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What Else do Epileptic Data Reveal

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Abstract: Problem statement: Aggregating and analyzing data of all patients using statistical methodologies as often done in macro sense would be not useful when physician's professional interest was only to provide the best medical care to the patient. For this purpose, individual data of the involved patient should be analyzed and modeled in a micro sense for the physician to notice whether the treatment was helping the particular patient as demonstrated in this article. Understandably, a medical treatment would work in some patients but not in all patients. The physician would be more helped to know whether the treatment worked in a patient. Otherwise, the physician might switch to another treatment for the patient. No appropriate methodology existed in the literature to perform such a profile analysis. Hence, this article introduced a new statistical methodology and demonstrated the methodology using epileptic data. **Approach:** A probabilistic approach was necessary, as the number of epilepsy seizure in a patient happened to involve a degree of uncertainty. In some patient, the chance for a large number of seizures might be more depending on his/her proneness. The proneness would be a latent and non-measurable factor and hence, it could be captured only as a parameter. The traditional Poisson distribution was not suitable as it assumed homogeneous patients with respect to the proneness. The probability model should match the reality. A generalized Poisson model with an additional parameter to describe individual patient's proneness was necessary as the article demonstrated. The author introduced such a model and investigated several statistical properties before in another article A new methodology with that probability was devised in this article for assessing the efficacy of a treatment for a chosen patient in epilepsy study. **Results:** Physicians pondered over whether epilepsy seizure incidences data support their hunch that their treatment was successful for a patient. This kind of case-by-case profiling was necessary to exercise the option of switching to another treatment for the patient. Aggregated medical data analysis of all patients did not help in making decision for a particular patient. The results of this article demonstrated about how the new methodology worked in epilepsy data to confirm when the treatment was successful. Patients, nurses and physicians were eager to develop an early warning system about how successful the treatment was in a patient. Such an early warning system was feasible, after finding the probability pattern of the data, because of the new methodology in this article. The discussions in this article could be emulated for other medical data analysis to address patient's profile. **Conclusions/Recommendations:** As demonstrated with an example using epilepsy data, other medical data could be fit, analyzed and interpreted using the incidence rate restricted Poisson model. Not only the incidence rate but also the restriction level on the incidence rate due to the treatment could be estimated and tested. The proximity of the patients could then be identified using the indices based on mapping the principal components of their data as demonstrated in the article.

Key words: Placebo patients, incidence rate, pregabide group, seizure incidence, epilepsy seizure, hypothesis, characteristic cube, epileptic seizure, restriction level, rate versus restriction

INTRODUCTION

The frontiers of medical discovery are expanding remarkably in this 21st century with inter-disciplinary cooperative research efforts. To advance medical discoveries, researchers are in great need of powerful and appropriate statistical methodologies to extract and interpret pertinent medical information. Applied statisticians are constantly inventing new methodologies to meet the needs. Yet, data like the seizure incidences remain under-utilized. Finding an appropriate underlying probability model for the data pattern has to be innovative and tailored to the needs of medical researchers as demonstrated in this article.

To be specific, consider the epilepsy seizure incidences data in Table 1 and 2 (Lu and Wang, 2003 for clinical details). The data were collected from fifty-nine patients who experienced repeatedly epilepsy

seizures. Twenty-seven of them were in a control group and they received "placebo" drug. The remaining thirty-two patients received progabide drug. The patient's age and number of seizures prior to the beginning of the treatment period were noted. The numbers of seizures in each of the four treatment years were recorded. The first task is to frame a modeling strategy to extract and best utilize data information to address patient's profile and the treatment effectiveness as demonstrated in this article.

First, let me start with the medical background. What is seizure? Seizure is just a transient symptom of irregular neuron activities. Seizure is not confined to only humans. Animals exhibit this episode. Recurring seizures is recognized as epilepsy in medical discipline. Is epilepsy curable? Is a particular treatment effective? Do the patient's age, frequency and severity of the seizures have significant influence in its cure? Medical community is split on this issue. Some physicians believe that the epileptic seizure incidence can be significantly reduced by a successful treatment. Neurologists are actively tracing out the root-causes of epileptic seizures. In curing epilepsy, does age make any difference? About 30-50% of the patients above 80 years age seem to experience a second seizure. What else do the chosen epilepsy incidences data reveal? This tutorial article explores the data to answer this and other pertinent questions.

The seizures impair body movements, conscious awareness and cognitive behaviors. A loss of memory occurs after every episode. Some patients express dizziness, lightheadedness, tight chest prior to the episode. Studies show that some seizures are unnoticed as they occur even during sleep. For recent accounts on medical advancements to cure epilepsy, Fisher *et al*. (2005); Berg (2008); Shukla *et al*. (2004) and Binjadhnan and Ahmad (2010).

Epileptic patients and physicians who are treating them are eager to develop an early warning system. Is it feasible? It all depends on complete and correct capturing of patient's data information. Such a capturing requires best possible underlying probability pattern and it is often a challenge. The challenge is intense due to hidden restrictions on the seizure incidence rate because of the treatment effect.

To identify the probability pattern in count data with rarity, Poisson probability model $\Pr[Y = y|\lambda] = e^{-\lambda}\lambda^{y} / y!$ is commonly employed in medical studies provided there is no over or under data dispersion where λ is the incidence rate. The number of epilepsy seizures in Table 1 and 2 are rare counts. What is over or under dispersion? The ideal equal dispersion means that the data average and variance are equal and it is the unique property of the commonly used Poisson model. This equal dispersion does not exist in the data of Table 1 and 2.

Table 1: Nimber of epileptic seizures in placebo group

Placebo patient	prior se izure	year 1	year 2	year 3	year 4	age
1	11	5	3	3	3	31
2	11	3	5	3	3	30
3	66	7	18	3	21	22
4	27	5	2	8	7	29
5	12	6	4	0	2	31
6	52	40	20	23	12	42
7	23	5	6	6	5	37
8	10	14	13	6	0	28
9	52	26	12	6	22	36
10	33	12	6	8	5	24
11	18	4	4	6	2	23
12	42	7	9	12	14	36
13	87	16	24	10	9	26
14	50	11	0	0	5	26
15	18	0	0	3	3	28
16	111	37	29	28	29	31
17	18	3	5	2	5	32
18	20	3	0	6	7	21
19	12	3	4	3	4	29
20	9	3	4	3	4	21
21	17	2	3	3	5	32
22	28	8	12	2	8	25
23	55	18	24	76	25	30
24	9	2	1	2	1	40
25	10	3	1	4	2	19
26	47	13	15	13	12	22

Table 2: Number of epileptic seizures in pregabide group

Progabic patient	Prior Seizure	year 1	year 2	year 3	year 4	age
1	76	11	14	9	8	18
2	38	8	17	9	4	32
3	19	0	4	3	0	20
4	10	3	6	1	3	20
5	19	2	6	7	4	18
6	24	4	3	1	3	24
7	31	22	17	19	16	30
8	14	5	4	7	4	35
9	11	2	4	0	4	57
10	67	3	7	7	7	20
11	41	4	18	72	5	22
12	7	2	1	1	0	28
13	22	0	2	4	0	23
14	13	5	4	0	3	40
15	46	11	14	25	15	43
16	36	10	5	3	8	21
17	38	19	7	6	7	35
18	7	1	1	2	4	25
19	36	6	10	8	8	26
20	11	2	1	0	0	25
21	151	102	65	72	63	22
22	22	4	3	2	4	32
23	41	8	6	5	7	25
24	32	1	3	1	5	35
25	56	18	11	28	13	21
26	24	6	3	4	0	41
27	16	3	5	4	3	32
28	22	1	23	19	8	26
29	25	2	3	0	1	21
30	13	0	0	0	0	36
31	12	1	4	3	2	37

To check the existence of this unique property in the collected data, the mean and variance of the number of seizures in 1, 2, 3 and year 4 are calculated using the number of prior seizures before the beginning of the treatment. The prior numbers of seizures in placeo group with patient ID # 16 and with patient ID # 21 in pregabide group are outliers (Fig. 1 and 2).

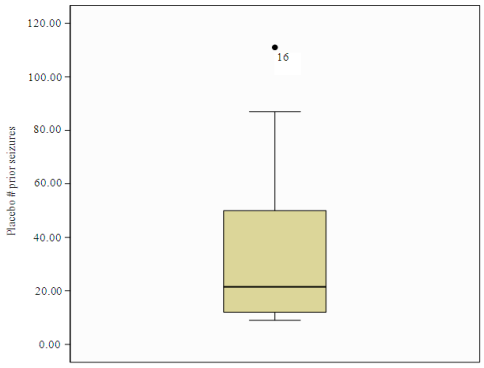

Fig. 1: Prior seizures in placebo group

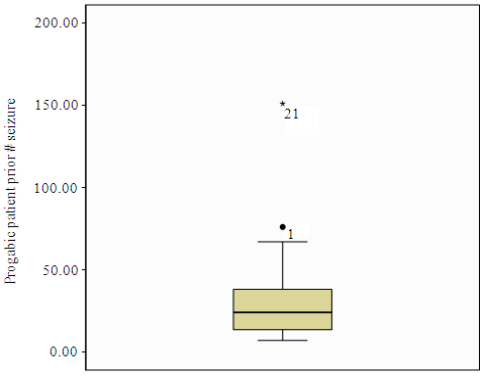

Fig. 2: Prior seizures in pregabide group

Table 3: Patients with equal dispersion and their # epileptic seizure in Placebo group

placebo patient	prior Seizure	year1	year2	year3	year4	age
3	6	2	4	0	5	25
4	8	4	4	1	4	36

However, these two patients of the placebo group exhibit equal dispersion in year 2 as they are displayed in Table 3. Even these two patients do not possess equal dispersion in 1, 3 and year 4. These two patients' data in Table 3 are excluded from our analysis.

Other patients in both groups possess under dispersion with some exceptions. The placebo patients with ID # 13 and # 4 have over dispersion effect in year 3 and in year 4. Therefore, the commonly used Poisson probability model is clearly inappropriate for the data in Table 1 and 2. However, the Incidence Rate Restricted Poisson (IRRP) model would study even for the exception cases because the usual Poisson model is a particular case of IRRP model.

What is IRRP model? Shanmugam (1991) introduced the IRRP model to understand traffic accident patterns. This model is probably not familiar to all medical researchers. No other article or book exists in the literature for medical researchers to learn to interpret data patterns. To fulfill this apparent need, this tutorial article with discussions is worthwhile and hence, is prepared. The discussions in this article can be emulated in other medical data analysis to address patient's profile. Patients, nurses and physicians are often eager to develop an early warning system. Is it feasible? An answer is affirmative if the data pattern is correctly identified. An appropriate underlying model for the collected data is an unavoidable necessity. Could it be IRRP model?

Could the prior number of seizures before beginning the treatment and the patient's age be valuable predictors in an early warning system to project the future number of seizures? The age of the patients (except pregabide patient with ID # 9) range from 18-43. Such a regression could address whether the epilepsy illness has progressively worsened or cured. The parameters of IRRP regression are seizure incidence rate and its restriction level. This article demonstrates on how to test the significance of the estimated restriction level using a property of non-central chi-squared probability model and test the significance of the estimated seizure incidence rate using normal probability model. The receiver operating characteristic curve of the cumulative model function of the seizure incidence rate in terms of the cumulative model function of the restriction level reveals the dynamics of the medical treatment as shown in Fig. 3 through Fig. 10. In the end, a principal component analysis is performed using the estimated incidence rate and its restriction level for all four years in both groups. The principal component results are displayed in Fig. 11 and 12 and interpreted subsequently.

Incidence rate restricted Poisson model: Let Y be the number of seizures experienced by a patient. This number could be anyone in the observable collection of possibilities {0, 1, 2, 3, ….}. The random variable Y is a Poisson type because of its rarity. The seizure incidence rate, λ is understandably restricted due to non-measurable treatment effect, patient's biologic and neurologic defects among others. The directly measurable factors in epilepsy data are his/her age and prior number of seizures before the beginning of the treatment but not the treatment effect. The collective impact of all non-measured factors on the seizure incidence rate is portrayed here as the restriction parameter β. A negative amount for β is indicative of under dispersion (that is, variance is smaller than the mean) and a positive amount for β is indicative of over dispersion (that is, variance is larger than the mean).

The infinite value for β is indicative of equal dispersion (that is, variance is equal to the mean).

In a scenario of equal dispersion, the IRRP model in (1) with $\beta = \infty$ reduces to usual Poisson model as the underlying probability pattern. That is, $\Pr[Y = y|\lambda,\beta = \infty] = e^{-\lambda}\lambda^{y} / y!$. In this scenario of equal dispersion, restrictions on the incidence rate do amount to no medicine/treatment effect.

In all other scenarios with a finite level of restrictions on the seizure incidence rate, Shanmugam (1991) Incidence Rate Restricted Poisson *(*IRRP*)* model in (1) with a probability mass function:

$$\Pr[Y = y|\lambda,\beta] = (1+\frac{y}{\beta})^{y-1}(\lambda e^{-\lambda/\beta})^{y} / y!e^{\lambda}$$

Would capture it and it is appropriate for the non-negative integer random variable Y, where the incidence parameter λ is restricted by an unknown restriction parameter β and y = 0,1,2,….,.

The estimate of the seizure Incidence Rate and Its Restriction Parameter of the IRRP model in (1) are respectively:

$$\hat{\lambda} = \overline{y}^{3/2} / s_{y} \quad (2)$$

and:

$$\hat{\beta} = \hat{\lambda} / (1-(\overline{y} / s^{2})^{1/2}) \quad (3)$$

where, $\overline{y}$ and s^{2} denote the data mean and variance respectively.

In the scenario of equal dispersion, recall that $s^{2} = \overline{y}$ and consequently $\hat{\beta} = \infty$ according to (3) and the probability mass function of the IRRP model in (1) reduces to the usual Poisson probability model. A graphical view of equal dispersion is the locus of positive diagonal line in Fig. 1 through Fig. 13.

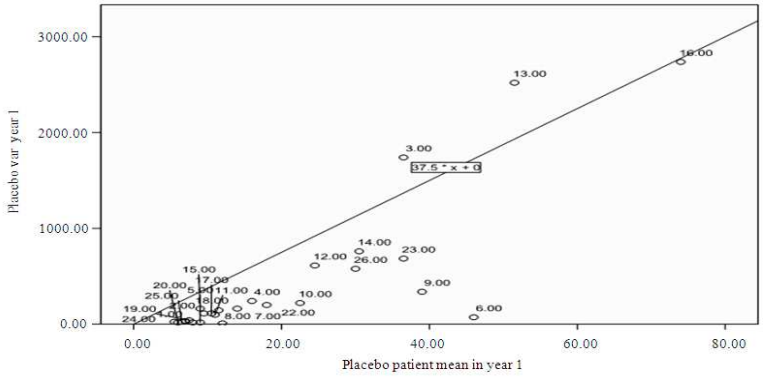

Fig. 3: Twenty-six placebo patients in Year 1

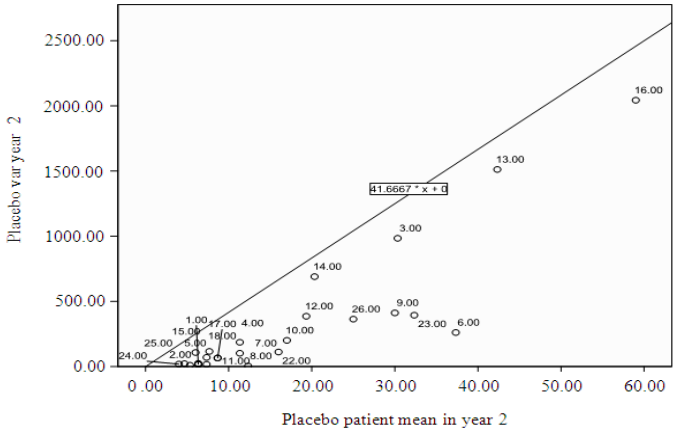

Fig. 4: Twenty-six placebo patients in Year 2

The placebo patients with ID #3 and ID #13 exhibit over dispersion while placebo patient with ID #18 exhibit equal dispersion in year 1 (Fig. 3). All other placebo patients exhibit under dispersion in year 2 (Fig. 4). The placebo patients with ID # 13 and ID # 14 exhibit over dispersion while none exhibits equal dispersion in year 3. All others exhibit under dispersion (Fig. 5). The placebo patients with ID #13 and ID #14 exhibit over dispersion while patient with ID #18 exhibit equal dispersion in year 4 (Fig. 7).

The pregabide patients with ID #1, 2, 3, 4, 10, 11, 12, 18, 19, 2, 24, 25, 27, 28and 29 exhibit over dispersion while no patient exhibits equal dispersion in year 1 (Fig. 7). Pregabide patients with ID # 2, 8, 9, 15and 16 exhibit equal dispersion in year 2 and those with ID # 1, 3, 10, 11, 12, 13, 18, 20, 21, 23, 24and 25 exhibit over dispersion in year 2 (Fig. 8). All pregabide patients exhibit under dispersion in year 3 (Fig. 9). The pregabide patients with ID # 1, 3, 9, 10, 11, 16, 21, 23and 24 exhibit over dispersion while pregabide patients with ID # 15, 17and 25 exhibit equal dispersion in year 4 (Fig. 10).

A unique property of the usual Poisson model (that is, $\beta = \infty$) is the equality of mean and variance. The usual Poisson model is inappropriate with the absence of this property in the data. Obviously the seizure incidence rate is restricted. Shanmugam (1991) for full inferential properties of the IRRP model. The needed results for discussions are quoted below.

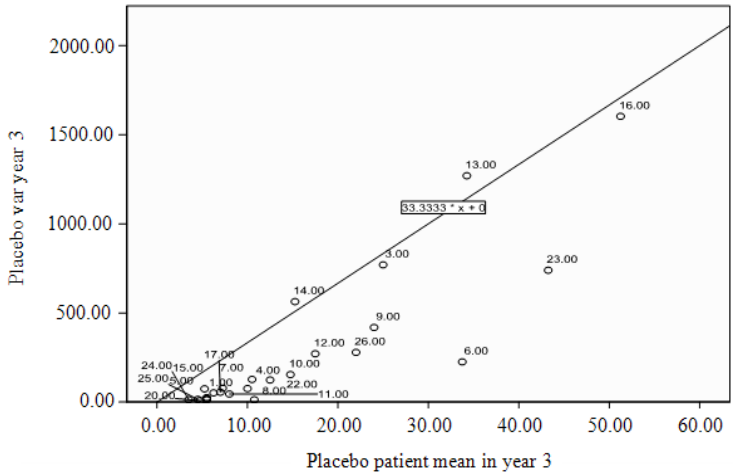

Fig. 5: Twenty-six placebo patients in Year 3

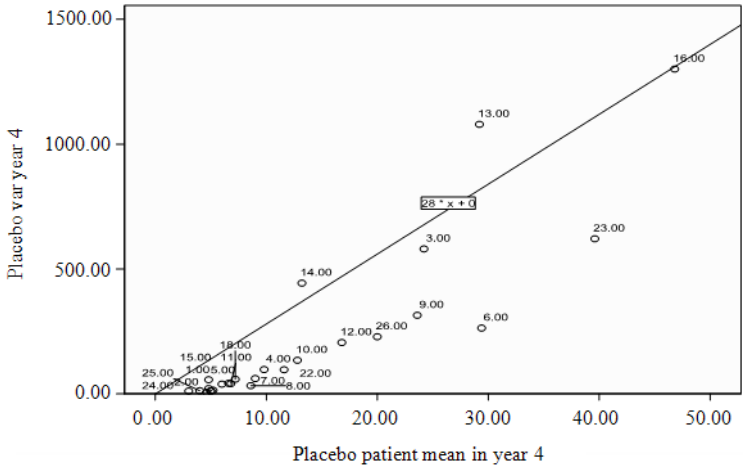

Fig. 6: Twenty-six placebo patients in Year 4

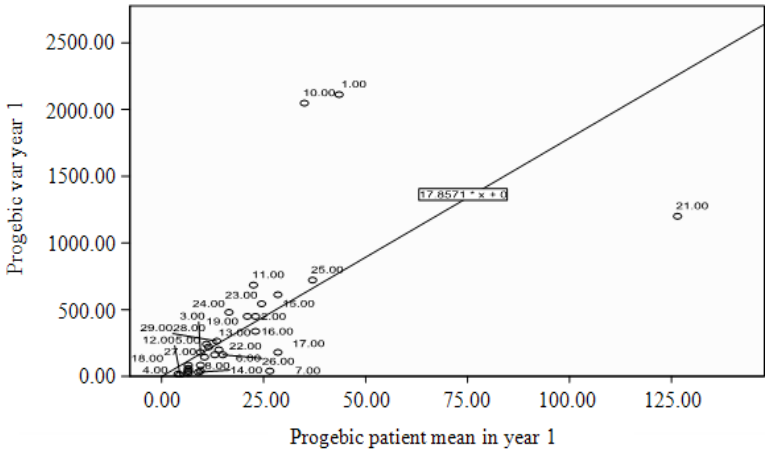

Fig. 7: Thirty-one pregabide patients in Year 1

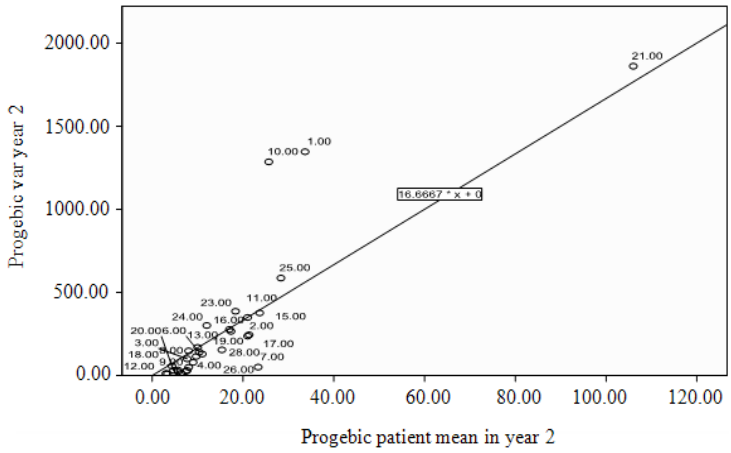

Fig. 8: Thirty-one Pregabide patients in Year 2

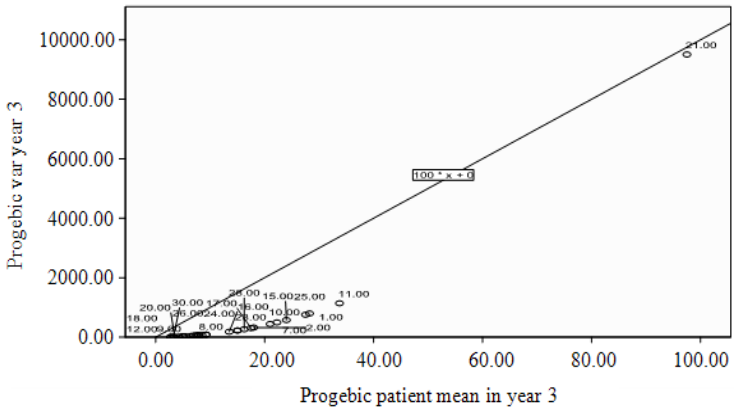

Fig. 9: Thirty-one Pregabide patients in Year 3

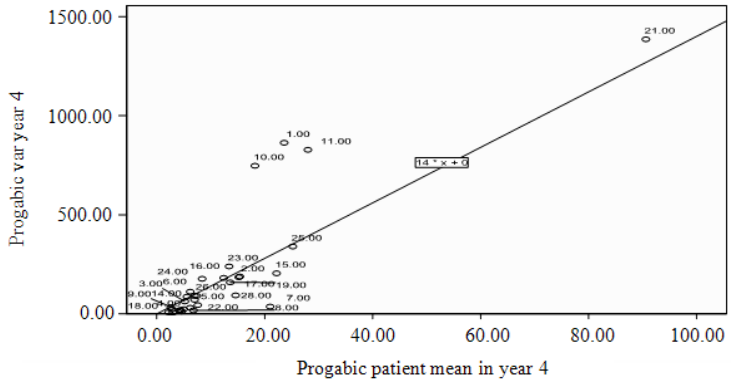

Fig. 10: Thirty-one Pregabide patients in Year 4

The probability of rejecting the true null hypothesis that $H_0\ \beta = \infty$ (meaning that the seizure incidence rate is unrestricted or equivalently the treatment is not effective) in favor of the false alternative $H_1\ \beta < \infty$ (meaning that the seizure incidence is restricted or equivalently the treatment is effective) is (Shanmugam 1991 for details):

$$\Phi[Z \geq (n-1)\left|s_y^2 - \bar{y}\right| / \bar{y}\sqrt{(n-1)}] \tag{4}$$

where, $\alpha = \Phi[Z \geq z_\alpha]$ is the upper tail area under standard normal curve for a given significance level $0<\alpha<1$. The unrestriction on the seizure incidence rate is synonymous to ineffective treatment/treatment.

The power is the probability of rejecting the false null hypothesis that $H_0\ \beta = \infty$ in favor of the true alternative $H_1\ \beta = \hat{\beta} < \infty$ is:

$$1 - \Phi[\frac{\hat{\beta}^2\{z_\alpha\sqrt{1+\bar{y}} + \sqrt{(n-1)}\} - \sqrt{(n-1)}(\bar{y}+\hat{\beta})^2}{(\bar{y}+1)\sqrt{\bar{y}\{\bar{y}+\hat{\beta}^2+\hat{\beta}\}\{\bar{y}\{\bar{y}+\hat{\beta}^2+\hat{\beta}\}+(\bar{y}+\hat{\beta})^2\}}}] \tag{5}$$

where, $\Phi[a]$ is the normal cumulative model function (cdf).

Likewise, the true null hypothesis $H_0\ \lambda = \lambda_0$ the seizure incidence rate is rejected in favor of false alternative hypothesis $H_1 : \lambda > \lambda_0$ at significance level α, if the test statistic $T_{\chi^2} = \frac{\bar{y}(\hat{\lambda} - \lambda_0)^2}{S_y}$ exceeds the critical chi-squared percentile $\chi^2_{1df,\alpha}$ with a significance level α. The power is the probability of rejecting false $H_0\ \lambda = \lambda_0$ in favor of true $H_1\ \lambda = \lambda_1$ is:

$$1 - \Phi_{\chi^2_{\delta^*_\lambda df}}[\frac{\bar{y}(\hat{\lambda} - \lambda_0)^2}{\rho_\lambda S_y}] = \Pr[\chi^2_{\delta^*_\lambda df} > \frac{\bar{y}(\hat{\lambda} - \lambda_0)^2}{\rho_\lambda S_y}] \tag{6}$$

where the degrees of freedom is:

$$\delta^*_\lambda = 1 + \frac{n(\lambda_1 - \lambda_0)^2}{\lambda_1(\lambda_1+2)[n(\lambda_1-\lambda_0)^2 + 0.25\lambda_1(\lambda_1+2)]} \tag{7}$$

and the non-centrality parameter is:

$$\rho_\lambda = 1 + \frac{2n(\lambda_1 - \lambda_0)^2}{\lambda_1(\lambda_1+2)[2n(\lambda_1-\lambda_0)^2 + \lambda_1(\lambda_1+2)]} \tag{8}$$

The formulas in (2) through (8) are demonstrated in Section 3 with the data in Table 1 and 2.

A demonstration of epileptic data analysis with IRRP model: The first task is to utilize the seizure data in Table 1 and 2 to estimate the IRRP model parameters. The incidence pattern for each patient should be captured for each year. To notice such pattern for year 1, the mean $\bar{y}$ and dispersion s^2 for his/her seizure incidences up to year 1 are computed using the number of seizures before beginning the treatment and the number of seizures in year 1. Substituting them in (2) and (3), the seizure incidence rate and restriction level for year 1 are estimated.

With inclusion of the observed seizure incidence in year 2, the mean $\bar{y}$ and dispersion s^2 for his/her seizure incidences up to year 2 are updated and substituted again in (2) and (3) to estimate the model parameters for year 2. This process of calculations and estimations are continued for all four years. These estimates are displayed in Table 4 for Placebo group (excluding the two patients who exhibited equal dispersion) and in Table 5 for Treatment group.

To reject the hypothesis $H_0\ \beta = \infty$ (meaning that the seizure incidence is unrestricted) in favor of the alternative $H_1\ \beta < \infty$ (meaning that the seizure is

restricted), the data based test statistic $Z = (n-1)\left|s_y^2 - \bar{y}\right|$ should exceed the critical value $z_\alpha \bar{y}\sqrt{n-1} = 1.645\bar{y}\sqrt{n-1}$ where n is the sample size and the significance level is α=0.05. The restriction is synonymous to the effective treatment. The test statistic Z and the critical value for each of the four years are displayed in Table 6 for placebo group and in Table 7 for pregabide group. The significant ones are displayed in boldface.

For an example, the hypothesis H_0 β = ∞ is not rejected for placebo patient 1 in year 1 but is rejected in 2, 3and year 4. Another example is pregabide patient 4 in year 2 and in which case, the hypothesis H_0 β = ∞ is not rejected in year 2 but is rejected in 1, 3and year 4. The boldface entries in 6 and Table 7 indicate the scenarios in which the hypothesis H_0 β = ∞ is rejected.

There appears to be relationships among the prior # of seizures, age and # of seizures in year 1 of patients as exhibited in Fig. 9 for placebo patients and in Fig. 10 for pregabide patients. The prior number of seizures is lower in older ages in both groups.

What relationships exist among the estimates of the incidence rate and the restriction level? The Fig. 11 through Fig. 14 reveal the pattern among placebo patients over the 4 years. Similar patterns among pregabide patients over the four years are exhibited in Fig. 15 through Fig. 18. In year 1, the restriction level is stable irrespective of the seizure rate in the Placebo group (Fig. 11). In year 2, year 3and year 4, the restriction level is increasing along with increasing seizure rate due to effective treatment (Fig. 12 through 14). In 1, 2, 3and year 4, the restriction level is increasing along with increasing seizure rate due to effective treatment (Fig. 15 through 18). There are some anomalies in both groups as evidenced in the Fig. 11 through Fig. 18.

In medical studies like this, the ideal incidence rate to attain is λ_0 =0. Is it attained among the epilepsy patients in our data? Could the null hypothesis H_0 λ = λ_0 =0 about the ideal incidence rate be rejected at significance level α = 0.05 according to the collected data? The answer is affirmative, if the test statistic $T_{\chi^2_{1df}} = \frac{\bar{y}(\hat{\lambda})^2}{S_{\bar{y}}}$ exceeds its critical (percentile) value $\chi^2_{1df,0.05} = 3.84$. The bold-faced values in Table 8 and in Table 9 are indicative of rejecting H_0 λ = λ_0 =0 respectively for placebo patients and so for pregabide patients. For example, the null hypothesis H_0 λ = λ_0 =0 is not rejected for placebo patient with ID # 14 in 1, 2, 3 and year 4 and for pregabide patient with ID # 3 in 1, 2 and year 3 only. The null hypothesis H_0 λ = λ_0 =0 is rejected for pregabide patient with ID # 3 in year 4.

Table 4: The estimate of incidence rate and the restriction level in Placebo group

Placebo Patient	year 1 Lembda	year 2 Lembda	year 3 Lembd	year 4 Beta	year 1 Beta	year 2 Beta	year 3 Beta	year 4 Beta
1	5.333333	3.828313	3.406987	3.22749	16.0	9.679	6.28	9.10
2	3.27395	3.828313	3.406987	3.22749	6.15	9.679	6.28	9.10
3	5.285697	5.324871	4.504687	4.94023	6.18	6.459	5.78	6.21
4	4.114076	2.795061	3.019132	3.10379	5.54	3.710	4.44	4.54
5	6.363961	4.76992	2.579729	2.28399	21.7	13.65	5.08	4.36
6	36.76804	14.11067	13.05441	9.81485	1830	22.68	15.9	14.7
7	4.115613	3.77162	3.643396	3.44291	5.83	5.653	5.49	5.58
8	14.69694	20.80701	9.807029	4.40363	-65.4	-30.3	14.6	9.02
9	13.24764	8.095306	5.746226	6.46176	20.1	11.09	7.45	8.90
10	7.187361	4.943965	4.561161	3.94576	10.6	6.971	6.33	5.70
11	3.685327	3.156536	3.360672	2.76258	5.54	4.965	5.32	4.65
12	4.90000	4.324929	4.447054	4.80117	6.13	5.571	5.94	6.72
13	7.36152	7.082718	5.625489	4.80201	8.59	8.506	6.94	5.75
14	6.108016	3.489663	2.508567	2.27675	7.64	4.213	3.56	2.75
15	2.12132	1.414214	1.396017	1.39659	2.78	1.850	2.62	1.97
16	12.16553	10.02392	9.164005	8.87558	14.6	12.08	10.8	11.0
17	3.207803	3.132653	2.489738	2.60703	4.62	4.906	4.30	4.31
18	3.244239	1.968148	2.206809	2.52162	4.52	2.648	3.57	3.88
19	3.227486	3.23108	2.959152	3.09276	5.67	6.596	5.46	7.63
20	3.464102	3.83158	3.604238	3.93067	8.2	13.61	7.01	27.0
21	2.760636	2.367945	2.175531	2.35339	3.89	3.497	3.84	3.87
22	5.400000	6.047432	3.974099	4.01559	7.71	9.722	5.84	6.14
23	8.428544	9.258571	10.45889	9.99752	11.0	12.97	12.0	13.4
24	2.605919	1.835326	1.771213	1.53226	4.95	3.391	4.13	3.13
25	3.348012	2.133209	2.464752	2.26274	6.90	3.929	4.74	5.21
26	6.834676	6.55178	6.181466	5.91054	8.85	8.879	8.00	8.39

Table 5: The estimate of incidence rate and the restriction level in Pregabide group

Progabic patient	year 1L	year 2L	year 3L	year 4L	year 1B	year 2B	year 3B	year 4B
1	6.24	5.3	4.5	3.902	7.29	6.324	5.311	4.67
2	5.20	6.3	5.5	4.360	6.72	8.900	7.885	6.11
3	2.18	2.1	1.9	1.498	2.83	2.929	2.783	2.10
4	3.35	4.5	2.9	2.813	6.90	16.010	6.656	7.24
5	2.83	3.0	3.4	3.148	3.87	4.585	5.619	5.37
6	3.70	2.8	2.1	1.936	5.04	3.848	2.860	2.68
7	21.40	16.0	17.0	15.930	112.00	49.780	71.510	66.00
8	4.60	3.9	4.6	4.215	8.92	7.751	11.600	11.10
9	2.60	2.9	1.8	2.075	4.34	5.752	3.215	4.10
10	4.58	3.6	3.1	2.840	5.26	4.224	3.681	3.37
11	4.08	5.2	6.6	5.151	4.98	6.826	8.202	6.31
12	2.70	1.9	1.6	1.176	6.75	4.382	3.757	2.53
13	2.35	1.9	1.8	1.422	2.98	2.423	2.474	1.91
14	4.77	4.0	2.4	2.306	10.20	8.926	4.159	4.28
15	6.15	5.9	7.4	7.311	7.84	7.921	10.730	10.90
16	6.00	4.2	3.2	3.243	8.12	5.598	4.272	4.39
17	11.30	6.3	4.9	4.404	18.80	8.948	6.839	6.17
18	1.89	1.5	1.6	2.038	3.57	3.000	3.757	6.36
19	4.54	4.4	4.1	3.980	5.79	5.951	5.683	5.63
20	2.60	1.8	1.3	1.006	4.34	3.012	2.049	1.57
21	41.10	25.0	25.0	23.170	60.80	33.230	32.930	31.10
22	3.68	2.8	2.3	2.198	5.14	3.963	3.196	3.20
23	5.20	4.0	3.3	3.171	6.60	5.106	4.302	4.15
24	3.06	2.4	1.9	1.831	3.75	2.994	2.315	2.34
25	8.38	6.2	7.6	6.864	10.80	7.983	10.390	9.43
26	4.56	3.2	2.8	2.113	6.56	4.537	4.095	2.96
27	3.19	3.2	3.1	2.786	4.79	5.424	5.432	5.06
28	2.63	4.8	6.4	5.775	3.40	7.058	10.440	9.56
29	3.05	2.4	1.8	1.461	3.94	3.214	2.284	1.91
30	1.80	1.2	0.9	0.721	2.49	1.663	1.247	1.00
31	2.13	2.4	2.3	2.101	3.17	4.081	4.309	4.02

Table 6: Beta (bold is significant) values in Placebo group at alpha = 0.05

Placebo patient	TBYear1	TBYear2	TBYear3	TBYear4	CritiYear1	CritiYear2	CritiYear3	CritiYear4
1	10	22.0	46.0	28.0	13.1600	14.7340	15.6710	16.450
2	25	22.0	46.0	28.0	11.5150	14.7340	15.6710	16.450
3	1704	1908.0	2006.0	2226.0	60.0430	70.5670	71.2310	79.618
4	226	350.0	323.0	352.0	26.3200	26.3660	29.9170	32.242
5	9	20.0	66.0	65.6	14.8050	17.0600	15.6710	15.792
6	26	448.0	1419.0	938.0	75.6700	86.8520	96.1610	96.726
7	148	182.0	230.0	210.0	23.0300	26.3660	28.4920	29.610
8	4	16.0	83.7	96.8	19.7400	28.6920	30.6290	28.294
9	299	764.0	1401.0	1165.0	64.1550	69.7910	68.3810	77.644
10	198	368.0	505.0	488.0	37.0130	39.5480	42.0260	42.112
11	87	113.3	138.0	138.0	18.0950	20.1620	22.7940	22.372
12	588	734.0	812.0	756.0	40.3030	44.9770	49.8610	55.272
13	2469	2940.0	3558.0	4202.0	84.7180	98.4830	97.5860	96.068
14	730	1340.0	1040.0	1722.0	50.1730	47.3030	43.4510	43.428
15	153	204.0	120.0	208.0	14.8050	13.9580	14.9580	15.792
16	2664	3970.0	6002.0	5018.0	121.7300	137.2600	146.0200	153.970
17	102	115.3	135.0	143.0	17.2730	20.1620	19.9450	21.714
18	133	217.3	171.0	206.0	18.9180	17.8360	20.6570	23.688
19	33	36.0	55.4	38.0	12.3380	14.7340	15.6710	17.108
20	12	10.0	26.7	6.8	9.8700	12.4070	13.5340	15.134
21	103	126.0	116.0	132.0	15.6280	17.0600	17.8080	19.740
22	182	192.0	380.0	341.0	29.6100	37.2220	35.6150	38.164
23	648	724.0	3399.0	2327.0	60.0430	75.2200	123.2300	130.280
24	19	30.0	28.3	34.0	9.0475	9.3055	9.9723	9.870
25	18	35.33	38.8	34.0	10.6930	10.8560	12.8220	13.160
26	548	678.0	1036.0	836.0	49.3500	58.1600	62.6830	65.800

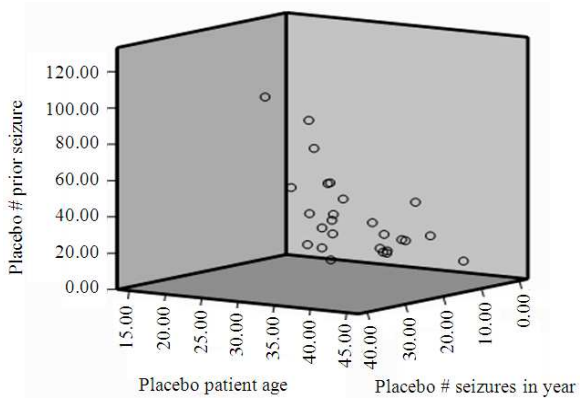

Fig. 11: Relationship among patient' age, # prior and year 1 seizures in placebo group

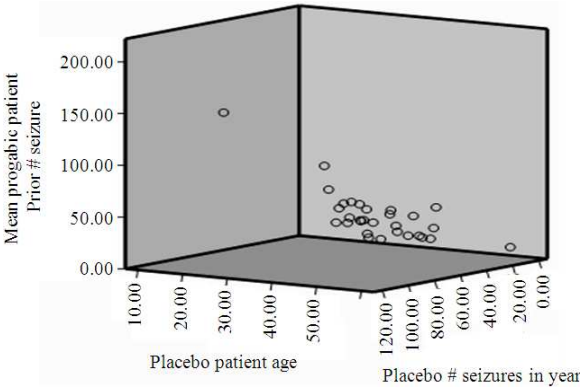

Fig. 12: Relationship among patient' age, # prior and year 1 seizures in pregabide group

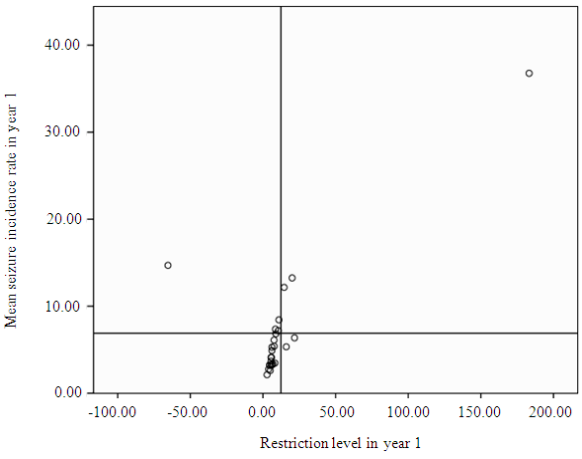

Fig. 13: Incidence rate versus restriction level among placebo patients in year 1

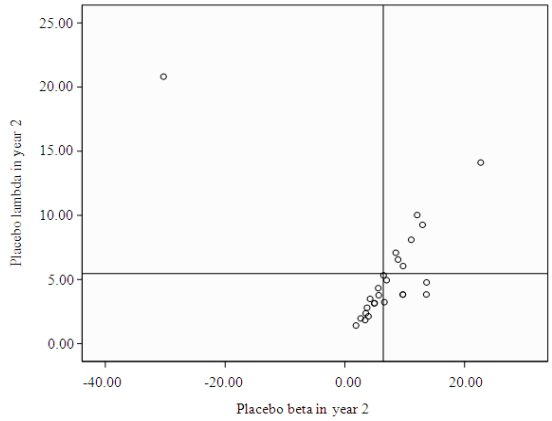

Fig. 14: Incidence rate versus restriction level among placebo patients in year 2

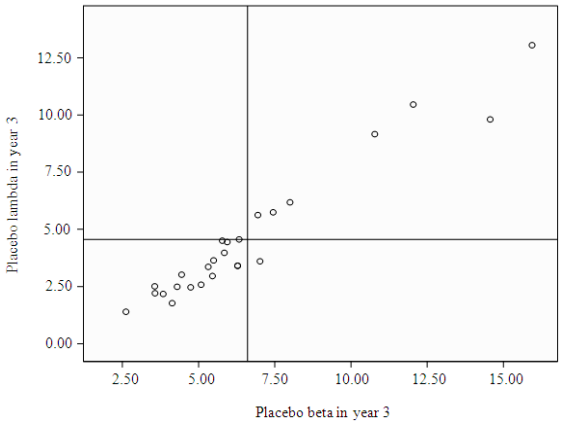

Fig. 15: Incidence rate versus restriction level among placebo patients in year 3

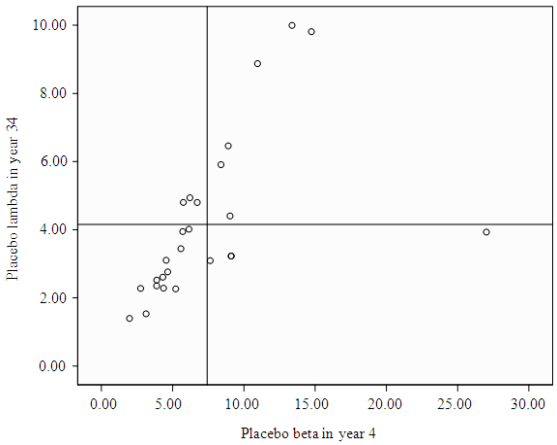

Fig. 16: Incidence rate versus restriction level among placebo patients in year 4

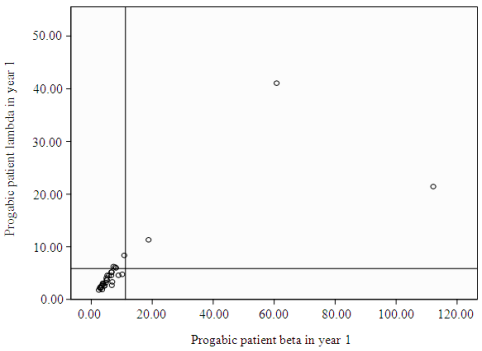

Fig. 17: Incidence rate versus restriction level among pregabide patients in year 1

The power of rejecting the false ideal incidence rate H_0 $\lambda = \lambda_0 = 0$ in favor of the true estimated incidence rate $H_1 : \lambda = \hat{\lambda}$ is calculated using chi-squared model $\Pr[\chi^2_{\delta^*_\lambda df} > \frac{\overline{y}(\hat{\lambda})^2}{\rho_\lambda S_y}]$ where the approximate chi-squared degrees of freedom is $\delta^*_\lambda \approx 1 + \frac{n\hat{\lambda}^2}{\hat{\lambda}+2}$ and the non-centrality parameter is $\rho_\lambda \approx 1 + \frac{2n\hat{\lambda}/(\hat{\lambda}+2)}{1+2n\hat{\lambda}/(\hat{\lambda}+2)}$.

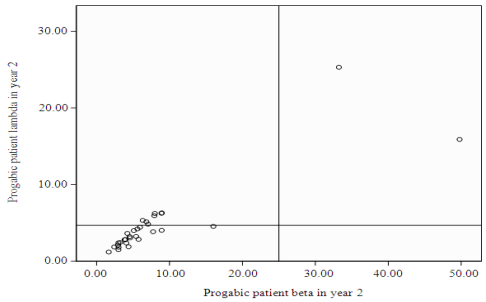

Fig. 18: Incidence rate versus restriction level among pregabide patients in year 2

These power values are displayed in Table 8 for placebo patients and in Table 9 for pregabide patients.

The receiver operating characteristic curve of the cumulative model function of the seizure incidence rate $\Phi[Z \le (n-1)|s_y^2 - \overline{y}| / \overline{y}\sqrt{(n-1)}]$ in terms of the cumulative model function $\Phi_{\chi^2_{\delta^*_\lambda df}}[\frac{\overline{y}(\hat{\lambda}-\lambda_0)^2}{\rho_\lambda S_y}]$ of the restriction level reveals the dynamics of the medical treatment as shown in Fig. 19 through Fig. 22 for placebo and in Fig. 23 through Fig. 26 for pregabide patients. The pattern is disappearing after year 1 and it is indicative of effective treatment.

Table 7: Beta (bold is significant) values in Pregabide group at alpha = 0.05

Progabic patient	TB year 1	TB year 2	TB year 3	TB Year 4	Criti year 1	Criti year 2	Criti year 3	Criti year 4
1	2069.00	2625.00	1439.000	2044.00	71.5580	78.3220	78.3540	77.6440
2	427.00	432.00	617.200	352.00	37.8350	48.8540	51.2860	50.0080
3	171.00	185.30	64.470	131.70	15.6280	17.8360	18.5200	17.1080
4	18.00	12.00	42.980	20.67	10.6930	14.7340	14.2460	15.1340
5	134.00	140.00	126.700	90.33	17.2730	20.9370	24.2180	25.0040
6	186.00	260.00	104.300	214.70	23.0300	24.0390	22.7940	23.0300
7	1400.00	54.00	975.900	32.00	43.5930	54.2820	63.3950	69.0900
8	31.00	45.33	101.500	25.67	15.6280	17.8360	21.3690	22.3720
9	34.00	33.33	26.670	37.33	10.6930	13.1830	12.1090	13.8180
10	2013.00	2519.00	810.300	1846.00	57.5750	59.7100	59.8340	59.8780
11	662.00	656.00	2241.000	1698.00	37.0130	48.8540	96.1610	92.1200
12	8.00	14.00	8.696	11.00	7.4025	7.7546	7.8354	7.2380
13	231.00	280.00	73.670	191.30	18.0950	18.6110	19.9450	18.4240
14	23.000	34.00	50.630	48.33	14.8050	17.0600	15.6710	16.4500
15	584.00	705.30	1113.000	454.70	46.8830	55.0580	68.3810	73.0380
16	315.00	520.00	331.200	440.30	37.8350	39.5480	38.4650	40.7960
17	152.00	446.00	581.200	408.30	46.8830	49.6290	49.8610	50.6660
18	14.00	18.00	8.197	11.00	6.5800	6.9791	7.8354	9.8700
19	429.00	496.00	417.400	367.30	34.5450	40.3240	42.7380	44.7440
20	34.00	51.33	13.480	44.33	10.6930	10.8560	9.9723	9.2120
21	1074.00	3510.00	18926.000	2864.00	208.0900	246.6000	277.8000	298.0700
22	149.00	209.30	98.740	166.30	21.3850	22.4880	22.0810	23.0300
23	520.00	736.00	410.700	574.00	40.3030	42.6500	42.7380	44.0860
24	464.00	578.00	136.400	443.30	27.1430	27.9170	26.3550	27.6360
25	685.00	1116.00	1548.000	725.30	60.8650	65.9140	80.4910	82.9080
26	147.00	236.00	148.400	178.00	24.6750	25.5900	26.3550	24.3460
27	75.00	82.00	84.000	59.33	15.6280	18.6110	19.9450	20.3980
28	209.00	278.00	503.300	180.00	18.9180	35.6710	46.3000	48.0340
29	251.00	318.00	86.500	260.30	22.2080	23.2640	21.3690	20.3980
30	78.00	104.00	6.114	78.00	10.6930	10.0810	9.2600	8.5540
31	54.00	53.33	38.630	36.67	10.6930	13.1830	14.2460	14.4760
Ave	245.00	347.70	412.300	286.20	33.0590	37.9480	42.2560	43.4700
Var	99.60	161.90	591.800	137.10	36.6700	43.0970	49.8310	53.0880

Table 8: Power for $H_0 \lambda = \lambda_0 = 0$ and power for $H_0 \beta = \beta_0 = \infty$ placebo patients

Placebo patient	ChiCdfYear1	ChiCdfYr2	ChiCdfYear3	ChiCdfYear4	NPwrYear1	NPwrYear2	NPwrYear3	NPwrYear4
1	1.00000	0.9979731	0.973159	0.911336	0.48908	0.47442	0.4631	0.4632
2	0.97918	0.9979731	0.973159	0.911336	0.47541	0.47442	0.4631	0.4632
3	0.99910	0.9982802	0.980544	0.989009	0.49712	0.49622	0.4950	0.4947
4	0.99349	0.8386845	0.800376	0.726617	0.49064	0.48454	0.4829	0.4811
5	1.00000	0.9999395	0.741310	0.600959	0.49316	0.48067	0.4612	0.4537
6	1.00000	1.0000000	1.000000	1.000000	0.49928	0.49728	0.4968	0.4961
7	0.99543	0.9881432	0.960193	0.879147	0.48883	0.48486	0.4818	0.4791
8	1.00000	1.0000000	1.000000	0.996308	0.50898	0.49412	0.4848	0.4788
9	1.00000	1.0000000	0.999888	0.999994	0.49746	0.49619	0.4947	0.4946
10	1.00000	0.9989633	0.996104	0.943406	0.49435	0.49137	0.4894	0.4870
11	0.98751	0.9497555	0.937576	0.775197	0.48465	0.47834	0.4757	0.4696
12	0.99892	0.9830488	0.990183	0.993861	0.49487	0.49275	0.4916	0.4911
13	1.00000	0.9999986	0.999060	0.972562	0.49827	0.49768	0.4968	0.4960
14	0.99999	0.9278584	0.473023	0.377116	0.49627	0.49323	0.4898	0.4874
15	0.61362	0.2861089	0.285394	0.124229	0.47891	0.46285	0.4566	0.4501
16	1.00000	1.0000000	1.000000	1.000000	0.49899	0.49858	0.4983	0.4980
17	0.94902	0.9462972	0.639929	0.707688	0.48340	0.47831	0.4707	0.4682
18	0.94716	0.5449593	0.469657	0.643004	0.48522	0.47347	0.4717	0.4714
19	0.97228	0.9764656	0.890714	0.863045	0.47632	0.47045	0.4620	0.4622
20	0.99286	0.9988578	0.991487	0.995601	0.47733	0.48059	0.4596	0.4972
21	0.86589	0.7506934	0.483618	0.590437	0.48083	0.47239	0.4660	0.4639
22	0.99998	0.9999989	0.978098	0.962312	0.49218	0.49080	0.4866	0.4852
23	1.00000	1.0000000	1.000000	1.000000	0.49715	0.49659	0.4978	0.4975
24	0.89223	0.5882679	0.563839	0.233977	0.46746	0.44515	0.4366	0.4205
25	0.98633	0.7218455	0.726206	0.630289	0.47531	0.45440	0.4524	0.4463
26	1.00000	0.9999991	0.999981	0.999938	0.49620	0.49503	0.4940	0.4931

Table 9: Power for $H_0 \lambda = \lambda_0 = 0$ and power for $H_0 \beta = \beta_0 = \infty$ pregabide patients

Progabic patient	ChiCdf Year 1	ChiCdf Year 2	ChiCdf Year 3	ChiCdf Year 4	NPwr Year 1	NPwr Year 2	NPwr Year 3	NPwr Year 4
1	0.999973	0.99991	0.98006	0.97196	0.5031	0.50615	0.5102	0.5146
2	0.999777	0.99992	0.99994	0.93049	0.5037	0.50363	0.5067	0.5132
3	0.632874	0.89375	0.55432	0.40841	0.5149	0.52476	0.5363	0.5612
4	0.986329	0.96951	0.95515	0.60809	0.4908	0.47828	0.4961	0.4943
5	0.872164	0.96843	0.90286	0.76657	0.5094	0.51237	0.5115	0.5165
6	0.980622	0.95150	0.45743	0.61321	0.5060	0.51649	0.5327	0.5440
7	1.000000	1.00000	1.00000	1.00000	0.4957	0.49576	0.4951	0.4949
8	0.999889	0.96759	0.99865	0.86254	0.4943	0.49734	0.4912	0.4921
9	0.870601	0.92358	0.67382	0.54408	0.5030	0.49944	0.5302	0.5232
10	0.990573	0.99844	0.72049	0.94056	0.5047	0.51009	0.5158	0.5215
11	0.984070	0.99961	0.99997	0.90155	0.5060	0.50635	0.5058	0.5102
12	0.935054	0.66360	0.52019	0.36377	0.4780	0.49306	0.5056	0.5483
13	0.684976	0.85481	0.45817	0.41650	0.5135	0.52919	0.5393	0.5630
14	0.999970	0.92630	0.79641	0.54058	0.4914	0.49320	0.5192	0.5233
15	0.999996	0.99985	1.00000	0.99987	0.5028	0.50488	0.5036	0.5045
16	0.999997	0.98616	0.88194	0.86238	0.5023	0.50889	0.5177	0.5213
17	1.000000	0.99673	0.99952	0.94484	0.4986	0.50361	0.5088	0.5130
18	0.844701	0.60347	0.45845	0.58500	0.4983	0.51416	0.5056	0.4795
19	0.997179	0.99598	0.97971	0.94375	0.5049	0.50807	0.5119	0.5152
20	0.870601	0.73068	0.33132	0.36218	0.5030	0.52381	0.5590	0.5975
21	1.000000	1.00000	1.00000	1.00000	0.4998	0.50019	0.5003	0.5005
22	0.982098	0.94635	0.53512	0.69487	0.5055	0.51600	0.5296	0.5370
23	0.999707	0.99645	0.87203	0.86850	0.5039	0.50989	0.5168	0.5218
24	0.872637	0.94866	0.48359	0.67159	0.5092	0.52015	0.5354	0.5439
25	1.000000	0.99985	1.00000	0.99974	0.5014	0.50478	0.5041	0.5061
26	0.999153	0.96457	0.76688	0.60573	0.5029	0.51286	0.5208	0.5393
27	0.953334	0.96521	0.88066	0.75819	0.5050	0.50712	0.5109	0.5174
28	0.793284	0.99415	0.99998	0.99114	0.5114	0.50563	0.5027	0.5051
29	0.895792	0.93432	0.48259	0.43688	0.5091	0.52053	0.5403	0.5594
30	0.761393	0.59554	0.12796	0.29381	0.5186	0.55129	0.5899	0.6312
31	0.678038	0.88789	0.60027	0.56533	0.5121	0.51254	0.5161	0.5253

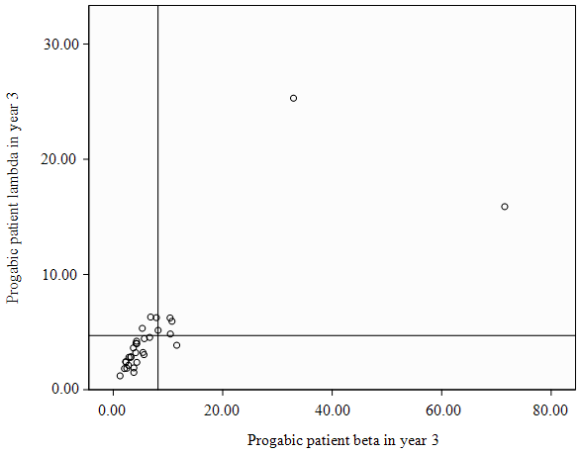

Fig. 19: Incidence rate versus restriction level among pregabide patients in year 3

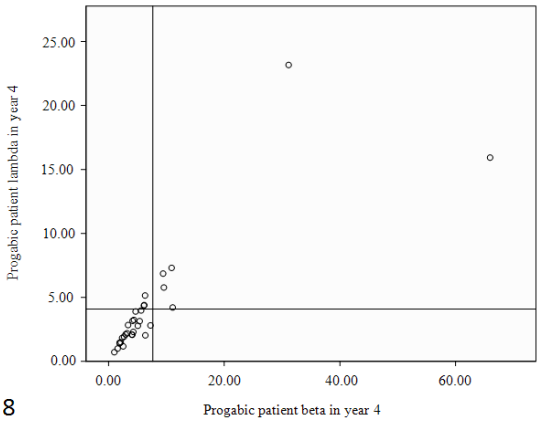

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Fig. 20: Incidence rate versus restriction level among pregabide patients in year 4

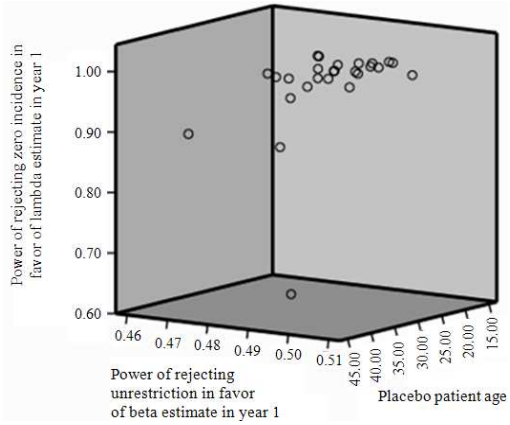

Fig. 21: Receiver operating characteristic cube in year 1

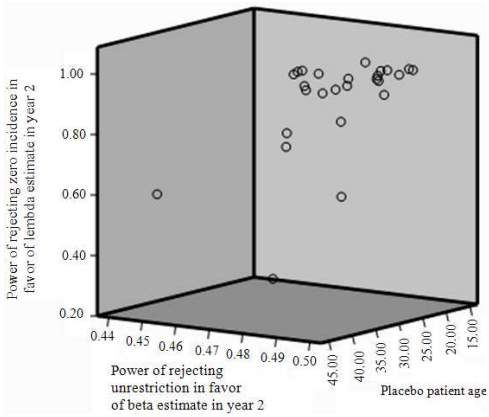

Fig. 22: Receiver operating characteristic cube for placebo patients in year 2

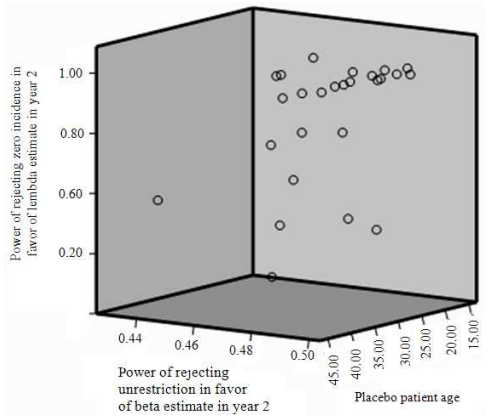

Fig. 23: Receiver operating characteristic cube for placebo patients in year 3

The powers for the seizure incidence rate and its restriction level due to treatment effect are displayed for all years in Fig. 19 through Fig. 22 for placebo group and in Fig. 23 through Fig. 26 for pregabide group of epilepsy patients.

Notice that the power about the incidence rate is stable in year 1 for placebo group and not so for pregabide group. The power is quite varying across all ages in both groups in all years. In a way, the power about the restriction level is varying considerably in all years for both groups of epilepsy patients. This phenomenon is just a tip of the "iceberg" in a medical sense that there must have been some unique personal metabolic characteristics among the patients. A scrutiny of patients' personal characteristics is necessary to detect the full details. Because of the lack of such information about the patients in these two groups, this line of research study is not pursued in this article.

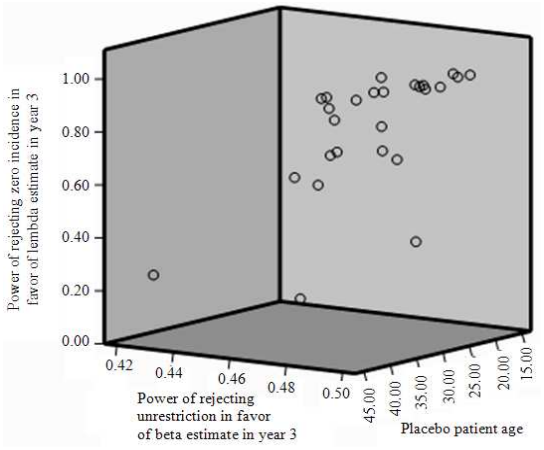

Fig. 24: Receiver operating characteristic cube for placebo patients in year 4

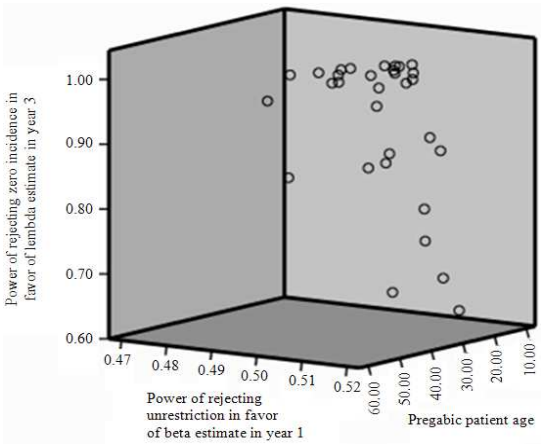

Fig. 25: Receiver operating characteristic cube for pregabide patients in year 1

A next natural statistical analysis to perform with the data involves principal components. The estimated seizure incidences and the restriction levels in year 1 through year 4 are considered for the principal components analysis. The Fig. 27 for Placebo patients and Fig. 28 for Pregabide patients portray the results for the first three principal components. There is no other pattern among the estimates of the incidence rates and their restriction levels to comment.

To check whether a pattern exists, a principal component analysis was performed with the estimates of seizure rate and restriction level for placebo and pregabide patients. The first two principal components explained 77% of the data variations in the placebo group and 90% of the total variations in pregabide group.

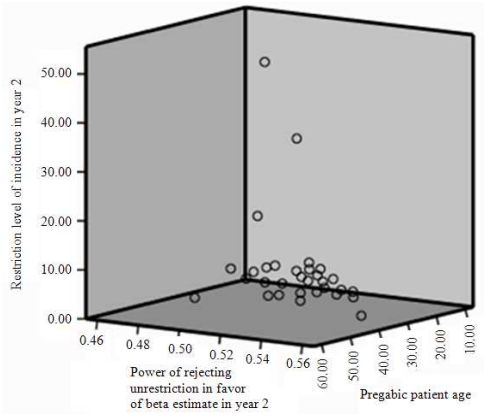

Fig. 26: Receiver operating characteristic cube for pregabide patients in year 2

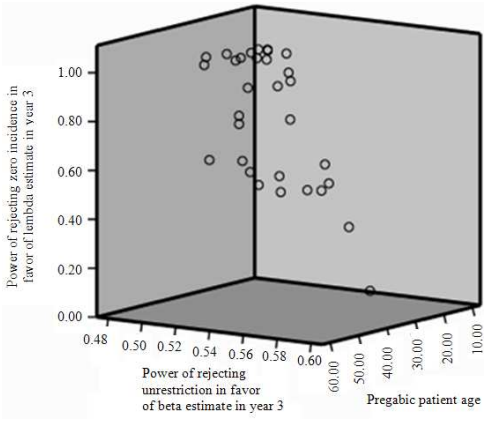

Fig. 27: Receiver operating characteristic cube for pregabide patients in year 3

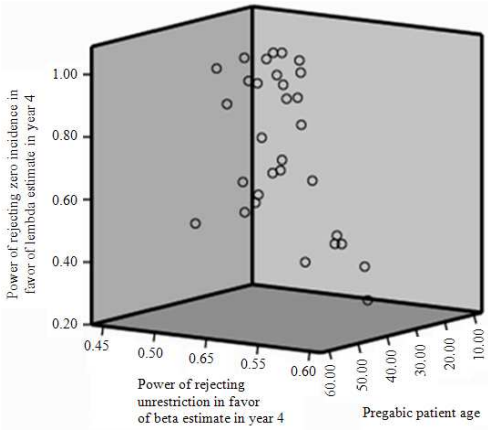

Fig. 28: Receiver operating characteristic cube for pregabide patients in year 4

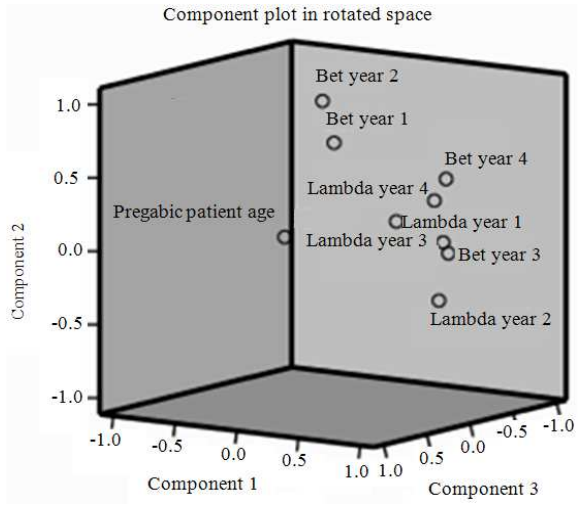

Fig. 29: Closeness of variables with three principal components in placebo group

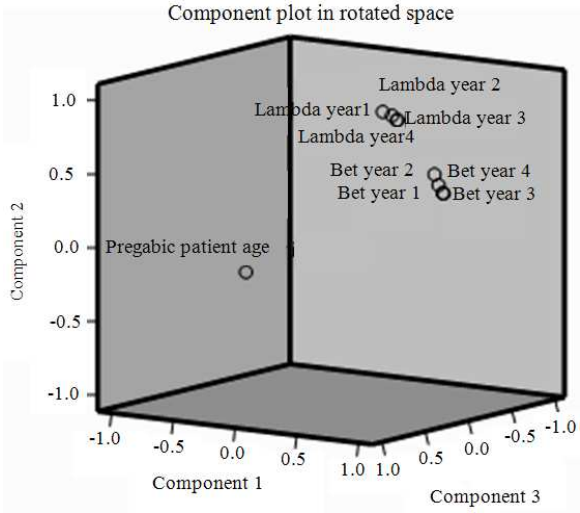

Fig. 30: Closeness of variables with three principal components in pregabide group

In the Placebo group, the first principal component picked up the restriction level in year 3, the seizure incidence rate in 1-4 year as significant factors. In the Pregabide group, the first principal component picked up the restriction level in 1-4 year and the seizure incidence rate in 1-4 year as significant factors.

In the Placebo group, the second principal component picked up the restriction level in 1 and year 2 as significant factors. In the Pregabide group, the second principal component picked up only the age as significant factor.

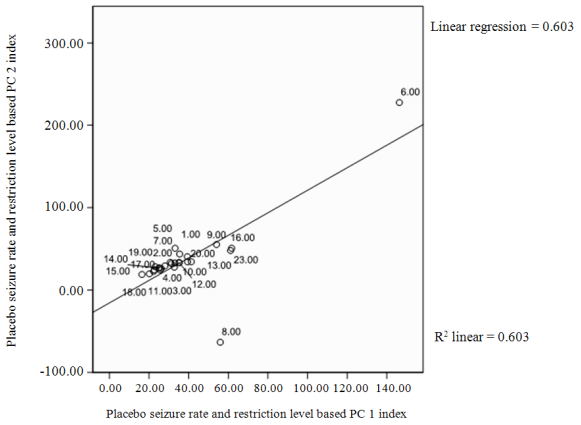

Fig. 31: Proximity of placebo patients according to the first two principal components

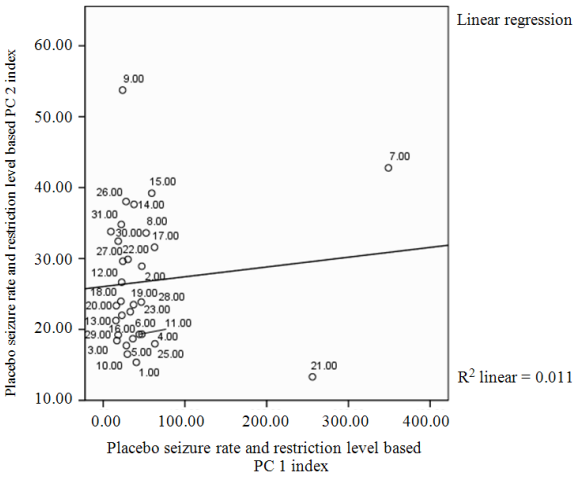

Fig. 32: Proximity of placebo patients according to the first two principal components

Using the factor loadings of the two principal components, two indices are computed for each patient. The two indices are used to graphically classify the proximity of patients in each group. Figure 29 for Placebo patients' proximity and Fig. 30-32 for Pregabide patients' proximity.

CONCLUSION

As this example, other medical data can be fit, analyzed and interpreted using the IRRP model. Not only the incidence rate but also the restriction level on the incidence rate due to treatment can be estimated and tested. The first two principal components can be computed using factor loadings. The proximity of the

patients can then be identified using the indices based on mapping the principal components.

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