J Atheroscler Thromb, 2018; 25: 570-579.
http://doi.org/10.5551/jat.42812

Original Article

The Association between Glomerular Filtration Rate Estimated on Admission and Acute Stroke Outcome: The Shiga Stroke Registry

Aryandhito Widhi Nugroho[1, 2, 3], Hisatomi Arima[4, 5], Itsuko Miyazawa[6], Takako Fujii[1], Naomi Miyamatsu[7], Yoshihisa Sugimoto[8, 9], Satoru Nagata[9], Masaru Komori[10], Naoyuki Takashima[5], Yoshikuni Kita[5, 11], Katsuyuki Miura[3, 5] and Kazuhiko Nozaki[1, 3]

[1]Department of Neurosurgery, Shiga University of Medical Science, Otsu, Japan
[2]Department of Neurosurgery, University of Indonesia, Jakarta, Indonesia
[3]Center for Epidemiologic Research in Asia, Shiga University of Medical Science, Otsu, Japan
[4]Department of Preventive Medicine and Public Health, Faculty of Medicine, Fukuoka University, Fukuoka, Japan
[5]Department of Public Health, Shiga University of Medical Science, Otsu, Japan
[6]Department of Medicine, Shiga University of Medical Science, Otsu, Japan
[7]Department of Clinical Nursing, Shiga University of Medical Science, Otsu, Japan
[8]Department of Cardiovascular and Respiratory Medicine, Shiga University of Medical Science, Otsu, Japan
[9]Department of Medical Informatics and Biomedical Engineering, Shiga University of Medical Science, Otsu, Japan
[10]Department of Fundamental Biosciences, Shiga University of Medical Science, Otsu, Japan
[11]Department of Nursing Science, Tsuruga Nursing University, Tsuruga, Japan

***Aim*: Although renal dysfunction has been identified as a novel risk factor affecting stroke prognosis, few have analyzed the association within large-scale population-based setting, using wide-range estimated glomerular filtration rate (eGFR) category. We aimed to determine the association of admission eGFR with acute stroke outcomes using data from a registry established in Shiga Prefecture, Japan.**

***Methods*: Following exclusion of patients younger than 18 years, with missing serum creatinine data, and with onset more than 7 days prior to admission, 2,813 acute stroke patients registered in the Shiga Stroke Registry year 2011 were included in the final analysis. The Japanese Society of Nephrology equation was used to estimate GFR. Multivariable logistic regression was performed to analyze the association of eGFR with all-cause in-hospital death (modified Rankin Scale [mRS] 6), and at-discharge death/disability (mRS 2−6). Separate analyses were conducted within stroke subtypes.**

***Results*: Compared to eGFR 60−89 mL/min/1.73 m^2, adjusted odds ratios (ORs) and 95% confidence interval [95% CI] for in-hospital death (in the order of eGFR <45, 45−59, and ≥90 mL/min/1.73 m^2) were 1.54 [1.04−2.27], 1.07 [0.72−1.58], and 1.04 [0.67−1.59]. Likewise, adjusted ORs [95% CI] for at-discharge death/disability were 1.54 [1.02−2.32], 0.97 [0.73−1.31], and 1.48 [1.06−2.05]. Similar pattern was further evident in the eGFR <45 mL/min/1.73 m^2 group for both outcomes within acute ischemic stroke patients.**

***Conclusions*: Our study has ascertained that in acute stroke, particularly ischemic stroke, low eGFR was significantly associated with in-hospital death and at-discharge death/disability. Additionally, high eGFR was found to be associated with at-discharge death/disability.**

See editorial vol. 25: 566-567

Key words: Stroke, Glomerular filtration rate, Mortality, Morbidity

Introduction

Stroke is one of the major non-communicable diseases causing global burden for its high mortality and morbidity[1-3]. In Japan, it is currently one of the leading causes of death and was the most prominent

killer in the past[4, 5]. Although being a developed country, Japan still suffers from immense healthcare cost for its stroke survivors[6]. Improvement of stroke outcome by refined detection of high-risk patients with poor prognosis is thus mandatory to alleviate the situation. In the past few years, renal dysfunction has been identified as a novel risk factor affecting stroke prognosis, and estimated glomerular filtration rate (eGFR) is one of the parameters used as its proxy[7-17]. Few, however, have analyzed the association within large-scale population-based setting, using wide-range eGFR category. It is therefore necessary to ascertain it using bigger and more comprehensive data. We aimed to determine the association of on-admission eGFR with in-hospital death and at-discharge death/disability in acute stroke patients using data from a registry established in Shiga Prefecture, Japan.

Methods

Subjects

The Shiga Stroke Registry (SSR) is a multicenter population-based stroke registry developed to provide comprehensive information on acute ischemic and nontraumatic hemorrhagic stroke in Shiga Prefecture, a region populated by 1.4 million people and located in the middle of Honshu Island, Japan[18]. Of 41 acute care hospitals inside the prefecture with neurology/neurosurgery facilities, as well as smaller hospitals with rehabilitation facilities, data of all stroke cases were obtained retrospectively from medical records by trained investigators and put together in an encrypted database in Shiga University of Medical Science. Civil registration death certificates were also used to identify stroke cases leading to death outside the hospital. The current study focused on 2,956 stroke patients registered from 1 January to 31 December 2011. Following exclusion of patients younger than 18 years ($n=5$), with missing admission serum creatinine data ($n=65$), and with onset more than 7 days prior to admission ($n=73$), 2,813 acute stroke patients were included in the final analysis. The Institutional Review Board of Shiga University of Medical Science has approved the study protocol.

Determination of Stroke

Stroke was defined as rapidly developing clinical signs of focal or global disturbance of cerebral function, lasting more than 24 h or leading to mortality, with no apparent cause other than that of vascular origin[19]. Stroke was further categorized as ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage, with the latter two grouped into hemorrhagic stroke. All cases were confirmed both clinically and radiologically, and the final diagnosis was made by more than 2 independent investigators.

Address for correspondence: Hisatomi Arima, Department of Public Health, Shiga University of Medical Science, Seta Tsukinowa-cho, Otsu, Shiga, 520-2192, Japan
E-mail: arima@belle.shiga-med.ac.jp
Received: September 27, 2017
Accepted for publication: November 14, 2017

Variables and Outcome

Data gathered included age, gender, comorbidities (hypertension, diabetes, myocardial infarction, atrial fibrillation, dyslipidemia), previous stroke, smoking status, admission details (systolic and diastolic blood pressure, modified Rankin Scale (mRS), Japan Coma Scale [JCS])[20], interventional/surgical therapy performed, tissue plasminogen activator administered, days from onset until death/hospital discharge, and discharge mRS score. Interventional therapy consisted of endovascular recanalization and coil embolization, whereas surgical therapy involved decompression, hematoma evacuation, cerebrospinal fluid diversion, thrombectomy, and aneurysm clipping by means of endoscopic and/or conventional cranio/ectomy. The outcomes of this study were all-cause in-hospital death (mRS of 6) and at-discharge death/disability (mRS 2−6).

Renal Function Evaluation

Admission serum creatinine was measured using enzymatic method in local laboratories and used to estimate GFR based on the Japanese Society of Nephrology equation: eGFR (mL/min/1.73 m^2) = 194 × (serum creatinine [mg/dL])$^{-1.094}$ × (age [year])$^{-0.287}$ × 0.739 (for female)[21]. The estimated GFR was then categorized as <45, 45−59, 60−89, and ≥ 90 mL/min/1.73 m^2, with eGFR 60−89 mL/min/1.73 m^2 being the reference group[22]. Patients with eGFR <45 mL/min/1.73 m^2 were pooled together due to small number, whereas patients on renal replacement therapy (RRT) were gathered into a separate group due to their particular feature.

Statistical Analysis

Continuous variables were presented as mean (standard deviation) or median (interquartile range) as appropriate, and categorical variables as proportions. Differences in means or medians between two groups were analyzed using Student's t-test or Mann−Whitney U test, respectively, while χ^2 or Fisher exact test was conducted to find differences in proportions as appropriate. Probability trends were determined by treating eGFR in its continuous nature and fitting it into linear/logistic regression models with variables of interest. Next, multivariable logistic regression analyses, adjusting for covariates regarded and/or identified from literatures to

Table 1. Basic characteristics of study subjects by renal replacement therapy status

	Non-RRT ($n=2743$)	RRT ($n=70$)	p
Age, mean years ± SD	74.1 ± 13.3	70.1 ± 13.4	0.04
Female, n (%)	1276 (46.5)	27 (38.6)	0.19
Comorbidities, n (%)			
Hypertension	1973 (72.7)	59 (85.5)	0.02
Diabetes	726 (26.7)	30 (43.5)	0.002
Myocardial infarction	165 (6.1)	3 (4.4)	0.79
Atrial fibrillation	559 (20.6)	15 (22.1)	0.76
Dyslipidemia	951 (36.7)	20 (30.8)	0.32
Previous stroke, n (%)	706 (25.8)	30 (42.9)	0.001
Smoking status, n (%)			0.54
Never	1634 (65.6)	38 (63.3)	
Ex	325 (13)	6 (10)	
Current	532 (21.4)	16 (26.7)	
SBP, mean mmHg ± SD	161.8 ± 33	166.7 ± 41	0.32
DBP, mean mmHg ± SD	88.7 ± 20.4	85.8 ± 22.5	0.26
Japan Coma Scale, n (%)			0.03
0	1241 (45.4)	32 (46.4)	
1-3 (1-digit)	693 (25.3)	9 (13)	
10-30 (2-digit)	357 (13.1)	9 (13)	
100-300 (3-digit)	444 (16.2)	19 (27.6)	
eGFR, mL/min/1.73 m^2, median (IQR)	67.5 (52.9-82.7)	6.2 (4.7-10.1)	<.0001
Admission mRS, n (%)			<.0001
0	1703 (62.1)	17 (24.3)	
1	322 (11.7)	17 (24.3)	
2	173 (6.3)	8 (11.4)	
3	212 (7.7)	11 (15.7)	
4	243 (8.9)	11 (15.7)	
5	90 (3.3)	6 (8.6)	
Intervention/surgery, n (%)	296 (10.8)	9 (12.9)	0.59
r-tPA, n (%)	77 (2.8)	1 (1.5)	0.99
Onset-death/discharge days, median (IQR)	25 (13-46)	19.5 (10-39)	0.09
Final diagnosis, n (%)			0.83
Ischemic	1803 (65.7)	45 (64.3)	
Haemorrhagic	935 (34.1)	25 (35.7)	
Discharge mRS, n (%)			0.09
0	202 (7.4)	4 (5.7)	
1	509 (18.6)	11 (15.7)	
2	318 (11.6)	8 (11.4)	
3	287 (10.5)	8 (11.4)	
4	628 (22.9)	11 (15.7)	
5	390 (14.2)	8 (11.4)	
In-hospital death, n (%)	409 (14.9)	20 (28.6)	0.002

RRT, renal replacement therapy; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; mRS, modified Rankin Scale; r-tPA, recombinant tissue plasminogen activator

be significantly associated with stroke outcomes, were performed to determine the association of eGFR with both outcomes. Separate analyses were done within stroke subtypes. Finally, sensitivity analyses were conducted for the outcome of at-discharge death/dependency (mRS 3-6) on all stroke subtypes. All analyses were conducted using SAS Version 9.4 software (SAS Institute). Differences with two-tailed p-value <0.05

Table 2. Characteristics of the study subjects not on renal replacement therapy

	eGFR (mL/min/1.73 m^2)				
	≤45 (*n*=431)	45-59 (*n*=571)	60-89 (*n*=1306)	≥90 (*n*=435)	*p*-trend
Age, mean years ± SD	80.9 ± 10.9	78 ± 10.4	72.5 ± 12.9	66.7 ± 15.4	<.0001
Female, n (%)	229 (53.1)	265 (46.4)	572 (43.8)	210 (48.3)	0.25
Comorbidities, n (%)					
Hypertension	351 (82.4)	433 (76.6)	917 (70.8)	272 (63.6)	<.0001
Diabetes	152 (35.8)	141 (24.7)	329 (25.3)	104 (24.3)	0.001
Myocardial infarction	45 (10.6)	39 (6.9)	61 (4.7)	20 (4.6)	<.0001
Atrial fibrillation	135 (31.8)	145 (25.6)	226 (17.4)	53 (12.2)	<.0001
Dyslipidemia	136 (33.8)	210 (38.9)	462 (37.4)	143 (35)	0.67
Previous stroke, n (%)	126 (29.6)	176 (30.9)	322 (24.7)	82 (18.9)	<.0001
Smoking status, n (%)					<.0001
Never	283 (74.3)	364 (70.8)	751 (62.7)	236 (59.2)	
Ex	52 (13.7)	74 (14.4)	153 (12.8)	46 (11.5)	
Current	46 (12.1)	76 (14.8)	293 (24.5)	117 (29.3)	
SBP, mean mmHg ± SD	157.2 ± 35.1	160.3 ± 32.8	163.7 ± 32.1	162.4 ± 33.4	0.05
DBP, mean mmHg ± SD	83.1 ± 20.9	86.9 ± 21.4	90.5 ± 19.8	90.9 ± 19.4	<.0001
Japan Coma Scale, n (%)					0.03
0	140 (32.6)	258 (45.2)	651 (50)	192 (44.4)	
1-3 (1-digit)	127 (29.6)	158 (27.7)	314 (24.1)	94 (21.8)	
10-30 (2-digit)	58 (13.5)	77 (13.5)	164 (12.6)	58 (13.4)	
100-300 (3-digit)	104 (24.2)	78 (13.7)	174 (13.4)	88 (20.4)	
eGFR, mean mL/min/1.73 m^2 ± SD	33.4 ± 9.5	53.4 ± 4.1	73.7 ± 8.4	108.5 ± 21.2	<.0001
Admission mRS, n (%)					<.0001
0	205 (47.6)	316 (55.3)	872 (66.8)	310 (71.3)	
1	59 (13.7)	79 (13.8)	152 (11.6)	32 (7.4)	
2	36 (8.4)	41 (7.2)	79 (6.1)	17 (3.9)	
3	59 (13.7)	59 (10.3)	80 (6.1)	14 (3.2)	
4	58 (13.5)	60 (10.5)	93 (7.1)	32 (7.4)	
5	14 (3.3)	16 (2.8)	30 (2.3)	30 (6.9)	
Intervention/surgery, n (%)	29 (6.8)	44 (7.7)	137 (10.5)	86 (19.8)	<.0001
tPA, n (%)	11 (2.6)	22 (3.9)	38 (2.9)	6 (1.4)	0.31
Onset-death/discharge days, median (IQR)	24 (12-51)	27 (13-48)	25 (13-45)	25 (13-46)	0.36
Final diagnosis, n (%)					<.0001
Ischemic	322 (74.7)	418 (73.2)	850 (65.1)	213 (49)	
Haemorrhagic	108 (25.1)	153 (26.8)	455 (34.8)	219 (50.3)	

SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; mRS, modified Rankin Scale; tPA, tissue plasminogen activator

is considered to be statistically significant.

Results

Characteristics of Patients by RRT Status

Table 1 shows basic characteristics of adult acute stroke patients by RRT status. Compared with non-RRT group, several significant differences were identified in RRT group: patients' age was younger; hypertension, diabetes, previous stroke, and pre-admission significant disability were more prevalent; admission JCS score was worse; admission eGFR was extremely lower; and in-hospital death was higher.

Characteristics of Study Subjects by eGFR Category

Table 2 presents basic characteristics of study subjects by eGFR category. Of 2,743 non-RRT patients, 15.7% presented with eGFR of <45 mL/min/1.73 m^2, 20.8% with eGFR 45−59 mL/min/1.73 m^2, 47.6% with eGFR 60−89 mL/min/1.73 m^2, and 15.9% with

Table 3. Prevalence and odds ratio (95% confidence interval) of each eGFR category for outcomes in all stroke

	eGFR (mL/min/1.73 m^2)				
	RRT (n=70)	<45 (n=431)	45-59 (n=571)	60-89 (n=1306)	≥90 (n=435)
Death (mRS 6)					
N (%)	20 (28.6)	113 (26.2)	81 (14.2)	152 (11.6)	63 (14.5)
Unadjusted	3.04 (1.76-5.24)	2.70 (2.05-3.55)	1.26 (0.94-1.68)	1.00	1.29 (0.94-1.76)
Model 1[a]	3.33 (1.91-5.81)	2.09 (1.57-2.77)	1.06 (0.79-1.43)	1.00	1.55 (1.12-2.14)
Model 2[b]	2.03 (0.90-4.58)	1.54 (1.05-2.27)	1.07 (0.72-1.58)	1.00	1.04 (0.67-1.59)
Death/disability (mRS 2-6)					
N (%)	55 (78.6)	376 (87.2)	437 (76.5)	913 (69.9)	306 (70.3)
Unadjusted	1.58 (0.88-2.83)	2.94 (2.17-4.00)	1.40 (1.12-1.76)	1.00	1.02 (0.81-1.30)
Model 1[a]	1.87 (1.01-3.46)	1.95 (1.42-2.69)	1.04 (0.82-1.33)	1.00	1.40 (1.08-1.82)
Model 2[b]	0.89 (0.39-2.03)	1.54 (1.02-2.32)	0.97 (0.73-1.31)	1.00	1.48 (1.06-2.05)

eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy; mRS, modified Rankin Scale
[a]Adjusted for age and sex
[b]Adjusted for age, sex, hypertension, diabetes, myocardial infarction, atrial fibrillation, previous stroke, smoking status, diastolic blood pressure, admission Japan Coma Scale and modified Rankin Scale, intervention/surgery, and recombinant tissue plasminogen activator administration
All regression analyses result are in odds ratio (95% confidence interval)

eGFR ≥90 mL/min/1.73 m^2. Compared to other groups, in the eGFR ≤45 mL/min/1.73 m^2 group, patients were significantly older; prevalence of hypertension, diabetes, myocardial infarction, atrial fibrillation, recurrent stroke, and never smokers were higher; admission systolic and diastolic blood pressure were lower, admission mRS and JCS were worse, intervention/surgery was less performed, and, lastly, ischemic stroke was more prevalent.

Prevalence of Outcomes by eGFR Category and the Association of eGFR with Outcomes in All Stroke

Table 3 shows prevalence of outcomes by eGFR category and the association of eGFR with outcomes in all stroke. Both in-hospital death and at-discharge death/disability display reverse relationship with eGFR. For multivariable adjustment, age, sex, hypertension, diabetes, myocardial infarction, atrial fibrillation, previous stroke, smoking status, diastolic blood pressure, admission JCS and mRS, intervention/surgery, and recombinant tissue plasminogen activator administration were selected as covariates. Compared to the reference group, only eGFR <45 mL/min/1.73 m^2 group maintained its significant association with in-hospital death (from unadjusted OR [95% CI] of 2.70 [2.05−3.55] to multivariable-adjusted OR [95% CI] of 1.54 [1.05−2.27]) and with at-discharge death/disability (from unadjusted OR [95% CI] of 2.94 [2.17−4.00] to multivariable-adjusted OR [95% CI] of 1.54 [1.02−2.32]). Moreover, following further adjustment, a maintained significant association with at-discharge disability was seen in eGFR >90 mL/min/1.73 m^2 group (multivariable-adjusted OR [95% CI] of 1.48 [1.06−2.05]). RRT group, particularly, did not display any significant association with both outcomes after adjustments.

Prevalence of Outcomes by eGFR Category and the Association of eGFR with Outcomes in Ischemic and Hemorrhagic Strokes

Tables 4 and **5** show prevalence of outcomes by eGFR category and the association of eGFR with outcomes in ischemic and hemorrhagic strokes. In-hospital death and at-discharge death/disability had similar reverse relationship with eGFR in both stroke subtypes as in all stroke. In the same manner, eGFR <45 mL/min/1.73 m^2 group in ischemic stroke displayed maintained significant association with in-hospital death (from unadjusted OR [95% CI] of 3.46 [2.37−5.05] to multivariable-adjusted OR [95% CI] of 1.60 [1.00−2.57]) and with at-discharge disability (from unadjusted OR [95% CI] of 3.53 [2.50−4.99] to multivariable-adjusted OR [95% CI] of 1.74 [1.10−2.76]). Still within the same stroke subtype, eGFR >90 mL/min/1.73 m^2 group also showed maintained significant association with at-discharge disability (multivariable-adjusted OR [95% CI] of 1.52 [1.01−2.31]). As for hemorrhagic stroke, with the exception of RRT group that preserved its significant association with in-hospital death (from unadjusted OR [95% CI] of 3.64 [1.61−8.25] to multivariable-adjusted OR [95% CI] of 5.27 [1.43−19.50]), no other significant associations were identified.

Table 4. Prevalence and odds ratio (95% confidence interval) of each eGFR category for outcomes in ischemic stroke

	eGFR (mL/min/1.73 m^2)				
	RRT (n=45)	<45 (n=322)	45-59 (n=418)	60-89 (n=850)	≥90 (n=213)
Death (mRS 6)					
N (%)	8 (17.8)	66 (20.5)	46 (11)	59 (6.9)	18 (8.5)
Unadjusted	2.90 (1.29-6.51)	3.46 (2.37-5.05)	1.66 (1.11-2.49)	1.00	1.24 (0.71-2.15)
Model 1[a]	2.97 (1.29-6.85)	2.17 (1.46-3.23)	1.26 (0.83-1.91)	1.00	1.66 (0.94-2.92)
Model 2[b]	0.91 (0.27-3.07)	1.60 (1.00-2.57)	1.20 (0.74-1.94)	1.00	0.92 (0.45-1.86)
Death/disability (mRS 2-6)					
N (%)	35 (77.8)	277 (86)	305 (73)	540 (63.5)	133 (62.4)
Unadjusted	2.01 (0.98-4.11)	3.53 (2.50-4.99)	1.55 (1.20-2.00)	1.00	0.95 (0.70-1.30)
Model 1[a]	1.89 (0.89-4.02)	2.08 (1.44-3.01)	1.02 (0.78-1.35)	1.00	1.41 (0.99-2.00)
Model 2[b]	0.96 (0.36-2.57)	1.74 (1.10-2.76)	0.91 (0.65-1.28)	1.00	1.54 (1.02-2.33)

eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy; mRS, modified Rankin Scale
[a]Adjusted for age and sex
[b]Adjusted for age, sex, hypertension, diabetes, myocardial infarction, atrial fibrillation, previous stroke, smoking status, diastolic blood pressure, admission Japan Coma Scale and modified Rankin Scale, intervention/surgery, and recombinant tissue plasminogen activator administration
All regression analyses result are in odds ratio (95% confidence interval)

Table 5. Prevalence and odds ratio (95% confidence interval) of each eGFR category for outcomes in hemorrhagic stroke

	eGFR (mL/min/1.73 m^2)				
	RRT (n=25)	<45 (n=108)	45-59 (n=153)	60-89 (n=455)	≥90 (n=219)
Death (mRS 6)					
N (%)	12 (48)	46 (42.6)	35 (22.9)	92 (20.2)	42 (19.2)
Unadjusted	3.64 (1.61-8.25)	2.93 (1.88-4.57)	1.17 (0.75-1.82)	1.00	0.94 (0.62-1.41)
Model 1[a]	4.53 (1.92-10.66)	2.46 (1.56-3.88)	1.05 (0.67-1.64)	1.00	1.09 (0.72-1.66)
Model 2[b]	5.27 (1.43-19.50)	1.66 (0.80-3.42)	0.85 (0.42-1.72)	1.00	1.00 (0.54-1.83)
Death/disability (mRS 2-6)					
N (%)	20 (80)	98 (90.7)	132 (86.3)	372 (81.8)	170 (77.6)
Unadjusted	0.89 (0.33-2.45)	2.19 (1.09-4.37)	1.40 (0.84-2.36)	1.00	0.77 (0.52-1.15)
Model 1[a]	1.30 (0.45-3.77)	1.61 (0.79-3.28)	1.20 (0.70-2.05)	1.00	1.04 (0.68-1.58)
Model 2[b]	0.51 (0.11-2.25)	0.71 (0.28-1.81)	1.08 (0.55-2.12)	1.00	1.18 (0.68-2.06)

eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy; mRS, modified Rankin Scale
[a]Adjusted for age and sex
[b]Adjusted for age, sex, hypertension, diabetes, myocardial infarction, atrial fibrillation, previous stroke, smoking status, diastolic blood pressure, admission Japan Coma Scale and modified Rankin Scale, intervention/surgery, and recombinant tissue plasminogen activator administration
All regression analyses result are in odds ratio (95% confidence interval)

Sensitivity Analyses: The Association of eGFR With At-Discharge Death/Dependency in All Strokes and Its Subtypes

Table 6 presents the association of eGFR with at-discharge death/dependency in all strokes and its subtypes as sensitivity analyses. Compared to the reference group, significant association was maintained only in eGFR <45 mL/min/1.73 m^2 in ischemic stroke (from unadjusted OR [95% CI] of 3.56 [2.50−4.99] to multivariable-adjusted OR [95% CI] of 1.74 [1.10−2.76]).

Discussion

In the current study, low eGFR (<45 mL/min/1.73 m^2) was shown to be significantly and positively associated with all stroke outcome: its ORs for in-hospital death and at-discharge death/disability were 1.54 times higher than the reference group. Additionally, high eGFR (≥90 mL/min/1.73 m^2) was significantly

Table 6. Prevalence and odds ratio (95% confidence interval) of each eGFR category for death/dependency (mRS 3-6) in all stroke and its subtypes

	eGFR (mL/min/1.73 m^2)				
	RRT	<45	45-59	60-89	≥90
All stroke					
Unadjusted	1.48 (0.89-2.47)	2.75 (2.13-3.55)	1.27 (1.03-1.55)	1.00	1.01 (0.81-1.26)
Model 1[a]	1.82 (1.05-3.15)	1.79 (1.36-2.36)	0.92 (0.74-1.15)	1.00	1.41 (1.10-1.80)
Model 2[b]	1.02 (0.46-2.27)	1.23 (0.85-1.79)	0.77 (0.57-1.03)	1.00	1.32 (0.94-1.84)
Ischemic stroke					
Unadjusted	1.89 (1.01-3.53)	3.56 (2.65-4.77)	1.52 (1.20-1.93)	1.00	0.98 (0.72-1.32)
Model 1[a]	1.87 (0.95-3.71)	2.07 (1.50-2.86)	1.01 (0.78-1.31)	1.00	1.49 (1.05-2.11)
Model 2[b]	1.18 (0.46-3.05)	1.54 (1.01-2.35)	0.81 (0.57-1.14)	1.00	1.56 (1.00-2.45)
Hemorrhagic stroke					
Unadjusted	0.87 (0.35-2.14)	1.81 (1.04-3.17)	1.02 (0.67-1.56)	1.00	0.69 (0.49-0.98)
Model 1[a]	1.39 (0.53-3.68)	1.27 (0.71-2.28)	0.83 (0.53-1.30)	1.00	0.94 (0.64-1.38)
Model 2[b]	0.54 (0.13-2.29)	0.49 (0.22-1.10)	0.63 (0.35-1.17)	1.00	0.91 (0.54-1.52)

eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy; mRS, modified Rankin Scale
[a]Adjusted for age and sex
[b]Adjusted for age, sex, hypertension, diabetes, myocardial infarction, atrial fibrillation, previous stroke, smoking status, diastolic blood pressure, admission Japan Coma Scale and modified Rankin Scale, intervention/surgery, and recombinant tissue plasminogen activator administration
All regression analyses result are in odds ratio (95% confidence interval)

associated with at-discharge death/disability, its OR was 1.48 higher than the reference group. Further analyses within each stroke subtypes, as well as sensitivity analyses, discovered the same pattern to be strongly evident in the ischemic stroke. In regard to RRT patients, this group displayed a notable association with death only within hemorrhagic stroke.

Despite growing interest in similar subject, divulging the association either in overall stroke[7-9], ischemic[10-14] or hemorrhagic subtypes[15-17], in-between study findings have been contradictory, for example, while Yahalom *et al*[9] and Tsagalis *et al*[7] showed significant and positive result between low eGFR and mortality and poor outcome after stroke, the opposite was reported by Yang *et al*[8]. Result interpretations were complicated by small sample size[7-9, 12-15, 17], non-population-based setting[7-9, 11, 12, 14], narrow-range eGFR category[7, 11, 13-15], or lack of control for stroke severity[12, 15]. The present study deals with these issues by employing data from a large-scale population-based setting registry, implementing wide-range eGFR category, and separating analyses between non-RRT and RRT patients. The latter, particularly, is paramount as serum creatinine level in RRT patients is unreliable; thus, its inclusion will confound the study results[23].

The mechanism underlying the relationship between renal function and poor stroke outcome has not been clearly understood. In our study, low eGFR group exhibited the highest prevalence of traditional vascular risk factors linked to stroke, e.g. hypertension, diabetes, and aging, all were perceived to cause poor outcome[13]. Various theories have been proposed to explain this, from aging-related mechanism[24, 25] to structure-related mechanisms of renal and cerebral blood vessels[26, 27]. These theories, especially the one related to aging and atherosclerosis, may explain our finding related to the detrimental effect of low eGFR, especially in patients with ischemic stroke. Although atherosclerosis of large cerebral arteries was reported to be related to the development of atherothrombotic brain infarction, the role of serum high-density lipoprotein cholesterol and non−high-density lipoprotein cholesterol may be different in both stroke subtypes[28, 29]. On the contrary, the adverse outcome in relation to high eGFR found in this study is probably related to kidney hyper filtration, which has been associated with unfavorable cardiovascular outcomes[10, 30]. High eGFR, however, may not represent true renal function in patients with atypically reduced muscle mass, such as the elderly, amputees, and others suffering from chronic muscle diseases[31, 32]. Vis-à-vis the association of RRT with in-hospital death within hemorrhagic stroke, similar result was identified in a study by Lin *et al*[33], in which prior stroke and diabetes, both were prevalent among RRT group in our study, strongly predict mortality in this particular group. A more extensive investigation in the future on this particular issue will be of importance. In addition, we realize that our finding is inconsistent with other studies describing the "U"- or "J"-shaped association[12, 14]. This may be due to inevi-

table differences in study population, eGFR equations, or study design. Recently, non-traditional vascular risk factors, such as oxidative stress, decreased platelet function, and anemia caused by reduced erythropoietin production[34, 35], have been suggested to adding up clot formation and infarct growth by decreasing perfusion distal to obstruction. They might also contribute to secondary cerebral injury due to metabolic stress and tissue hypoxia[36], promoting hematoma growth and perihematomal edema, eventually worsening hemorrhagic stroke outcome[17, 37].

As a consequence of undesirable effects associated with renal dysfunction, a more vigilant management of acute stroke patients with this condition is warranted. Increased risk of intracerebral hemorrhage with thrombolysis administration[38], decreased responsiveness of antiplatelet[39], and limited use of anticoagulants[40] are few of the limitations critical to be recognized in providing medical therapy to these high-risk patients. Should any indication for interventional/surgical therapy arise, cautious peri-, intra-, and postoperative management is imperative, covering aspects such as fluid and electrolytes therapy, anesthetic agent selection, and contrast agent use[41, 42]. Promotion and preventive measures to manage cardiovascular disease risk factors in community level, specifically in renal dysfunction patients, is of no less importance. A recent study investigating lipid management targets in Japan showed inadequate attainment rates in the population, raising alarm for its improvement[43].

Besides the aforementioned strength of this study, eGFR 60−89 mL/min/1.73 m^2 was selected as the reference group, considering the specific range of which to better represent the aging nature of stroke patients by taking into account study subjects' mean eGFR and age. However, because only Japanese patients were studied, results may not be applicable to other populations. Serum creatinine was only measured on admission and in individual centers, thereby influencing its accuracy. Furthermore, admission NIHSS, a strong predictor of stroke outcome[43], was not incorporated due to its high rate of missing data. However, we perceive this issue to be overcome by using JCS, a Japanese-based consciousness level score developed in the same year as the Glasgow Coma Scale, which has been proven to have good predictability of stroke outcome[22].

In conclusion, our study has ascertained that in acute stroke, particularly in ischemic stroke, low eGFR was associated with in-hospital death and at-discharge death/disability. Additionally, high eGFR was also found to be associated with at-discharge death/disability. These findings reemphasize the importance of having great awareness among clinicians managing these stroke patients with renal dysfunction.

Acknowledgement and Notice

None.

Conflict of Interest

None.

References

1) Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, De Ferranti S, Despres JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jimenez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW, Turner MB: Heart disease and stroke statistics-2016 update: a report From the American Heart Association. Circulation, 2016; 133: e38-360
2) Johnston SC, Mendis S, Mathers CD: Global variation in stroke burden and mortality: estimates from monitoring, surveillance, and modelling. Lancet Neurol, 2009; 8: 345-354
3) GBD 2013 and Causes of Mortality Collaborators: Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of mortality, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet, 2015; 385: 117-171
4) World Health Organization: Noncommunicable disease country profile 2014. Geneva, 2014; 99
5) Miura K: Epidemiology and prevention of hypertension in Japanese: how could Japan get longevity? EPMA J, 2011; 2: 59-64
6) Yoneda Y, Okuda S, Hamada R, Toyota A, Gotoh J, Watanabe M, Okada Y, Okeda K, Ibayashi S, Hasegawa Y: Hospital cost of ischemic stroke and intracerebral hemorrhage in Japanese stroke centers. Health Policy, 2005; 73: 202-211
7) Tsagalis G, Akrivos T, Alevizaki M, Manios M, Stamatellopoulos K, Laggouranis A, Vemmos KN: Renal dysfunction in acute stroke: an independent predictor of long-term all combined vascular events and overall mortality. Nephrol Dial Transplant, 2009; 24: 194-200
8) Yang J, Arima H, Zhou J, Zhao Y, Li Q, Wu G, Zhang Y: Effects of low estimated glomerular filtration rate on outcomes after stroke: a hospital-based stroke registry in China. Eur J Neurol, 2014; 21: 1143-1145
9) Yahalom G, Schwartz R, Schwammenthal Y, Merzeliak O, Toashi M, Orion D, Sela BA, Tanne D: Chronic kidney disease and clinical outcome in patients with acute stroke. Stroke, 2009; 40: 1296-1303
10) Wang X, Wang Y, Wang C, Zhao X, Xian Y, Wang D, Liu L, Luo Y, Liu G, Wang Y: Association between estimated glomerular filtration rate and clinical outcomes in patients with acute ischaemic stroke: results from China National Stroke Registry. Age Ageing, 2014; 43: 839-845
11) Kumai Y, Kamouchi M, Hata J, Ago T, Kitayama J,

Nakane H, Sugimori H, Kitazono T: Proteinuria and clinical outcome after ischemic stroke. Neurology, 2012; 78: 1909-1915
12) Mostofsky E, Wellenius GA, Noheria A, Levitan EB, Burger MR, Schlaug G, Mittleman MA: Renal function predicts survival in patients with acute ischemic stroke. Cerebrovasc Dis, 2009; 28: 88-94
13) Naganuma M, Koga M, Shiokawa Y, Nakagawara J, Furui E, Kimura K, Yamagami H, Okada Y, Hasegawa Y, Kario K, Okuda S, Nishiyama K, Minematsu K, Toyoda K: Reduced estimated glomerular filtration rate is associated with stroke outcome after intravenous rt-PA: the Stroke Acute Management with Urgent Risk-Factor Assessment and Improvement (SAMURAI) rt-PA registry. Cerebrovasc Dis, 2011; 31: 123-129
14) Hojs Fabjan T, Penko M, Hojs R: Cystatin C, creatinine, estimated glomerular filtration, and long-term mortality in stroke patients. Ren Fail, 2014; 36: 81-86
15) Kai S, Jiaoyan Q, Weihua S, Yinhui Z, Channa Z, Li S, Yan S, Rutai H, Jingzhou C: Low estimated glomerular filtration rate is associated with high recurrence rate and poor prognosis of hemorrhage stroke. Curr Neurovasc Res, 2015; 12: 11
16) Zheng D, Sato S, Arima H, Heeley E, Delcourt C, Cao Y, Chalmers J, Anderson CS: Estimated GFR and the effect of intensive blood pressure lowering after acute intracerebral hemorrhage. Am J Kidney Dis, 2016; 68: 94-102
17) Miyagi T, Koga M, Yamagami H, Okuda S, Okada Y, Kimura K, Shiokawa Y, Nakagawara J, Furui E, Hasegawa Y, Kario K, Arihiro S, Sato S, Minematsu K, Toyoda K: Reduced estimated glomerular filtration rate affects outcomes 3 months after intracerebral hemorrhage: the stroke acute management with urgent risk-factor assessment and improvement-intracerebral hemorrhage study. J Stroke Cerebrovasc Dis, 2015; 24: 176-182
18) Takashima N, Arima H, Kita Y, Fujii T, Miyamatsu N, Komori M, Sugimoto Y, Nagata S, Miura K, Nozaki K: Incidence, management and short-term outcome of stroke in a general population of 1.4 Million Japanese: Shiga Stroke Registry, Circ J, 2017; 81: 1636-1646
19) Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, Elkind MS, George MG, Hamdan AD, Higashida RT, Hoh BL, Janis LS, Kase CS, Kleindorfer DO, Lee JM, Moseley ME, Peterson ED, Turan TN, Valderrama AL, Vinters HV: An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke, 2013; 44: 2064-2089
20) Shigematsu K, Nakano H, Watanabe Y: The eye response test alone is sufficient to predict stroke outcome--reintroduction of Japan Coma Scale: a cohort study. BMJ Open, 2013; 3: e002736
21) Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A: Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis, 2009; 53: 982-992
22) Kidney Disease Improving Global Outcomes: KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl, 2013; 3: 163
23) Kooman JP: Estimation of renal function in patients with chronic kidney disease. J Magn Reson Imaging, 2009; 30: 1341-1346
24) Etgen T: Kidney disease as a determinant of cognitive decline and dementia. Alzheimers Res Ther, 2015; 7: 29
25) Wang JC, Bennett M: Aging and atherosclerosis: mechanisms, functional consequences, and potential therapeutics for cellular senescence. Circ Res, 2012; 111: 245-259
26) O'Rourke MF, Safar ME: Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy. Hypertension, 2005; 46: 200-204
27) Sato S, Delcourt C, Heeley E, Arima H, Zhang S, Al-Shahi Salman R, Stapf C, Woo D, Flaherty ML, Vagal A, Levi C, Davies L, Wang J, Robinson T, Lavados PM, Lindley RI, Chalmers J, Anderson CS: Significance of cerebral small-vessel disease in acute intracerebral hemorrhage. Stroke, 2016; 47: 701-707
28) Imamura T, Doi Y, Ninomiya T, Hata J, Nagata M, Ikeda F, Mukai N, Hirakawa Y, Yoshida D, Fukuhara M, Kitazono T, Kiyohara Y: Non-high-density lipoprotein cholesterol and the development of coronary heart disease and stroke subtypes in a general Japanese population: the Hisayama Study. Atherosclerosis, 2014; 233: 343-348
29) Usui T, Nagata M, Hata J, Mukai N, Hirakawa Y, Yoshida D, Kishimoto H, Kitazono T, Kiyohara Y, Ninomiya T: Serum non-high-density lipoprotein cholesterol and risk of cardiovascular disease in community dwellers with chronic kidney disease: the Hisayama Study. J Atheroscler Thromb, 2017; 24: 706-715
30) Reboldi G, Verdecchia P, Fiorucci G, Beilin LJ, Eguchi K, Imai Y, et al. Glomerular hyperfiltration is a predictor of adverse cardiovascular outcomes. Kidney Int, 2017 In Press
31) Odden MC, Shlipak MG, Tager IB: Serum creatinine and functional limitation in elderly persons. J Gerontol A Biol Sci Med Sci, 2009; 64: 370-376
32) Delanaye P, Schaeffner E, Ebert N, Cavalier E, Mariat C, Krzesinski JM, Moranne O: Normal reference values for glomerular filtration rate: what do we really know? Nephrol Dial Transplant, 2012; 27: 2664-2672
33) Lin CY, Chien CC, Chen HA, Su FM, Wang JJ, Wang CC, Chu CC, Lin YJ: The impact of comorbidity on survival after hemorrhagic stroke among dialysis patients: a nationwide population-based study. BMC Nephrol, 2014; 15: 186
34) Thekkedath UR, Chirananthavat T, Leypoldt JK, Cheung AK, Mohammad SF: Elevated fibrinogen fragment levels in uremic plasma inhibit platelet function and expression of glycoprotein IIb-IIIa. Am J Hematol, 2006; 81: 915-926
35) Ganguly P, Alam SF: Role of homocysteine in the development of cardiovascular disease. Nutr J, 2015; 14: 6
36) Lutz J, Menke J, Sollinger D, Schinzel H, Thurmel K: Haemostasis in chronic kidney disease. Nephrol Dial Transplant, 2014; 29: 29-40
37) Molshatzki N, Orion D, Tsabari R, Schwammenthal Y, Merzeliak O, Toashi M, Tanne D: Chronic kidney disease in patients with acute intracerebral hemorrhage: association with large hematoma volume and poor outcome. Cerebrovasc Dis, 2011; 31: 271-277
38) Angiolillo DJ, Bernardo E, Capodanno D, Vivas D, Sabate M, Ferreiro JL, Ueno M, Jimenez-Quevedo P, Alfonso F, Bass TA, Macaya C, Fernandez-Ortiz A: Impact of chronic

kidney disease on platelet function profiles in diabetes mellitus patients with coronary artery disease taking dual antiplatelet therapy. J Am Coll Cardiol, 2010; 55: 1139-1146
39) Chan KE, Lazarus JM, Thadhani R, Hakim RM: Anticoagulant and antiplatelet usage associates with mortality among hemodialysis patients. J Am Soc Nephrol, 2009; 20: 872-881
40) Hirano T: Thrombolysis and hyperacute reperfusion therapy for stroke in renal patients. Contrib Nephrol, 2013; 179: 110-118
41) Toyoda K, Ninomiya T: Stroke and cerebrovascular diseases in patients with chronic kidney disease. Lancet Neurol, 2014; 13: 823-833
41) Craig RG, Hunter JM: Recent developments in the perioperative management of adult patients with chronic kidney disease. Br J Anaesth, 2008; 101: 296-310
42) Adams HP, Jr., Davis PH, Leira EC, Chang KC, Bendixen BH, Clarke WR, Woolson RF, Hansen MD: Baseline NIH Stroke Scale score strongly predicts outcome after stroke: A report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). Neurology, 1999; 53: 126-131
43) Tada H, Kawashiri MA, Nohara A, Inazu A, Kobayashi J, Yasuda K, Mabuchi H, Yamagishi M, Hayashi K: Lipid management in a Japanese community: attainment rate of target set by the Japan Atherosclerosis Society guidelines for the prevention of atherosclerotic cardiovascular diseases 2012. J Atheroscler Thromb, 2017; 24: 338-345