VNU Journal of Science: Medical and Pharmaceutical Sciences

Journal homepage: https://js.vnu.edu.vn/MPS

Original Article

Applying Logistic Regression to Predict Diabetic Nephropathy Based on Some Clinical and Paraclinical Characteristics of Type 2 Diabetic Patients

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Abstract: Today, the incidence of type 2 diabetes mellitus is increasing rapidly on global. This disease is shown with many complications that significantly affect public health. One of them is kidney complications, which have a high incidence among diabetic patients in Vietnam (25.6-33.1%). Age, history of hypertension, and dyslipidemia are considered to be the main risk factors for diabetic nephropathy. Thus, early detection of these factors for kidney damage is significant for diagnosing, monitoring, treatment, and prognosis of diabetic patients. Our descriptive, cross-sectional study conducting on 120 diabetic patients at E Hospital has observed that blood cholesterol levels, HbA1c levels were independently related to eGFR decline below 60 mL/min/1.73m². From those data, an equation to predict the risk of diabetic kidney disease was estimated as $p = \frac{k}{1+k}$ with $k = e^{-56.333 + 0.704.[Chlesterol] + 0.469.[HbA1c]}$

Keyword: Type 2 diabetes, Diabetic nephropathy, Risk factor.

1. Introduction

The rapidly increasing incidence of diabetes makes diabetes one of the top health concerns in many countries worldwide. According to the International Diabetes Federation (IDF) 2019, there are 88 million people with diabetes in Southeast Asia. At 2045, it is estimated that this number will increase by 74% with 153 million people living with the disease [1]. Progressive

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diabetes causes severe complications for many body systems. In particular, kidney damage is a common complication with silent clinical symptoms in the early stage, which only manifests when the kidney function has declined, leading to chronic kidney disease [2-4]. Impaired renal function is a factor that aggravates other complications of diabetes and increases the mortality of the patient [4]. Therefore, early detection of kidney damage is crucial for diagnosing, monitoring, treating, and diagnosing diabetic patients. Many studies conducted in Vietnam and the world have shown many risk factors for diabetic kidney disease, such as the age of onset, prolonged duration, hypertension, dyslipidemia, hyperglycemia, and proteinuria [5, 6]. But it has no study predict the risk of kidney damage in the Vietnamese diabetes patients. Thus, we carried out this study to investigate some of the risk factors associated with diabetic nephropathy and building an equation to predict the risk of diabetic nephropathy based on them in a population of Vietnamese diabetic patients in a central hospital.

2. Objects and Research Methods

Study subjects: diabetic type 2 patient treated at General Internal Medicine Department - E Central Hospital.

Selection criteria: patient were diagnosed with type 2 diabetes (According to the American Diabetes Association Guidelines 2020) [7] and volunteered in research study.

Exclusion criteria: patient has one of the following cases: acute medical condition; other kidney diseases: kidney stones, nephritis, pyelonephritis,...

Time and location of the study: the study was conducted from May 2020 to December 2020, data were collected from the General Internal Medicine Department - E Hospital.

Research method: Descriptive, cross-sectional study.

Complete clinical information (Age, sex, weight, height, history of hypertension and diabetes mellitus), subclinical information (Creatinine, glucose, cholesterol, triglyceride, HDL, LDL blood levels).

Method of outcome assessment: estimated glomerular filtration rate (eGFR) based on blood creatinine calculated using formula MDRD (Modification of Diet in Renal Disease) [8].

$$eGFR_{cre} = 186.3 \times Scr^{-1,154} \text{ (mg/dL)} \times age^{-0,203} \times 0.742 \text{ (if female) [8]}$$

(eGFRcre: Estimated glomerular filtration rate based on Creatinine; Scre: serum creatinine concentration)

Standards used in research:

- BMI is calculated by the formula: $\frac{weight\ (kg)}{height\ (m) \times height\ (m)}$ [9]

- Criteria for increasing blood lipid according to NCEP III (National Cholesterol Education Program) [10]:

Table 1. Criteria for increasing blood lipid [10]

	Reference range	Pathological range
Total cholesterol	5.17 - 6.19 mmol/L (200 - 239 mg/dL)	≥6.2 mmol/L (≥ 240 mg/dL)
Triglycerides	1.69 - 2.25 mmol/L (150 - 199 mg/dL)	≥2.26 mmol/L (≥200 mg/dL)
HDL	≥ 1.03 mmol/L (≥ 40 mg/dL)	<1.03 mmol/L (<40 mg/dL)
LDL	3.34 - 4.09 mmol/L (130 - 159 mg/dL)	≥ 4.1 mmol/L (≥ 160 mg/dL)

- Reduced MLCT when eGFR<60 mL/min/1.73 m^2 [11].

Data processing: SPSS 26.0 software with appropriate statistical tests such as Kolmogorov-

Smirnov test, χ^2 test, T-test, ANOVA analysis, Mann-Whitney U test, Kruskal-Wallis test, regression analysis, and correlation analysis.

Table 2. General clinical characteristics

Features	Male ($\bar{x}$ ± SD)	Female ($\bar{x}$ ± SD)	Total ($\bar{x}$ ± SD)	p
Age (years)	66.0 ± 9.1	67.1 ± 8.1	66.6 ± 8.6	0.531[b]
BMI (kg/m^2)	22.9 ± 3.1	23.4 ± 3.1	23.2 ± 3.1	0.337[a]
Systolic blood pressure (mmHg)	131.0 ± 19.7	130.5 ± 26.4	130.7 ± 23.7	0.386[b]
Diastolic blood pressure (mmHg)	76.7 ± 9.7	74.7 ± 12.0	75.5 ± 11.0	0.097[b]
[a] Independent T-test; [b] Mann-Whitney U test				

3. Results

3.1. General Clinical Characteristics

Our study was conducted on 120 patients with 51 male and 69 female diagnosed with type 2 diabetes at Hospital E. After analyzing the data, we obtained the results of the general characteristics of the study subjects in Table 2.

The female patients had higher average age, BMI, and lower blood pressure than male patients, but the difference was not statistically significant (p> 0.05).

Table 3. General paraclinical characteristics

Features	Men ($\bar{x}$ ± SD)	Women ($\bar{x}$ ± SD)	Total ($\bar{x}$ ± SD)	p
Glucose (mmol/L)	11.2 ± 6.2	9.0 ± 4.0	10.0 ± 5.1	0.046[a]
Creatinin (µmol/L)	85.9 ± 18.4	69.1 ± 17.5	76.2 ± 19.7	<0.05[a]
eGFR (mL/phút/1.73 m^2)	87.5 ± 24.8	83.9 ± 22.6	85.4 ± 23.5	0.627[a]
Cholesterol (mmol/L)	4.5 ± 1.2	5.2 ± 1.3	4.9 ± 1.3	0.003[a]
Triglycerid (mmol/L)	2.4 ± 1.6	2.9 ± 2.1	2.7 ± 1.9	0.091[a]
HDL-C (mmol/L)	1.5 ± 0.7	1.8 ± 1.0	1.7 ± 0.9	0.044[a]
LDL-C (mmol/L)	2.0 ± 1.0	2.0 ± 1.1	2.0 ± 1.1	0.824[a]
eGFR: estimated glomerular filtration rate; [a] Mann-Whitney U test. HDL-C: High-density lipoprotein; LDL-C: Low-density lipoprotein.				

3.2. General Paraclinical Characteristics

The patients participated in the study were tested some blood biochemical inidcators. The obtained results showed in the Table 3.

Table 3 showed that the concentration of glucose, creatinine in male patients is significantly higher than female patients (with p=0.046 and p<0.05, respectively). The concentration of total cholesterol, triglycerides,

and HDL-C in blood at female group was higher than male group (p=0.003, p=0.091, and p=0.044). There was a similarity at both groups when comparing eGFR and LDL-C (p> 0.05).

Method of calculating eGFR based on serum creatinine concentration is an important indicator of renal function in patients. Therefore, we analyzed the eGFR and some clinical characteristics, the results are shown in Table 4.

Table 4. eGFR and some clinical factors

Features		eGFR (mL/min/1.73 m^2)	p
Gender	Men	87.5 ± 24.8	0.407
	Women	83.9 ± 22.6	
Age	< 60	99.0 ± 27.3	0.002
	≥ 60	82.4 ± 21.6	
Historical of hypertension	No	98.8 ± 26.7	< 0.001
	Yes	79.4 ± 19.3	

It was seen that there was a decrease in eGFR, which was evident in the subjects over 60 years old compared to the lower 60 years old group (p=0.002). The difference was also found in the group with a combination of hypertension and diabetes, with a decline in eGFR in this group (79.4 ± 19.3 mL/min/1.73m^2), while the eGFR recorded a normal result (98.8 ± 26.7 mL/min/1.73m^2) in the group without associated hypertension (p <0.001). It was not difference in eGFR between the two genders groups (p=0.047).

3.3 Between Risk Factors Diabetes with Two Groups of Patients Based on Estimated Glomerular Filtration Rate

According to KDIGO2020, the eGFR<60 mL/min/1.73m^2 is considered as indicator of the beginning kidney damage [12]. Therefore, we analyzed the relationship between some risk factors for kidney damage with two groups of patients classify based on eGFR<60 mL/min/1.73m^2 and eGFR ≥ 60 mL/min/1.73m^2. The results were presented in Tables 5, 6.

Table 5. Clinical and paraclinical factors and two group patients based on eGFR

Features	eGFR≥60 mL/min/1.73m^2	eGFR<60 mL/min/1.73m^2	p
Age	66.0 ± 8.7	72.6 ± 3.0	<0.001[a]
Duration of diabetes (years)	8.2 ± 7.4	11.7 ± 7.5	0.118[a]
Systolic blood pressure (mmHg)	129.9 ± 22.7	138.8 ± 31.0	0.314[a]
Diastolic blood pressure (mmHg)	74.9 ± 10.7	80.8 ± 12.9	0.101[a]
BMI (kg/m^2)	23.2 ± 3.1	23.1 ± 2.6	0.929[b]
Round the waist (cm)	88.1 ± 7.9	90.6 ± 12.3	0.397[b]
Waist (cm)	84.2 ± 6.8	83.4 ± 9.0	0.278[b]
Glucose (mmol/L)	10.0 ± 5.3	9.4 ± 2.3	0.454[a]
Cholesterol (mmol/L)	4.8 ± 1.2	5.7 ± 1.5	0.036[a]
Triglycerid (mmol/L)	2.7 ± 1.9	3.1 ± 1.7	0.234[a]
HDL-C (mmol/L)	1.7 ± 0.9	1.9 ± 1.1	0.462[a]
LDL-C (mmol/L)	2.0 ± 1.1	2.2 ± 1.3	0.707[a]
HbA1c (mmol/L)	9.4 ± 2.4	11.9 ± 3.7	0.014[b]
BMI – Body Mass Index; eGFR unit: mL/min/1,73m^2; [a]Chi Square Test; [b]T-test; [c]Fisher's Exact Test			

When analyzing some clinical features between the two groups with and without eGFR reduction, we found no effect of diabetes duration, diabetes, blood pressure, BMI, waist circumference, glucose concentration, triglyceride, HDL-C, and LDL-C concentrations on eGF (p>0.05). In addition, it was seen that the more eGFR decreased with the higher age (p<0.001), the higher the total cholesterol concentration (p=0.036) and the higher HbA1c concentration (p=0.014).

Table 6. Clinical factors and two groups of patients with and without a decrease in eGFR

n (%)		eGFR>60 (mL/min/1.73 m²)	eGFR<60 (mL/min/1.73 m²)	OR	CI 95%	p
Gender	Men	48 (94.1)	3 (5.9)	2.400	0.616 – 9.357	0.163^c
	Women	60 (87)	9 (13)			
Age (years)	<60	22 (100)	0 (0.0)	1.140	1.058 – 1.227	0.077^c
	≥60	86 (87.8)	12 (12.2)			
Historical of hypertension	No	37 (100)	0 (0.0)	1.169	1.070 – 1.277	0.009^c
	Yes	71 (85.5)	12 (14.5)			
Historical of hypertension (years)	<10	71 (94.7)	4 (5.3)	3.883	1.061 –14.210	0.037^c
	≥10	32 (82.1)	7 (17.9)			
Historical of the family with	No	70 (90.9)	7 (9.1)	1.316	0.391 – 4.429	0.440^a
	Yes	38 (88.4)	5 (11.6)			
Historical of smoking	No	96 (88.9)	12 (11.1)	0.889	0.832 – 0.905	0.265^c
	Yes	12 (100)	0 (0.0)			
Historical of drinking	No	88 (89.8)	10 (10.2)	0.880	0.179 – 4.332	0.618^c
	Yes	20 (90.9)	2 (9.1)			
BMI – Body Mass Index; eGFR's unit: mL/min/1.73m²; ^{a} Chi-Square Test; ^{b} T-test; ^{c} Fisher's Exact Test						

From the above results, we found that age, blood cholesterol, and concentration of HbA1c differ between 2 groups of eGFR that express kidney damage. Therefore, we conducted logistic regression analysis between the possibility of eGFR depletion below 60 mL/min/1.73m² with these factors. Results are showed d in Table 7.

Table 7. Several factors are associated with impaired eGFR

Factors	Regression coefficient	p	Percentage correct
Age	0.099	0.334	
Cholesterol	0.704	0.039	
HbA1c	0.469	0.038	93.8%
Hypertension	19.346	0.998	
Constant	-56.333	0.996	

Table 7 showed that age, hypertension, cholesterol concentration, HbA1c all increase the likelihood of eGFR decline below 60 mL/min/1.73m², in which age has the strongest impact then on cholesterol, HbA1c, and have hypertension. Of these factors, cholesterol and HbA1c levels were independently related to eGFR decline below 60 mL/min/1.73m² (p<0.05). From there, we have equations to predict the risk of kidney damage based on the eGFR subtype below 60 mL/min/1.73m2 with a correct prediction rate of 94.8% as follows:

Equation of risk of kidney damage $p = \frac{k}{1+k}$ with $k = e^{-56.333+ 0.704.[Cholesterol] + 0.469.[HbA1c]}$

4. Discussion

4.1. Clinical and Subclinical Characteristics of Research Subjects

Our study was conducted on 120 type 2 diabetic patients, the male: female ratio in our study was 1: 1.4. This ratio is different from many other studies in other provinces of

Vietnam. At Thai Nguyen National Hospital, research by B. T. T. Huong (2020), the ratio of male: female is 1.55: 1 [13]. At District 2 Hospital, Ho Chi Minh City, research by Le Xuan Truong (2019), the rate is 1: 2 [14]. This difference may be due to the characteristics of population, nutrition, and living of each region.

We found no difference between men and women in age, BMI, systolic blood pressure, and diastolic blood pressure (p>0.05). Meanwhile, there were differences in blood glucose, creatinine, total cholesterol, triglycerides and HDL-C levels. The mean blood glucose concentration in men was 11.2 ± 6.2 mmol/L, higher than that in women of 9.0 ± 4.0 mmol/L (p=0.046). This result is consistent with the observations on the changes by age of the mean glucose levels of men and women by Yi Sang Wook (2017). Accordingly, in general, men and women have the same mean blood glucose levels at the age of 18 to 23. Then, men have higher blood glucose levels than women until the age of 72 to 73, female blood glucose levels become higher than men [15].

Mean serum creatinine levels in men (85.9 ± 18.4 µmol/L) were higher than in women (69.1 ± 17.5 µmol/L) with p <0.05. This is easily explained that there are differences in weight and muscle mass in men and women, leading to differences in creatinine levels by sex. In contrast, the total cholesterol levels of women (5.2 ± 1.3 mmol/L) were higher than that in men (4.5 ± 1.2 mmol/L) (p=0.003), the triglyceride levels in women also higher than in men (2.9 ± 2.1 mmol/L compared with 2.4 ± 1.6 mmol/L). This result is consistent with the hypothesis that after menopause, the concentration of total cholesterol and triglyceride in women tends to increase higher [16, 17]. Blood HDL-C levels in women were reported higher than in men throughout their lifetime, similar to our results when we obtained HDL-C levels in women of 1.8 ± 1.0. mmol/L, while this result for men is 1.5 ± 0.7 mmol/L with p=0.044 [16].

4.2. Some Risk Factors and Decrease of eGFR in Type 2 Diabetic Patients

Many studies conducted in Vietnam and over the world have shown some risk factors for diabetic kidney disease such as age, diabetes duration, hypertension, dyslipidemia, elevated blood sugar, and proteinuria [5, 6].

According to KDIGO 2012, the GFR<60 mL/min/1.73m^2 is the sign of starting kidney damage [11]. Thus, we analyzed some clinical and paraclinical factors between two groups which classify by eGFR (eGFR<60 mL/min/1.73m^2 and eGFR>60 mL/min/1.73m^2). There was no difference in sex and diabetes duration between these two groups with p=0.163 and p=0.118. (Table 5, 6). This result is similar to the results of Plazhy (2017) [18].

Mean age of patients with eGFR<60 mL/min/1.73m^2 was clearly higher than the patient's group with eGFR $\geq$ 60 ml/min/1.73m^2 with p<0.001. In addition, the mean eGFR was 99.0 ± 27.3 mL/min/1.73 m^2 in the under 60 years old group, while this index was 82.4 ± 21.6 mL/min/1.73m^2 in over 60 years old group (p=0.006). It can be seen that the glomerular filtration rate decreases with age. After the age of 40, the level of glomerular filtration in normal people tends to decrease gradually and increase rapidly after 60 years of age [19]. Studies in the laboratory have observed some biochemical deterioration in aging kidney cells, including fewer mitochondria, lower enzyme levels, and ATPase activity, decreased sodium transport, and oxygen consumption and decreased renal tubular transport [20]. In diabetic patients, high blood sugar levels affect the glomerular vessels, there are nephrons disappear and glomerular filtration cells also impaired function. These problems lead to damage to the renal tubules and decrease eGFR.

The patients with a history of hypertension also decrease in eGFR comparing with those without a history of hypertension with p < 0.001. This result showed that people with a history of hypertension have a higher risk of impaired eGFR less than 60 mL/min/1.73m^2 than

those without hypertension. Besides, in the diabetic patient groups with a history of hypertension over 10 years, the risk of kidney damage increased by 3.883 times compared to the other patients (p=0.037). This is evidenced by the results of Giacomo Zoppini performed in 2012 on patients with type 2 diabetes who have hypertension, microalbuminuria, eGFR decline 1 ± 0.1 mL/min/1.73m^2 per year, whereas in those patients without hypertension, eGFR decline 0.3 ± 0.1 mL/min/1.73m^2 per year [21].

Hyperlipidemia are one of the important factors contributing to change the development of kidney damage in diabetic kidney disease [22]. Accordingly, as energy intake gradually exceeds the body's ability to store fat in adipose tissue, circulating lipids from various sources flow into non-fat tissue, such as muscles, liver, kidneys, and pancreas [23]. In the kidneys, lipids can be deposited in most types of cells, from mesoderm to shell cells and proximal tubular epithelial cells. Furthermore, lipid concentrations continue to increase with the progression of kidney damage [24]. Thus, we compared the mean blood cholesterol levels between 2 groups of eGFR. The results showed that blood cholesterol levels were significantly higher in group patients with eGFR<60 mL/min/1.73m^2 than in other patient groups (p=0.036). Also, high triglycerides have also been linked to impaired renal function in diabetic nephropathy [25, 26]. Therefore, we compare eGFR between 2 groups with increased and no hypertriglyceridemia. However, there is no correlation between triglyceride concentration and eGFR in our study.

4.3. The Equation to Predict the Risk of Diabetic Kidney Disease

Predicting the progression of diabetic nephropathy is an important and challenging matter. In many countries, diabetes is the main cause of end-stage kidney disease, and 1/4 to 1/2 diabetic patients will progress to chronic kidney disease [27]. Many studies have been done to give predictive models of diabetic kidney damage based on patients' clinical and sub-clinical indicators. Research by Dan Dan Miao et al performed in 2017 on 11,771 Chinese people introduced models predict kidney disease risk based on indicators of age, place of residence, BMI, HDL-C, creatinine, hypertension, dyslipidemia, diabetic retinopathy, dietary control, and daily physical activity [28]. Another study by Robert G. Nelson (2019) on 5,222,711 subjects from 34 multinational studies obtained a model that predicts an estimated 5-year impaired eGFR in diabetic patients based on diabetes medication factors, HBA1c, age, sex, race/ethnicity, eGFR, history of cardiovascular disease, history of smoking, hypertension, sBMI and albuminuria. Both models demonstrate high predictability and correction in diverse populations [29].

In our study, we recognized that the factors of age, cholesterol concentration, and history of hypertension were different between the two groups of eGFR. We conducted a logistic regression analysis between the possibility of impaired eGFR with these factors. Results were shown in Table 7. By the prediction equation, it is possible to estimate the probability of kidney damage based on the patient's age, cholesterol level, and history of hypertension or not, with a correct prediction of 93.8 %.

Although it is simple and convenient for clinical application, our predictive model has many deficiencies due to the small sample size and the factors that show a correlation with the decrease of eGFR. Thus, it is necessary to conduct research with larger sample sizes, extensive studies and manage more of the risk factors.

5. Conclusions

Research conducted on 120 type 2 diabetic patients showed blood Cholesterol, HbA1c levels are independently related to the impairment of eGFR. Besides, hypertensive patients with a history of over 10 years increase

the likelihood of reduced eGFR $<60mL/min/1.73m^2$ higher 3.883 times than other patients. The risk of diabetic kidney disease is predicted by the equation $p = \frac{k}{1+k}$ with $k = e^{-56.333+0.704.[cholesterol]+0.469.[HbA1c]}$, the ability to predict correctly is 93.8%.

Acknowledgements

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