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The Exploring Based on Nonlinear Logistic Model in Forecasting Curative Effect for AIDS

Yifei Bian, Zhongdi Cen, Jian Huang, Lifeng Xi *
Institute of Mathematics, Zhejiang Wanli University, Ningbo, 315100, P.R. China
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Abstract: The paper uses the improved model based on the traditional Logistic Model to forecast the effect of the curative way for AIDS. We have a conclusion about the best time to stop the treatment by the analysis on the clinical data.

Key words: HIV ; CD4; curative effect; nonlinear Logistic Model

1 Introduction

AIDS is the one of the most serious illnesses. It has killed $3,000,000$ people since 1981. In January 1988, the World Heath Organization(WHO) called the December 1 of every year the world day of AIDS to propagandize the knowledge of AIDS. AIDS is caused by the HIV, which can destroy the human's immune system, and cause the loss of resistant ability or even lives.

The cell of CD4 in the immune system is the quite effective to resist HIV. When the CD4 breaks down with the inroad of HIV, the number of CD4 will decrease rapidly and the number of HIV will increase, which could cause the outbreak of AIDS.

So the purpose of the treatment about AIDS is to reduce the number of HIV in the human's system, and to add the number of CD4, or reduce the rate of decreasing of CD4 at least.

But now, people still have not found an effective cure for AIDS. And then, the ways we are now using have not only some side-effect, but also higher costs. So many countries and the medical treatment are still looking for the best treatment for AIDS.

We will set up a model to forecast the curative effect for AIDS through the data from ACTG (American Cure Treatment Government for AIDS), which show the chroma of the CD4 and HIV about more than 300 cases, taking medicines of zidovudine, lamivudine and indinavir. If we set up the forecasting model, we could compare the treatments for AIDS, and also we may have a conclusion about the best time to stop the treatment.

2 Model Introduction

2.1 Confirming the variables

Generally, the curative effect depends on the infecting grade at the beginning. Meanwhile, we have the index number at the beginning of the treatment, and also the index number among the treated time from the clinical data. As the standard sort on CD4 and HIV by the CDC (Center of Disease Control in America) and WHO, we divided more than 300 cases into 4 kinds. These kinds are the early time (the number of CD4 is more than $100/\mu l$), the middle time(the number of CD4 is between $40/\mu l$ and $200/\mu l$), the latter time(the

*Corresponding author. Tel. : +86-574-8822 2249. *E-mail address*: xilf@zwu.edu.cn

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number of CD4 is between $10/\mu l$ and $40/\mu l$) and the last time(the number of CD4 is less than $10/\mu l$)(see [1-2]). Then, we found that the clinical data had the distinct observing time, based on the distributing figure of the frequency (Figure 1).

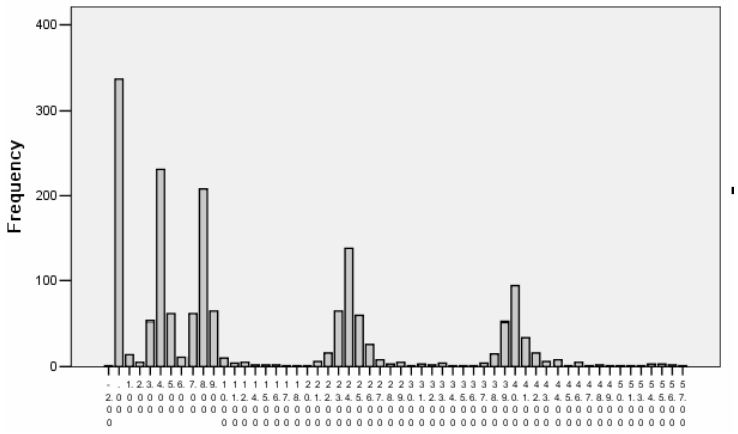

Figure 1: Bar chart on the frequency of the treated time.

From the Figure 1, we found the observing time could be divided into 5 periods. The first period, which is from the $-2nd$ week to $2nd$ week, is the early time of treatment. The latter periods is the curative time. It is composed of 4 periods. They are the second period(the $3rd\sim6th$ week), the third period(the $7th\sim16th$ week), the fourth period(the $17th\sim33rd$ week) and the fifth period(more than the $33rd$ week).

Then we made discriminant analysis on the two indexes of the CD4and HIV of the five different curative period from more than 300 clinical data. The discriminant analysis is the T-Test of the paired numbers. The result is the Figure 2.

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	cd4count1 - cd4count2	-48.163	104.472	5.537	-59.052	-37.273	-8.698	355	.000
Pair 2	cd4count1 - cd4count3	-70.641	128.275	6.926	-84.265	-57.018	-10.199	342	.000
Pair 3	cd4count1 - cd4count4	-84.643	129.027	6.867	-98.149	-71.137	-12.325	352	.000
Pair 4	cd4count1 - cd4count5	-93.157	138.944	8.718	-110.327	-75.988	-10.686	253	.000
Pair 5	vload1 - vload2	1.838	1.173	.063	1.714	1.962	29.186	346	.000
Pair 6	vload1 - vload3	2.085	1.293	.071	1.945	2.224	29.338	330	.000
Pair 7	vload1 - vload4	2.109	1.487	.082	1.948	2.271	25.660	326	.000
Pair 8	vload1 - vload5	2.166	1.522	.108	1.954	2.378	20.132	199	.000

Figure 2: analysis of variance on the indexes of CD4 and HIV.

From the Figure 2, we could find the distinct differences of the two indexes among the different curative period. It shows the curative effect varies in the different curative periods. This also explains why we could forecast the change of the curative effect according to the treating time or the curative period.

There are many variables of two characters in Medicine. For example, the variable on effect and illness are two characters. One is the affirmance, and the other is the denial. It is not easy to explain this problem if we use the linear model. Therefore, we chose the Logistic Model to solve the problem.

We wanted a probability of the curative effect. First, we used the variable Y_j of two kinds of character.

$$Y_j = \begin{cases} 1 & \text{the medicine is effective} \\ 0 & \text{otherwise} \end{cases} \tag{1}$$

The variable Y_j comes down to the curative effect, so we must make a demarcation of curative effect to the clinical data. Since we only have two indexes and the information for AIDS we have collected , we use the changes of these two indexes to define the curative effect. The medicine is defined effective if the number of CD4 increases by 80% and the chroma of HIV decreases, or the speed of decreasing the number of CD4 is slow. Otherwise, it is not defined effective.

2.2 Setting up the model

The Logistic Model(see[3]) is

$$\ln[\frac{P_j}{1-P_j}] = \alpha + \sum \beta_i X_{ij} \tag{2}$$

The P_j thereinto model (2) is the event probability in the condition of $X_{ij} = (x_{ij}$. And $1 - P_j$ is the probability of the event not happening in the same condition. In model (2), $i = 1, \cdots, m$ is the number of the independent variables. α is the intercept, and β_j is the parameters of the independent variables.

If we want to forecast the curative effect for AIDS, we must estimate the under probability of P_j.

$$P_j = P(Y_j = 1 | X_{ij} = x_{ij}) \tag{3}$$

From the experience of the medicine, we know the curative effect is relative to the severity of sickening and the time of treatment or the period of treatment. So we chose X_{1j}(the severity of sickening) and X_{2j} (the period of treatment) as the independent variables. Meanwhile, we didn't know whether these two independent variables are independent. So we may consider the mutual influence of the two independent variables in the model. Then, we could get the conditional probability of the curative effect:

$$P_j = \frac{\exp(\alpha + \beta_1 X_{1j} + \beta_2 X_{2j} + \beta_3 X_{1j} X_{2j})}{1 + \exp(\alpha + \beta_1 X_{1j} + \beta_2 X_{2j} + \beta_3 X_{1j} X_{2j})} \tag{4}$$

In the equation (4),we know

$$X_{1j} = \begin{cases} 1 & \text{the case is in early time,} \\ 2 & \text{the case is in middle time,} \\ 3 & \text{the case is in latter time,} \\ 4 & \text{the case is in last time.} \end{cases} \tag{5}$$

$$X_{2j} = \begin{cases} 1 & \text{the treatment is in the first period,} \\ 2 & \text{the treatment is in the second period,} \\ 3 & \text{the treatment is in the third period,} \\ 4 & \text{the treatment is in the fourth period} \\ 5 & \text{the treatment is in the fifth period.} \end{cases} \tag{6}$$

3 Improved Model

We used the statistical software of SPSS(see[4]), and got the result as the figure in the underside(Figure 3).

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	x1			.000	3	1.000	
	x1(1)	-1.267	990.818	.000	1	.999	.282
	x1(2)	-.430	931.152	.000	1	1.000	.650
	x1(3)	-.129	867.395	.000	1	1.000	.879
	x2			14.648	4	.005	
	x2(1)	13.700	1472.281	.000	1	.993	891298.8
	x2(2)	-11.487	1244.304	.000	1	.993	.000
	x2(3)	6.315	736.140	.000	1	.993	553.077
	x2(4)	-2.442	278.235	.000	1	.993	.087
	x1 * x2			9.030	12	.700	
	x1(1) by x2(1)	-.525	3133.241	.000	1	1.000	.591
	x1(1) by x2(2)	1.373	2648.072	.000	1	1.000	3.948
	x1(1) by x2(3)	-.593	1566.621	.000	1	1.000	.553
	x1(1) by x2(4)	.111	592.127	.000	1	1.000	1.118
	x1(2) by x2(1)	-.320	2944.562	.000	1	1.000	.726
	x1(2) by x2(2)	.197	2488.609	.000	1	1.000	1.218
	x1(2) by x2(3)	-.263	1472.281	.000	1	1.000	.769
	x1(2) by x2(4)	.330	556.470	.000	1	1.000	1.391
	x1(3) by x2(1)	-.163	2742.945	.000	1	1.000	.850
	x1(3) by x2(2)	.157	2318.212	.000	1	1.000	1.170
	x1(3) by x2(3)	.058	1371.473	.000	1	1.000	1.060
	x1(3) by x2(4)	-.326	518.368	.000	1	.999	.722
	Constant	-4.109	465.576	.000	1	.993	.016

a. Variable(s) entered on step 1: x1, x2, x1 * x2 .

Figure 3: The result of the Logistic Model.

From the result, we could find that the test probability of the coefficient is more than 0.05 except the variable of X_{2j}. So the independent variables X_{1j} and $X_{1j} * X_{2j}$ is not marked. But this contravenes the general theory. For the reason of the general knowledge of Medicine, the independent variable X_{1j} surely affects the curative effect. In other words, the variable X_{1j} must be in the model. Thus,we had to adjust the two independent variables. Since we used the independent variables X_{1j} and X_{2j} in the original model,we could change X_{2j} to T_j. Both X_{2j} and T_j show the time of treatment. So one could replace another. But the maximum of T_j is 57 and it could be infinite. If $T_j \longrightarrow \infty$, then $\lim P_j = 0$. In other words, this kind of treatments has no effect at last. Please see [5-8] for related topics.

It is in conflict with any medical treatment. Meanwhile, from the figure of the spot about the effective probability and the treated time, we could find the effective probability inclines to the stable probability as the passing treated time.

Therefore, we improved the model to be the following form.

$$P_j = \frac{\exp(\alpha + \beta_1 X_{1j} + \beta_2 \exp^{-\frac{T_j}{4}} + \beta_3 X_{1j} T_j)}{1 + \exp(\alpha + \beta_1 X_{1j} + \beta_2 \exp^{-\frac{T_j}{4}} + \beta_3 X_{1j} T_j)} \tag{7}$$

In model (7), we used $\exp^{-\frac{T_j}{4}}$ to T_j because of two reasons. One is that the effective probability must be surely stable as the treated time going on. The other is based on the numerical computer. We divided T_j into 4 to prevent the numerical computer from overflow. We chose 4 because it is the cycle of the test since the case took the treatment.

Then we used SPSS to estimate coefficients again. The result is Figure 4.

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	560.823	7	.000
	Block	560.823	7	.000
	Model	560.823	7	.000

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	x1			78.104	3	.000	
	x1(1)	-1.623	.216	56.418	1	.000	.197
	x1(2)	-.763	.198	14.774	1	.000	.466
	x1(3)	-.145	.178	.663	1	.416	.865
	x2	-3.836	.267	205.752	1	.000	.022
	cd4date * x1			1.898	3	.594	
	cd4date by x1(1)	.003	.010	.076	1	.783	1.003
	cd4date by x1(2)	.011	.009	1.467	1	.226	1.011
	cd4date by x1(3)	-.003	.008	.107	1	.743	.997
	Constant	.602	.082	53.774	1	.000	1.825

a. Variable(s) entered on step 1: x1, x2, cd4date * x1 .

Figure 4: The result of the improved Logistic Model.

The chi-square of the Model is 560.823, and it is marked(Sig. is less than 0.05)from the table of Omnibus Tests of Model Coefficients. By the table of Variables in the Equation, the variables of X_{1j} and the $X_{2j}(= \exp^{\frac{-T_j}{4}})$ are not markedly zero. (The Sig. of X_{1j} and X_{2j} is less than 0.05). But the mutual influence of X_{1j} and T_j is not marked, because the Sig. is 0.594,more than 0.05. So we could not consider the mutual influence of X_{1j} and T_j in the improved model. Again,we used SPSS to get the coefficients estimate, and

after the test of the model and the coefficients we got the model

$$P_j = \begin{cases} \frac{\exp(0.596-1.552-3.782\exp^{-\frac{T_j}{4}})}{1+exp(0.596-1.552-3.782\exp^{-\frac{T_j}{4}})} & X_{1j}=1, \\ \frac{\exp(0.596-0.574-3.782\exp^{-\frac{T_j}{4}})}{1+exp(0.596-0.574-3.782\exp^{-\frac{T_j}{4}})} & X_{1j}=2, \\ \frac{\exp(0.596-0.180-3.782\exp^{-\frac{T_j}{4}})}{1+exp(0.596-0.180-3.782\exp^{-\frac{T_j}{4}})} & X_{1j}=3, \\ \frac{\exp(0.596-3.782\exp^{-\frac{T_j}{4}})}{1+exp(0.596-3.782\exp^{-\frac{T_j}{4}})} & X_{1j}=4. \end{cases} \tag{8}$$

4 The application of the improved Logistic Model

From the spot figure of the effective probability and the treated time (Figure5), we could find the difference among the cases of the different sicken degree. In Figure 5, 4 different curves can be seen. The effective probability of each kind of sicken degree is represented by each curve. However, for any kind of sicken degree, the most effective probability could be reached at some time between 15 weeks and 20 weeks after having the treatment. If the patient keep receiving the treatment, the curative effect will not be better. So the best cure period should be at some time between 15 and 20 weeks. In other words, we should terminate the treatment in the period 4.

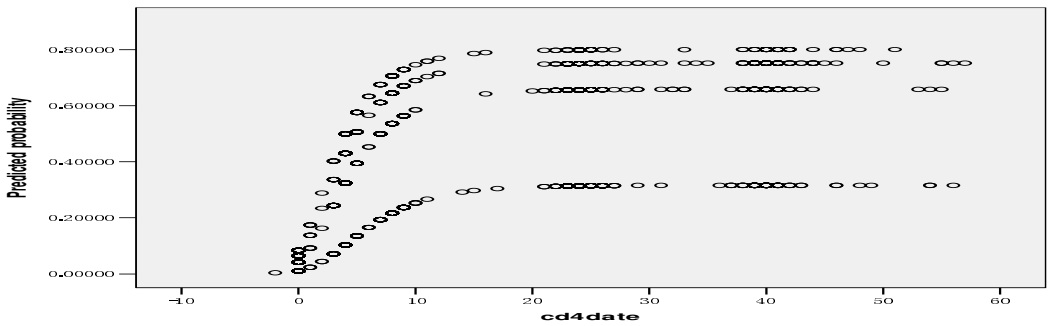

Figure 5: The spot figure of the effective probability and the treated time.

5 Conclusion

This paper does research on the curative effect for AIDS by the mathematical model. Based on the Logistic Model,we improved it. But there are many points to be improved for absence of the medical knowledge and the experiences, such as the criteria to define the medical effect, the cases' classification, and the validation of the provided Logistic model from the theory.

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