OCULAR AND SYSTEMIC MANIFESTATIONS RELATED TO THE CD4 COUNTS OF HIV/AIDS PATIENTS-A STATISTICAL APPROACH

Statistics

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ABSTRACT

HIV/AIDS is a multi-system disorder of opportunistic infections caused by the Human Immunodeficiency Virus (HIV). People with advanced HIV infection are vulnerable to a wide range of infections which affect the entire body parts. Methods The data on 182 patients was collected at Vittala International Institute of Ophthalmology (VIIO), Bangalore, India. Data were entered and analyzed using SPSS 7.5 for windows and Matlab 5.3. In order to know the association between pairs of attributes, to predict number of patients requiring ART in the future, that are of medical interest, various statistical methods are used such as Independence of Attributes, Bayesian predictive distribution, Goodness of fit , discriminant Analysis. Results From the discriminant analysis, we observed that the probability of misclassification is very high, this indicates that even though CD4 is a precursor, it is not a predictor for ocular manifestation. While using Bayesian predictive distribution, we observed that out of 20 patients, 4 patients will require ART with the probability 0.06. which can be useful for the hospital management for future demand.

KEYWORDS

HIV/AIDS, Discriminant Analysis, Multinomial distribution, CD4 Count

1 Introduction:

HIV/AIDS is a multi-system disorder of opportunistic infections caused by the Human Immunodeficiency Virus (HIV). This disorder is transmitted via contaminated bodily fluids, often of a sexual nature. HIV/AIDS is encountered more frequently in socio-economically depressed populations. However, AIDS respects no age, sexual, social, cultural or racial boundaries. The mechanism of AIDS can be explained from the pathophysiological viewpoint as follows: The HIV organism selectively invades and attacks the T-helper cells of its host at the CD4 receptor site. It then incorporates its own DNA into the host genome, and induces the cells to produce viral particles. Here, CD4 (cluster of differentiation 4) is a glycoprotein expressed on the surface of T helper cells, regulatory T cells, monocytes, macrophages, and dendritic cells , and is also a primary receptor used by HIV-1 to gain entry into host T cells. Normally, the lymphocytes recognize the foreign pathogens and initiate an appropriate immune response. Unfortunately, viral infection interrupts this activity and ultimately destroys the lymphocytes. When enough CD4 T-lymphocytes have been depleted, the immune system becomes susceptible to opportunistic infections, and illness results. When the CD4 T-lymphocyte count falls below 200 cells/cubic mm, or when other recognized opportunistic infections or secondary conditions ensue, the patient is said to have AIDS. HIV/AIDS infections leads to a progressive reduction in the number of T cells possessing CD4 receptors and therefore, the CD4 count is used as an indicator to help physicians decide when to begin treatment in HIV infected patients. People with advanced HIV infection are vulnerable to a wide range of infections which affect the entire body parts which may be classified as systemic manifestations and ocular manifestations. Some of the common diseases with systemic manifestations which are frequently used in this data are pulmonary and abdominal tuberculosis and oral candidiasis. Some of the most common AIDS related ocular manifestations are HIV retinopathy, HIV optic neuropathy and CMV retinitis. In this paper, we have analyzed the data in order to know the association between pairs of attributes that are of medical interest , to predict number of patients requiring for ART in the future experiment and so on. The data was collected from Vittala International Institute of Ophthalmology(VIIO) Bangalore, India.Thus helping the hospital management to plan and schedule the availability of costly medicine.

2 Data Description:

The data on 182 patients was collected at (VIIO), Bangalore, India.

Individuals who tested positive for HIV at Freedom Foundation were sent to VIIO, where they were examined for ocular disease. Along with the ocular manifestations, various other systemic observations on each patient were recorded. Some of the observations on the patients are described as follows: Age, which is taken as a discrete variable ranging from 20 to 72 years. Most of the patients in the study are from the age group 30 to 40 years. Sex is taken as a binary variable. Most of the patients in the data are male. Antiretroviral Treatment (ART) is taken as a binary in nature. In this data, most of the patients are not under antiretroviral treatment. CD4 count, which ranges from 10 to 603, this variable is regarded as continuous in the context of our study. CD4 count is a blood cell count used as an indicator to detect AIDS. A lower CD4 count value implies lesser resistance and hence a more advanced stage of AIDS. In other words, as CD4 count increases, the resistance of the patient to diseases increases. Systemic manifestations, which is taken as a categorical variable gives information about any systemic disease that the patient is suffering from, like tuberculosis, oral candidiasis, hypertension, etc. The data here consists of 23 systemic manifestations. Ocular manifestations, is a categorical variable which consists of the diagnosis about the ocular diseases of the patients, based on the observations made on the eye. There are 20 ocular manifestations in this data.

3 Methods:

The data was analyzed in five sections, namely

(1) The application of Maximum Likelihood Estimation of covariance in Multinomial Distribution in order to estimate the probability of a patient belonging to a particular disease.
(2) Testing for Independence of Attributes related to ocular and systemic manifestations in order to examine the association between pairs of attributes.
(3) Bayesian Predictive distribution for number of patients opting for ART in a future experiment given the number of patients taking ART out of n patients in the current study.
(4) Testing for Goodness of Fit of modeled CD4 count distributions
(5) Discriminant Analysis in order to discriminate an observation into one of five main categories of ocular diseases, based on only CD4 counts

3.1 Maximum Likelihood Estimation of covariance in Multinomial Distribution

In order to know the prevalence of systemic manifestations and ocular

diseases in AIDS patients, we estimated the probability that an AIDS patient will have a particular ocular or systemic manifestation or both. The number of AIDS patients in each category is recorded. This constitutes a multinomial experiment. The probability mass function of the Multinomial distribution obtained from this experiment is given below.

$$f(x_1, x_2, ..., x_k; p_1, p_2, ..., p_k) = \frac{n!}{x_1! x_2! ... x_k!} p_1^{x_1} p_2^{x_2} ... p_k^{x_k}$$

$$0 < p_i < 1, i = 1, 2, ..., k, n = x_1 + x_2 + ... + x_k. 0 \le x_i \le n$$

Here, k is the number of categories of manifestations. The variables are defined as X_i : Number of patients belonging to the ith category. We used the maximum likelihood method of estimation to obtain estimates of p_i's . The MLE of pi is given by

$$\hat{p}_i = \frac{X_i}{n}$$

It is also of interest to estimate the measure of relationship between X_i and X_j, i≠j. The MLE of the covariance between X_i and X_j is given by

$$\hat{cov}(x_i, x_j) = -n\hat{p}_i\hat{p}_j, i, j = 1, 2, ..., k.$$

3.1.1 Systemic manifestations
Here the categories are classified as X_1 represents Abdominal tuberculosis, X_2 represents pulmonary tuberculosis, X_3 represents OSM(Other systemic manifestations-other than abdominal and pulmonary tuberculosis), X_4 represents pulmonary tuberculosis +OSM, X_5 represents Abdominal tuberculosis+OSM, X_6 represents NSM (no systemic manifestation)

Here X_1=9, X_2=41, X_3=20, X_4= 28, X_5=2, X_6=77 and the ML estimates are

$$\hat{p}_1 = 0.0494 \quad \hat{p}_2 = 0.2252 \quad \hat{p}_3 = 0.1099 \quad \hat{p}_4 = 0.1538 \quad \hat{p}_5 = 0.1098 \quad \hat{p}_6 = 0.4230$$

Table 1: Estimated covariance matrix of Systematic manifestation

Cov	X_1	X_2	X_3	X_4	X_5	X_6
X_1	-	-1.9691	-0.96094	-1.3448	-0.09601	-3.69863
X_2	-1.95077	-	-4.38066	-6.13053	-0.43767	-16.8609
X_3	-0.952	-4.38066	-	-2.99176	-0.21359	-8.22832
X_4	-1.33227	-6.13053	-2.99176	-	-0.2989	-11.5152
X_5	-0.09511	-0.43767	-0.21359	-0.2989	-	-0.82208
X_6	-3.69863	-16.8609	-8.22832	-11.5152	-0.82208	-

From Table 1, we observe that the MLE of p1 is 0.05, which means that approximately 5% of AIDS patients coming to VIIO are expected to have abdominal tuberculosis. In the estimated covariance matrix, we see that all the covariances are negative, which is obvious since the categories are non -overlapping. The MLE of the correlation between X_i and X_j is

$$\hat{\rho}_{ij} = \frac{n\hat{p}_i\hat{q}_j}{\sqrt{n\hat{p}_i\hat{q}_i}\sqrt{n\hat{p}_j\hat{q}_j}}$$

Here, the MLE of the correlation between X_1 and X_2 is

$$\hat{\rho}_{12} = -0.2448$$

and the MLE of the correlation between X_1 and X_5 is

$$\hat{\rho}_{15} = -0.1193.$$

Clearly, the first two categories have a higher negative correlation than the first and the fifth categories.

3.1.2 Ocular manifestations:
The different categories here are classified as Y_1 represents CMV retinitis, Y_2 represents HIV retinopathy, Y_3 represents HIV optic neuropathy, Y_4 represents NOD (no ocular diagnosis), Y_5 represents OOD (other ocular diagnosis-other than CMV retinitis, HIV retinopathy and HIV optic neuropathy), Y6 represents CMV retinitis+

NOD, Y_7 represents CMV retinitis + OOD, Y_8 represents NOD+OOD.

Here Y_1=10, Y_2=24, Y_3=4, Y_4=113, Y_5=15, Y_6=2, Y_7=5, Y_8=2. We also estimated p_i's, i=1, 2,...,8 using the method of maximum likelihood as

$$\hat{p}_1 = 0.0549 \quad \hat{p}_2 = 0.1263 \quad \hat{p}_3 = 0.0604 \quad \hat{p}_4 = 0.6263 \quad \hat{p}_5 = 0.0824 \quad \hat{p}_6 = 0.0109 \quad \hat{p}_7 = 0.0274$$

$$\hat{p}_8 = 0.0109$$

Table 2: The estimated covariance matrix of Ocular manifestation

Cov	Y_1	Y_2	Y_3	Y_4	Y_5	Y_6	Y_7	Y_8
Y_1	-	-0.1262	-0.6035	-0.8233	-6.2578	-0.1907	-0.2737	-0.1089
Y_2	-0.1262	-	-1.3883	-1.894	-14.396	-0.4388	-0.6298	-0.2505

From Table 2, we observe that the MLE P_3 is 0.06, which means that approximately 6% of AIDS patients coming to the hospital are expected to have HIV optic neuropathy. Here, the MLE of the correlation between Y_2 and Y_3 is given by

$$\hat{\rho}_{23} = -0.1002$$

And the MLE of the correlation between Y2 and Y5 is given by

$$\hat{\rho}_{25} = -0.9006.$$

Clearly, the second and the fifth categories have a higher negative correlation than the second and the third categories.

3.1.3   Combination of ocular and systemic manifestations:
The different categories are classified as follows: Z_1 represents HIV retinopathy + pulmonary tuberculosis, Z_2 represents OOD + NSM, Z_3 represents NOD + pulmonary tuberculosis, Z_4 represents NOD + abdominal tuberculosis, Z_5 represents NOD +OSM, Z_6 represents NOD+NSM, Z_7 represents pulmonary TB+OSM+HIV retinopathy and Z8 represents pulmonary TB+OSM+NOD.

Here Z_1=8, Z_2=11, Z_3=21, Z_4=5, Z_5=11, Z_6=55, Z_7=7, Z_8=15. The maximum likelihood estimates of pi,i=1,2,….,8 are obtained as

$$\hat{p}_1 = 0.0549 \quad \hat{p}_2 = 0.1263 \quad \hat{p}_3 = 0.0604 \quad \hat{p}_4 = 0.6263 \quad \hat{p}_5 = 0.0824 \quad \hat{p}_6 = 0.0109 \quad \hat{p}_7 = 0.0274$$

$$\hat{p}_8 = 0.0109$$

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$\hat{p}_8 = 0.0109$

Table 3: The estimated covariance matrix of Ocular and systematic manifestations

Cov	Z_1	Z_2	Z_3	Z_4	Z_5	Z_6	Z_7	Z_8
Z_1	-	-0.3192	-0.6384	-0.1596	-0.3192	-1.596	-0.2128	-0.4788
Z_2	-0.3192	-	-0.9576	-0.2394	-0.4788	-2.394	-0.3192	-0.7182
Z_3	-0.6384	-0.9576	-	-0.4788	-0.9576	-4.788	-0.6384	-1.4364
Z_4	-0.1596	-0.2394	-0.4788	-	-0.2394	-1.197	-0.1596	-0.3591
Z_5	-0.3192	-0.4788	-0.9576	-0.2394	-	-2.394	-0.3192	-0.7182
Z_6	-1.596	-2.394	-4.788	-1.197	-2.394	-	-1.596	-3.591
Z_7	-0.2128	-0.3192	-0.6384	-0.1596	-0.3192	-1.596	-	-0.4788
Z_8	-0.4788	-0.7182	-1.4364	-0.3591	-0.7182	-3.591	-0.4788	-

From the above Table 3, we see that the MLE of p1 is 0.05, which means that approximately 5% of AIDS patients coming to the hospital are expected to have a combination of HIV retinopathy and pulmonary tuberculosis. In the estimated covariance matrix, we see that all the co variances are negative, since the categories are non-overlapping. Here, the MLE of the correlation between Z_4 and Z_1 is given by and the MLE of the correlation between Z_4 and Z_3 is given by Clearly, the fourth and the third categories have a higher negative correlation than the fourth and the first categories.

3.2 Testing for Independence of Attributes related to ocular and systemic diseases:

Here testing for association between- **1**.Ocular and systemic manifestations. **2**. Antiretroviral treatment and ocular manifestations. **3**. Age and ocular manifestations.

In order to test for association, we applied the chi-square test, the Hypotheis is defined as

H0 : The two categories are independent against   H1: The two categories are associated. The test procedure is to reject H_0 at level of significance α, if

$$\chi^2 \geq \chi^2_{((r-1)(c-1),1-\alpha)}$$

where   r = number of categories of attribute A and c= number of categories of attribute B.

3.2.1 Ocular diagnoses and systemic manifestation

Table 4: Association between Ocular and Systemic manifestations

SM \ OD	HIVR	HIVO	CMVR	Total
Pulm TB	15 15.17	7 6.6	9 9.23	31
Abd TB	1 1.47	0 0.64	2 0.89	3
Oral Candidiasis	7 6.36	3 2.77	3 3.87	13
Total	23	10	14	47

Table 4 shows the Association between Ocular and Systemic manifestations and We obtain χ^2 (cal value) =2.4951 and $\chi^2_{((r-1)(c-1),1-\alpha)}$ = 9.488. Hence, we accept H0 at 5% level of significance and conclude that systemic and ocular manifestation are not associated.

3.2.2 Antiretroviral treatment and ocular manifestations

Table 5: Association between ART and Ocular manifestation

OD \ ART	HIVR	HIVO	CMVR	NL	Others	CMVR + Others	CMVR+ NL	NL+ Others	Totals
YES	23 20.44	9 9.37	9 8.52	94 96.24	11 12.77	2 1.70	5 4.26	2 1.70	155
NO	1 3.56	2 1.63	1 1.48	19 16.76	4 2.23	0 0.30	0 0.74	0 0.30	27
Totals	24	11	10	113	15	2	5	2	182

Table 5 shows the Association between ART and Ocular manifestation and We obtain $\chi^2_{=6.0246}$ and $\chi^2_{((r-1)(c-1),(1-\alpha))}$ = 14.067. Hence we accept at 5% level of significance and conclude that antiretroviral treatment and ocular manifestation are not associated.

3.2.3 Age and ocular manifestations

Table 6: Association between Age and Ocular manifestation

OD AGE	HIVR	HIVO	CMVR	NL	Others	CMVR + Others	CMVR + NL	NL + Others	Totals
20-29	10 5.01	1 2.30	3 2.09	21 23.59	3 3.13	0 1.04	0 0.42	0 0.42	38
30-39	10 13.32	5 6.10	6 5.55	67 62.71	7 8.32	3 2.77	2 1.11	1 1.11	101
40-49	3 3.96	4 1.81	1 1.65	17 18.63	2 2.47	2 0.82	0 0.33	1 0.33	30
50-59	0 0.92	1 0.42	0 0.38	5 4.35	1 0.58	0 0.19	0 0.08	0 0.08	7
60-69	1 0.66	0 0.30	0 0.27	2 3.10	2 0.41	0 0.14	0 0.05	0 0.05	5
70-79	0 0.13	0 0.06	0 0.05	1 0.62	0 0.08	0 0.03	0 0.01	0 0.01	1
Totals	24	11	10	113	15	5	2	2	182

Table 6 shows the Association between Age and Ocular manifestation and We obtain χ2= 29.2537 and χ2((r-1)(c-1),(1-α))=45. Hence we do not reject the null hypothesis at 5% level of significance and conclude that age and ocular manifestation are not associated.

3.3 Bayesian predictive distribution for number of patients opting for Antiretroviral treatment.

Let X denote whether the AIDS patient who visits VIIO takes the antiretroviral treatment or not. Then X|θ follows B(n=15, θ). That is, the distribution from which we sample is B(15, θ). That is

$$f(x \mid \theta) = \begin{cases} \binom{15}{x} \theta^x (1-\theta)^{15-x}, & x = 0,1,2,\dots,15 \\ 0, & \text{otherwise,} \end{cases}$$

where Θ={θ: 0<θ<1}. We model the prior distribution of θ using the past data. For this we **have the following observed frequency distribution.** For this observed data, we fitted Beta distribution of the first kind with parameters   α=2.5547 and β = 13.415 and found it to be a good fit using the chi-square goodness of fit criterion. Using the prior distribution and the B(15,θ) distribution we obtain the posterior distribution of θ given by shown in Table 7. For a future B(20,θ) experiment , the predictive distribution of a future observation y given the current observation equal to x=3 is the Beta-binomial distribution .

For N=20 and x=3, the predictive probabilities are shown in Table 8.

Table 7: Sample Number of people requiring ART

Sample Number	Number of people taking ART $\sum_{i=1}^{15} Xi$	
1	1	0.0667
2	5	0.3333
3	4	0.2667
4	1	0.0667
5	1	0.0667
6	3	0.2000
7	3	0.2000
8	3	0.2000
9	0	0.0000
10	2	0.1333
11	1	0.0667

Table 8: Sample Number of people requiring ART for N=20 and x=3, the predictive probabilities are

Y	0	1	2	3	4	5	6	7	8	9	10
f(y|x=3)	0.36	0.26	0.17	0.10	0.06	0.03	0.01	0.01	0.00	0.00	0.00
Y	11	12	13	14	15	16	17	18	19	20	
f(y|x=3)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	

By using the Predictive distribution Beta-Binomial Distribution , we can predict the number of patients who will be on ART out of N patients in a future experiment, given that x out of n patients are on ART in the current experiment. Suppose that in the current experiment x=3 patients take ART out of n=15 patients, then in a future experiment , if N=20 patients come to VIIO, the probability that 4 patients requiring ART is 0.06. The same procedure can be used prediction for various values of N, n and x and this can be very useful to the hospital management.

3.4 Disriminant Analysis based on only CD4 counts

We have modeled the CD4 counts corresponding to the patients of each category mentioned in the first section. The sample fitted model HIV retinopathy are shown in Figure1
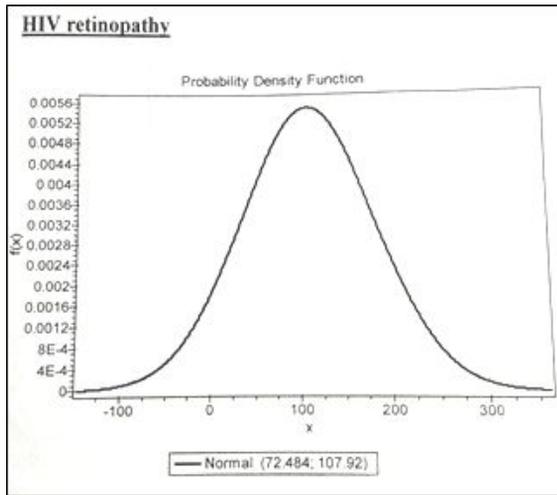

Figure 1: Sample Fitted Model of HIV Retinopathy

Which follows normal distribution with mean 72.484 and variance 107.92 Similarly, HIV Optic Neuropathy follows normal distribution with mean 75.95 and variance 138.27,CMV retinitis follows shifted lognormal distribution with location parameter 0.18174 scale parameter 5.3038 and shift of -116.04, OOD follows normal distribution with mean 137.78 and variance 200.67, CMV retinitis + OOD follows normal distribution with mean 57.977 and variance 104.4, NOD follows normal distribution with mean 87.33 and variance 159.26, Abdominal tuberculosis follows normal distribution with mean 146.02 and variance 145.75., NSM follows normal distribution with mean 94.082 and variance 195.62, OSM follows normal distribution with mean 779.462 and variance 130.63, Pulmonary tuberculosis follows normal distribution with mean 61.424 and variance 134.05,Pulmonary tuberculosis + OSM follows normal distribution with mean 41.265 and variance 75.7. When we began we talked about 5 non-overlapping categories of ocular disease. Now if an AIDS patient arrives at VIIO, we classified the AIDS patient as belonging to one of the 5 categories.

For this we used the squared distance(univariate case) .The classification rule is to assign the value x (that is, the patient corresponding to the CD4 count x) to the ith population, if the squared distance is minimum for the ith population. We used the first 170 observations in the data for obtaining the classification rule. The remaining 12 observations are used to validate the rule.

Table 9: Classification Rule to assign the value X corresponding to CD4 count.

Obsn. No	Cd⁴ Count	Squared Distance						Observed Popln.	True Popln
		HIVR	CMVR	HIVO	Others	NL	Minimum		
1	177	2.0128	5.1105	0.249	0.0315	0.0299	0.029	5	4
2	61	0.495	0.4888	0.923	0.979	1.2978	0.488	2	1
3	341	19.53	41.54	6.438	0.943	4.114	0.942	4	1
4	79	0.14	0.0575	0.541	0.746	0.8754	0.057	2	5
6	94	0.01	0.0204	0.301	0.576	0.5866	0.01	1	5
7	10	2.6785	4.0016	2.553	1.814	2.9453	1.814	4	5
8	110	0.0372	0.3037	0.122	0.418	0.3421	0.037	1	5
9	145	0.6944	2.0856	0.008	0.161	0.0357	0.007	3	5
10	163	1.3516	3.623	0.099	0.076	0.0002	0.000	5	5
11	224	5.1922	11.971	1.157	0.023	0.4966	0.023	4	5
12	142	0.6059	1.8704	0.003	0.179	0.0497	0.002	3	3
5	192	2.8668	6.9874	0.457	0.005	0.1175	0.005	4	5

From Table 9, we observed that only 2 out of 12 observations are correctly classified. There is a very high probability of misclassification (0.83). This is because there are several other factors that cause ocular manifestations, not only CD4 count. Here, we come to conclusion that CD4 counts are only precursors and not predictors for ocular diseases.

1 Conclusion

(1) The application of the multinomial probabilities of a patient belonging to an ocular, systemic or a combination of both have been estimated.

(2) We have studied the association between various pairs of attributes that are of medical interest. Firstly, ocular and systemic manifestations are not associated. Secondly Antiretroviral treatment and ocular diagnoses are not associated. This indicates that ART does not prevent the onset of ocular manifestation. Thirdly, Age and ocular diagnoses are not associated , this is because the ocular diseases in this data are HIV/AIDS related and not age related. So the probability of an aged HIV/AIDS patient being affected by a particular ocular disease is not significantly different from the probability of a young AIDS patient being affected by the same ocular disease.

(3) Given that X patients out of n are taking ART in the current study, we have obtained the predictive distribution for the number of patients Y out of N patients . This is very useful tool to the hospital management. It can be used to plan and schedule the availability of costly medicines, doctors, technicians and equipment required for ART according to the number of patients requiring ART.

(4) In the discriminant analysis, we observe that the probability of misclassification is very high. This indicates that even though CD4 is a precursor, it is not a predictor for ocular diagnoses. This high probability of misclassification is attributed to the non-availability of any data other than the CD4 count. If there is multivariate data, then discriminant analysis is expected to yield better results.

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