Araştırma Makalesi / ***Research Article***

İzmir Eğitim ve Araştırma Hastanesi Tıp Dergisi (Medical Journal of İzmir Hospital) 25 (1): 23-27, 2021

EVALUATION OF VIRAL LOAD, CD4 T LYMPHOCYTE COUNT, eGFR, COMPLETE BLOOD COUNTS AND VITAMIN D METABOLISM PARAMETERS IN HIV-INFECTED PATIENTS AT THE TIME OF DIAGNOSIS

HIV İLE ENFEKTE OLAN HASTALARDA TANI SIRASINDA VİRAL YÜK, CD4 T LENFOSİT SAYISI, eGFR, TAM KAN SAYIMI VE D VİTAMİN METABOLİZMA PARAMETRELERİNİN DEĞERLENDİRİLMESİ

Ilter BOZACI[1] Hulya OZKAN OZDEMIR[2]

[1]Department of Nephrology, University of Health Sciences Bozyaka Training and Research Hospital, Izmir, Turkey
[2]Department of Clinical Microbiology and Infectious Diseases, University of Health Sciences Bozyaka Training and Research Hospital, Izmir, Turkey

Anahtar Sözcükler: HIV, CD4 T lenfosit, viral yük
Keywords: HIV, CD4 T lymphocyte, viral load

Yazının alınma tarihi: 14.11.2020 *Yazının Kabul tarihi: 05.01.2021* *Online basım tarihi: 11.03.2021*

SUMMARY

Introduction: *Kidney, liver and heart disease have become the leading cause of death rather than infections in HIV-infected patients. We aimed to investigate the relationship between HIV related results and other laboratory variables at the time of diagnosis.*

Material and Methods: *Patients with viral load below 100.000 copies/ml were in group-1; patients with viral load above 100.000 copies/ml were in group-2. Patients were also staged according to their CD4 T lymphocytes count.*

Results: *A sum of 292 naïve HIV positive patients were enrolled in the study. HIV viral load was positively correlated with creatinine and alkaline phosphatase levels, negatively correlated with eGFR, CD4+ T lymphocyte count, CD4+ T lymphocyte percentage, platelet, hemoglobin and hematocrit levels. HIV viral load was independently associated with CD4+ T lymphocyte percentage in logistic regression analysis (odds ratio, 0.937; 95% confidence interval, 0.896 to 0.981; p=0.005). CD4 positive T lymphocyte counts was found negatively correlated with age, HIV viral load and ALP levels; positively correlated with serum leucocyte levels, lymphocyte levels, platelet levels, hemoglobin levels, hematocrit levels, calcium levels, phosphorus levels and vitamin D levels.*

Conclusion: *Initial evaluation of HIV-infected patients must include possible organ involvement parameters such as urea, creatinine, complete blood counts and parameters those associated with vitamin D metabolism in addition to CD4 T lymphocytes counts and HIV viral load.*

ÖZ

Giriş: *Böbrek, karaciğer ve kalp hastalıkları HIV ile enfekte hastalarda enfeksiyonlardan ziyade önde gelen ölüm nedeni haline gelmiştir. Tanı anında HIV ile ilgili sonuçlar ile diğer laboratuvar degişkenleri arasındaki ilişkiyi araştırmayı amaçladık.*

Gereç ve Yöntem: *Viral yükü 100.000 kopya/ml'nin altında olan hastalar grup-1'de; 100.000 kopya/ml'nin üzerinde viral yükü olan hastalar grup-2'de yer aldı. Hastalar ayrıca CD4 T lenfosit sayılarına göre evrelendirildi.*

Bulgular: *Çalışmaya toplam 292 yeni tanı HIV pozitif hasta dahil edildi. HIV viral yük: eGFR; CD4 T lenfosit sayısı, CD4 T lenfosit yüzdesi, trombosit, hemoglobin, hematorit seviyeleri ile negatif; kreatinin ve alkalen fosfataz seviyeleri ile pozitif korelasyon gösterdi. HIV viral yükü, lojistik regresyon analizinde CD4 T lenfosit yüzdesi ile bağımsız olarak ilişkilendirildi (olasılık oranı, 0.937, %95 güven aralığı, 0.896-0.981; p=0.005). CD4 T lenfosit sayıları: yaş, HIV viral yükü ve alkalen fosfataz seviyeleri ile negatif; lökosit, lenfosit, trombosit, hemoglobin, hematokrit, kalsiyum, fosfor ve D vitamin seviyeleri ile pozitif korelasyon gösterdi.*

Sonuç: *HIV ile enfekte hastaların ilk değerlendimesi, CD4 T lenfosit sayıları ve HIV viral yüküne ek olarak üre, kreatinin, hemogram ve D vitamini metabolizması ile ilişkili parametreler gibi olası organ tutulumu parametrelerini içermelidir.*

INTRODUCTION

Human immunodeficiency virus (HIV) infection is a global health problem. Although opportunistic infections were the leading cause of death in the HIV environment in the past, improvements in survival and disease progression led to complications such as kidney, liver and heart disease as the leading cause of death (1). Therefore, initial evaluation of HIV-positive patients and risk stratification is crucial.HIV is an infection characterized by the targeting and destruction of CD4 T lymphocytes, loss of which will result in the inability to have a proper immune response (2,3). Although World Health Organization (WHO)'s 2016 recommendation to treat all people diagnosed with HIV regardless of immune status led to loss of one of the primary indications for CD4 testing, viral load and CD4 testing have been recognized as mainstays of the management of HIV disease (4,5). Myelosuppression frequently occurs in patients with HIV-infection in association with the decline of adaptive immunity (6).Besides, acute kidney injury (AKI) and chronic kidney disease (CKD) risk is enhanced at patients with HIV(7,8). Risk factors for AKI and CKD among HIV-positive patients can be divided into two groups: similar risk factors in the general population (older age, diabetes mellitus, preexisting CKD and acute or chronic liver disease) and HIV-specific risk factors (diagnosis of acquired immunodeficiency syndrome (AIDS), low CD4+ T lymphocytes count, high viral load (VL), co-infection with hepatitis C virus (HCV)) (9,10). Syphilis is an infectious disease which is caused by a spirochete, have been shown to be increased in studies from developed countries among HIV-infected populations (11,12).In terms of opportunistic infections syphilis is an important issue in HIV-infected patients.

In HIV-infected patients, observational studies have demonstrated very high rates of low vitamin D levels (13). In addition to interacting with PTH at the bone and kidney and stimulating intestinal calcium absorption for delivery to target organs, vitamin D plays a critical role in immune system (14). In the present study, we aimed to investigate the relationship between HIV viral load, CD4 T lymphocytes count and laboratory and demographical data at the time of diagnosis in our HIV-infected patients.

MATERIAL AND METHODS

Study Design

This study was conducted in an out-patient clinic of a department of clinical microbiology and infectious disease at a training and research hospital over 1-year period between April 2019 and May 2020. Patients were initially divided into two groups. Group-1 was composed of patients with viral load below100.000copies/ml; group-2 was composed of patients with viral load above 100.000copies/ml based on the classification in the literature (15). Besides, patients were also staged according to CD4 T lymphocytes count according to the World Health Organization (WHO) classification(16).Patients were in stage-1, stage-2, stage-3 and stage-4 with CD4 T lymphocytes count >500x10$^{3/\mu L}$, 349-500x10$^{3/\mu L}$, 199-350x10$^{3/\mu L}$ and <200x10$^{3/\mu L}$, respectively. The study was approved by institutional ethics committee. Glomerular filtration rate (GFR) was estimated from the serum creatinine using the CKD Epidemiology Collaborative Study Equation (17).Medical records in terms of medical history of patients and laboratory results were recruited from registry data.

Statistical Analysis

Continuous parametric variables were reported as means ± standard deviation and non-parametric continuous variables were reported as median with 25-75 interquartile range.

Categorical variables were reported as percentages. Categorical variables were compared using the chi-square test. Student's t test was used to compare continuous variables.

Pearson correlation was used to evaluate association between CD4 T lymphocyte count, HIV viral load and laboratory parameters. Multiple logistic regression analysis was used to study unadjusted and adjusted association between predictor variables including creatinine, eGFR, CD4 T lymphocyte count and percentage, hemoglobin, hematocrit, platelet, ALP and syphilis antibody by using Enter Method. All statistical analyses were performed using SPSS 18.0 (Chicago,IL USA).For all tests, p value of <0.05 was considered statistically significant.

RESULTS

A sum of 292 naive HIV positive patients were enrolled in the study. In terms of viral load, 134 patients were in group-1 and 158 patients were in group-2. There was statistically significant difference between group-1 and group-2 in terms of age (34±10 years vs 37±12 years; p=0.024). Statistically significant difference was found between group-1 and group-2 in terms of lymphocyte (2.3±9 x10$^{3/\mu L}$ vs 1.7±9x10$^{3/\mu L}$; p=0.021), hemoglobin (14.5±1.5 g/dL vs 13±2 g/dL; p=0.001), hematocrit (44±4 % vs 41±6; p=0.001), calcium (9.4±0.4 mg/dl vs 9.2±0.4 mg/dl; p= 0.001) and vitamin D (19±7 ng/ml vs 17±8 ng/ml; p=0.033)levels. CD4 T lymphocyte count (523±266 x10$^{3/\mu L}$vs 379±285x10$^{3/\mu L}$; p= 0.001) and CD4T lymphocyte cell percentage (23±3 % vs 17±9 %; p= 0.001) were significantly lower in group-2 compared to group-1. Demographical and laboratory results of group-1 and group-2 are presented in table.1.HIV viral load was positively correlated with creatinine and alkaline phosphatase levels; negatively correlated with eGFR, CD4 T lymphocyte count, CD4 T lymphocyte percentage, platelet, hemoglobin and hematocrit levels.In logistic regression analysis (variables: creatinine, eGFR, CD4T lymphocyte count, CD4 T lymphocyte percentage, platelet, hemoglobin, hematocrit, alkaline phosphatase) HIV viral load was independently associated with CD4 T lymphocyte percentage(odds ratio, 0.937; 95% confidence interval, 0.896 to 0.981; p=0.005). Besides, logistic regression analysis made by excluding biochemical parameters (variables: syphilis seropositivity and CD4 positive cell percentage), HIV viral load was independently associated with CD4 T lymphocyte percentage (odds ratio, 0.931; 95% confidence interval, 0.905 to 0.958; p=0.000) and syphilis seropositivity (odds ratio, 1.966; 95% confidence interval, 1.056 to 3.661; p=0.033).In another classification of patients according to theCD4 T lymphocyte count, 111 patients were in stage-1; 52 patients were in stage-2; 75 patients were in stage-3 and 54 patients were in stage-4.The laboratory results of patient groups in terms of CD4 T lymphocyte counts are presented in table.2.We found significant difference between patients in stage-1, stage-2, stage-3 and stage-4 in terms of HIV-RNA (0.42±1.8x10^{6} copy vs 0.28±0.6x10^{6} copy vs 0.75±1.7x10^{6} copy vs 1.93±3.4 x10^{6} copy; p=0.00); leucocyte (7.1±1.9x10$^{3/\mu L}$vs 6±1.4 x10$^{3/\mu L}$vs 5.5±1.5 x10$^{3/\mu L}$vs 4.3±1.8 x10$^{3/\mu L}$; p=0.00); lymphocyte (2.8±0.9x10$^{3/\mu L}$ vs 2.1±0.5x10$^{3/\mu L}$ vs 1.8±0.7x10$^{3/\mu L}$ vs 1.3±0.8x10$^{3/\mu L}$; p=0.00); platelet (229±69 x10$^{3/\mu L}$ vs 205±81x10$^{3/\mu L}$vs 189±81 x10$^{3/\mu L}$ vs 176±66x10$^{3/\mu L}$; p=0.00); hemoglobin (15±1.3g/dL vs 14±1.4g/dL vs 14±1.8g/dL vs 12±2g/dL; p=0.00); hematocrit (45±3.9 % vs 44±3.8 % vs 42±5.0 % vs 37±6.2 %; p=0.00); calcium (9.5±0.4 mg/dl vs 9.3±0.4 mg/dl vs 9.4±0.4 mg/dl vs 9.1±0.5 mg/dl; p=0.00) and vitamin D levels (19±7.9 ng/ml vs 18±6.9ng/ml vs 18±6.3 ng/ml vs 15±6.7ng/ml; p=0.005). In Pearson's correlation analysis, CD4 Tlymphocyte count was found negatively correlated with age, HIV viral load and ALP levels. On the other hand, CD4 T lymphocyte count was found positively correlated with serum leucocyte, lymphocyte, platelet, hemoglobin, hematocrit, calcium, phosphorus and vitamin D levels.The Pearson's correlation analysis of CD4 T lymphocyte count and HIV viral load is presented in table 3.

DISCUSSION

The present study investigated the demographical features, laboratory results and the association between those results and viral markers such as HIV viral load and CD4 T lymphocyte count of 292 naïve HIV positive patients at the time of diagnosis. In our study, we found negative correlation between CD4 T lymphocyte count and HIV viral load in return, in accordance with the results of the study of Schultze A et al. (18). Syphilis infection is associated with a significant decrease in CD4 T lymphocyte count and a significant increase in plasma HIV viral load (19).In our study we determined syphilis seropositivity in 21% of our patients. We also determined highest seropositivity rates in patients with lowest CD4 T lymphocyte count. In our study, the negative correlation of HIV viral load with eGFR revealed a possible direct effect of the virus on kidney function. Also, myelosuppression in patients with higher viral load were found more determined compared to patients with lower viral load. Besides, bone mineral metabolism markers such as serum calcium, phosphorus, vitamin D and ALP levels were found significantly correlated with CD4 T lymphocyte count. Patients with higher viral load were older and this might be related to late acceptance of the disease process.

Myelosuppression characterized by granulocytopenia, thrombocytopenia and anemia frequently occurin patients with HIV infection related to the decline of adaptive immunity and the degree of the hematopoietic pathology correlates with the stage of disease progression (20). In a study, Nixon et al. revealed the direct effect of infection of intermediate CD34+CD38+ hematopoietic progenitor cells (HPCs) by HIV-1, resulting in pancytopenia(21). Our results revealed the association between HIV and hematopoietic cells even in the early period of the disease course. Although the introduction of combined antiretroviral therapy (ART) resulted a dramatic shift from the weight loss and wasting to healthy weight, weight loss occurs in the course of HIV infection and increases in severity with progression of the disease (22).However, decreasing levels were found in patient groups in terms of CD4 T lymphocyte count in our study which might reflect advanced disease course. Low bone mineral density is a common finding in HIV infected patients (23). Multiple factors including HIV viral protein appear to be involved in the pathogenesis of bone loss in HIV infected patients (24). Vitamin D plays a prominent role in bone and mineral metabolism in HIV-infected patients as well as in general population (25). In accordance with the results of the studies in the literature, in our study we found lower vitamin D levels both in patient groups with higher viral load and patient groups with lower CD4T lymphocytes count. Positive correlation between ALP and HIV viral load and negative correlation between ALP and CD4T lymphocytes count might be due to increased bone metabolism in patients with advanced disease course.

Limitations of our study were as follows: number of total individuals enrolled in the study was few; renal prognostic laboratory parameters such as proteinuria could not be obtained from the medical records.

CONCLUSION

Initial evaluation must also include demographical parameters and laboratory parameters those might reflect possible organ involvements such as urea, creatinine, complete blood counts and parameters those associated with vitamin D metabolism in addition to CD4 T lymphocytes count and HIV viral load.

REFERENCES

1. Mirani G, Williams PL, Chernoff M, Abzug MJ, Levin MJ, Seage GR 3rd et al. Changing trends in complications and mortality rates among US youth and young adults with HIV infection in the era of combination antiretroviral therapy. Clin Infect Dis 2015; 61(12): 1850-61.
2. Nacher M, Huber F, Adriouch L, Djoaaou F, Adenis A, Couppie P. Temporal trend of the proportion of patients presenting with advanced HIV in French Guiana: stuck on th asymptote? BMC Res Notes 2018; 11(1): 831.
3. Carr A, Richardson R, Liu Z. Success and failure of initial antiretroviral therapy in adults: an updated systemic review. AIDS 2019; 33(3): 443-53.
4. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection recommendations for a public health approach. Second edition Geneva, Switzerland: WHO; 2016.
5. US Department of Health and Human Services. Panel on antiretroviral guidelines for adults and adolescents. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents 2018.

6. Razzak CS, Workeneh BT, Montez-Rath ME, Zolopa AR, Klotman PE, Winkelmayer WC. Trends in outcomes of end-stage renal disease secondary to human immunodeficiency virus-associated nephropathy. Nephrol Dial Transplant 2015; 30: 1734-40.
7. Lopes JA, Melo MJ, Viegas A, Raimundo M, Camara I, Antunes F et al. Acute kidney injury in hospitalized HIV-infected patients: a cohort analysis. Nephrol Dial Transplant 2011; 26(12): 3888-94.
8. Randall DW, Brima N, Walker D, Connolly J, Laing C, Copas AJ et al. Acute kidney injury among HIV-infected patients admitted to the intensive care unit. Int J STD AIDS 2015; 26(13): 915-21.
9. Wald R, McArthur E, Adhikari NK, Bagshaw SM, Burns KE, Garg AX et al. Changing incidence and outcomes following dialysis-requiring acute kidney injury among critically ill adults: a population-based cohort study. Am J Kidney Dis 2015; 65(6): 870-7.
10. Nadkarni GN, Patel AA, Yacoub R, Benjo AM, Konstantinidis I, Annapureddy N et al. The burden of dialysis-requiring acute kidney injury among hospitalized adults with HIV infection: A Nationwide Inpatient Sample Analysis. AIDS 2015; 29(9): 1061-6.
11. Paz-Bailey G, Meyers A, Blank S, Brown J, Rubin S, Braxton J et al. A case-control study of syphilis among men who have sex with men in New York City: association with HIV infection. Sex Transm Dis 2004; 31(10): 581-7.
12. Simms I, Fenton KA, Ashton M, Turner KME, Crawley- Boevey EE, Gorton R et al. The re-emergence of syphilis in the United Kingdom: the new epidemic phases. Sex Transm Dis 2005; 32(4): 220-6.
13. Von Roenn JH, Roth EL, Craig R. HIV-related cachexia: potential mechanisms and treatment. Oncology 1992; 49: 50-4.
14. Stone B, Dockrell D, Bowman C, McCloskey E. HIV and bone disease. Arch Biochem Biophys 2010; 503: 66-7.
15. Socias ME, Sued O, Laufer N, Lazaro ME, Mingrone H, Pryluka D et al. Acute retroviral syndrome and high baseline viral load are predictors of rapid HIV progression among untreated Argentinean seroconverters. J Int AIDS Soc 2011; 14(1): 40.
16. World Health Organization. Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy Geneva, Switzerland: WHO; July 2017.
17. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009; 150: 604-12.
18. Schultze A, Torti C, Cozzi-Lepri A, Vandamme A-M, Zazzi M, Sambatakou H et al. The effect of primary drug resistance on CD4+ cell decline and the viral load set-point in HIV-positive individuals before the start of antiretroviral therapy. AIDS 2019; 33(2): 315-26.
19. Buchacz K, Patel P, Taylor M, Kerndt PR, Byers RH, Holmberg SD et al. Syphilis increases HIV viral load and decreases CD4 cell counts in HIV-infected patients with new syphilis infections. AIDS 2004; 18(15): 2075-9.
20. Sloand E. Hematologic complications of HIV infection. AIDS Rev 2005; 7: 187-96.
21. Nixon CC, Vatakis DN, Reichelderfer SN, Dixit D, Kim SG, Uittenbogaart CH et al. HIV-1 infection of hematopoietic progenitor cells in vivo in humanized mice. Blood 2013; 122(13): 2195-204.
22. Swanepoel CR, Atta MG, D'Agati VDet al. Kidney disease in the setting of HIV infection: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int 2018; 93:545.
23. Atteritano M, Mirarchi L, Venanzi-Rullo E, Santoro D, Iaria C, Catalano A et al. Vitamin D status and relationship with bone fragility fractures in HIV-infected patients: A case control study. Int J Mol Sci 2018; 19(1): 119.
24. Bang UC, Shakar SA, Hitz MF, Jespersen MS, Andersen O, Nielsen SD et al. Deficiency of 25-hydroxyvitamin D in male HIV-positive patients: a descriptive cross-sectional study. Scand J Infect Dis 2010; 42(4): 306-10.
25. Villamor E. A potential role for vitamin D on HIV infection? Nutr Rev 2006; 64: 226-33.

Sorumlu yazar

Ilter BOZACI (Uzm.Dr.)
Sağlık Bilimleri Üniversitesi, İzmir Bozyaka Eğitim ve Araştırma Hastanesi,
Nefroloji Kliniği, İzmir
Phone:0232 2505050/2136
E- mail:ilterbozaci@gmail.com
ORCID: 0000-0001-7535-9403

Hulya OZKAN OZDEMIR(Uzm.Dr.) ORCID:0000-0002-0041-1710