

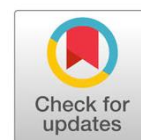


Original Research



Does gender affect immune response in HIV patients?

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Abstract: Gender differences affect the frequency and course of many diseases. This study aimed to determine the gender distribution in HIV-infected patients and investigate the relationship between gender and immune response. The study included HIV-infected patients who followed up in our hospital in 2018. The patients were divided into HIV RNA negative patients (Group 1) and HIV RNA positive patients (Group 2). Patients with diseases that may affect the immune system and those using drugs that affect the immune system were excluded from the study. The evaluation was made of 549 patients, as 305 patients (45 females 14.75%) in Group 1 and 224 patients (23 females, 9.43%) in Group 2. When the CD4/CD8 ratio of male and female patients was compared in both groups, a lower rate was determined in females (0.71-0.58) than males (0.82-0.93). A negative correlation was determined between HIV RNA and the CD4/CD8 ratio in premenopausal females ($p=0.045$) and males (≤ 45 years $p=0.0001$). Clinical studies of HIV infection have demonstrated better initial viremia control in females with primary infection, faster disease progression, and stronger immune activation than males for the same level of viral replication.

Keywords: HIV; AIDS; Gender; Immune Response.

INTRODUCTION

Approximately 38 million people worldwide are infected with the human immunodeficiency virus (HIV). As most of these individuals do not have access to appropriate treatment, HIV infection eventually leads to serious immune deficiency, resulting in a condition called AIDS (Acquired Immune Deficiency Syndrome), resulting in morbidity and mortality.^{1,2,3} However, the CD4: CD8 ratio is usually less than 1 in HIV infection. The primary mechanism leading to immunodeficiency, opportunistic infections, and ultimately death in HIV infection is the continuous loss of CD4 T cells.⁴

Gender differences affect the incidence and course of many diseases. Gonadal sex steroids are particularly focused on gender-specific risk factors.⁵ A combination of environmental factors, host genetics, and viral characteristics determines transmission and pathogenesis in HIV infection.⁶ The objective of this study was to determine the gender distribution in patients infected with HIV

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In Istanbul, the most populous city in Turkey, and to investigate the relationship between gender and immune response in this patient group.

MATERIAL AND METHOD

Approval for this retrospective study was granted by the Local Ethics Committee(2019-18/16.09.2019). The study included HIV-infected patients who followed up in our hospital in 2018. The patients were divided into HIV RNA negative (Group 1) and HIV RNA positive patients (Group 2). Patients were divided into two groups as under 45 age and 45 and above age according to sex hormones effects. Patient information was obtained from the hospital data system and immunology laboratory. The informed consent form was not obtained from the patients due to the retrospective study. The identity of the patients or the information to disclose their identity was never used, and all patient data was stored in encrypted files on personal computers. Patients were excluded if they were aged <18 years, pregnant, had any disease affecting the immune system, a diagnosed malignancy, chronic renal failure, receiving estrogen-progesterone or androgen-containing hormone therapy, or if they were receiving estrogen-progesterone or androgen-containing were taking drugs that could affect the immune system. Flow cytometric analyses were performed with Navios cytometer (BECLS)-Kaluza Software. Whole blood was stained with anti-human FITC-CD45, PE-CD4, ECD-CD8, PE-CY5.5-CD3 (Beckman Coulter, Brea, California) antibodies. The percent and count of CD4+ and CD8+ cell are expressed CD3+CD4+ and CD3+CD8+ cells in CD45+ leukocyte gating. The HIV RNA level was measured with the PCR method (Real-time PCR, Rotor gene Q, QIAGEN, Germany).

Statistical analyses were performed using NCSS 11 software (Number Cruncher Statistical System, 2017 Statistical Software). Chi-square analysis was applied to determine relationships between categorical variables. The Independent Samples t-test was used to compare two groups of continuous independent variables with normal distribution. The Mann-Whitney U test was used to compare two independent groups of variables that did not fulfill the normal distribution assumption. Spearman correlation analysis was applied to determine the correlational relationships between variables that did not meet the normal distribution assumption. A value of $p < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

The evaluation was made of a total of 549 patients, comprising 68 females and 481 males. Group 1 included 305 patients (45 females, 14.75%) HIV RNA negative after appropriate antiretroviral therapy (ART). Group 2 included 224 patients (23 females, 9.43%) who had not yet received treatment or had not completed treatment and were HIV RNA positive. In both groups, there was no significant age difference between male and female patients ([Table 1](#)). When the female patients were evaluated alone, WBC, CD4 T cells, and CD4 / CD8 values were lower, and lymphocyte and CD8 T cells values were higher in Group 2, although not statistically significant ([Table 2](#)). The CD4 / CD8 ratio was 0.71 ± 0.56 in Group 1 and 0.58 ± 0.47 in Group 2 ($p > 0.05$). When the male patients have evaluated alone, WBC and CD4 cells values were significantly lower ($p < 0.0001$), and CD8% and CD4 / CD8 values were significantly higher ($p < 0.0001$) in Group 2 ([Table 3](#)). The CD4 / CD8 ratio was 0.82 ± 0.9 in Group 1 and 0.93 ± 6.64 in Group 2 ($p < 0.0001$). The CD4 / CD8 ratio of female and male patients in Group 1 was compared; the CD4 / CD8 ratio in females was 0.71 ± 0.56 , which

was lower than that of males (0.82 ± 0.9). The ratio in patients in Group 2 was similar to that in Group 1, with a CD4 / CD8 ratio of 0.58 ± 0.47 in females and lower than in males (0.93 ± 6.64). A significant negative correlation was determined between HIV RNA and the CD4 T cells in premenopausal women ($p = 0.005$, $r = -0.700$) and males (≤ 45 years $p < 0.0001$, $r = -0.322$, >45 years $p < 0.001$, $r = -0.486$). There was a positive correlation between HIV RNA and the CD8 T cells in males (45 years $p = 0.022$, $r = 0.178$). A significant negative correlation was determined between HIV RNA and the CD4 / CD8 ratio in premenopausal women ($p = 0.045$, $r = -0.542$) and males (≤ 45 years $p = 0.0001$, $r = -0.486$, >45 years $p = 0.001$, $r = -0.447$) (Table 4). When the RNA count was compared in Group 2, the median RNA value was lower in females than in males (433-655 copy/ml) (Table 5).

The progression of the disease in HIV infection is determined by the number and percentage of CD4 T cells. CD4 is a T cell helper T cell and regulates the immune response by interacting with other immune cells via inflammatory cytokines such as interleukin-1 (IL-1), IL-6, or tumor necrosis factor α (TNF- α).^{7,8} Specific cytotoxic CD8 T cells recognize virus antigens on the surface of HIV-infected cells and need help in immunological memory and the cytolytic response of CD4 T cells while killing cells by lysis through antigen-specific cytotoxic mechanisms.⁹

In the early stage of infection with HIV, CD8 T cells initiate a severe specific HIV response and increase in number by approximately 20-fold. Specific anti-HIV cytotoxic CD8 + T cells are present even before specific antibodies are detected.¹⁰ In acute infection, most of the cells in the immune response become active and contribute to infection progression. In the current study, CD8+ T cells levels were high in both male and female patients in the group with acute HIV infection (Group 2). CD8 + T cells exhibit antiviral activity with soluble factors that inhibit the HIV replication they secrete and with their HIV-specific cytotoxins.¹¹

The absolute number of CD4 T cells is considered the main criterion in determining the risk of opportunistic infection, deciding to initiate ART, and predicting AIDS-related cancers and deaths. However, the CD4 / CD8 ratio is also used as a parameter to predict prognosis.^{12,13} In the general population, a CD4 / CD8 ratio of <1.0 is considered the predictor of immunosenescence and is an independent predictor of overall mortality.¹⁴

Studies have shown that in both HIV-infected and non-HIV-infected populations, females have higher CD4 cell counts than males.^{15,16} Zapata et al. showed that the CD4 / CD8 ratio of male patients was lower than that of females, regardless of age and duration of treatment.¹⁷ However, in contrast to that study, the CD4 / CD8 ratios were higher in males in both Group 1 and Group 2 in the current study. In a long-term cohort study by Sacarino et al., multivariate analyses including age, sex, rare CD4, CD4 T cell count, and ART duration were performed in 407 patients to predict non-AIDS events, including malignancies, cardiovascular and renal diseases. A low CD4 / CD8 ratio was an independent factor for both non-AIDS morbidity and mortality in long-term HIV-positive patients independent of the absolute CD4 T cell count.¹⁸ As the current study did not include long-term follow-up data, no comment on mortality and morbidity can be made. All these studies show that the CD4 T cell number has lost its predictive value, while the CD4 / CD8 ratio remains a predictor of morbidity and mortality associated with AIDS or not, even after prolonged ART.¹⁹

The incidence, severity, and course of some diseases may be different for men, and women.²⁰ Autoimmune diseases, in particular, are more common in females.²¹ In addition, the incidence, and severity of many microbial infections, including malaria and tuberculosis,²² influenza,²³ hepatitis²⁴, and HIV, have been reported to differ between the genders.²⁵ In the current study, 87.64% (n: 481) of the patients who were followed up for HIV infection and included in the study

within one year were male, and there was a statistically significant male predominance in the current patient population. In HIV infection, clinical research has shown that females have faster disease progression and stronger immune activation than males for the same level of viral replication and better control of the first viremia in women during primary infection.²⁶ In the current study patient population, 66,17% (n: 45) of the female patients had viremia control, and HIV RNA was negative, whereas this rate was 54.05% (n: 260) for males, similar to the above-mentioned study.

Despite advances in the pathogenesis and treatment of HIV infection, the biological mechanisms leading to gender-specific differences have not been fully elucidated. Gender-specific environmental risk factors, differences in the microbiome by sex,²⁷ steroid hormones secreted by gonads²⁸, and the direct effects of X and Y chromosome-related factors²⁹ may be responsible for this. Of these factors, gonadal sex steroids have mainly been focused on.

The level of immune activation is an essential predictor of the course of HIV disease.³⁰ The level of immune activation contributes to the progression of HIV disease and has been shown to differ between males and females.²⁸

In a multi-center cohort study that included many countries such as the United States of America, Australia, Canada, and Brazil, it was seen that in primary HIV infection, females tend to have lower plasma viral load levels than men.³¹ Similarly, in the current study patient population, the viral load in female patients in Group 2 was much lower than in male patients. Another study stated that the risk of developing AIDS was 1.6 times higher in HIV-infected females with the same viral load as males.³² In the current study, as the HIV RNA increased in premenopausal patients, the CD4 / CD8 ratio decreased, and the absence of this decrease in postmenopausal women supports this view. Differences in immunoreaction in reproductive and postmenopausal periods in women suggest that sex-related changes in HIV infection may be due to gonadal sex hormones in the foreground. Sex hormones can affect the susceptibility of CD4 T cells to infection by altering the density of coreceptors and receptors in the target cells. The effects of progesterone on human cervical cells have also been investigated and shown to increase expression of HIV receptors CD4, CCR5, and CXCR4 in cervical CD4 + T cells.³³

CONCLUSION

Clinical studies of HIV infection have demonstrated better initial viremia control in females with primary infection, faster disease progression, and stronger immune activation than males for the same level of viral replication. Further studies are needed to clarify the role of gender in HIV pathogenesis. Particular focus on gonadal sex steroids in the pathogenesis may be of guidance for new trends in preventing or treating HIV infection.

AUTHORS' CONTRIBUTIONS

- Gülçin Şahingöz Erdal : Conceived, designed the review, and wrote the manuscript.
- Ramazan Korkusuz : Performed the search of articles and gathered the information and valid biomarkers from the articles, and wrote the manuscript.
- Pınar Kasapoğlu : Performed the search of articles.
- Nilgün Işıksaçan : Read the literature and applied the exclusion criteria, and interpret the data.
- Kadriye Kart Yaşar : Substantial contribution to the interpretation of data.

All authors critically revised the manuscript for important intellectual content, approved the final version to be submitted, and agreed to be accountable for the manuscript's content.

FOUNDING INFORMATION

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DATA AVAILABILITY STATEMENT

The utilized data to contribute to this investigation are available from the corresponding author on reasonable request.

DISCLOSURE STATEMENT

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors. This article was previously presented as an oral presentation at the "25th National Immunology Congress".

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Table 1. Gender Distribution of the Groups

Gender	Group 1	Group 2	p-value
	n (%)	n (%)	
Female	45	23	0.060
Male	260	221	
Chi-square test			

Table 2. Comparison of Variables of Female Patients According to Groups

Female	Group 1	Group 2	p-value
	n=45	n=23	
	Mean±SD Med. (Min.-Max.)	Mean±SD Med. (Min.-Max.)	
Age (years)	42.31±9.3 41- (26-65)	41.39±13.52 38- (18-61)	0.673
white blood cell 10 ³ /ul	6542.89±2159.65 6650- (2670-11410)	6070±1472.41 6240- (3710-9120)	0.292
Lymphocytes %	31.82±9.38 32.3- (8.9-51.7)	34.56±8.62 36.8- (20.6-51)	0.247
CD3+	74.34±11.12 76.3- (48.7-92)	74.53±11.55 76.9- (49.8-92.8)	0.945
% CD3+CD4+	26.08±11.63 26.4- (1.53-56.2)	22.57±12.43 20.8- (1.4-42.9)	0.291
CD3+CD4+ Cell/ul	545.62±319.97 514- (11-1432)	508.04±345.53 503- (20-1230)	0.657
%CD3+CD8+	43.44±12.22 44.1- (19.2-72.9)	47.47±13.98 47.3- (25.4-72)	0.224
CD3+CD8+ Cell/ul	873.87±401.49 882- (144-2022)	1029.22±504.27 823- (431-2284)	0.484
CD4/CD8	0.71±0.56 0.51- (0.03-2.32)	0.58±0.47 0.47- (0.02-1.64)	0.235
Mann Whitney U test Independent Samples t-test			

Table 3. Comparison of Variables of Male Patients According to Groups

Male	Group 1 n=260	Group 2 n=221	p-value
	Mean±SD Med. (Min.-Max.)	Mean±SD Med. (Min.-Max.)	
Age (years)	38.11±11.87 36-(18-70)	37.18±11.28 35-(18-69)	0.437
white blood cell 10 ³ /ul	7350.04±2081.98 7080-(3620-16980)	6548.42±1959.86 6290-(2270-13470)	<0.0001*
Lymphocytes %	34.48±9.03 34.8-(6.2-67.2)	33.15±10.05 32.4-(6.6-67.1)	0.129
CD3 Cell/ul	75.77±8.57 76-(50.1-96.4)	77.02±10.36 78.4-(32-96.5)	0.133
%CD3+CD4+	28.39±9.83 28.1-(0.9-56.4)	20.88±9.67 19.8-(0.76-46.9)	<0.0001*
CD3+CD4+ Cell/ul	697.62±309.38 672-(11-1703)	452.86±266.93 431-(2-1531)	<0.0001*
%CD3+CD8+	41.64±11.53 41.5-(16.9-83)	51.55±29.69 49.6-(16.6-447)	<0.0001*
CD3+CD8+ Cell/ul	1025.08±528.43 871-(10.56-3826)	1076.3±553.59 961-(129-4051)	0.259
CD4/CD8	0.82±0.9 0.67-(0.01-13)	0.93±6.64 0.4-(0-99)	<0.0001*

Mann Whitney U test
* Independent Samples t-test

Table 4. Relationships between variables with HIV RNA level according to the age limit of 45 years in males and females (Group 1)

		Female		Male	
		≤45 years	>45 years	≤45 years	>45 years
r		-0.542*	0.083	-0.486*	-0.447*
CD4/CD8	p	0.045	0.831	0	0.001
	n	14	9	165	56

*Spearman Correlation analysis

Table 5. Examination of HIV RNA positive cases by Gender

	Female (n=23) Mean±SD Med. (Min.-Max.)	Male (n=221) Mean±SD Med. (Min.-Max.)	p-value
HIV RNA Copy/ml	45230±1460 433-(27-695017)	200842106±2962484 655-(5-44041392)	0.506

Mann Whitney U test