Original article

Use of Quintile Regression to Find Factors Influencing CD4 Cell Count in Iranian Newly Recognized HIV-Infected People (1987–2016)

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ABSTRACT

Background: The number of CD4 cell counts is one of the markers that are widely used to assess the level of disease progression. Potential risk factors may have a different relationship at different points in the CD4 distribution. For example, some factors may have a weak link with the CD4 mean. While their relationship at the lower levels of CD4 is very strong. Understanding such a different relationship to identify a population at risk based on different levels of CD4 is very beneficial. Accordingly, this study aimed to use quantile regression to provides a more comprehensive analysis of the factors associated across different quantiles of CD4 counts at the time of diagnosis in Iranian newly recognized HIV-infected people.

Methods: This retrospective cohort study included 4402 HIV-infected patients from 31 provinces of Iran from 1987 to 2016. Patients' information included baseline CD4 cell count, age, sex, marital status, educational level, job status, way of HIV transmission, year of diagnosis, TB co-infected, clinical stage at the time of diagnosis. Quantile regression models were fitted to the data.

Results: The study findings indicated that variables, such as older age, clinical stage, transmission way, and year of HIV diagnosis could play the role of risk factors for CD4 counts at the time of diagnosis in HIV patients. However, the relationship between different variables was not uniformly distributed in many different quantiles.

Conclusions: The results of this study will be helpful for public health policymakers to adopt targeted policies aimed at improving the survival of these patients.

1. Introduction

CD4 (cluster of differentiation 4) cell counts can be used as surrogate markers to estimate the extent of damage to the immune system in AIDS patients. The number of these cells decreases a few weeks after HIV infection and then increases again in the following months but does not reach their initial level before infection.¹ CD4 cell counting is a tool to measure the number of CD4 cells in the blood.² A CD4 cell count is used to monitor the progress of AIDS and to assess the health of the immune system, and the greater the number of cells, the greater the immune system's health.³ Due to a variety of environmental, immunological, demographic, and genetic factors, CD4 cell counts vary between healthy

individuals and between patients.^{1,3–5} Factors that lead to CD4 cell changes in AIDS patients are complex and multiple.⁶ For AIDS patients to live longer information should be provided on factors that alter the CD4 cell count in the early stages of their disease.⁵

One of the most important predictors of HIV disease progression and AIDS (acquired immune deficiency syndrome)-related mortality is the count of CD4 lymphocytes in HIV-infected people. The increased risk of opportunistic infections and HIV-related malignancies is the consequence of the loss of CD4 cells. To determine the onset of a highly active antiretroviral therapy (HAART), CD4 counting, along with HIV viral load and clinical symptoms, are used.³

A low number of CD4 counts is associated with a higher risk for

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opportunistic HIV infections, which can lead to advanced disease and death.⁷

However, in addition to HIV, there are other factors such as age that can affect the number of CD4 cells. For example, reducing the CD4 response to ART in older people is more predictable.⁸

Identifying factors affecting the level of CD4 apart from ART helps health professionals and patients to help manage and monitor health-care interventions in people with HIV. Therefore, modeling and analyzing the factors affecting the number of CD4 cells in AIDS research is more and more important. In this case, one of the special problems to be considered is that on average, the effect of covariates on age, sex, education level, and other factors on the number of CD4 cells is studied.^{3,5,9,10}

It should be noted that potential risk factors may have a different relationship at different points of CD4 distribution. For example, some factors may have a weak link with the CD4 mean, while their relationship at the lower levels of CD4 is very strong. Understanding such a different relationship to identify a population at risk based on different levels of CD4 is very beneficial.⁸ Accordingly, the use of regression methods such as quantile regressions, in comparison with other regression models based on the mean response, provides a more comprehensive analysis of the factors associated with CD4 cell counting. Therefore, this study aims to use quantile regression to identify and estimate the socio-demographic factors influencing the CD4 cell count at the time of HIV diagnosis in patients followed by a Behavioral Diseases Counseling Centers (BDCC) from 31 provinces of Iran from 1987 to 2016.

2. Materials and methods

2.1. Study design

In this retrospective cohort study, information on the number of CD4 cells and risk factors associated with HIV patients was extracted from 158 behavioral disease counseling centers (BDCCs) from 31 provinces in Iran from 1987 to 2016.¹¹

The quantile regression model was applied to determine the effect of different variables on CD4 counts at diagnosis and different levels of the CD4 distribution. The CD4 cells count measured up to 3 months later at the time of HIV diagnosis was considered as the response variable and the demographic and clinical variables such as age at the diagnosis time, gender, and the date of HIV diagnosis, the mode of HIV transmission, level of education, employment status and TB co-infection was considered as the predictor variables. The coefficients were estimated for each 5 percentile from 5th to 95th quantile of CD4 count. Standard errors and 95% confidence intervals (CI) were estimated using bootstrapping with 1000 replications. The coefficients corresponding to each quantile were plotted along with their 95% CI. R software was used for statistical calculations.

2.2. Statistical analysis

2.2.1. Quantile regression for count data

In the simple linear regression model, it is supposed that ε_i s have normal distributions with zero mean and unknown variance σ^2 are independent.¹²

$$y_i = \beta_0 + \beta_1 x_i + \varepsilon_i$$

Due to the assumption of the mean zero, the function of $\beta_0 + \beta_1 x_i$ is fitted to data with a conditional mean ($E(y|x)$) corresponding to the mean in the population of y values with a constant value of the independent variable x. The quantile regression model corresponding to the linear regression model can be shown as follows [13]:

$$y_i = \beta_0^p + \beta_1^p x_i + \varepsilon_i^p$$

Table 1

Demographic and clinical characteristics of newly diagnosed HIV-infected people in Iran (1987–2016).

Variable	N (%)	Mean	1st Quintile	Median	3rd Quintile
All	4402 (100)	344.77	113.00	288.50	506.00
Age (year)					
<30	1445 (32.8)	449.08	213.00	410.00	628.00
30–40	1856 (42.2)	308.03	104.00	258.00	449.75
40–50	784 (17.8)	281.10	82.25	203.50	392.75
>50	317 (7.2)	241.88	72.00	172.00	334.50
Sex					
Male	1372 (31.2)	388.65	154.25	343.00	549.75
Female	3030 (68.8)	324.90	98.00	262.00	478.00
Marital Status					
Single	1429 (32.5)	368.82	120.50	321.00	540.00
Married	2133 (48.5)	337.22	119.50	284.00	492.00
Widow	265 (6)	307.27	79.00	238.00	452.00
Divorce	508 (11.5)	333.14	96.75	252.50	505.50
Unknown	67 (1.5)	308.63	52.00	208.00	405.00
Education					
Illiterate	319 (7.2)	330.55	105.00	250.00	469.00
Primary School	1020 (23.2)	334.22	108.00	271.00	497.75
Secondary School	1261 (28.6)	346.34	123.00	300.00	502.50
High School	919 (20.9)	358.21	114.00	302.00	530.00
Academic	274 (6.2)	344.16	141.50	324.50	494.50
Unknown	609 (13.8)	346.64	95.00	285.00	495.50
Job					
Employed	1521 (34.6)	345.21	104.50	292.00	509.00
Unemployed	1740 (39.5)	347.36	117.00	285.00	511.00
Unknown	1141 (25.9)	340.24	115.00	290.00	492.50
Transmission Way					
Injecting drug users	2104 (47.8)	324.54	105.00	261.00	477.00
Unsafe sexual	1646 (37.4)	370.39	143.75	329.00	527.00
Mother to child	122 (2.8)	618.61	282.50	589.50	897.00
Blood transfusion	14 (0.3)	309.71	62.50	116.00	706.25
Unknown	516 (11.7)	281.70	75.50	213.50	427.50
WHO Clinical Stage					
Stage 1	1997 (45.4)	420.55	210.00	381.00	575.00
Stage 2	594 (13.5)	333.39	123.00	276.00	454.25
Stage 3	575 (13.1)	181.67	48.00	114.00	250.00
Stage 4	372 (8.5)	157.14	36.00	86.50	200.75
Unknown	846 (19.6)	366.77	124.50	317.50	549.50
Year of HIV Diagnosis					
Before 2006	530 (12)	432.85	212.75	389.50	622.00
2006–2011	1388 (31.5)	325.31	105.00	268.00	465.50
After 2011	2484 (56.5)	336.85	103.00	276.50	499.75
TB co-infection					
No	4142 (94.1)	350.03	118.00	299.00	510.00
Yes	260 (5.9)	260.91	68.25	175.00	379.00

Table 2Quantile count regression for **factors influencing CD4 cell count** in newly diagnosed HIV-infected people in Iran (1987–2016).

Variable	CD4 count at diagnosis					
	1st Quintile		Median		3rd Quintile	
	Coefficient	P-value	Coefficient	P-value	Coefficient	P-value
Intercept	6.780	<0.001	6.99	<0.001	7.219	<0.001
Age						
<30	Reference					
30–40	–0.343	0.041	–0.25	0.127	–0.214	0.017
40–50	–0.497	0.012	–0.37	0.031	–0.316	0.043
>50	–0.487	0.095	–0.53	<0.001	–0.336	<0.001
Sex						
Female	Reference					
Male	–0.203	0.077	–0.11	0.422	–0.084	0.472
Marital Status						
Single	Reference					
Married	0.048	0.765	–0.009	0.969	–0.041	0.675
Widow and Divorce	–0.077	0.698	–0.002	0.993	0.031	0.831
Unknown	–0.302	0.349	–0.125	0.668	–0.078	0.356
Education						
Illiterate	Reference					
Primary School	0.008	0.962	–0.011	0.935	0.018	0.848
Secondary School	0.153	0.366	0.008	0.934	0.029	0.811
High School	0.083	0.744	–0.004	0.976	0.034	0.454
Academic	0.089	0.696	–0.052	0.734	–0.038	0.752
Unknown	–0.141	0.612	–0.094	0.462	–0.011	0.951
Job						
Employed	Reference					
Unemployed	–0.005	0.966	–0.012	0.963	0.017	0.864
Unknown	–0.090	0.645	–0.018	0.885	–0.006	0.950
Transmission						
Mother to child	Reference					
Injecting drug users	–0.390	0.121	–0.392	0.194	–0.406	0.035
Unsafe sexual	–0.333	0.139	–0.318	0.038	–0.371	0.040
Blood transfusion & Unknown	–0.575	0.115	–0.456	0.013	–0.500	0.001
WHO Clinical Stage						
Stage 1	Reference					
Stage 2	–0.492	0.019	–0.370	0.028	–0.216	0.168
Stage 3	–1.425	<0.001	–1.118	0.001	–0.806	<0.001
Stage 4	–1.756	<0.001	–1.377	<0.001	–1.048	<0.001
Unknown	–0.599	0.003	–0.224	0.056	–0.085	0.599
Year of HIV Diagnosis						
Before 2006	Reference					
2006–2011	–0.722	<0.001	–0.477	0.052	–0.359	0.051
After 2011	–0.728	<0.001	–0.418	0.077	–0.306	0.050
TB co-infection						
No	Reference					
Yes	0.204	0.122	0.187	0.561	0.160	0.419

In which the value of $0 < p < 1$ represents the contribution of the population below to the quantile p . For quantile regression models, the p th quantile is as follows:¹⁴

$$Q^p(y_i|x_i) = \beta_0^p + \beta_1^p x_i$$

This model is analogous to the OLS regression model, hence the estimation of the parameters is via the minimization procedure. For a random sample of Y it is well known that the $\hat{\beta}_1^p, \hat{\beta}_0^p$ are estimated with the Least Absolute Deviations method that minimizes the following sum of the absolute deviations:

$$p \sum_{y_i \geq \beta_0^p + \beta_1^p x_i} |y_i - \beta_0^p - \beta_1^p x_i| + (1-p) \sum_{y_i < \beta_0^p + \beta_1^p x_i} |y_i - \beta_0^p - \beta_1^p x_i|$$

One problem with using quantile regression to count data is that the cumulative distribution function of the response parameter is not continuous, and so the quantiles are not continuous, so they can't be presented as a continuous function of the covariates. Adding uniform random noise (jittering) to the counts can overcome this problem.¹³

3. Results

Between 1987 and 2016, data on 4402 patients aged from 16 to 78-

year-old, whose CD4 cells count were measured in the first three months later of diagnosis, as well as no missing information, was included in this study. The average age of study participants was 34.86 ± 10.43 SD (standard deviation) and 3030 (68.8%) of them were males. Most of the participants 1740 (39.5%) had an unemployed job status. Similarly, most participants had baseline WHO clinical stage I 1997 (45.4%) and transmission way in 2104 (47.8%) of patients was through injecting a drug. Other information about the variables associated with these patients is presented in Table 1.

The results of fitting the quantile count regression model are presented in Table 2. Also, results of the quantile regression analysis for every quantile as well as their 95% CI are presented in Fig. 1. It is noted that for this plot the x-axis represents quantiles of CD4 count, and the y-axis represents the change in CD4 count associated with a one-unit change in the studied covariate, holding other covariates constant.

Male gender was negatively associated with CD4 count at diagnosis for all quantiles (25, 50, and 75). All the age group of the diagnosis has a significant effect for the third quantile, while for the first quantile, the age groups of 30–40 and 40–50 have been significant effect and for the second quantile, the age groups of 40–50 and above 50 have been the significant effect the CD4 counts. For all age groups in all quantile, the CD4 counts decrease with increasing age group. Marital status, job employment, and education level have no significant effect on CD4

Fig. 1. Coefficients of quantile regression model for CD4 count for every quantiles as well as their 95% CI.

counts in different quantiles.

In the first quantile, the transmission way has no significant effect on the CD4 counts. However, in the second quantile patients infected by unsafe sex and blood transition had significantly lower CD4 counts than mother to child transition people. Also, in the third quantile drug user patients and people infected by unsafe sex and blood transition had significantly lower CD4 counts than mother to child transition people.

In the first quantile, all people with WHO Clinical Stage (II, III, IV, and unknown) had significantly lower CD4 counts than the people with WHO Clinical Stage I. For the third quantile, only people with WHO Clinical Stage III and IV had significantly lower CD4 counts than the people with WHO Clinical Stage I.

Year of HIV diagnosis had a significant effect on the CD4 counts for the first quantile. Also, TB co-infection had no significant effect on CD4

counts for all quantiles.

4. Discussion

In this study, the quantile regression model was used to account for potential heterogeneity in the association of various explanatory variables across different quantiles of CD4 counts at the time of diagnosis in HIV patients. Traditional regression models such as the log-linear model assume that the impact of the independent variables is the same at different quantiles of the CD4 distribution. Therefore based on these models the picture of the relationship is incomplete. Quantile regression provides a more accurate description of the conditional variable distribution and its determinants. Most statistical models that describe the relationship between CD4 cell counts and the factors that affect them use

models with count data and their variants to investigate the average effects of covariates on cell counts^{3, 5, 9-10} While using quantile regression for counts as a methodological alternative in analyzing CD4 counts allows various quantiles of a population to be estimated. Some factors that may be poorly related to average CD4 cell counts may be strongly related to lower cell counts. Insight regarding such differential associations is therefore essential for identifying populations at risk based on different levels of cell counts in the diagnosis of HIV.⁸ To achieve this goal, compared to standard regression models, the use of modern statistical methods such as quantile regression can allow a more comprehensive analysis of the factors associated with CD4 cell counting. Using this model can also quantify the relative loss of cells related to a specific risk factor.⁸

On the other hand, the assumption of the equality of mean and variance of the response distribution (over dispersion) in the log-linear model restricts their use in real.¹² Considering that the quantile regression model for count data has a separate scale parameter and over dispersion does not occur, the problem of over dispersion has been solved for this model.

Quantile regression was introduced in 1978 by Quincker and Bast, whose purpose is to model conditional quantiles as a function of predictors.¹³ Tang et al., in 2014, used a logistic regression method to identify the factors associated with baseline CD4 cell count (within 6 months of diagnosis). The variables studied in the Tong study include the year of diagnosis of HIV, age, gender, race, marital status, employment status, educational level, and the way of transmission of the virus. The results of the study indicate that older patients are more likely to be diagnosed late in the disease. Also, due to the use of preventive prophylaxis in China over the period from 2006 to 2012, the percentage of patients with a late diagnosis was declining. According to the authors, one of the limitations mentioned for their study is the use of local data and the non-use of country data. Also, in this study, the staging factor of the disease has not been investigated.⁹ Meier et al. (2007) used a multivariate regression method to identify factors affecting CD4 cell count in Senegalese patients infected with other infections (other than HIV). Also, separate models for men and women have been fitted in this study. The results indicate that the average CD4 count in men is significantly lower than that of women. Smoking also has an important impact on the number of CD4 cells.³ In the year 2016, Bruneau et al., employed multiple quantile regression methods to identify the factors affecting the number of CD4 cells in AIDS patients in France. The purpose of this study was to identify important factors on various levels of CD4 at the time of diagnosis of AIDS. The results of this study showed that in all studied cases, higher age, male status, external migrant patients, association with hepatitis B and C viruses, rural residency and homosexual transmission method have a negative association with CD4 cell count. However, the statistical significance of these factors varied in different quantile. Foreign migrant patients are the only variables that were significant in all of the quantiles.⁸ In 2016, Abbas Tabar et al., used a Poisson regression model to determine the factors affecting the CD4 count in AIDS patients in Shiraz. The results of this study showed that female gender, unemployment, addiction, injection from a common syringe, sexually transmitted infections, longer illness time and age had a negative effect on the CD4 count, while factors such as being present Health insurance, receiving HAART treatment and higher initial CD4 count have a positive effect on CD4 count. One of the weaknesses of this study is the lack of an examination of the appropriateness of fitting the model used for data.¹⁰

5. Conclusion

The study findings indicated that variables, such as older age, clinical stage, transmission way, and year of HIV diagnosis could play the role of risk factors for CD4 counts at the time of diagnosis in HIV patients. However, the relationship between different variables was not uniform distributed in many different quantiles. The late detection of HIV and the lack of awareness of people about their HIV status delay in receiving disinfection therapies, thereby reducing their life expectancy and transmission of HIV by these people. The results of this study can be particularly useful for the prevention, management and clinical care of people with HIV.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Hamadan University of Medical Sciences with IR.UMSHA.REC.1398.406.

Declaration of competing interest

There are no conflicts of interest.

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