



A Multivariate Analysis of Risk Factors for Diabetic Nephropathy

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Abstract: This paper uses multivariate methods on actual data from 267 patients with non-insulin-dependent (Type 2) diabetes mellitus in order to see how the various risk factors can affect the progression of diabetic nephropathy. The approach succeeds in identifying preliminary risk factors such as smoking for males, although the females had higher fasting blood glucose at diagnosis. Not surprisingly, hypertension is common among patients of both sexes and it has an association with proteinuria in female patients in the sample.

Keywords: Multivariate model, Univariate analysis, Glomerular filtration rate, Microalbuminuria, Proteinuria.

Introduction

In a previous paper [8], we used univariate analysis to look for risk factors for diabetic nephropathy. However, examination of each independent variable individually can only provide a preliminary idea of how important each variable is by itself. The relative importance of all the variables has to be examined simultaneously by multivariate methods. In this paper linear logistic regression analysis is adopted in attempt to identify the risk factors related to diabetic kidney disease.

The rationale for using linear logistic regression for analysis is that it is not required to assume the normal distribution for the independent variables. Now in our case, many of the independent variables are qualitative or measured in nominal or ordinal scales and often in such cases any such normality assumption is violated.

Thus, once we have an overview of the data by from univariate analysis, we can further our investigation by using multivariate analysis. The rationale for using the multivariate method is that the univariate approach may ignore the possibility that a collection of variables, each of which is weakly associated with the outcome, can become an important predictor of the outcome when taken together.

Proteinuria

Research suggests that measurement of proteinuria is the most accurate way for the screening and diagnosis of overt diabetic nephropathy. Moreover, protein measurement in spot urine is a reliable and simple method for the screening and diagnosis of overt diabetic nephropathy [11].

Persistent proteinuria is defined as a protein excretion > 0.5 g/24 h in at least four consecutive urine samples with an interval of at least 1 month in patients without renal infection. Persistent proteinuria is strongly associated with increased mortality in insulin-dependent diabetes mellitus (IDDM), and risk of this condition can be predicted many years in advance by subclinical increases in albumin excretion rate (microalbuminuria) [2]. It was found that the reduction in albumin excretion rate was accompanied by a significant fall in median glomerular filtration rate (GFR) and a fractional renal clearance of albumin. Kidney volume remained unchanged.

Microalbuminuria, the early phase of diabetic nephropathy, is associated with increased cardiovascular morbidity and mortality, but the reason for this is not clear [3]. Patrick et al. [6] assessed the prevalence of microalbuminuria, and its associations with other clinical features. The study showed that persistent microalbuminuria was found in a significant number of non-insulin-dependent diabetes (NIDDM) patients at the time of diagnosis.

Similarly, the impact of microalbuminuria on mortality among a large cohort of NIDDM and other risk factors was investigated by Schmitz et al. [7]. They found that age, urine albumin concentration (UAC), known duration, and serum creatinine were the only significant risk factors. More specifically, Turtle [9] explained that patients with microalbuminuria have an increased risk of developing diabetic nephropathy, hypertension, large vessel disease and retinopathy. Hence epidemiological studies have focused on the identification of risk factors for the development of microalbuminuria. In the same way, the United Kingdom Prospective Diabetes Study Group [10] concluded that urinary albumin excretion was associated with hyperglycaemia and hypertension, whereas urinary N-acetyglycaeminidase was primary associated with hyperglycaemia.

Data

The longitudinal data of the diabetic patients have been collected by Professor David Owens *CBE* and his team at the Diabetes Research Unit, University of Cardiff School of Medicine, with which the authors have worked over the years. The data set consists of measurements of age, sex, weight, height, blood glucose, cholesterol, high and low density lipoprotein, blood pressure, urea and creatinine, together with various demographic and biochemical data for 267 NIDDM patients (75 females, 192 males).

However, it is more informative to compare the means of different variables of the patients' characteristics classified by sex. The results are tabulated in Table 2.

Logistic regression analysis

Logistic regression is used for situations in which one wants to be able to predict the presence or absence of characteristics or outcomes based on values of a set of predictor variables. It is similar to a multiple linear regression model but is suited to models where the dependent variable is dichotomous. Thus the method is usually applied to the case when one considers the binary variable which gives the categories numerical values of 0 and 1, usually representing 'No' and 'Yes' respectively, so that the mean of these values in a sample of individuals is the same as the proportion of individuals with the characteristic.

Table 1. Summarized statistics of all the metric variables

Variable	N	Minimum	Maximum	Mean	Std. deviation
Age [year]	267	17	78	52.73	10.97
BMI [kg/m ²]	267	17.15	48.73	28.66	5.08
Cholesterol [mmol/l]	248	2.8	11.4	5.33	1.24
Creatinine [μmol/l]	257	44.00	176	86.00	17.25
Dia_BP [mm Hg]	262	58	120	85.08	10.00
HBA _{1c} [%]	265	6.7	19.3	11.2	2.4
HDL [mmol/l]	243	0.4	2.2	1.08	0.32
Height [m]	267	1.49	1.95	1.69	0.09
LDL [mmol/l]	239	0.7	7.5	3.25	1.06
MTT [mmol/l]	267	5.6	20.5	11.75	3.37
OGTT [mol/l]	267	5.8	22.8	12.0	3.5
Sys_BP [mmHg]	262	92	210	138.8	20.4
Triglyceride [mmol/l]	248	0.4	10.7	2.1	1.3
Urea [mmol/l]	261	2.2	11.5	5.4	1.3
Weight [kg]	267	45	135.5	81.5	14.7
Valid N [listwise]	232				

Table 2. Means of patient characteristics

Variable	Female			Male			p Value
	Mean	SD	N	Mean	SD	N	
Age	50.38	11.25	75	53.64	10.29	192	0.029
BMI	31.10	6.13	75	27.71	4.27	192	< 0.000
Cholesterol	5.56	1.30	71	5.23	1.35	177	0.059
Creatinine	73.02	12.48	71	90.95	16.65	186	< 0.000
Dia_BP	83.22	10.43	73	85.79	9.41	189	0.0620
HBA _{1c}	11.69	2.42	73	11.06	2.27	192	0.056
HDL	1.15	0.34	71	1.04	0.32	172	0.016
Height	1.59	0.066	75	1.72	0.079	192	< 0.000
LDL	3.45	1.03	71	3.15	1.07	168	0.048
MTT	12.42	3.35	75	11.49	3.36	192	0.042
OGTT	12.70	3.408	75	11.68	3.466	192	0.033
Sys_BP	139.30	22.31	73	138.58	19.46	189	0.800
Triglyceride	1.97	1.18	71	2.18	1.19	177	0.278
Urea	5.08	1.53	72	5.57	1.26	189	0.010
Weight	79.53	16.69	75	82.30	14.09	192	0.169

Now suppose that there are n diabetic patients for some of whom the health-related event (for instance, presence of proteinuria) has occurred. They are called successes, while the others are failures. Let $y_i = 1$ if the i^{th} individual is a success and $y_i = 0$ if the i^{th} individual is a failure. Suppose that for each of the n individuals, p independent variables x_{i1}, \dots, x_{ip} are measured. These variables can be qualitative, such as sex and race, or quantitative, such as blood pressure and body mass index. The problem now is to relate the independent variables x_{i1}, \dots, x_{ip} to the dichotomous dependent variable y_i .

One obvious method often suggested is the ordinary multiple linear regression technique. Assume that the y_j 's are normally distributed with mean P_i and variance σ^2 , and P_i , defined as the probability of success, or

$$\begin{aligned} P_i &= P(y_i = 1 \mid x_{i1}, \dots, x_{ip}) \\ 1 - P_i &= P(y_i = 0 \mid x_{i1}, \dots, x_{ip}) \quad i = 1, \dots, n \end{aligned} \quad (1)$$

is linearly dependent on x_{ij} 's. The model may be written as

$$P_i = \sum_{j=1}^p b_j x_{ij} \quad (2)$$

Then a least-squares technique is applied to estimate the coefficients b_j . Consequently, for a new individual patient, P_i can be estimated by substituting its x_{ij} values into Eq. (2). However, using this method and treating the dichotomous dependent variable as if it is quantitative, has at least two limitations. Firstly, the y_j 's are not normally distributed and hence the ordinary linear regression may not be validly applied in this situation. Secondly, it may also be possible that the least-square estimate for P_i obtained from Eq. (2) may have the result that the fitted value does not satisfy the condition $0 \leq P_i \leq 1$. Due to these limitations a more appropriate model, known as the logistic regression model, will be used to solve this kind of problem where the dependent variable is dichotomous.

The logistic regression model

The basic principle of logistic regression is much the same as for ordinary multiple regression. The main difference is that instead of developing a model that uses a linear combination of the values of a group of predictor variables to predict the value of a dependent variable, the group of predictor variables is used to predict a transformation of the dependent variable.

Thus in the linear logistic model, the dependence of the probability of success on the independent predictor variables is assumed to be

$$P_i = \frac{\exp\left(\sum_{j=1}^p b_j x_{ij}\right)}{1 + \exp\left(\sum_{j=1}^p b_j x_{ij}\right)} \quad (3)$$

and

$$1 - P_i = \frac{1}{1 + \exp\left(\sum_{j=1}^p b_j x_{ij}\right)} \quad (4)$$

Hence the logarithm of the ratio of P_i and $1 - P_i$, known as the logit transformation, is given by

$$\text{logit}(P_i) = \log \frac{P_i}{1-P_i} = \sum_{j=1}^p b_j x_{ij} \quad (5)$$

and is a simple linear function of the x_{ij} 's.

Eq. (5) is also called the log odds. The logistic regression coefficients b_j 's can be used to estimate odds ratio for each of the independent variables in the model. Thus from our model, if we wish to compare predictions for subjects with or without a particular characteristic, such as systolic blood pressure greater than 140 mm Hg, we will estimate $l_1 = \text{logit}(p_1)$ for one group of subjects and $l_2 = \text{logit}(p_2)$ for the other. Then we have

$$l_1 - l_2 = \text{logit}(p_1) - \text{logit}(p_2) = \log \left(\frac{p_1}{1-p_1} \right) - \log \left(\frac{p_2}{1-p_2} \right) = \log \left(\frac{p_1(1-p_2)}{p_2(1-p_1)} \right) \quad (6)$$

which is the logarithm of the odds ratio.

From the estimated regression Eq. (3) a predicted probability of success can be computed by substituting the values of the risk factors in the equation. Using these predicted probabilities, a goodness-of-fit test can be performed to test the hypothesis that the model fits the data adequately. Several such tests are applicable, such as the Pearson chi-square test, and the Hosmer-Lemeshow test, we are going to utilise them in testing the goodness-of-fit of the full model.

Results from the analysis of the diabetic patients' data

In this section we are going to utilize logistic regression to analyse the diabetic patients' data. The goal of the analysis is to investigate, by using logistic regression, which of the factors are predictive of proteinuria. In our data set we have 267 patients with some measure of their personal characteristics, such as age, sex, weight, height, and their fasting blood glucose, measured by oral glucose tolerance test (OGTT), or meal tolerance test (MTT), and the glycoslated hemoglobin (HbA_{1c}). Measurements are also made on their lipids level, such as cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), and triglyceride (TG). Moreover, their renal functions; such as urea and creatinine levels are recorded. Apart from these, their systolic and diastolic blood pressure, body mass index (BMI) and their smoking habit are also noted.

Full model

Extensive data analysis, using the logistic regression technique, reveals that among 267 patients, only 128 patients have records of presence/absence of proteinuria, hence these 128 patients' data will be utilized in the logistic regression. The logistic regression method is used to identify the most important risk factors and to predict the probability of proteinuria on the basis of these risk factors. By using MINITAB, the final result is tabulated in Fig. 1.

From Fig. 1 the procedure identifies that the most important risk factors for proteinuria (hence diabetic nephropathy) are mainly from lipid levels, namely, cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), and triglyceride (TG). Moreover, the other two risk factors identified are retinopathy and body mass index (BMI).

Binary Logistic Regression

NOTE: BEST FULL MODEL for the diabetic patients
Link Function: Logit

Response Information

Variable	Value	Count
PROT	1	28 (Event)
	0	100
	Total	128

128 cases were used
139 cases contained missing values

Logistic Regression Table

Predictor	Coef	StDev	Z	P	Odds Ratio	95% CI	
						Lower	Upper
Constant	-4.810	1.965	-2.45	0.014			
CHOL	1.4114	0.5860	2.41	0.016	4.10	1.30	12.93
HDL	-2.2020	0.9234	-2.38	0.017	0.11	0.02	0.68
LDL	-0.9621	0.5411	-1.78	0.075	0.38	0.13	1.10
TG	-1.3776	0.4527	-3.04	0.002	0.25	0.10	0.61
RET(2)	1.7119	0.7024	2.44	0.015	5.54	1.40	21.95
BWI	0.13619	0.04786	2.85	0.004	1.15	1.04	1.26

Log-Likelihood = -57.311
Test that all slopes are zero: G = 19.860, DF = 6, P-Value = 0.003

Goodness-of-Fit Tests

Method	Chi-Square	DF	P
Pearson	117.137	121	0.582
Deviance	114.622	121	0.646
Hosmer-Lemeshow	11.037	8	0.200

Fig. 1 Estimated coefficients for a linear regression model using data from diabetic patients

Validation of the model

In order to test the goodness of fit of the model, we refer to Fig. 1 which provides us with details of the test. In the first place we observed that when testing the null hypothesis that all slopes are zero, the G value is 19.860, with a *p* value of 0.03, hence we can conclude that at least one of the slope (that is, the risk factor) is significantly different from zero. Also from the Hosmer-Lemeshow test, the *p* value is 0.2, indicating that the data fits the model. Actually from the MINITAB output we observe that practically all the other two methods, namely the Pearson test and the Deviance test show that the model is a good-fit (that is, with all their *p* values greater than 0.05).

Now we can further investigate whether the data set contains any outlier. The best way to investigate this is by referring to the analysis of residuals. The delta deviance vs. probability plot is shown in Fig. 2. The plot is used to identify factor/covariate patterns that have not been fit well by the model. The delta deviance measures the change in the deviance goodness-of-fit statistic due to deleting a particular factor/covariate pattern. Now from the Fig. 2 we observe that all the data are distributed evenly and there are no particular outliers being noted. Hence we can conclude that there is no outlier being identified with the set of data.

Bias due to missing data

In order to investigate the bias due to missing data, it is better to divide the data set into two portions. One is for those data which are included in the model, and the other is not included. Then we can compare the mean of different characteristics of the two set of data, at baseline, and investigate the difference between them.

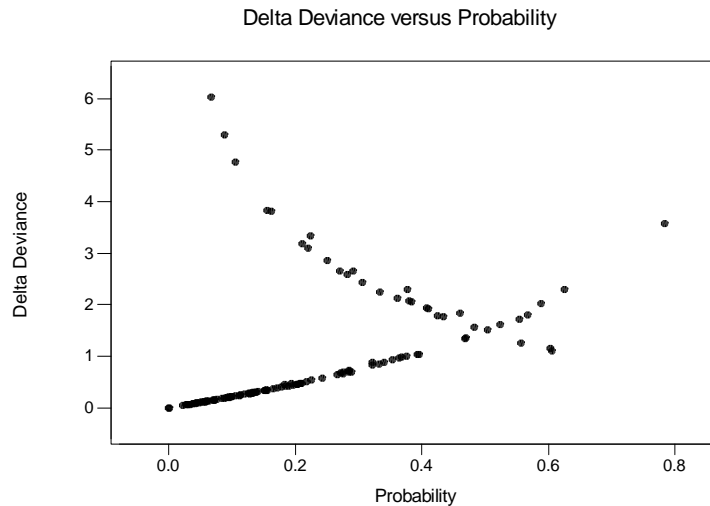


Fig. 2 Delta deviance versus probability

Table 3. Table of means of patients’ characteristics classified by included/not included in model

Variable	Included in model			Not included			p Value
	Mean	SD	N	Mean	SD	N	
Age	52.5	11.4	128	52.9	10.6	139	0.76
BMI	29.04	5.12	128	28.32	5.04	139	0.25
Cholesterol	5.05	1.00	128	5.62	1.40	120	0.00
Creatinine	88.2	16.7	126	83.9	16.65	186	0.043
Dia_BP	87.44	9.6	124	82.96	9.92	138	0.00
HBA _{1c}	87.44	9.6	124	82.96	9.92	138	0.00
HDL	1.135	0.342	128	1.01	0.298	115	0.028
Height	1.694	0.091	128	1.68	0.095	139	0.561
LDL	3.027	0.95	128	3.5	1.13	111	0.11
MTT	11.52	3.37	128	11.97	3.38	139	0.28
OGTT	11.7	3.49	128	12.21	3.59	139	0.237
Sys_BP	144.3	20.3	124	113.9	19.2	138	0.00
Triglyceride	1.96	1.24	128	2.29	1.47	120	0.061
Urea	5.35	1.41	128	5.53	1.34	133	0.289
Weight	83.1	14.8	128	80.1	14.6	139	0.1

Also for those characteristics presented as categorical data, we can use the chi-square test to find whether there is any association between those included in model and those not included, and the result is given in Table 4.

Now we discuss the results of Table 3 and Table 4 in terms of $p < 0.01$, due to the fact that there are so many variables under consideration. From Table 3 we observe that for the majority of the characteristics their mean values have no significant difference between the two groups, except only for cholesterol, diastolic BP, systolic BP, HBA_{1c}. Now the model we obtained consisted of the variables of BMI, cholesterol, HDL, LDL, TG, RET(2), and BMI, out of which only cholesterol shows a significant difference between the two groups of patients (that is, included/not included). As a matter of fact the mean value for cholesterol for

those not included is 10% higher than those included in the model. So this may be the only risk factor which needs further investigation as reflected from the data. While for all the other factors, the mean values show no significant difference between two groups. From Table 4 we also observe that for retinopathy, there is no significance between two groups, hence we can say that we are justified in using the model for diagnostic purposes for patients who are most likely to develop proteinuria with later onset of nephropathy.

Table 4. Table of chi-square test p values for categorical data classified by included/not included in model

Variables	Chi-square test p values
Sex	0.795
Smoke	0.001
Ret	0.411
Prot	0.076

However, it must be borne in mind that there may be some bias due to the missing data as we have seen that nearly half of the data have missing values, but as we have mentioned before, missing data are a common phenomena in collecting clinical data, and unfortunately we cannot do anything about it at the present stage.

Interpretation of results

In this chapter we have performed two kinds of data analysis. The first and preliminary one is the univariate analysis. Univariate analysis based on t -test or classification of the variables in contingency table in order to test the association of different variables with the status of presence/absence of proteinuria should provide us the information on which variables should be included into the experimental model.

From our results we observed that if the whole group of patients is taken into consideration, the only obvious risk factor for nephropathy so obtained is age. This is in accord with the literature (Lee et al., [4]). However, we know from Table 2 that there is a marked difference between the male and female characteristics from the patients' statistics classified by sex. Hence we suspect that sex may be a confounding factor. So it is beneficial to classify the patients' data by sex and perform further investigation. In doing so we discovered that if we classified the age into four categories and using chi-square test, the association between age and proteinuria is significant among male patients, while such association among female patients is considered to be non-significant. Hence this reinforces our conviction that sex may be a confounding factor.

Another possible risk factor of interest is BMI, for obesity should be associated with diabetes and nephropathy. However, such a hypothesis is not supported by the univariate data analysis. Even when the data are subdivided by sex, the results are still not significant. In fact, the only significant association observed is between retinopathy and BMI (Fig. 3).

Hypertension is another possible risk factor often mentioned in the literature. However, in our data analysis, only hypertension in terms of diastolic BP among female patients was found to have strong association with proteinuria. For hypertension in terms of systolic blood pressure, no such association with proteinuria is obtained.

Fat * RETINOPATHY * SEX Crosstabulation								
SEX	Fat	normal	Count	RETINOPATHY				Total
				absence	presence	moderate	serious	
Female		normal	Count	12	1	2	1	16
			% within Fat	75.0%	6.3%	12.5%	6.3%	100.0%
	fat >26.5	normal	Count	49	4	3	3	59
			% within Fat	83.1%	6.8%	5.1%	5.1%	100.0%
	Total	normal	Count	61	5	5	4	75
			% within Fat	81.3%	6.7%	6.7%	5.3%	100.0%
Male		normal	Count	58	5	16	6	85
			% within Fat	68.2%	5.9%	18.8%	7.1%	100.0%
	fat >26.5	normal	Count	92	3	7	5	107
			% within Fat	86.0%	2.8%	6.5%	4.7%	100.0%
	Total	normal	Count	150	8	23	11	192
			% within Fat	78.1%	4.2%	12.0%	5.7%	100.0%

Chi-Square Tests				
SEX		Value	df	Asymp. Sig. (2-sided)
Female	Pearson Chi-Square	1.176 ^a	3	.759
	N of Valid Cases	75		
Male	Pearson Chi-Square	9.422 ^b	3	.024
	N of Valid Cases	192		

a. 6 cells (75.0%) have expected count less than 5. The minimum expected count is .85.
b. 3 cells (37.5%) have expected count less than 5. The minimum expected count is 3.54.

Fig. 3 Two way table of BMI group and retinopathy group for diabetic patients classified by sex

When we subdivide the patients further according to smoking habit, we observe that the triglyceride level shows a significant difference between different proteinuria status (i.e. absence/presence of proteinuria). Hence lipid level does become a risk factor for nephropathy among some particular patients with certain characteristics. Table 5 shows that nearly all the significance difference between the patients with status of proteinuria are male. Hence we can conclude that male patients may be at higher risk of developing proteinuria or nephropathy than female patients.

Table 5. Summary statistics for variables from patients with different characteristics by proteinuria status

Patient characteristics	Variable	Proteinuria Status				p value
		No		Yes		
		Mean	SD	Mean	SD	
Male	Age	56.13	10.35	50.00	8.84	0.003
Male	Triglyceride	2.08	1.32	1.648	0.567	0.027
Smoker	Triglyceride	2.54	1.72	1.77	0.51	0.031
Male non-smoker	Age	56.40	11.18	51.19	8.06	0.046
Male non-smoker	MTT	11.59	3.55	9.71	2.39	0.019
Male smoker	Age	55.61	8.65	48.54	9.84	0.038
Male smoker	Triglyceride	2.48	1.84	1.70	0.45	0.055
Male hypertension (SBP)	Age	57.37	10.60	52.55	8.91	0.059
Male hypertension (DBP)	LDL	3.11	0.87	2.37	1.26	0.047

Now the result of the multivariate logistic regression shows that the risk factors for nephropathy are mainly associated with lipid levels, namely, cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), and triglyceride (TG). When compared

with the univariate analysis, only triglyceride is classified as risk factor among male smokers. Thus multivariate analysis enables us to include more variables under consideration. The significant association between lipid levels and nephropathy is supported by Boemi et al. [1] who conducted a study to examine the hypothesis that kidney function is an independent determinant of lipoprotein (a) [Lp(a)] concentrations in people with diabetes. They discovered that for both type 1 and type 2 patients, renal disease (i.e., macroalbuminuria) is a determinant of increased Lp(a) concentration. Thus it is not surprised to see that there is a strong association of proteinuria with lipids level in our data analysis.

The other two risk factors identified by logistic regression are BMI and retinopathy. Both were not revealed in the univariate analysis. As mentioned previously they may be only weakly associated with proteinuria and hence they were overlooked when univariate analysis was performed. Relatively high BMI can be associated with low physical exercise, obesity, and stress, which increase insulin demand [5].

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