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BINARY RESPONSES OF RETINOPATHY IN T2DM USING GEE MODELING AND GOODNESS OF FIT TESTS

V.Rajagopalan[1], M.Vijayasankar[1*] & S.Lakshmi[2]

[1]Department of Statistics, Annamalai University, Annamalai nagar-608 002, Chidambaram, Tamil Nadu, India.
[2]Chief Civil Surgeon, Govt .E.S.I Hospital, Trichy -620 001, Tamil Nadu, India.

ABSTRACT

Retinopathy is a major cause of blindness in DM worldwide. We aimed to study the prevalence of retinopathy in DM by screening and its complications. The risk factors are uncontrolled DM prolonged duration of the disease and lack of regular screening. The above factors are studied using GEE modeling for binary responses from patients of diabetic retinopathy. Two models are fitted and obtained their estimate, standard error and significance of the main effects and interaction. Also two goodness-of-fit tests are proposed for GEE modeling.

Keywords: DM (Diabetes Mellitus), DR (Diabetic Retinopathy), GEE (Generalized Estimation Equations), Goodness-of-fit test.

INTRODUCTION

DR is a dreaded complication of diabetes and a leading cause of blindness though it is preventable. It occurs when diabetes damages the tiny blood vessels inside the retina, the light-sensitive layer of the eye (See Fig 1 below). A healthy retina is necessary for good vision. DR causes by changes in the blood vessels of the retina. The blood vessels may swell and leak fluid or abnormal new blood vessels may grow on the surface of the retina. These vessels may leak and cause blindness. At the onset, DR is totally a symptomatic. But, over a period, when it gets worsened, it may even lead to total blindness.

DR has Four Stages:

1. **Mild Non-proliferative Retinopathy.** At this earliest stage, micro-aneurysms occur. They are small areas of balloon-like swelling in the retina's tiny blood vessels.
2. **Moderate Non-proliferative Retinopathy.** As the disease progresses, some blood vessels that nourish the retina are blocked.
3. **Severe Non-proliferative Retinopathy.** Many more blood vessels are blocked, depriving several areas of the retina with their blood supply. These areas of the retina send signals to the body to grow new blood vessels for nourishment.
4. **Proliferative Retinopathy.** At this advanced stage, the signals sent by the retina for nourishment trigger the growth of new blood vessels. This condition is called proliferative retinopathy. These new blood vessels are abnormal and fragile. They grow along the retina and along the surface of the clear, vitreous gel that fills the inside of the eye (Fig 1). By themselves, these blood vessels do not cause symptoms or vision loss. However, they have thin, fragile walls. If they leak blood, severe vision loss and even blindness can result.

Blood Vessels Damaged From DR Can Cause Vision Loss in Two Ways:

1. Fragile, abnormal blood vessels can develop and leak blood into the center of the eye, blurring vision. This is **proliferative retinopathy** and is the fourth and most advanced stage of the disease.
2. Fluid can leak into the center of the macula, the part of the eye where sharp, straight-ahead vision occurs. The fluid makes the macula swell and blur vision. This condition is called **macular edema**. It can occur at any

Corresponding Author**: - M.Vijayasankar** Email**: -** auvs81@yahoo.in

stage of DR, although it is more likely to occur as the disease progresses. About half of the people with proliferative retinopathy also have macular edema.

Causes

✓ Diabetes damages small blood vessels throughout the body, leading to reduced blood flow. When these changes affect the tiny blood vessels in the eyes, DR may occur.

✓ DR tiny blood vessels in the eye weaken and develop small bulges that may burst and leak into the retina. Later new fragile blood vessels grow on the surface of the retina. These blood vessels may break and bleed into the eye, clouding vision and causing scar tissue to form.

✓ The scar tissue may pull on the retina, leading to retinal detachment. This can lead to vision loss.

Symptoms

✓ Reduced vision
✓ Eye swelling
✓ Double vision accompanied by headaches
✓ Blurred, double, or distorted vision or difficulty reading
✓ Floaters or spots in your vision
✓ Pain , pressure, or constant redness of the eye.

Symptoms of Proliferative Retinopathy

DR does not usually cause any noticeable symptoms until it has reached an advanced stage. If it is not identified and treated, it can lead to sudden blindness. Symptoms of DR mainly include: sudden changes in vision, blurred vision, slow vision loss over time, pain in the eye, double vision, floaters in vision and difficult to see at night times [1]. Many people with early diabetic retinopathy have no symptoms before major bleeding occurs in the eye as shown in figure 3. In the early stage of diabetic retinopathy i.e., non-proliferative the blood vessels in the eye are larger in certain spots, sometimes blood vessels that are blocked, small amounts of bleeding i.e., retinal hemorrhages and fluid may leak into the retina. In more advanced retinopathy i.e., proliferative we can see new blood vessels starting to grow in the eye that are fragile that can bleed, small scars develop on the retina and in other parts of the eye [2].

Diagnosis of DR

Macular edema and DR are detected during a comprehensive eye exam that includes:

✓ Visual acuity test. This eye chart test measures how well you see at various distances.

✓ Dilated eye exam. Pupils are dilated using drops and the optic nerve is examined for signs of damage and other eye problems.

✓ Tonometry: An instrument measures the pressure inside the eye.

✓ Fluorescin Angiography. In some cases, this special test is performed to examine retinal blood flow by injecting a dye into vain and taking pictures of retina.

✓ Examination can reveal any of the following:
✓ Leaking blood vessels.
✓ Retinal swelling (macular edema).
✓ Pale, fatty deposits on the retina signs of leaking blood vessels.
✓ Damaged nerve tissue.
✓ Any changes to the blood vessels.

Risk for DR

All people of DM are at risk for DR - both Type 1 and Type 2 diabetes. That's why everyone with diabetes should get a comprehensive dilated eye exam at least once a year. Between 40 to 45 percent of Indian diagnosed with diabetes have some stage of DR. During pregnancy, DR may be a problem for women with diabetes. To protect vision, every pregnant woman with diabetes should have a comprehensive dilated eye exam as soon as possible. In general, people with diabetes who also have high blood pressure are more likely to develop complications that affect the blood vessels in the body, including those in the eyes. High blood sugar increases risk of DR.

The definition of screening that was adapted by the WHO [3] was “the presumptive identification of unrecognized disease of defect by the application of tests, examinations or other procedures which can be applied rapidly. Screening tests sort out apparently well persons who probably have a disease from those who probably do not. A screening test is not intended to be diagnostic. Persons with positive or suspicious findings must be referred to their physicians for diagnosis and necessary treatment.

DR is one of the major common complications of diabetes that affects the blood vessels by causing damage to retina [4]. The retina is the light-sensitive layer of cells at the back of the eye. It converts light into electrical signals. These signals are sent to the brain through the optic nerve and the brain interprets them to produce the images. So, retina needs a constant supply of blood, which it receives through a network of tiny blood vessels. Over time, a continuously high blood glucose level can cause these blood vessels to become blocked or to leak. This damages the retina and stops it from working. It is an ocular manifestation of systemic disease which affects up to 80-85% of all patients who have had diabetes for 10 years or more [5].

The research indicates that it could be reduced if there was proper treatment and monitoring of the eyes [6]. The longer a person suffers with diabetes, the higher is the chances of developing DR. There are mainly three stages of DR. First stage is called Non-proliferative stage and the Pre-proliferative DR is second stage and the third stage Proliferative DR, which is more advanced and even more severe. The various stages of DR are shown in figure 2. Other complications that may develop mainly include: Cataracts- indicated by the cloudiness of the eye lens, Glaucoma- mainly due to increased pressure in the eye that

can lead to blindness, Macular edema- blurry vision mainly due to fluid leaking into the area of the retina that provides sharp central vision and retinal detachment- scarring that may cause part of the retina to pull away from the back of eyeball position [7, 8].

Treatment of DR

The patient with proliferative DR will need prompt surgical treatment. But people with the non-proliferative DR may not need surgical treatment. However, they should be closely followed by an eye doctor who is trained to treat diabetic eye diseases. Once the doctor notices new blood vessels growing in retina (neovascularization) or develop macular edema, treatment is usually needed [9] Sometimes surgery is also recommended for severe non-proliferative DR depending on specific problem of retina various options include:

Focal Laser Treatment

It is also known as photocoagulation [10], it stops or slows the leakage of blood and fluid from the eye. In laser treatment, leaks from abnormal blood vessels are treated with laser burns. Focal laser treatment is usually done in single session. The vision will be blurred for about a day after the procedure. It is usually done in single session. Sometimes small spots can be seen in visual field that is usually related to the laser treatment. The spots will usually disappear within week days [11].

Scatter Laser Treatment

This laser treatment, also known as pan retinal photocoagulation. The abnormal blood vessels are shirked the area of retina away from the macula are treated with scattered by laser burns. The burns cause the abnormal new blood vessels to shrink. It is done in doctor's clinic. It is usually done in two or more sessions. There may be some loss of peripheral vision or night vision after the procedure [5]

Vitrectomy

Surgeries are the main treatment for DR. It is done in surgery center or hospitals by using local or general anesthesia. It involves removal of blood from the middle of the eye i.e., vitreous as well as scar tissue that tugging on the retina by using delicate instruments and replace with salt solution, which helps to maintain eye's in normal shape. And sometimes a gas bubble must be placed in the eye cavity to help reattach the retina. Vitrectomy may be accompanied by laser treatment. It often stops the progression of DR, but it is not a permanent cure. As diabetes is a lifelong condition, so future retinal damage and loss of vision are possible. Even after treatment the patient need regular eye exam. Sometimes, additional treatment may also be needed [12]. New treatment for DR, include medication that may help to prevent abnormal blood vessels forming in the eye. These medications are directly injected into the eye. These appear promising, but still long trials yet to be done [13].

MATERIALS AND METHODS

Data have been collected from 850 DM patients from Aravind Eye Hospital at Pondicherry. These 850 DM patients were classified into low and high according to their Blood Glucose Level [(BGL), (1= high, 0= low)], and the Consumption of Drug (CD) is classified into standard and new drug (1= new drug, 0= standard drug) during their stipulated periods of visits to the hospital over the first month, second month and fourth month are termed as the category "Time" (0, l, 2). The above kind of classification with their diabetic status (N=Normal, A=Abnormal) is provided in Table 1 below.

Out of the 850 DM patients, 408 were identified as DR. The data relating to eye specific covariate such as refractive error and intraocular pressure and the other clinical parameters refractive error, intraocular pressure, age at diagnosis of diabetes (years), duration of diabetes (years), Glycosylated hemoglobin level, systolic blood pressure, diastolic blood pressure, BMI, pulse rate, Gender, proteinuria, doses of insulin per day, and residence were observed for univariate analysis of the DR study. We apply the GEE model for binary responses goodness-of-fit test which are analyzed by using the SAS software.

GEE METHODOLOGY

Binary responses occur commonly in clinical studies the logistic regression model its mostly used for such analysis on the method are existing for testing the fitness of the model [14,15,16]. Generalized estimating equations (GEE) are useful for analyzing such correlated data with categorical or continuous responses for parameter estimation [17, 18].

Some methods are available for assessing the fit of GEE regression models with binary responses. A goodness-of-fit test for assessing such model fit is developed in [19]. Also a goodness-of-fit statistic for ordinary logistic regression is studied in [13]. Their proposed test statistic has an approximate chi-squared distribution when the model is specified correctly. A goodness-of-fit statistic for assessing the fit of GEE binary regression models is proposed in [20]. The extension for assessing the fit of ordinary logistic regression models is proposed in [14]. This approach involves partitioning the space of covariates into distinct regions and forming score statistics that are asymptotically distributed as chi-square random variables with the appropriate degrees of freedom. Barnhart and Williamson's approach is best employed in the situation when there are only discrete covariates available because then there is no need to partition the covariates. A goodness of- fit tests for GEE with correlated binary data is proposed in [21]. Pan's two tests result in the Pearson chi-square and an unweighted sum of residual squares, both of which are based on the residuals. These

two tests can only be used when there is at least one continuous covariate available. Assessment of the adequacy of the fitted GEE model is cumbersome since no likelihood exists and the residuals are correlated with in a cluster.

A test for the logistic regression model which is asymptotically estimated as Chi-squared distribution based on the difference between the observed and expected counts is proposed by [14]. A test statistic based on nonparametric kernel methods for models with continuous covariates of binary data is introduced by [22].

GEE Modeling

The GEE modeling for binary response has the following form

$$\text{logit}(\mu_i) = X_i\beta \quad (1)$$

where $Y_i = (y_{i1}, y_{i2}, \ldots y_{iT})'$ be a T×1 vector of binary outcomes and

$$X_i = \begin{bmatrix} X_{i11} & X_{i12} & \ldots & \ldots & X_{i1k} \\ X_{i21} & X_{i22} & \ldots & \ldots & X_{i2k} \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ X_{iT1} & X_{iT2} & \ldots & \ldots & X_{iTk} \end{bmatrix}_{T\times k} = (X_{i1} \;\; X_{i2} \ldots X_{iT})^T$$

where, $X_{ij} = \begin{pmatrix} X_{ij1} & X_{ij2} \ldots X_{ijk} \end{pmatrix}$; $j = 1,2, \ldots, T$ is a matrix for the i^{th}individual (i=1,2, …N). Where N is the sample size and the i^{th} individual has $T_i$binary measurements (0 or 1). Let us assume that $T_o = T$for all i. With

$$\mu_i = \begin{bmatrix} \mu_{i1} \\ \mu_{i2} \\ \vdots \\ \mu_{iT} \end{bmatrix}_{T\times 1} = \begin{bmatrix} E(Y_{i1}) \\ E(Y_{i2}) \\ \vdots \\ E(Y_{iT}) \end{bmatrix} = \begin{bmatrix} \pi_{i1} \\ \pi_{i2} \\ \vdots \\ \pi_{iT} \end{bmatrix} = \pi_i$$ is the mean vector and $\mu_{ij} P\left(Y_{ij} = \frac{1}{X_{ij}}\right) = \pi_{ij}$ the variance of Y_{ij} is $\mu_{ij}(1-\mu_{ij}) = p_{ij}(1-p_{ij})$and the Dispersion matrix of y_i is

$$\text{var}(y_i) = \begin{bmatrix} V(Y_{i1}) & Cov(Y_{i1}, Y_{i2}) & \ldots & Cov(Y_{i1}, Y_{iT}) \\ Cov(Y_{i1}, Y_{i2}) & V(Y_{i2}) & \cdots & Cov(Y_{i2}, Y_{iT}) \\ \vdots & \vdots & \vdots & \vdots \\ Cov(Y_{i1}, Y_{iT}) & Cov(Y_{i2}, Y_{iT}) & \ldots & V(Y_{iT}) \end{bmatrix}_{T\times T}$$

Estimation of β is obtained by solving the GEE [17,18].

$$\sum_{i=1}^{N}\left(\frac{\partial \mu_i}{\partial \beta_p}\right) V_i^{-1}(Y_i - \mu_i) = 0\,, \quad p = 1,2, \ldots p+1 \quad (2)$$

with $V_i = A_i^{\frac{1}{2}} R_i A_i^{\frac{1}{2}}$, $A_i = \text{diag}(\text{var}(y_{i1}), \ldots \ldots, \text{var}(y_{iT}))$, where, R_i is the working correlation matrix for Y_i.

GOODNESS-OF-FIT TESTS

We describe the proposed goodness- of-fit statistics by first partitioning the covariate space $X = (x_1, \ldots, x_p)'$ into M distinct regions in P-dimensional space. Let $I_{it} = (I_{it1}, \ldots, I_{itM})'$ be an $M \times 1$ vector, where I_{itm} is the indicator variable that equals one if the i^{th} subject is in the m^{th} region at the t^{th} occasion and zero otherwise. We define the $T \times M$ matrix $I_i$as

$$I_i = [I_{i1}, \ldots, I_{iT}]' \quad (3)$$

Let Z_T be the $T \times (T-1)$ matrix where the first row has entries zero and the remaining $(T-1)$ rows from a $(T-1) \times (T-1)$ identity matrix. Consider the model

$$\text{logit}(\mu_i) = X_i\beta + Z_T\tau + I_i\gamma + S_i\rho, \quad (4)$$

where $S_i = [0, \text{diag}(I_{i2}, \ldots I_{iT})]'$ is a $T \times (T-1)M$ matrix and 0 is a $(T-1)M \times 1$ vectors of zeros. Note that τ is the $(T-1) \times 1$ vector of time effects (the first occasion is the reference time point), γ is the $M \times 1$ vector of region effects, and ρis the $(T-1)M \times 1$ vector of time and region interaction effects because each column of S_i results from component wise multiplication of two column vectors, one column vector from Z_T and the order from I_i. A goodness-of-fit test statistic consists of testing $H_o: \theta = 0$, where $\theta = [\tau', \gamma', \rho']'$ is a $J \times 1$ vector with $J = (T-1) + M + (T-1)M$.

Let $L = P + 1 + J$ be the number of parameters in the model presented in (4). Denote U be the $L \times 1$ vector with l^{th} component

$$U_l = \sum_{i=1}^{N} \hat{D}_{il}' \hat{V}_i^{-1}(Y_i - \hat{\mu}_i) \text{ for } l = 1, \ldots, L. \quad (5)$$

where $\hat{D}_{il} = \partial\hat{\mu}_i/\partial\beta_l$ for $l \le P+1$,

$\hat{D}_{il} = \partial\hat{\mu}_i/\partial\theta_{l-P-1}$ for $l > P+1$,

$\hat{\mu}_i = \text{logit}^{-1}(X_i\hat{\beta} + Z_T\tau + I_i\gamma + S_i\rho)$

and $\hat{\beta}$ is obtained as the solution to (2). Then, under $H_o: \theta = 0$, the asymptotic distribution of U is multivariate normal with mean zero and covariance matrix [17]

$$W_R = \sum_{i=1}^{N} \hat{D}_i'\hat{V}_i^{-1}\text{cov}(Y_i)\,\hat{V}_i^{-1}\hat{D}_i', \quad (6)$$

here $\hat{D}_i = [\hat{D}_{i1}, \ldots, \hat{D}_{iL}]$ is a $T \times L$ matrix Note that $\text{cov}(Y_i)$ can be consistently estimated by

$$(Y_i - \hat{\mu}_i)(Y_i - \hat{\mu}_i)'\,.$$

If the correlation matrix R_i is correctly specified, then the asymptotic covariance matrix of U reduces to $W = \sum_{i=1}^{N} \hat{D}_i'\hat{V}_i^{-1}\hat{D}_i$.

$$\text{Let } U = \begin{pmatrix} U_1 \\ U_2 \end{pmatrix} W_R = \begin{pmatrix} A_R & B_R' \\ B_R & C_R \end{pmatrix} W = \begin{pmatrix} A & B' \\ B & C \end{pmatrix}$$

be the partitioning for U, W_R, and W, where U_2 is the $J \times 1$ vector and C_R and C are $J \times J$ matrices. Under $H_o: \theta = 0$, both the proposed roubst (empirically corrected) goodness-of-fit test test statistic

$$Q_R = U_2'(C_R - B_R A_R^{-1} B_R^{-1})^- U_2$$

and the proposed model-based goodness-of-fit test statistic

$$Q = U_2'(C - BA^{-1}B')^- U_2$$

are asymptotically distributed as Chi-square random variables with $d.f. = rank((C_R - B_R A_R^{-1} B_R')^-) = rank((C - BA^{-1}B')^-)$.

Where G^- is any generalized inverse of the matrix G. The degree-of-freedom for the chi-square random variables do not equal the number of parameters in θ because of linear dependencies between the covariates in the model and the covariates from the region portioning,

i.e., $(C_R - B_R A_R^{-1} B_R')$ and $(C - BA^{-1}B')$

are singular matrices. Let H_1 and H_2 be the design matrices in models (1) and (4), respectively. Then intuitively, the degree-of-freedom of the above chi-square random variables is equal to $rank(H_2) - rank(H_1)$. Let $H_{2i} = \{h_{itj}\} = [X_i, Z_T, I_i, S_i]$ be the $T \times (P + 1 + J)$ design matrix for the i^{th} subject in model (4). It can be easily shown that the tj^{th} element of $\widehat{D}_i$ is equal to $\hat{\mu}_{it}(1 - \hat{\mu}_{it})h_{itj}$. Therefore, the goodness-of-fit test statistics Q and Q_R can be readily calculated once $\hat{\beta}$ is obtained from the estimating equations (2).

PROPOSED MODELS FOR THE STUDY

Here we propose two models for the data observed and test the goodness-of-fit test of those proposed models. The null and alternative hypotheses of the two models are

Model I:

H_o : logit(μ_{it})=β_0+$\beta_1 x_{i1}$+$\beta_2 x_{it2}$,
H_1: logit(μ_{it})=β_0+$\beta_1 x_{i1}$+$\beta_2 x_{it2}$+ β_3 $x_{i1}x_{it2}$,

Model II:

H_o : logit(μ_{it})=β_0+$\beta_1 x_{i1}$+$\beta_2 x_{t2}$+ β_3 x_{i3},
H_1: logit(μ_{it})=β_0+$\beta_1 x_{i1}$+$\beta_2 x_{t2}$+ β_3 x_{i3}+ β_4 $x_{i1}x_{i3}$,

for i = 1. . . N (850) denoting subject and t = 1. . .T (0, 1, 2) denoting the responses of the occasions of visiting first, second and fourth month. For Model I, x_1 is a time – independent binary covariate and x_2 is a time – dependent continuous covariate. For Model II, x_1 is again a time – independent binary covariate, x_2 is an indicator variable for the second occasion, and x_3 is a time – independent continuous covariate.

MODEL FITTING AND ANALYSIS

We fit two models to the data as proposed above. The first model namely, Model I includes the main effects such as Time (0, 1, 2), BGL (0,1) and CD (0, 1) and for the second model namely, Model II, we studied the above main effects apart from this interaction effect of treatment and time. Because all the covariates are discrete, the covariate categories were used to from four categories with frequencies provided in the last column of Table 1. The robust parameter estimates and goodness-of-fit test are tabulated below in Table 2 and Table 3.For Model I, Q = 34.7923 and Q_R= 37.2517. It shows that the Model I which has only main effects did not fit the data by both the goodness of fit tests, since p < 0.0001. However, there is a significant interaction effect (time × treatment), since $\beta_4 = 0.3542$ with p < 0.0014, indicating that patients with new drug treatment improved significantly faster than a patients with the standard drug. The model with this interaction term included has a good fit to the data (Q = 12.9979, Q_R= 13.5993; p = 0.0722, p = 0.0588). Thus the proposed goodness-of-fit test successfully detected the interaction effect. From the 850 DM patients, it was observed that 408 were identified as DR patients. Those DR patients are classified according to the retinopathy of their eyes as follows.A univariate analysis is performed with 13 variables is fitted to the data. The goodness-of-fit tests are also performed along with each logit model. From the above analysis, it is found that the p-values shows that the covariates such as duration of diabetes, BMI are alone significant where as the robust p-values shows that the covariates intraocular pressure, duration of diabetes, BMI, systolic blood pressure, diastolic blood pressure and proteinuria are highly significant. Hence the above factors are significant for the study of DR.

Table 1. Cross – Classification of Responses at Three Times (Normal =N, Abnormal =A) by Diagnosis and Treatment of DM Patients

Response at 1st month, 2nd month and 4th month										
BGL	Treatment	NNN	NNA	NAN	NAA	ANN	ANA	AAN	AAA	TOTAL
Low	Standard	57	38	28	14	26	17	23	16	219
Low	New Drug	65	22	13	1	51	9	17	6	184
High	Standard	19	16	38	34	39	45	87	59	337
High	New Drug	11	8	12	6	19	13	32	9	110

Table 2. Parameter estimates and goodness of fit tests for the data of Model I from the DM patients (Main effects only)

Covariates	Model I		
	Estimate	S.E	p- value
Intercept	0.1115	0.0871	0.2007
Time (0,1,2)[a]	0.4149	0.0514	<0.0001
Diagnosis(0 =Low, 1= High)	-0.9188	0.0852	<0.0001
Treatment(0–standard, 1-Newdrug	0.3776	0.0899	<0.0001

Table 3. Parameter estimates and goodness of fit tests for the data of Model II from the DM patients (Main effects and interaction between treatment and time)

Covariates	Model II		
	Estimate	S.E	p- value
Intercept	0.2283	0.0944	0.0155
Time (0,1,2)[a]	0.3008	0.0622	<0.0001
Diagnosis(0 =Low, 1= High)	-0.9224	0.0854	<0.0001
Treatment(0–standard, 1-Newdrug	0.0424	0.1377	0.7580
Treatment × Time interaction	0.3542	0.1108	<0.0014
[a]The values for time 0,1,2, correspond to the logarithm to the base 2 of months 1, 2 and 4.			

Table 4. Goodness-of-Fit

Model I				Model II		
Statistic		d.f	p-value	Statistic	d.f	p-value
Q	34.7923	7	<0.0001	12.9979	7	0.0722
Q_R	37.2517	7	<0.0001	13.5993	7	0.0588
Q denotes the proposed model-based goodness-of-fit test statistic and $Q_R$denotes the robust goodness-of-fit test statistic.						

Table 5. Frequency of DR

Right eye	Left eye		Total
	Absence	Presence	
Absence	216	37	253
Presence	104	51	155
Total	320	88	408

Table 6. Univariate analysis of the DR study

Covariate[a]	Parameter estimate	Roubust p-value	Q_R	d.f	p-value
Eye specific Covariate					
Refractive error	0.013	0.41	21.3	7	<0.0001
Intraocular pressure	0.040	0.001	8.5	7	0.2810
Clinical Measurement					
Age at Diagnosis of Diabetes(Years)	0.021	0.38	6.5	7	0.66
Duration of Diabetes (Years)	0.231	<0.0001	44.7	7	<0.0001
Glycosylated Hemoglobin Level	0.88	0.0161	17.2	7	0.0232
Body Mass Index(kg/m)^2	0.812	<0.0001	20.2	7	<0.0001
Systolic Blood Pressure(mm Hg)	0.27	<0.0001	3.5	7	0.8932
Diastolic Blood Pressure(mm Hg)	0.101	<0.0001	9.2	7	0.2401
Pulse rate (beats/30 Seconds)	0.105	0.0023	5.0	7	0.24
Gender(Male –M, Female-F)	0.160	0.3801	2.1	2	0.4700
Proteinuria (Absent =0 , Present =1)	0.105	<0.0001	0.8	2	0.3111
Does of insulin per day (0,1,2)	0.29	0.0713	6.0	3	0.704
Residence (Rural=0, Urban=1)	0.015	0.6752	0.6	2	0.787
* [a]One covariate, macular edema (absent = 0, present = 1), was not used in the model fitting because individuals with macular edema had DR.					

Figure 1. Structure of Eye Ball

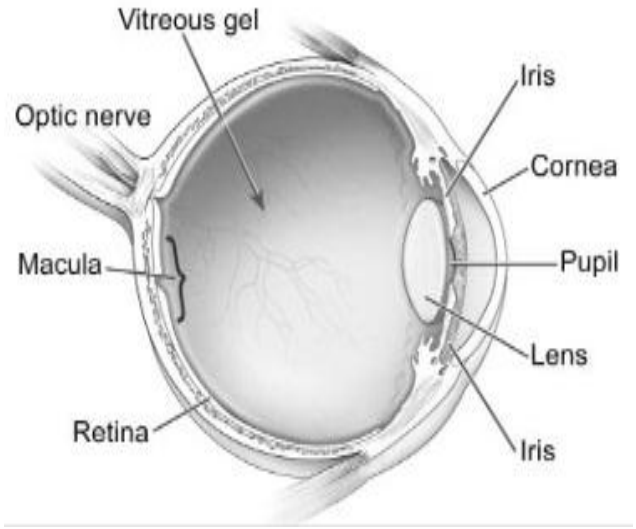


Figure 2. Diabetic Retinopathy

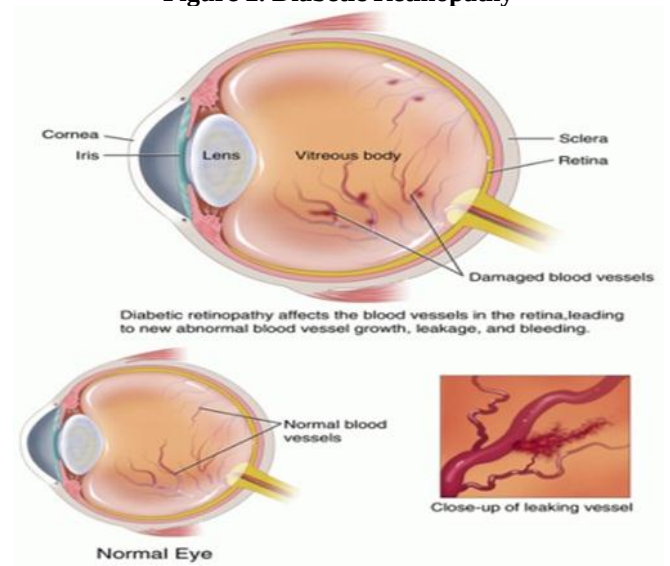


Figure 3. DR vision changes before and after

Normal vision

same scene viewed by a person with DR

Figure 4. Difference between Normal Retina and DR

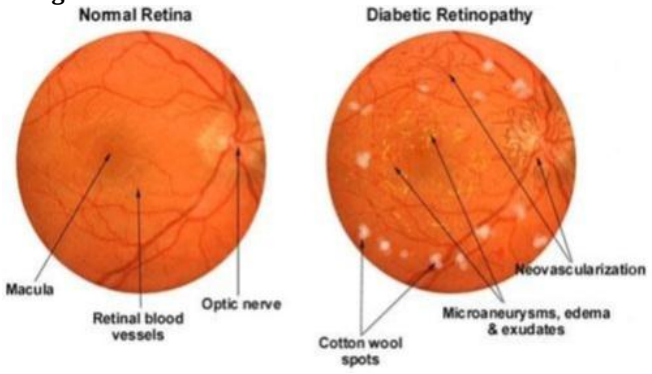
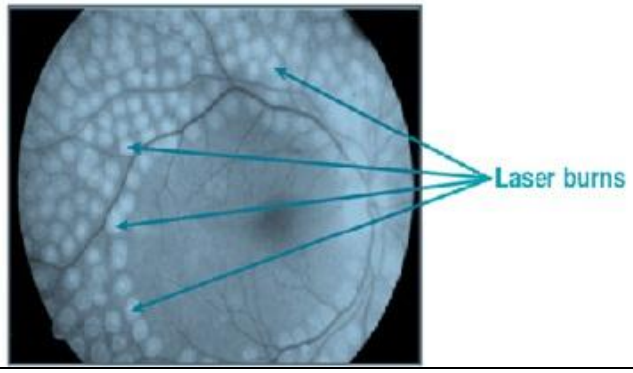


Figure 5. Scatter laser treatment



DISCUSSION

We have studied two models (one with only main effects and another with main effects and the interaction effect) and robust goodness-of-fit test for GEE modeling with binary responses. The proposed goodness-of-fit test have high power for detecting Model II (which included interaction effect) but have low power for detecting Model I (without interaction effect). The robust goodness of fit performs better than the model based goodness-of-fit test DR is a dreaded complication of diabetes and leading cause of blindness, though it is preventable. Retina is the light sensitive layer of eye. A healthy retina is necessary for good vision. Hence the factors namely, intraocular

pressure, duration of diabetes, BMI, systolic blood pressure, diastolic blood pressure and proteinuria are significant for DR. DR causes changes in the blood vessels of retina. It causes neo vascularisation which may cause bleeding into the retina and subsequent blindness. These vascular changes of retina can be diagnosed and treated before the onset of complication by regular eye screening. Between 40 to 45 percent of Indian diagnosed with diabetes have some stage of DR. DR is proportional to the duration of diabetes, severity and lack of follow up for eye care. Hence these factors are analyzed. It is seen that regular eye screening once in a year, better management of DM from the earlier stage itself plays a major role in prevention of blindness due to DR.

PREVENTION

These are steps we can take to reduce vision loss from DR and its complications:

- Control your blood sugar levels, keep blood sugar levels in a target range by eating a balanced diet ie., Eating Healthy food that support to reduce your DR and monitoring your blood sugar levels.
- Get adequate exercise. Exercise helps keep blood sugar levels in a target range, which can reduce the risk of vision damage from DR.
- Blood pressure should be kept under control as the combination of DM and HT can progress DR.
- Keep up to date with regular medical exams to ensure that your blood pressure readings are normal.
- Getting regular physical exercise, and taking insulin or medicines for type 2 diabetes if prescribed.
- Avoid hazardous activities. Certain physical activities like weight lifting or some contact sports may trigger bleeding in the eye through impact or increased pressure. Avoiding these activities when you have DR can help reduce the risk of damage to your vision.
- People with type 1 diabetes who are age 10 and older should have a dilated eye exam within 5 years after diabetes is diagnosed and then every year.
- People with type 2 diabetes should have an exam as soon as diabetes is diagnosed and then every year.

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CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

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