



IDENTIFYING PATIENTS WITH DIABETIC NEPHROPATHY BASED ON SERUM CREATININE UNDER ZERO TRUNCATED MODEL

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Abstract: *Diabetes mellitus is a clinical syndrome characterized by hyperglycemia due to absolute or relative insufficiency of insulin in the body. Diabetic nephropathy is a generic term referring to deleterious effect on renal structure and/or function caused by diabetes mellitus. In this paper, we estimate the probability of occurrence of diabetic nephropathy, taking serum creatinine as a marker for renal function/dysfunction. We adopted a Zero truncated binomial distribution (ZTBD) with parameters (n_i, p) , where p , the probability that serum creatinine \geq cutoff value, was unknown. Maximum likelihood and residual bootstrapping methods were used to estimate p . Retrospective data was collected from 132 patients diagnosed as diabetic as per ADA standards. Out of the available data of 132 patients, 72 patients had no diabetic renal complications with serum creatinine mean \pm s.d as 0.9774 ± 0.12508 and 60 patients had certain diabetic complications with serum creatinine mean \pm s.d. as 1.6462 ± 0.28827 . The mean \pm s.d. for duration of disease for 60 patients came out to be 15.46667 ± 5.54 (yrs) and median as 17.1 yrs. The two groups of patients were found to be significantly different with $p < .001$. The value of \tilde{p} came out to be 0.4555397 and 0.445545 using maximum likelihood and residual bootstrapping methods respectively. It was found that 60 patients had non -zero probability of renal disease under ZTBD. From this study, it was concluded that the duration of diabetes along with elevated levels of serum creatinine defines a high risk group for the diabetic nephropathy.*

Keywords: *Diabetic Nephropathy, Maximum likelihood, Residual bootstrapping, Serum creatinine, Type 2 diabetes, Zero truncated binomial distribution.*

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1. Introduction

Diabetes mellitus is a clinical syndrome characterized by hyperglycemia due to absolute or relative insufficiency of insulin in the body. Diabetic Nephropathy (DN) is a generic term referring to deleterious effect on renal structure and/or function caused by diabetes mellitus. Type 2 diabetes usually starts in middle age or later [1]. According to World Health Organization estimates diabetes affects more than 170 million people worldwide and this number may rise to 370 million by 2030 [3]. The prevalence of DN is the highest among the Asians and is a growing public health concern. Diabetic nephropathy develops in 20 - 40% of patients within 10 to 15 years after the onset of diabetes [13]. Estimating Glomerular filtration rate (GFR) is the most rational noninvasive method of assessing the renal status in patients [4,5]. With the development of DN, serum creatinine (SrCr) levels start to increase and GFR starts to fall. The rate of rise in SrCr, a well-accepted marker for the progression of DN, (creatinine value 1.4 to 3.0 mg/dl) is the indicator for impaired renal function [7]. BioStratum at their 64th Scientific Sessions ADA Meet accepted rate of rise in serum creatinine as a marker for the progression of diabetic nephropathy. Diabetic nephropathy is a leading cause of end stage renal failure [9].

Andersen [18] proposed multistate proportional hazards regression models with time dependent covariates to find mortality and incidence of nephropathy in diabetic patients. He also computed the transition intensities and probabilities. Frydman Halina [12] used three state time homogenous Markov process with irreversible transitions to find transition intensities and probabilities and illustrated this model with diabetic survival data. Enzo Ballone and others [17] applied conditional probability to find that a diabetic patient will develop a second complication, given that they had already developed the first complication. They also proposed the Bayes' formula for the same problem. Gunnes Nina and others [10] developed non-Markov multistage models under dependent censoring for estimating stage occupation probabilities. They showed that the individual transition and censoring mechanisms are linked together through covariate processes that affect both the transition intensities and the censoring hazard for the corresponding subjects. Study on development of nephropathy among diabetic patients is used as demonstration on how the estimation method works in practice.

Based on the previous results, in this study also SrCr is taken as a marker for predicting renal health. Present study deals with diabetic patient's renal health. We applied zero truncated binomial distribution (ZTBD) with parameters (n_i, p) where n_i , denoting the number of times the test was recommended to the i^{th} patient, were known and p , denoting the probability that $\text{SrCr} \geq$ cutoff value (considered as success), was unknown. The estimated value of p , i.e. \tilde{p} , is derived using maximum likelihood and residual bootstrapping methods. Mean, variance and the 95% confidence band of both the estimators are also compared. The p estimators obtained from both the methods are used to obtain the probability of occurrence of diabetic Nephropathy under ZTBD. We found that 60 subjects had non-zero probability of renal disease under ZTBD. Further, 27 out of 60 were found to be with advanced diabetic Nephropathy.

Although much work has already been done on diabetic nephropathy but to the best of our knowledge this is the first investigation about the estimation of occurrence of nephropathy arising out of type-2 diabetes only. This study clearly points out the number of times the value of serum creatinine, if crossed normal range, could lead to renal complications. This could be an important pointer for medical fraternity to guide the patients about likely outcome i.e. end-stage renal disease.

Besides introduction this paper includes three more sections. Section-2, which is further divided into two sections, 2.1 section contains details of the material used and in section 2.2 the model is introduced. In section-3 the model is applied to the type-2 diabetic patient data and section 4 contains discussion.

2. Materials and Methods

2.1 Materials

Retrospective data from 250 patients were short – listed who were diagnosed of diabetes [as per ADA standards] from the data base of Dr. Lal’s Path Lab, a reputed NABL certified path lab. Requests were sent to patients for sharing their pathological history in terms of up-to-date reports. Out of this 164 patients responded positively. These 164 patients were contacted through a house to house survey and their pathological reports along with doctor’s prescription were collected for further verification. Reports from only 132 patients, with minimum 5 yrs diabetic history, were found suitable for this study as their reports indicated continuity of pathological follow-up always using the same lab. This was done to maintain benchmark of the data used. Patients included in this study were under medical supervision. ADA standards are taken as reference values for this study: $FBG \geq 126$ mg/dl for diabetes and $DBP > 90$ mmHg for hypertension, $LDL \geq 100$ mg/dl for elevated cholesterol concentration, $SrCr \geq 1.4$ mg/dl for onset of renal disease/nephropathy. Pathological history were recorded on SrCr, fasting blood glucose (FBG), diastolic blood pressure (DBP) and low density lipoprotein (LDL). Since the study is concentrated on the renal complication arising out of type-2 diabetes only, it automatically excludes its effect on eyes, heart etc. We also excluded the cases where renal complication had preceded the onset of diabetes. The descriptive statistics of 132 patients is given in table 1.

2.2 Methodology

The Model ZTBD is depicted in figure 1. All the patients under study experienced an initial event E1 (diagnosed as diabetes as per ADA standards) but not all of them experienced a second event E2 (onset of renal disease/diabetic nephropathy) till the study was terminated on 5th Nov 2007. Patients under study came with different history of disease & health condition. This model is explained with the help of figure 1 where X-axis denotes the duration of disease, and Y-axis denotes the level of SrCr. The total lines from X-axis for any patient represents number of times the serum creatinine test was recommended and height of each line indicates its SrCr value. The patient P_i ($i = 1, 8, 50$) belongs to group 1 and patients P_5 and P_{20} to control group or group 0. The number of lines which crossed the cutoff value for the i^{th} patient is the no. of successes for that respective patient. The number of lines below the cutoff value for the i^{th} patient is not considered or count of zeros is not observed. Based on the number of successes we are able to estimate the onset of diabetic nephropathy.

Table 1. Descriptive statistics of 132 patients giving minimum, maximum, range and mean± standard deviation of age at diagnosis, duration of diabetes, fasting blood glucose(FBG), systolic blood pressure(SBP), diastolic blood pressure(DBP), low density lipoprotein(LDL) and serum creatinine(SrCr) for two groups i.e. control(Group 0)and affected(Group 1).

Variable		Group 0	Group 1
Age at diagnosis (years)	minimum	35	29
	maximum	58	56
	range	23	27
	mean±S.D	44.011±4.36	45.003±5.28
Duration of disease (years)	minimum	5.6	29
	maximum	27	56
	range	21.4	27
	mean±S.D	10.2784±5.7	14.0931±5.0528
FBG (mg/dl)	minimum	62	120
	maximum	186	242
	range	124	122
	mean±S.D	133.8027±17.48	142.035±14.39
DBP (mm Hg)	minimum	68	76
	maximum	95	112.0
	range	27	36
	mean±S.D	82.3919±6.0789	91.9695±9.423
SBP (mm Hg)	minimum	110	110
	maximum	160	160
	range	50	50
	mean±S.D	125.1214±12.4007	142.8214±13.8815
LDL (mg/dl)	minimum	62	68
	maximum	186	132
	range	124	64
	mean±S.D	91.7973±18.75007	107.4417±14.2667
SrCr (mg/dl)	minimum	0.71	68
	maximum	1.39	132
	range	0.92	64
	mean±S.D	0.9982±0.15084	1.6686±0.28233

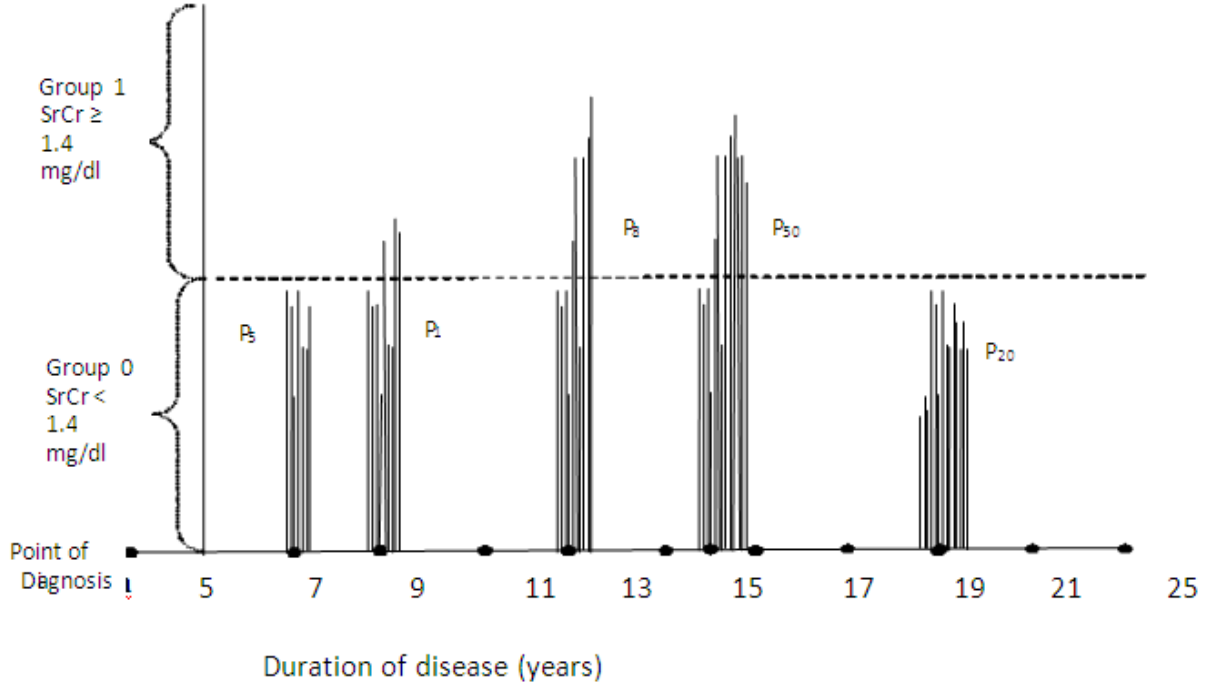


Figure 1. Zero truncated binomial model where X-axis denotes of the diabetes, Y-axis denoting the level of Serum Creatine in mg/dl and number of vertical lines indicating the number of times Serum Creatinine recommended for i^{th} patient.

2.2.1 Zero truncated binomial distribution Model

Zero truncated samples from discrete distribution arise when the count of zeros are not considered. Let X_1, X_2, \dots, X_n are independently distributed random variables following zero truncated binomial distribution with parameters n_i, p . Then probability mass function for the i^{th} patient, is given by Johnson and Kotz [21] as.

$$P(X_i = x_i) = \frac{{}^{n_i}c_{x_i} p^{x_i} (1-p)^{(n_i-x_i)}}{(1-(1-p)^{n_i})} \quad ; \quad x_i = 1, 2, \dots, n_i \quad (1)$$

where n_i , the number of times the test is recommended to the i^{th} patient, is known. $\text{SrCr} \geq 1.4$ mg/dl is considered as success, x_i denotes the number of successes and p is the probability of success. The parameter p is unknown and is estimated using maximum likelihood method as well as by residual bootstrapping method.

2.2.2 Maximum likelihood method to estimate the parameter p

The likelihood function for estimating p is given by:

$$L = \prod_1^n \frac{{}^{n_i}c_{x_i} p^{x_i} (1-p)^{(n_i-x_i)}}{(1-(1-p)^{n_i})} \quad (2)$$

Differentiating $\log L$ with respect to p and then, equating the derivative to zero, the resulting equation comes out to be

$$\frac{(p \sum_1^n n_i - \sum_1^n x_i)}{p(1-p)} - \frac{\sum_1^n n_i(1-p)^{n_i-1}}{(1-(1-p)^{n_i})} = 0 \quad (3)$$

Maximum likelihood estimate of p is obtained as \tilde{p} by solving the above equation by the method of iteration. This value of \tilde{p} , came out to be approximately equal to the proportion of patients belonging to group-1(affected group). We also computed $Var \tilde{p}$ and 95% confidence interval which may be considered as a special feature of this work.

$$Var \tilde{p} = p(1-p)/n = \tilde{p}(1-\tilde{p})/n \quad (4)$$

$$C.I(\tilde{p}) = \tilde{p} \pm 1.96 * \sqrt{\tilde{p}(1-\tilde{p})/n} \quad (5)$$

2.2.3 Residual Bootstrapping method to estimate the parameter p

In this method linear regression model is fitted by taking y_i , mean serum creatinine for the i^{th} patient, as response variable and x_i , the number of successes (no. of times the value of SrCr ≥ 1.4 mg/dl), as independent variable. Residual Bootstrapping is a method where resampling is applied for the errors alone and the entire vector of independent variables is not resampled suggested by Efron and Tibshirani [16].

$$y_i = \beta x_i + e_i \quad (6)$$

Algorithm applied for estimating p is given as follows:

- Step1- Using the full model (6), compute \hat{y}_i predicted value and standardized residuals as:

$$\hat{e}_i = (y_i - \hat{y}_i) / \sqrt{Var(y_i - \hat{y}_i)}.$$

- Step2- Generate the resample of residuals \hat{e}_i , giving dataset, $\{ e_i^* \}$.
- Step3- Create a new bootstrap sample dataset $\{ y_i^* \}$ by $y_i^* = \hat{y}_i + e_i^* \sqrt{Var(y_i - \hat{y}_i)}$.
- Step4- Use y_i^* to estimate the parameter p .

Repeat step 2-4 to generate y_i^* for 50 samples, each with size 132.

Estimated values of p are depicted in table 2. We also computed the expected value, \tilde{p} , with corresponding variance and 95% confidence interval. These values were compared with those obtained by maximum likelihood method.

2.2.4 The probability of renal disease /diabetic nephropathy for each patient with ZTBD model

Under the above ZTBD model, we obtained the probability of renal disease for each patient. From the \tilde{p} , derived using maximum likelihood and residual bootstrapping methods, we

calculated $P (X_i \leq \text{no of successes})$, the cumulative mass function for each patient, is given below.

$$F(x_i) = \sum_1^{x_i} \frac{{}^{n_i}C_{x_i} \tilde{p}^{x_i} (1 - \tilde{p})^{(n_i - x_i)}}{(1 - (1 - \tilde{p})^{n_i})} \quad ; \quad x_i = 1, 2, \dots, n_i \quad (7)$$

Then the expected number of successes required for i^{th} patient proceeding for diabetic nephropathy is given by.

$$E(X_i) = n_i p / (1 - (1 - p)^{n_i}) \quad (8)$$

3. Results

Up-to-date pathological reports / records of diabetic patients, using a common path lab, were collected through a house to house Survey. Retrospective study was conducted on the collected data. Since our study was focused on diabetic nephropathy only, patient's data indicating effect on eyes, heart etc was excluded. A total of 132 diabetic patients were selected, (60 with and 72 without renal complication), aged 44.45 ± 4.79 years (mean \pm SD). The demographic details recorded were Age at the time of diagnosis, Duration of disease, FBG, DBP, SBP, LDL and SrCr as depicted in table 1. Figure 2 depicted average value of SrCr under two groups (affected and controlled). It can be observed from the figure 2 that patients with average (SrCr) ≤ 1.0 mg/dl are in control group and the patients with average (SrCr) ≥ 1.25 mg/dl are in affected group. Further, the proportion of patients in the affected group was distributed according to their diabetic history (i.e. duration of disease) and facts are displayed in table 2 and graphically illustrated in figure 3.

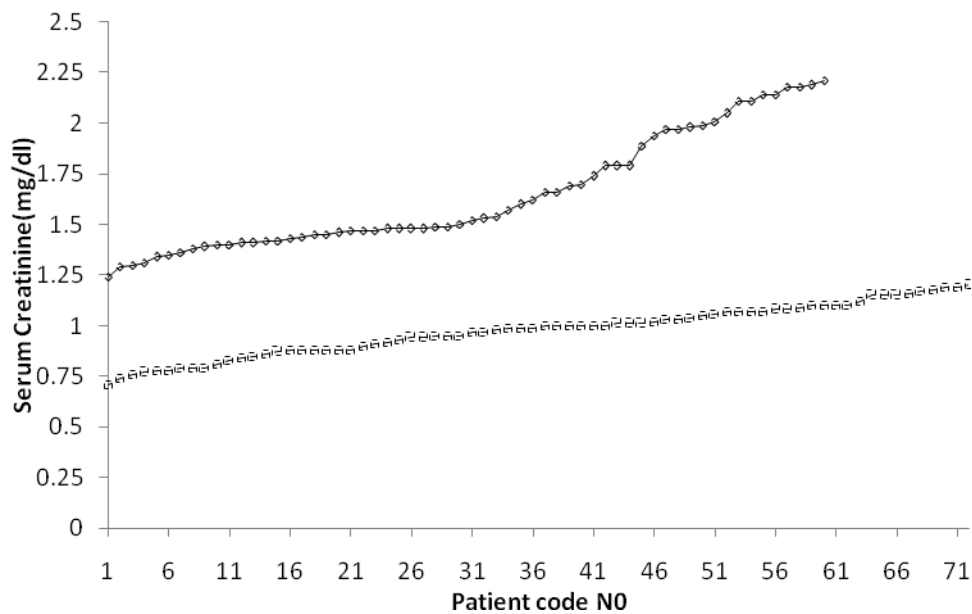


Figure 2. Patients in two groups, control and affected group, according to mean Serum Creatinine value measuring in mg/dl. Affected group is indicated by top line and bottom line indicates the cases under control group.

Table 2. Proportion of patients in the affected group was distributed according to their diabetic history.

Duration of diabetes(yrs)	Proportion of patients	Cumulated proportion
5-8	0.030303	0.030303
8-11	0.060606	0.090909
11-14	0.05303	0.143939
14-17	0.075758	0.219697
17-20	0.113636	0.333333
>20	0.121212	0.454545

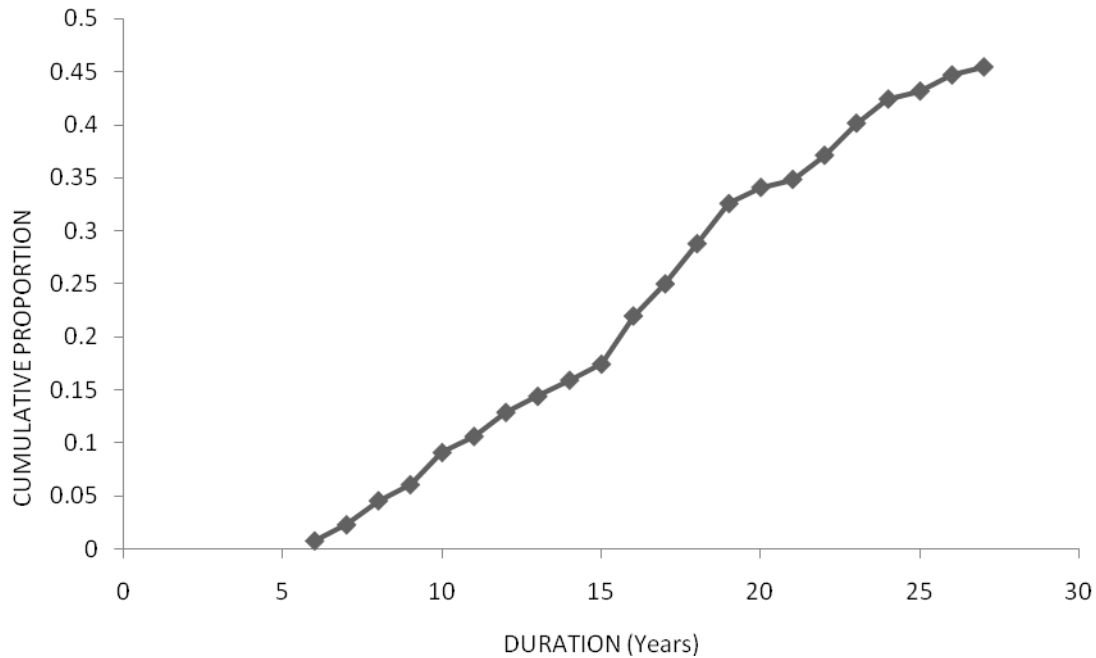


Figure 3. Proportion of patients belonging to group 1 or affected group with respect to their diabetic history.

3.1 Estimated value of p with corresponding variance and 95% confidence interval by the method of maximum likelihood and residual bootstrapping method

On substituting the values of the total number of times the SrCr test was recommended and the total number of times the value of SrCr ≥ 1.4 mg/dl as $\sum_{i=1}^n n_i = 996$ and $\sum_{i=1}^n x_i = 487$, respectively, in equation (3) for the patients who belong to affected group, the maximum likelihood estimate of p was obtained as $\tilde{p} = .4555397$. By applying residual bootstrapping method 50 different values of p were estimated from each sample of size 132, which are displayed in table 3. Further, t-test for single mean was applied to test for $\tilde{p} = 0.445545$ and calculated value of t came out to be 0.791, which showed that the generated sample was accepted for $p = \tilde{p}$. Thus, $\tilde{p} = 0.445545$, was considered as estimate of p obtained by residual bootstrapping method. The estimates of p , Expected (\tilde{p}), Variance (\tilde{p}) & 95% Confidence interval (\tilde{p}) were obtained by both the method of maximum likelihood and residual bootstrapping method and are displayed in table 4. The 95% Confidence interval (\tilde{p}) from

residual bootstrapping was found to be wider i.e. (0.4229133, 0.4681766) as compared to (0.4435269, 0.4675524), obtained by maximum likelihood method.

Table 3. Indicates 50 different values of p using Residual Bootstrapping.

0.445545	0.4924242	0.4090909	0.3257576	0.2878788	0.4621212	0.2727273
0.5227273	0.4469697	0.2424242	0.2878788	0.4621212	0.3257576	0.4166667
0.5151515	0.3863636	0.4848485	0.4318182	0.5757576	0.4242424	0.5909091
0.3560606	0.4015152	0.4772727	0.5151515	0.4469697	0.5681818	0.4242424
0.530303	0.530303	0.3636364	0.4015152	0.3560606	0.3560606	0.5227273
0.3560606	0.4469697	0.4848485	0.469697	0.4242424	0.5075758	0.5227273
0.3181818	0.4545455	0.4772727	0.4469697	0.4621212	0.4015152	0.4924242
0.5075758						

Table 4. The estimates of p , Expected (\tilde{p}), Variance (\tilde{p}) & 95% Confidence interval (\tilde{p}) obtained by the method of maximum likelihood and residual bootstrapping.

Method	p	Expected (\tilde{p})	Variance (\tilde{p})	95% Confidence interval (\tilde{p})
Maximum Likelihood	0.4555397	0.45454545	0.00187829	(0.4435269,0.4675524)
Residual Bootstrapping	0.445545	0.458743	0.000499	(0.4229133,0.4681766)

3.2 The probability of renal disease /diabetic nephropathy for every patient with ZTBD model

Based on \tilde{p} obtained by maximum likelihood method, $X_i \sim ZTBD(n_i, 0.4555397)$, with known n_i , Using this ZTBD model we calculated probability mass function and cumulative function for each patient, as the number of times the SrCr test was recommended was different for different patients. Using figure 1, for each patient under affected group, counted the number of times the serum creatinine value crossed the normal range for the i^{th} patient, and obtained x_i . We obtained $P(X_i \leq x_i)$ or probability of occurrence of diabetic nephropathy and mean number of successes for all 60 patients as depicted in column (2) and column (4) respectively in table 5. Here we used the value of \tilde{p} obtained by residual bootstrapping method, $X_i \sim ZTBD(n_i, 0.445545)$, with known n_i . Proceeding in the same manner as for maximum likelihood method, $P(X_i \leq x_i)$ or probability of occurrence of diabetic nephropathy and mean number of successes for all 60 patients were obtained and are depicted in column (3) and column (5) respectively in table 5.

Table 5 (a). Probability of occurrence of Diabetic Nephropathy, mean number of times the SrCr crossing the normal range, using maximum likelihood and Residual bootstrapping methods under ZTBD.

Duration (yrs)	Probability of diabetic nephropathy		Expected no. of successes		
	Maximum likelihood estimator	Bootstrapping estimator	Maximum likelihood estimator	Bootstrapping estimator	Proceeding for diabetic nephropathy
6	0.21241	0.24211	1	2	4
7	0.06078	0.03706	0	1	5
7	0.05987	0.05774	0	0	3
7.8	0.87266	0.79944	11	12	6
8	0.09377	0.0904	1	1	5
8	0.14242	0.13805	1	1	4
9	0.03601	0.03454	0	0	4
9	0.06078	0.05827	0	0	5
9.6	0.09617	0.09624	1	1	6
10	0.03713	0.035	1	1	8
10	0.01537	0.01449	0	0	4
10	0.25502	0.2484	3	2	5
10.4	0.26612	0.2541	3	2	5
11	0.05987	0.05774	0	0	6
11.4	0.00954	0.00547	0	0	7
12	0.01974	0.01753	0	0	7
12	0.87266	0.79944	12	11	6
13	0.64537	0.54807	11	9	8
13	0.99611	0.98955	16	16	7
13.4	0.18541	0.09974	3	2	7
13.6	0.80649	0.80649	12	11	7
15	0.97948	0.97808	18	18	7
15	0.91011	0.90566	15	15	8
15.2	0.15696	0.15122	2	2	6
15.6	0.99681	0.992	19	19	9
16	0.81062	0.71934	11	9	6
16	0.9467	0.85553	15	14	7
16	0.95359	0.91268	14	13	7
16	0.99566	0.99932	21	21	10
16.6	0.80396	0.79641	14	14	8
17	0.08797	0.08577	2	2	10
17	0.95947	0.90049	20	19	10
17	0.999	0.99091	21	21	10
17.2	0.72935	0.63529	12	10	7
17.6	0.94381	0.91011	16	15	8
18	0.00009	0.00005	0	0	9

Table 5 (b). Probability of occurrence of Diabetic Nephropathy, mean number of times the SrCr crossing the normal range, using maximum likelihood and Residual bootstrapping methods under ZTBD.

18	0.73441	0.64926	13	15	9
18	0.97948	0.97808	18	18	8
19	0.1058	0.1332	3	2	8
19	0.13581	0.13552	3	3	8
19	0.37327	0.36287	7	7	8
19	0.86174	0.85553	16	15	11
20	0.49482	0.481202	8	8	8
20	0.9944	0.99394	18	18	8
21	0.05438	0.035	1	1	8
21.2	0.03873	0.02397	0	0	7
21.4	0.02601	0.00664	0	0	11
22	0.00213	0.00044	0	0	11
22.2	0.00471	0.00432	0	0	11
22.6	0.00725	0.00668	0	0	10
23	0.99969	0.99874	17	17	8
23	0.00471	0.00432	0	0	11
23.6	0.00725	0.00668	0	0	10
24	0.11971	0.08338	2	1	10
24	0.18541	0.13103	3	2	9
24.4	0.86174	0.85553	16	15	8
26	0.85213	0.84433	21	21	12
26	0.85014	0.84006	21	21	12
26.6	0.99681	0.98382	23	23	11

3.3 Comparison between two groups, less advanced nephropathy with advanced nephropathy

The column (6) of table 5 is representing the expected number of successes required for i^{th} patient proceeding to advanced diabetic nephropathy. Patients in affected group were with different diabetic history and different renal health. To identify patients with advanced nephropathy, mean number of successes obtained through maximum likelihood method and residual bootstrapping method was compared with the mean number of successes required for any patient proceeding for DN. It was found that 27 patients i.e. 20.45% of 132 subjects, whose mean number of successes, obtained through maximum likelihood method and residual bootstrapping method, was greater than or equal to the number of successes required for any patient, proceeded to advanced diabetic nephropathy. Thus, under ZTBD model, 132 patients were classified under three groups, 72 under control, 33 had less advanced nephropathy and 27 had proceeded with advanced nephropathy. By applying t-test of difference of means on the two groups of patients, 33 less advanced nephropathy and 27 advanced nephropathy, under affected group of 60 patients were found to be significantly different and the calculated value of t came out to be 9.61 with $p < 0.001$. Results in table 6 indicate the details of 27 patients, belonging to advanced nephropathy group, with respect to duration of disease and mean number of times serum creatinine crossed normal range (using ML and bootstrapping methods) under ZTBD. These results regarding the expected number of successes obtained from both the methods have

been graphically illustrated in figure 4. It can be observed from the graph as well as from table 6 that the results obtained by both the methods are close to each other. SPSS for Windows, Version 15 statistical package was used for calculation and analysis.

Table 6. Mean number of successes only for those patients who proceeded for Advanced Diabetic Nephropathy along with their duration ,from maximum likelihood and residual bootstrapping methods.

Duration Of diabetes (years)	Expected no. of successes		
	Maximum Likelihood estimator	Bootstrap ping estimator	Proceeding for diabetic nephropathy
7.8	11	12	6
12	12	11	6
13	11	9	8
13	16	16	7
13.6	12	11	7
15	18	18	7
15	15	15	8
15.6	19	19	9
16	11	9	6
16	15	14	7
16	14	13	7
16	21	21	10
16.6	14	14	8
17	20	19	10
17	21	21	10
17.2	12	10	7
17.6	16	15	8
18	13	15	9
18	18	18	8
19	16	15	7
20	8	8	8
20	18	18	8
23	17	17	8
24.4	16	15	8
26	21	21	12
26	21	21	12
26.6	23	23	11

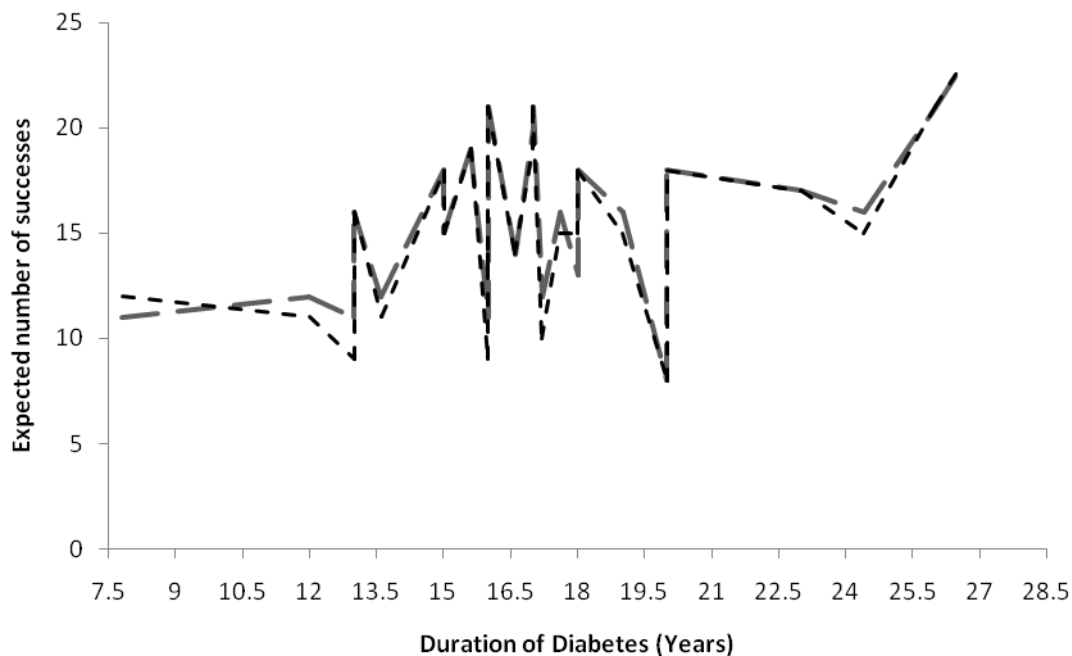


Figure 4. Mean number of successes only for those patients who proceeded for Advanced Diabetic Nephropathy obtained from maximum likelihood and residual bootstrapping methods.

4. Discussion

The present study demonstrates that an increase in value of serum creatinine in type-2 diabetic patients predicts the progression of nephropathy. The major use of estimating the probability of occurrence of diabetic nephropathy is that in future studies it may provide greater sensitivity for detecting patients with diabetic nephropathy. It may allow one to gain deeper insight into the various differences that may exist between the treatments suggested by previous studies i.e. by the DCCT Research Group and UK Prospective Diabetes Study Group [19,20] given to type -2 diabetic patients.

Under the present ZTBD model, out of 132 patients 45.45% had non zero probability of diabetic nephropathy with mean duration of diabetes as 15.99 yrs which is almost consistent with the previous findings which suggest that diabetic nephropathy develop in 20 – 40 % of patients within 10 to 15 years after the onset of diabetes [13]. Further, this model divides the 60 patients of affected group into two group sizes 33 and 27. In the first group with less advanced nephropathy, the expected number of times SrCr crossed the normal range, obtained from maximum likelihood and residual bootstrapping methods, came out to be less than the expected number required for proceeding for DN. In the second group with advanced nephropathy, the expected number of times SrCr crossed the normal range, obtained from maximum likelihood and residual bootstrapping methods, came out to be more than or equal to the expected number required for proceeding for DN. The findings of this paper through ZTBD model are consistent with the observed facts, i.e., out of total of 132 subjects, 72 had mean serum creatinine \leq 1.0mg/dl under control. Out of the remaining 60 patients of the affected group, 33 had mean SrCr equal to 1.42 mg/dl, under less advanced nephropathy and 27 had mean SrCr equal to

1.91mg/dl, under advanced nephropathy group as given in table 7. The classification obtained from the ZTBD model as well as from the observed almost matches with the results obtained by Abs-Lewis EJ.

Table 7. The descriptive statistics for the three groups, viz., control, less advanced nephropathy and advanced nephropathy.

Groups	Group size	Mean SrCr	Standard Deviation
Control Group	72	.9780	.12616
Less advanced DN group	33	1.4245	.07665
Advanced DN group	27	1.9137	.20888
Total	132	1.2810	.39610

Previous studies suggest that there is a constant deterioration of renal function of the diabetic patients over time or progression of nephropathy over time [20]. It can be observed from the present ZTBD model that out of a total of 56 patients with less than 10 years of diabetes duration, 8 are under less advanced nephropathy group and only 1 patient is under advanced nephropathy group. Where as in a total of 21 patients with greater than 20 years of diabetes duration, 11 are under less advanced nephropathy group and only 6 patients are under advanced nephropathy group. To show that the progression of nephropathy depends on the duration of diabetes we applied Karl-Pearson’s chi square goodness-of-fit test for independence of attributes, where calculated value of chi-square came out to be $\chi_{(6)}^2=51.39$ with $p<0.001$ Thus we conclude that there is a constant deterioration of renal function of the diabetic patients over time or progression of nephropathy over time. Complete detail of results is depicted in table 8. The results are completely in accordance with past studies which suggest a link between development and progression of diabetic nephropathy and duration of diabetes in type 2 diabetic patients [20].

Table 8. Progression of nephropathy depends on the duration of diabetes with 132 type-2 diabetic patients.

		Group accord disease progression			Total	
		0	1	2		
Duration of disease	<10	Counted	47	8	1	56
		Expected Count	30.5	14	11.5	56.0
	10-15	Counted	11	8	4	23
		Expected Count	12.5	5.8	4.7	23.0
	15-20	Counted	10	6	16	32
		Expected Count	17.5	8.0	6.5	32.0
	≥20	Counted	4	11	6	21
		Expected Count	11.5	5.3	4.3	21.0
Total	Counted	72	33	27	132	
	Expected Count	72.0	33.0	27.0	132.0	

In conclusion, the present study suggests that increased serum creatinine levels are strongly associated with the development of diabetic nephropathy and the results obtained in this paper, based on marker serum creatinine, are also comparable with the previous results which are based on albumin urea.

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