Hirosaki Med. J. **65**：65—73, 2014

ORIGINAL ARTICLE

MEASUREMENT OF ESTIMATED GLOMERULAR FILTRATION RATE IS USEFUL IN STROKE PATIENTS

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Abstract Background: Chronic kidney disease (CKD) is a major worldwide public health problem. Although CKD is widely known to cause stroke, evaluation of renal function in stroke patients is difficult.
Purpose: We aimed to determine the prevalence of CKD in stroke patients and demonstrate the validity of estimated glomerular filtration rate (eGFR) measurement to assess renal function in patients after stroke.
Subjects and Methods: We examined the prevalence of CKD in 545 stroke patients and assessed correlations between eGFR and biochemical data, prevalence of hypertension, diabetes mellitus, hypercholesterolemia, and atrial fibrillation (AF).
Results: Of the 545 patients, 178 (32.8%) had CKD with a low eGFR (<60 mL/min/1.73 m^2). eGFR was negatively correlated with age, serum uric acid and creatinine concentrations, and positively correlated with hemoglobin levels. Moreover, eGFR was correlated with the prevalence of hypertension and AF, but not diabetes mellitus or hypercholesterolemia.
Conclusions: High prevalence of CKD was observed in stroke patients. Measurement of eGFR can be useful in evaluating renal function in stroke patients.

Hirosaki Med. J. **65**：65—73, 2014

Key words: CKD; stroke; eGFR; hypertension; atrial fibrillation.

原　著

脳卒中患者において推定糸球体濾過値の有用性について

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抄録　背景：慢性腎臓病(CKD)は世界的な公衆衛生的問題であり，CKDは脳卒中発症の危険因子であることが明らかとなっているが，脳卒中患者の腎機能を評価することは一般に困難である．
目的：本研究は，脳卒中患者の腎機能評価に推定糸球体濾過率(eGFR)を用いることの妥当性を明らかにすることを目的とした．
対象と方法：対象は脳卒中で545例である．分析は，eGFRと生化学的データ，高血圧症，糖尿病，高コレステロール血症，心房細動の有病率との関連を評価した．
結果：178名(32.8％)はCKDの診断基準の一つであるeGFRが60 mL/min/1.73m^2)以下であった．eGFRは，年齢と血清尿酸値との間に負の相関，血清ヘモグロビン値とは正の相関を示した．eGFRは，高血圧と心房細動の有病率との相関はあったが，糖尿病や高コレステロール血症の有病率とは相関はみられなかった．
結論：脳卒中患者ではCKDの有病率が高い．また，eGFRの測定は，脳卒中患者の腎機能評価に有用である．

弘前医学　**65**：65—73, 2014

キーワード：慢性腎臓病；脳卒中；推定糸球体濾過値；高血圧；心房細動．

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Received for publication, November 20, 2013
Accepted for publication, December 16, 2013

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平成25年11月20日受付
平成25年12月16日受理

Introduction

Chronic kidney disease (CKD) is a major worldwide public health concern as it is associated with adverse outcomes such as kidney failure, cardiovascular disease (CVD), and premature death[1]. The number of patients with CKD is increasing despite recent progress in biomedical sciences. The global prevalence of CKD is estimated to be as high as 500 million[3, 4], and in Japan, there are approximately 13.3 million patients with CKD. Many prospective epidemiologic studies have shown that patients with CKD have high risk of developing CVD and stroke, although CKD is not considered a conventional cardiovascular risk factor[5, 6]. Early detection and early treatment of CKD are thus important.

Few studies have reported on the relationship between renal function and stroke. Accurate assessment of renal function is very important in providing proper medical treatment and nursing care; however, an evaluation of renal function is difficult in stroke patients, due to the presence of post-void residual urine associated with neurological disorders. Moreover, it is difficult for elderly patients to collect urine samples in a timed manner, and thus a clearance test is not easily performed to assess renal function. Recently, estimated glomerular filtration rate (eGFR), an easily calculated and useful staging index of CKD proposed by the Japanese Society of Nephrology, was recommended for use in renal function evaluations. An appropriate evaluation of renal function in stroke patients will help promote better nursing care, diet, exercise, daily life guidance, and self-management, but the difficulty lies in comparing eGFR values with clearance test results in these patients.

The purpose of this study was to determine the associations between eGFR and various data in stroke patients, and to demonstrate the prevalence of CKD as well as the validity of eGFR measurement.

Subjects and Methods

Subjects

Between June 2012 and February 2013, 545 patients (mean age ± SD, 72.3 ± 12.3 years; men, 55.0%) who presented with stroke symptoms within two months were treated at the Hirosaki Stroke and Rehabilitation Center. Data including medical history, current medication use, and clinical symptoms were collected using patient medical records from the time of hospitalization.

Measurements

In each patient, eGFR was calculated based on the serum creatinine value (S-Cr) and age using the abbreviated Modification of Diet in Renal Disorder (MDRD) Study equation modified for Japanese subjects, and further improved by including insulin clearance, as follows[7]:

if male: eGFR (mL/min/1.73 m^2) =194 × $Cr^{-1.094}$ × $Age^{-0.287}$

if female: eGFR (mL/min/1.73 m^2) =194 × $Cr^{-1.094}$ × $Age^{-0.287}$ × 0.739

Although eGFR is a simple method, the accuracy is high and values fall within the actual GFR value ± 30% measured in 75% of patients[7].

We examined the prevalence of CKD among our patients. CKD criteria consist of findings that suggest renal injury, such as abnormal urinalysis, abnormal renal imaging, abnormal blood biochemistry, abnormal renal histology, and low GFR (<60 mL/min/1.73 m^2)[8]. In this study, urinalysis was not carried out in many patients, and patients with only a decrease in eGFR (<60 mL/min/1.73 m^2) were defined as having CKD.

We examined correlations between eGFR

and age, hemoglobin levels, and serum uric acid and creatinine concentrations.

We divided patients according to their eGFR values and compared various data between groups with eGFR ≥60 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2, between groups with eGFR ≥50 mL/min/1.73 m^2 and <50 mL/min/1.73 m^2, and between groups with ≥40 mL/min/1.73 m^2 and <40 mL/min/1.73 m^2.

Hypertension was defined as high blood pressure with a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg; patients who were treated with anti-hypertensive agents or those with a history of hypertension were also included.

Diabetes mellitus was defined as a plasma glucose level ≥200 mg/dL and HbA1c (NGSP) ≥6.5%. Patients with a history of diabetic treatment were also considered to have diabetes mellitus.

Hypercholesterolemia was defined as a serum cholesterol >220 mg/dL, high-density lipoprotein cholesterol (HDL) <40 mg/dL, or low-density lipoprotein cholesterol (LDL) ≥140 mg/dL. Patients with a history of hypercholesterolemia treatment were also considered to have hypercholesterolemia.

Atrial fibrillation (AF) was defined as presence of AF in electro cardiogram. Patients with a history of AF treatment were also considered to have AF.

Statistical analyses

Data are expressed as mean ± SD unless otherwise indicated. The unpaired t-test or unpaired Mann-Whitney test was used to evaluate differences in mean values, and the chi-square test was used to evaluate differences in proportions. Correlation analysis was performed to examine the relationships between renal deterioration and associated factors. $P<0.05$ was considered statistically significant. All statistical analyses were performed using SPSS version 21 software (SAS Institute Inc., Cary, NC).

Ethical Considerations

The study protocols were approved by the Ethics Committee of Hirosaki University, and patient informed consent was waived.

Results

The characteristics of 545 patients are shown in Table 1. Of the 545 patients, 455 (83.5%) were over 60 years of age, 470 (86.2%) had hypertension, 178 (32.7%) had diabetes mellitus, 337 (61.8%) had hypercholesterolemia, 152 (27.9%) had atrial fibrillation (AF), and 178 (32.7%) had a low eGFR <60 mL/min/1.73 m^2. The types of stroke were ischemic stroke in 413 (75.8%), intracerebral hemorrhage in 103 (18.9%), and others in 29 (5.3%). Two hundred

Table 1 Patient characteristics

Total nunber of subjects	n=545(%)
Sex (male)	300(55.0)
Age (years)	72.3 ± 12.3
30-39	4(0.7)
40-49	25(4.6)
50-59	61(11.2)
60-69	107(19.6)
70-79	164(30.1)
80-89	163(29.9)
90-95	21(3.9)
Hypertension	470(86.2)
Diabetes	178(32.7)
Hypercholesterolemia	337(61.8)
AF	152(27.9)
BMI (kg/m^2)	22.87 ± 3.9
Uric acid (mg/dL)	5.47 ± 1.8
Hemoglobin (g/dL)	13.57 ± 2.1
Serum albumin (g/dL)	4.12 ± 1.8
eGFR (ml/min/1.73 m^2)	68.36 ± 22.1
Serum creatinine (mg/dL)	0.87 ± 0.6
eGFR (ml/min/1.73 m^2)	
≥60	367(67.3)
<60	178(32.7)
Stroke type	
Ischemic stroke	413(75.8)
Intracerebral hemorrhage	103(18.9)
Other	29(5.3)
Medical history of stroke	220(40.4)

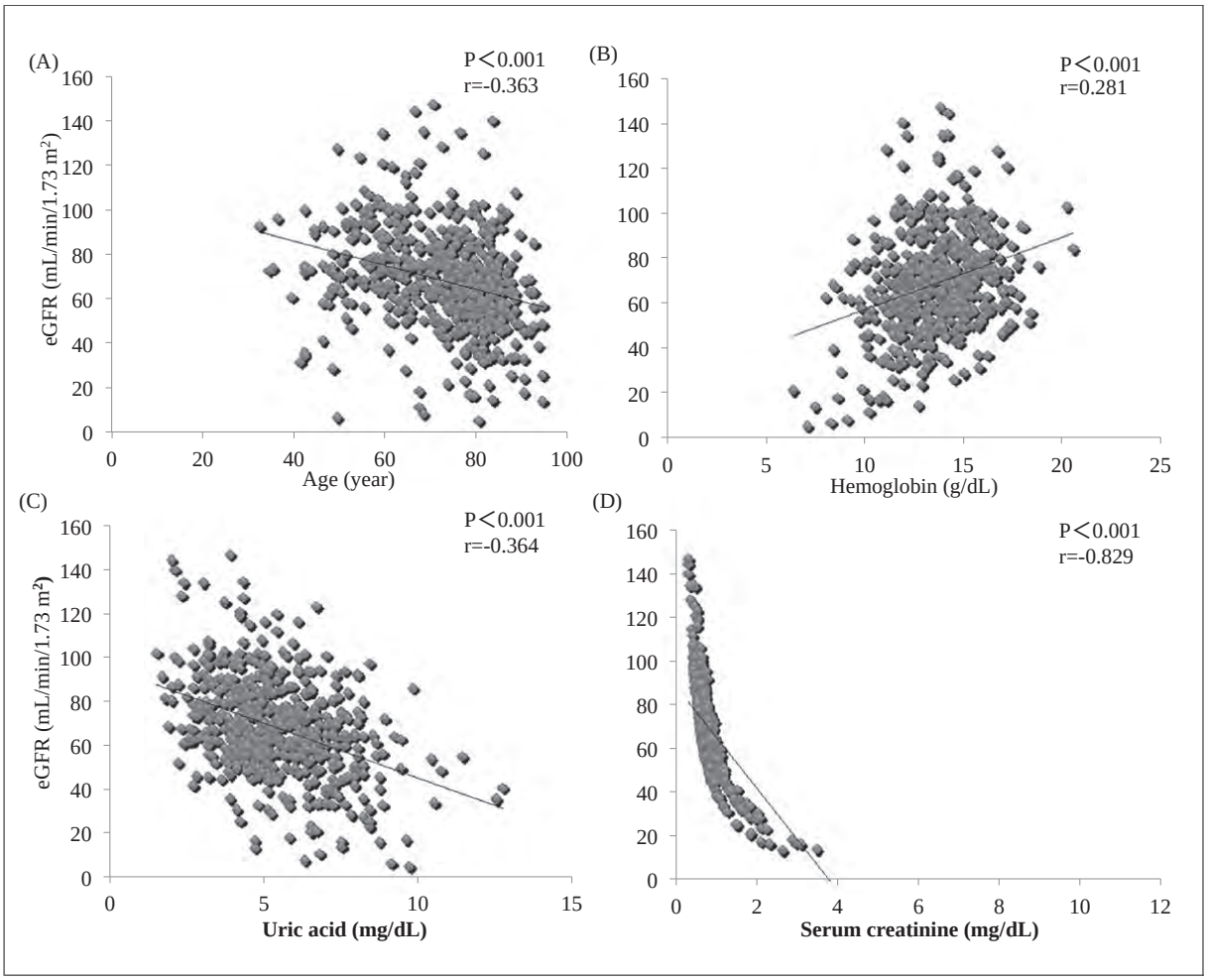

Figure 1. Correlation between eGFR and age (A), hemoglobin (B), uric acid (C), and serum creatinine (D).

and twenty (40.4%) patients had a history of previous stroke.

Of the 545 patients, 178 (32.8%) had CKD with a low eGFR (<60 mL/min/1.73 m^2).

Correlations between eGFR and age, hemoglobin levels, uric acid concentrations, and serum creatinine levels are shown in Figure 1. eGFR was negatively correlated with age (Fig 1A), uric acid concentrations (Fig 1C), and serum creatinine levels (Fig 1D), and positively correlated with hemoglobin levels (Fig 1B).

Comparisons between the group with eGFR ≥60 mL/min/1.73 m^2 and the group with eGFR <60 mL/min/1.73 m^2 are shown in Table 2. The group with lower eGFR (<60 mL/min/1.73 m^2) showed a higher median age (71.0 vs. 80.0 year, p<0.001), higher prevalence of AF (22.3% vs. 39.3%, p<0.001), higher concentration of uric acid (5.0 mg/dL vs. 6.0 mg/dL, p<0.001), and lower level of hemoglobin (13.9 g/dL vs. 13.0 g/dL) than the group with higher eGFR (≥60 mL/min/1.73 m^2). There were no significant differences in sex, body mass index (BMI), prevalence of diabetes mellitus, hypertension, hypercholesterolemia, history of previous stroke, and HbA1c levels between the two groups.

Comparisons between the group with eGFR ≥50 mL/min/1.73 m^2 and the group with eGFR <50 mL/min/1.73 m^2 are shown in Table 3. The group with lower eGFR (<50 mL/min/1.73 m^2) showed a higher median age (73.0 vs. 81.0 year, p<0.001), higher prevalence of hypertension

Table 2 Comparison of baseline characteristics of subjects between eGFR ≥60 mL/min/1.73 m^2 and < 60 mL/min/1.73 m^2.

		eGFR (mL/min/1.73 m^2)		
		≥60	<60	
		n = 367	*n* = 178	P value
Median age (years)		71.0 (61.0 – 79.0)	80.0 (73.8 – 84.0)	< 0.001
Sex (Male)[a]	(%)	208 (56.7)	92 (51.7)	0.272
BMI (kg/m^2)		22.8 (20.5 – 25.0)	22.4 (19.7 – 25.0)	0.126
Hypertension[a]	(%)	310 (84.5)	160 (89.9)	0.085
Diabetes mellitus[a]	(%)	121 (33.0)	57 (32.0)	0.825
Hypercholesterolemia[a]	(%)	226 (61.6)	111 (62.4)	0.861
AF[a]	(%)	82 (22.3)	70 (39.3)	< 0.001
Medical history of stroke[a]	(%)	145 (39.5)	75 (42.1)	0.558
HbA1c (%)		5.9 (5.6 – 6.3)	5.9 (5.5 – 6.33)	0.655
Total protein (g/dL)		7.0 (6.6 – 7.4)	7.0 (6.6 – 7.33)	0.128
Hemoglobin (g/dL)		13.9 (12.5 – 15.2)	13.0 (11.6 – 14.3)	< 0.001
Serum creatinine (mg/dL)		0.69 (0.59 – 0.80)	1.01 (0.84 – 1.28)	< 0.001
Uric acid (mg/dL)		5.0 (4.0 – 6.2)	6.0 (4.8 – 7.4)	< 0.001

Mann-Whitney test
[a]Chi-square tests

(84.6% vs. 93.2%, p=0.023), higher prevalence of AF (24.7% vs. 41.7%, p<0.001), higher concentration of uric acid (5.0 mg/dL vs. 6.8 mg/dL, p<0.001), and lower level of hemoglobin (13.9 g/dL vs. 12.4 g/dL, p<0.001) than the group with higher eGFR (≥50 mL/min/1.73 m^2). There were no significant differences in sex, BMI, prevalence of diabetes mellitus, hypercholesterolemia, history of previous stroke, and HbA1c levels between these two groups.

Comparisons between the group with eGFR ≥40 mL/min/1.73 m^2 and the group with eGFR <40 mL/min/1.73 m^2 are shown in Table 4. The group with lower eGFR (<40 mL/min/1.73 m^2) showed a higher median age (74.0 vs. 81.0 year, p<0.001), higher prevalence of hypertension (85.3% vs. 95.7%, p=0.048), higher concentration of uric acid (5.1 mg/dL vs. 7.1 mg/dL, p<0.001), and lower level of hemoglobin than the group with higher eGFR (≥40 mL/min/1.73 m^2). There were no significant differences in sex, BMI, prevalence of diabetes mellitus, hypercholesterolemia, AF, history of previous stroke, total protein, and HbA1c levels between these groups.

Discussion

CKD criteria consist of findings that suggest renal injury, such as abnormal urinalysis, abnormal renal imaging, abnormal blood biochemistry, abnormal renal histology, and low

Table 3 Comparison of baseline characteristics of subjects between eGFR ≥50 mL/min/1.73 m^2 and < 50 mL/min/1.73 m^2.

		eGFR (mL/min/1.73 m^2)		
		≥50	<50	
		n = 442	*n* = 103	P value
Median age (years)		73.0 (62.0 – 80.0)	81.0 (74.0 – 85.0)	< 0.001
Sex (Male)[a]	(%)	246 (55.7)	54 (52.4)	0.553
BMI (kg/m^2)		22.8 (20.4 – 25.0)	22.1 (19.6 – 24.9)	0.102
Hypertension[a]	(%)	374 (84.6)	96 (93.2)	0.023
Diabetes[a]	(%)	146 (33.0)	32 (31.1)	0.702
Hypercholesterolemia[a]	(%)	275 (62.2)	62 (60.2)	0.703
AF[a]	(%)	109 (24.7)	43 (41.7)	< 0.001
Medical history of stroke[a]	(%)	175 (39.6)	45 (43.7)	0.445
HbA1c (%)		5.9 (5.6 – 6.3)	5.9 (5.6 – 6.4)	0.769
Total protein (g/dL)		7.0 (6.7 – 7.4)	6.9 (6.5 – 7.3)	0.021
Hemoglobin (g/dL)		13.9 (12.4 – 15.2)	12.4 (11.4 – 13.7)	< 0.001
Serum creatinine (mg/dL)		0.71 (0.61 – 0.83)	0.77 (0.64 – 0.92)	< 0.001
Uric acid (mg/dL)		5.0 (4.1 – 6.2)	6.8 (5.2 – 7.9)	< 0.001

Mann-Whitney test
[a]Chi-square tests

GFR (<60 mL/min/1.73 m^2)[8]. Recently, eGFR has been used as GFR, given a good correlation between eGFR and actual measured GFR values[7]. In this study, urinalysis was not carried out in many patients, and patients with only a decrease in eGFR (<60 mL/min/1.73 m^2) were defined as having CKD.

Renal function is a very important barometer of health that medical staff members need to know in order to determine appropriate diet therapy, patient guidance, degree of physical activity, and amount of medicine. In stroke patients, a clearance test is very difficult to perform due to the presence of post-void residual urine and problems associated with collection of a timed urine specimen. Therefore, measurement of eGFR to assess renal function can be very useful in clinical settings.

Low eGFR (<60 mL/min/1.73 m^2) is an independent risk factor for ischemic and hemorrhagic stroke, with a relative risk of 1.4 to 2.0[5, 6]. In this study, the prevalence of low eGFR (<60 mL/min/1.73 m^2) was 32.7%, which is much higher than that in the general Japanese population (6.8%)[9], and close to the reported prevalence (29.7%)[10] among acute stroke patients. Moreover, the prevalence of low eGFR (<60 mL/min/1.73 m^2) was significantly correlated with age, as previously reported[10]. In this study, eGFR was negatively correlated with age in stroke patients, and positively correlated with hemoglobin levels. Renal anemia is known

Table 4 Comparison of baseline characteristics of subjects between eGFR ≥40 mL/min/m^2 and <40 mL/min/m^2.

		eGFR (mL/min/1.73 m^2)		
		≥40	<40	
		$n=498$	$n=47$	P value
Median age (years)		74.0 (63－81)	81.0 (74－85)	＜0.001
Sex (Male)[a]	(%)	273 (54.8)	27 (57.4)	0.729
BMI (kg/m^2)		22.8 (20.3－25.0)	22.1 (19.7－25.1)	0.384
Hypertension[a]	(%)	425 (85.3)	45 (95.7)	0.048
Diabetes[a]	(%)	163 (32.7)	15 (31.9)	0.909
Hypercholesterolemia[a]	(%)	309 (62.0)	28 (59.6)	0.185
AF[a]	(%)	135 (27.1)	17 (36.2)	0.185
Medical history of stroke[a]	(%)	196 (39.4)	24 (51.1)	0.188
HbA1c (%)		5.9 (5.6－6.4)	5.9 (5.4－6.2)	0.435
Total protein (g/dL)		7.0 (6.6－7.4)	6.9 (6.4－7.3)	0.101
Hemoglobin (g/dL)		13.8 (12.4－15.0)	11.6 (10.2－13.1)	＜0.001
Serum creatinine (mg/dL)		0.74 (0.62－0.87)	1.58 (1.44－2.11)	＜0.001
Uric acid (mg/dL)		5.1 (4.2－6.4)	7.1 (5.9－8.3)	＜0.001

Mann-Whitney test
[a]Chi-square tests

to progress as renal function decreases, as renal injury leads to abnormal erythropoietin production and decreased red blood cells.

The concentration of uric acid was negatively correlated with eGFR, similar to the results of previous studies. Uric acid is the most sensitive marker of renal impairment. Hyperuricacidemia first appears with a decline in renal function. Thus, eGFR properly reflects renal function in stroke patients, as well as in other diseases.

The prevalence of AF or hypertension was significantly higher in patients with a low eGFR. Several clinical and population-based studies have shown that the prevalence of AF is independently associated with decreased eGFR[11-13]. A recent study reported that decreased eGFR is associated with an increased risk of subsequent new AF onset in a large-scale community-based cohort[14].

The presence of AF could be related to cardiogenic cerebral embolism. Hypertension is closely related to renal function. The prevalence of hypertension increases as renal function decreases, while hypertension itself decreases renal function. In this study, the prevalence of hypertension increased with a decrease in eGFR in stroke patients. However, it remains unknown whether hypertension caused a decrease in eGFR, or decreased eGFR induced hypertension. Elderly patients showed decreased eGFR; therefore, age may be related to the high prevalence of hypertension.

The prevalence of hypercholesterolemia and diabetes mellitus had no significant effect on eGFR.

Rule and Glassock described criteria for choosing the best equation to estimate GFR, which are 1) accuracy in estimating a measured GFR; 2) optimal discrimination of clinical outcomes; and 3) association with CKD risk factors and outcomes similar to that of measured GFR. Therefore, we think that measurement of eGFR in stroke patients can be validated[15].

In conclusion, the prevalence of CKD was about 30% in stroke patients, which was significantly higher than that in the general population. eGFR correlated with age, hemoglobin levels, serum uric acid concentrations, and the prevalence of hypertension and AF in stroke patients. Therefore, low eGFR is thought to reflect risk of arteriosclerosis in stroke patients. Measurement of eGFR is thus useful in evaluating renal function in stroke patients, based on which appropriate care can be provided.

Acknowledgements

The authors are grateful to Mr. Osamu Tatebayashi and Ms. Ayako Abo for their technical assistance and data provided. We also would like to express our gratitude to staffs of the Hirosaki Stroke and Rehabilitation Center for their cooperation.

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