virus-1 (HIV)-positive and high-risk HIV-negative women. J Natl Cancer Inst. 1999;91:226-36.
9. Wada NI, Jacobson LP, Margolick JB, Breen EC, Macatangay B, Penugonda S, et al. The effect of HAART-induced HIV suppression on circulating markers of inflammation and immune activation. AIDS. 2015;29:463-71.
10. Boulware DR, Hullsiek KH, Puronen CE, Rupert A, Baker JV, French MA, et al. Higher levels of CRP, d-dimer, IL-6, and hyaluronic acid before initiation of antiretroviral therapy (ART) are associated with increased risk of AIDS or death. J Infect Dis. 2011;203:1637-46.
11. French MA, Cozzi-Lepri A, Arduino RC, Johnson M, Achhra AC, Landay A. Plasma levels of cytokines and chemokines and the risk of mortality in HIV-infected individuals. AIDS. 2015;29:847-51.
12. Guthrie GJ, Charles KA, Roxburgh CS, Horgan PG, McMillan DC, Clarke SJ. The systemic inflammation-based neutrophil–lymphocyte ratio: experience in patients with cancer. Crit Rev Oncol Hematol. 2013;88:218-30.
13. Wang X, Zhang G, Jiang X, Zhu H, Lu Z, Xu L. Neutrophil to lymphocyte ratio in relation to risk of all-cause mortality and cardiovascular events among patients undergoing angiography or cardiac revascularization: a meta-analysis of observational studies. Atherosclerosis. 2014;234:206-13.
14. Templeton AJ, McNamara MG, Šeruga B, Vera-Badillo FE, Aneja P, Ocaña A, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Natl Cancer Inst. 2014;106:dju124.
15. Raffetti E, Donato F, Pezzoli C, Digiambenedetto S, Bandera A, Di Pietro M, et al. Systemic inflammation-based biomarkers and survival in HIV-positive subject with solid cancer in an Italian multicenter study. J Acquir Immune Defic Syndr. 2015;69:585-92.
16. Chen F, Lin L, Yan L, Qiu Y, Cai L, He B. Preoperative neutrophil-to-lymphocyte ratio predicts the prognosis of oral squamous cell carcinoma: a large-sample prospective study. J Oral Maxillofac Surg. 2017;75:1275-82.
17. Coutlée F, Gravitt P, Kornegay J, Hankins C, Richardson H, Lapointe N, et al. Use of PGMY primers in L1 consensus PCR improves detection of human papillomavirus DNA in genital samples. J Clin Microbiol. 2002;40:902-7.
18. Bao Y, Wang Y, Li X, Pan M, Zhang H, Cheng Z, et al. Prognostic significance of platelet-to-lymphocyte ratio in urothelial carcinoma patients: a meta-analysis. Cancer Cell Int. 2019;19:315.
19. Saharia KK, Koup RA. T Cell susceptibility to HIV influences outcome of opportunistic infections. Cell. 2013;155:505-14.
20. Adler DH, Wallace M, Bennie T, Abar B, Meiring TL, Williamson AL, et al. Cumulative impact of HIV and multiple concurrent human papillomavirus infections on the risk of cervical dysplasia. Adv Virol. 2016;2016:7310894.
21. Ceccato Junior BP, Lopes AP, Nascimento LF, Novaes LM, Melo VH. Prevalência de infecção cervical por papilomavírus humano e neoplasia intraepitelial cervical em mulheres HIV-positivas e negativas. Rev Bras Ginecol Obstet. 2015;37:178-85.
22. Hawes SE, Critchlow CW, Sow PS, Touré P, N'Doye I, Diop A, et al. Incident high-grade squamous intraepithelial lesions in Senegalese women with and without human immunodeficiency virus tgype 1 (HIV-1) and HIV-2. J Natl Cancer Inst. 2006;98:100-9.
23. Zhang HY, Fei MD, Jiang Y, Fei QY, Qian H, Xu L, et al. The diversity of human papillomavirus infection among human immunodeficiency virus-infected women in Yunnan, China. Virol J. 2014;11:202.

24. Guedes DS, Carvalho AZ, Lima IC, Cunha GH, Galvão MT, Farias OO. Vulnerability of women with human immunodeficiency virus to cervical cancer. Esc Anna Nery. 2019;23:e20180203.
25. Moraes DC, Cabral JR, Oliveira RC, Souza VA. Quality of care and adherence to antiretroviral drugs in specialized HIV services in Pernambuco/Brazil, 2017-2018. Saude Debate. 2021;45:1088-100.
26. Liu G, Sharma M, Tan N, Barnabas RV. HIV-positive women have higher risk of human papilloma virus infection, precancerous lesions, and cervical cancer. AIDS. 2018;32:795-808.
27. Kutluturk F, Gul SS, Sahin S, Tasliyurt T. Comparison of mean platelet volume, platelet count, neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in the euthyroid, overt hypothyroid and subclinical hyperthyroid phases of papillary thyroid carcinoma. Endocr Metab Immune Disord Drug Targets. 2019;19:859-65.
28. Wu J, Chen M, Liang C, Su W. Prognostic value of the pretreatment neutrophil-to-lymphocyte ratio in cervical cancer: a meta-analysis and systematic review. Oncotarget. 2017;8:13400-12.
29. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell. 2010;140:883-99.
30. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature. 2008;454:436-44.
31. Fernandes Jr PC, Garcia CB, Micheli DC, Cunha FQ, Murta EF, Tavares-Murta BM. Circulating neutrophils may play a role in the host response in cervical cancer. Int J Gynecol Cancer. 2007;17:1068-74.
32. Tavares-Murta BM, Mendonça MA, Duarte NL, Silva JA, Mutão TS, Garcia CB, et al. Systemic leukocyte alterations are associated with invasive uterine cervical cancer. Int J Gynecol Cancer. 2010;20:1154-9.
33. Xu XR, Zhang D, Oswald BE, Carrim N, Wang X, Hou Y, et al. Platelets are versatile cells: new discoveries in hemostasis, thrombosis, immune responses, tumor metastasis and beyond. Crit Rev Clin Lab Sci. 2016;53:409-30.
34. Chao B, Ju X, Zhang L, Xu X, Zhao Y. A novel prognostic marker systemic inflammation response index (SIRI) for operable cervical cancer patients. Front Oncol. 2020;10:766.
35. Bilir F, Chkhikvadze M, Yilmaz AY, Kose O, Arıöz DT. Prognostic value of systemic inflammation response index in patients with persistent human papilloma virus infection. Ginekol Pol. 2022;93:705-9.
36. Palaia I, Tomao F, Di Pinto A, Pernazza A, Santangelo G, D'Alessandris N, et al. Response to neoadjuvant chemotherapy in locally advanced cervical cancer: the role of immune-related factors. In Vivo. 2021;35:1277-83.
37. Mogensen TH, Paludan SR. Molecular pathways in virus-induced cytokine production. Microbiol Mol Biol Rev. 2001;65:131-50.
38. Mesquita EC, Hottz ED, Amancio RT, Carneiro AB, Palhinha L, Coelho LE, et al. Persistent platelet activation and apoptosis in virologically suppressed HIV-infected individuals. Sci Rep. 2018;8:14999.