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Etiology and Outcome of Ischemic Stroke in Patients With Renal Impairment Including Chronic Kidney Disease

Japan Stroke Data Bank

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Abstract

Background and Objectives

Chronic kidney disease is a worldwide public health problem that is recognized as an established risk factor for stroke. It remains unclear whether its distribution and clinical impact are consistent across ischemic stroke subtypes in patients with renal impairment. We examined whether renal impairment was associated with the proportion of each stroke subtype vs ischemic stroke overall and with functional outcomes after each stroke subtype.

Methods

Study participants were 10,392 adult patients with an acute stroke from the register of the Japan Stroke Data Bank, a hospital-based multicenter stroke registration database, between October 2016 and December 2019, whose baseline serum creatinine levels or a dipstick proteinuria result were available. All ischemic strokes were classified according to the Trial of Org 10172 in Acute Stroke Treatment criteria. Unfavorable functional outcome was defined as modified Rankin Scale (mRS) score 3–6 at discharge. Mixed effect logistic regression was used to determine the relationship between the outcomes and the estimated glomerular filtration rate (eGFR), eGFR strata (<45, 45–59, ≥60 mL/min/1.73 m^2), or dipstick proteinuria ≥1 adjusted for covariates.

Results

Overall, 2,419 (23%) patients had eGFR 45–59 mL/min/1.73 m^2 and 1,976 (19%) had eGFR <45 mL/min/1.73 m^2, including 185 patients (1.8%) receiving hemodialysis. Both eGFR 45–59 and eGFR <45 mL/min/1.73 m^2 were associated with a higher proportion of cardioembolic stroke (odds ratio [OR], 1.21 [95% CI, 1.05–1.39] and 1.55 [1.34–1.79], respectively) and a lower proportion of small vessel occlusion (0.79 [0.69–0.90] and 0.68 [0.59–0.79], respectively). A similar association with the proportion of these 2 subtypes was proven in the analyses using decreased eGFR as continuous values. Both eGFR <45 mL/min/1.73 m^2 and proteinuria were associated with unfavorable functional outcomes in patients with cardioembolic stroke (OR, 1.30 [95% CI, 1.01–1.69] and 3.18 [2.03–4.98], respectively) and small vessel occlusion (OR, 1.44 [1.01–2.07] and 2.08 [1.08–3.98], respectively).

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Japan Stroke Data Bank Investigators coinvestigators are listed in the appendix 2 at the end of the article.

Glossary

CKD = chronic kidney disease; **eGFR** = estimated glomerular filtration rate; **JSDB** = Japan Stroke Data Bank; **mRS** = modified Rankin Scale; **NIHSS** = National Institutes of Health Stroke Scale; **TOAST** = Trial of Org 10172 in Acute Stroke Treatment.

Discussion

Renal impairment contributes to the different distributions and clinical effects across specific stroke subtypes, particularly evident in cardioembolic stroke and small vessel occlusion. This possibly indicates shared mechanisms of susceptibility and potentially enhancing pathways.

Chronic kidney disease (CKD) affects as many as 9.1% (95% CI, 8.5–9.8) of the population worldwide.[1] The overall incidence of stroke in patients with CKD is more than twice that in individuals with normal kidney function.[2] There is an inverse linear relationship between estimated glomerular filtration rate (eGFR) and the risk of stroke, with a 7% increase in risk per 10 mL/min/1.73 m^2 decrease in eGFR.[3] The presence of proteinuria independently conferred a 2-fold higher risk of stroke compared to the absence of proteinuria.[4]

The mechanisms of increased stroke risk in CKD remain unclear, with possible contributions from shared traditional vascular risk factors and nontraditional risk factors induced by renal dysfunction.[5,6] The diverse contributing factors can lead to subsequent systemic vascular injury and endothelial impairment, which can inferentially predispose to any of the stroke subtypes.[7] Although ischemic stroke is classified into specific subtypes that have inherently heterogeneous pathogeneses, there is uncertainty and controversy regarding the predominant stroke subtypes in patients with CKD. The population-based OXVASC study reported no significant differences in stroke subtypes classified by the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria between patients with and without CKD, after adjusting for age, sex, and hypertension.[8]

Furthermore, CKD is associated with both short-term and long-term mortality after ischemic stroke.[6,9-12] Some studies have shown a positive association between eGFR strata and disability and death at discharge,[12,13] whereas other studies showed no apparent association.[11,14] It remains uncertain how renal impairment affects functional outcomes after each subtype of stroke.

The Japan Stroke Data Bank (JSDB), with its large collection of individual case-level data from acute stroke centers throughout Japan, can deliver comprehensive estimates of acute stroke clinical data in Japan.[15-17] We aimed to quantify the association between renal impairment (decreased eGFR or proteinuria) and acute ischemic stroke, expressed in terms of the proportion of ischemic stroke subtypes and functional outcomes after each stroke subtype, using the JSDB registry.

Methods

Data Source

The JSDB is an ongoing hospital-based multicenter prospective registry of patients with acute stroke in Japan. The JSDB has a registered database aimed at standardizing the acute treatment of stroke and is used to verify and establish evidence for the treatment of acute stroke. The unique aspects of this nationwide multicenter hospital-based registry are standardized clinical information, valid diagnosis of stroke, and acute management by stroke specialists. Detailed information on the JSDB was described previously.[15-17] JSDB collects the clinical diagnosis of acute stroke based on the professional evaluation of stroke specialists from high-volume stroke centers and academic teaching hospitals. Ischemic stroke was diagnosed according to TOAST criteria.[18] A total of 199,599 patients from 130 academic or regional stroke centers were enrolled from 1999 to 2019. Routine blood test and optional urine test at admission were collected from October 2016.

Standard Protocol Approvals, Registrations, and Patient Consents

The study protocol was approved by the institutional ethical board. Due to the anonymous nature of the data, individual consent for entry into the database was waived by the institution. Instead, opt-out consent method was used.

Patients

For the current analyses, patients with acute ischemic stroke with available data on baseline eGFR levels or dipstick proteinuria were eligible for inclusion. The study cohort was abstracted from October 2016 to December 2019, leaving 10,575 eligible patients. Of these, 10,392 patients met the following criteria and were included in the analysis: (1) age ≥18 years, (2) a diagnosis of a subtype of ischemic stroke, (3) available data on blood tests or urinalysis on admission, and (4) without kidney transplantation.

Data Collection

Data on hospitalization attributed to acute stroke were recorded by the study physicians or clinical report coordinators in each institute using a standardized form of the registry database. Clinical information on demographics, stroke

subtypes, neurologic impairment (National Institutes of Health Stroke Scale [NIHSS]), medical history, risk factors, medications, and functional outcomes at discharge (modified Rankin Scale [mRS]) were available in the database. Detailed protocols for outcome collection are described elsewhere.[15-17] Ischemic stroke was classified into 5 subtypes according to TOAST criteria: large artery stroke, cardioembolic stroke, small vessel occlusion, other determined etiology stroke, or undetermined etiology stroke.[18]

We defined renal impairment as eGFR <60 mL/min/1.73 m^2, elevated proteinuria, or both, according to the baseline test. The eGFR was estimated using the CKD–Epidemiology Collaboration Equation by Japanese formula.[19] We had a semiquantitative assessment of proteinuria with a dipstick test, indicating negative, trace, 1+, 2+, or 3+. The outcomes assessed were ischemic stroke subtypes, unfavorable functional outcome defined as mRS 3–6 at discharge, and in-hospital deaths.

Statistical Analysis

Descriptive statistics were used to summarize the baseline characteristics of the cohort stratified by eGFR strata. Continuous data were given as mean (SD) or median (interquartile range), as appropriate; categorical data were given as n (%). Mann-Whitney *U* and χ^2 tests were used to test the significance of differences between 2 groups for continuous and categorical variables, respectively. First, we modeled eGFR measures as continuous covariates (eGFR 1 SD decrease) and categorized eGFR into 3 categories (eGFR ≥60, eGFR 45–59, eGFR <45) (mL/min/1.73 m^2) based on the Kidney Disease: Improving Global Outcomes (KDIGO) guideline.[20] For cohorts with available baseline proteinuria, the proteinuria was categorized into 2 groups: negative or trace (reference) and 1+ or higher (present). Mixed effect binary logistic regression analyses using institutions as random intercepts were performed to calculate the odds ratio (OR) and 95% CI for evaluating the association of CKD measures with each ischemic stroke subtype or unfavorable functional outcome. The model for ischemic stroke subtypes was adjusted for age, sex, hypertension, diabetes, previous statin use, and atrial fibrillation. The model for unfavorable functional outcomes was adjusted for age, sex, hypertension, diabetes, history of stroke, previous statin use, previous antiplatelet use, alteplase or endovascular treatment, premorbid mRS, and initial NIHSS, using the stratified cohorts of each ischemic stroke subtype. We repeated further analyses restricted to patients receiving hemodialysis. We also performed an analysis of the combined effects of eGFR and proteinuria, in which we generated 4 categories by renal impairment (eGFR [≥60/<60 mL/min/1.73 m^2] with or without proteinuria); the category of eGFR ≥60 without proteinuria was set as a reference. We tested interacting effects of renal impairment and key characteristics (median age [≤75 or >75 years], sex, hypertension, diabetes, history of stroke, previous antiplatelet, previous statin, premorbid mRS [≤1 or >1], initial NIHSS [≤4 or >4]) by including the respective interaction terms in the models. We completed a sensitivity analysis for unfavorable functional outcomes in which we excluded patients receiving hemodialysis. We performed restricted cubic spline analyses with 3 knots (at 30, 45, and 60 mL/min/1.73 m^2) to explore the overall association between eGFR and ischemic stroke subtypes or unfavorable functional outcomes, calculating ORs at each 1 mL/min/1.73 m^2 increment. An eGFR of 60 mL/min/1.73 m^2 was used as a reference. The analyses were based on all the patients who had complete information. We did not impute missing values. We acknowledge the overinflation of type I error probability from multiple testing. As this work is considered hypothesis generating, all *p* values were 2-sided and a *p* value of <0.05 was considered statistically significant. The analyses were performed using STATA version 16 (Stata Corp LP).

Results

In total, 10,392 patients with acute ischemic stroke were included in this analysis (eFigure 1, links.lww.com/WNL/B860). The mean age was 74.3 ± 12.3 years and 68% were men. Of all studied patients, 10,022 (96%) underwent brain MRI on admission. The baseline characteristics of the 3 patient groups categorized according to eGFR strata are outlined in Table 1.

Association Between Renal Impairment and Ischemic Stroke Subtypes

Of all studied patients, 4,395 (42%) had eGFR <60, of whom 2,419 (23%) had eGFR 45–59, and 1,976 (19%) had eGFR <45 (mL/min/1.73 m^2), including 185 patients (1.8%) receiving hemodialysis. Of the 3,524 patients with available data for dipstick proteinuria, 838 (23%) had proteinuria. Figure 1 demonstrates the distributions of ischemic stroke subtypes according to eGFR strata and proteinuria. Cardioembolic stroke was more common and small vessel occlusion was less common in patients with eGFR <45 mL/min/1.73 m^2 or with proteinuria than in those with eGFR ≥60 mL/min/1.73 m^2 or without proteinuria.

In multivariate analysis, renal impairment measures (i.e., eGFR 45–59 mL/min/1.73 m^2, eGFR <45 mL/min/1.73 m^2, decreases in eGFR as continuous values, or proteinuria) were significantly associated with a higher proportion of cardioembolic stroke and a lower proportion of small vessel occlusion (Figure 2).

The adjusted restricted cubic spline analysis was consistent with these results (Figure 3 and eFigure 2, links.lww.com/WNL/B860). Lower eGFR levels were linearly associated with a higher proportion of cardioembolic stroke and lower proportion of small vessel occlusion (Figure 3).

In the analysis using the 4 categories with the combined effects of eGFR and proteinuria, all 3 categories had a higher proportion of cardioembolic stroke and a lower proportion of small vessel occlusion than the reference category of eGFR

Table 1 Patient Characteristics by eGFR Strata

Variable	eGFR ≥60 (n = 5,997)	eGFR 59–45 (n = 2,419)	eGFR <45 without HD (n = 1,795)	On HD (n = 185)	*p* Value
Age, y	71.4 ± 12.8	78.0 ± 9.9	79.7 ± 10.5	71.7 ± 10.8	<0.001
Male sex	4,240 (69)	1,629 (67)	1,150 (65)	126 (68)	0.001
Premorbid mRS	0 (0–1)	0 (0–2)	1 (0–3)	1 (0–2)	<0.001
Hypertension	3,646 (61)	1,627 (67)	1,283 (72)	132 (71)	<0.001
Antihypertensive agents (n = 8,734)	2,632/4,754 (56)	1,352/2,145 (63)	1,154/1,653 (70)	123/182 (68)	<0.001
Diabetes	1,511 (25)	616 (25)	587 (33)	85 (46)	<0.001
Dyslipidemia	1,872 (31)	802 (33)	537 (30)	45 (24)	0.046
Statin (n = 8,734)	1,023/4,754 (21)	575/2,145 (27)	458/1,653 (28)	42/182 (23)	<0.001
Atrial fibrillation	834 (14)	495 (20)	427 (24)	30 (16)	<0.001
History of stroke	1,344 (22)	695 (29)	561 (31)	66 (35)	<0.001
Antiplatelet agents (n = 8,734)	1,369/4,754 (29)	734/2,145 (34)	659/1,653 (39)	113/182 (62)	<0.001
Anticoagulant agents (n = 8,887)	622/4,754 (13)	396/2,145 (18)	373/1,653 (23)	18/182 (10)	<0.001
eGFR	78.7 ± 14.9	53.1 ± 4.3	32.1± 10.7	7.5 ± 3.7	<0.001
Proteinuria (n = 3,524)	314/1,994 (15)	219/861 (25)	307/668 (45)	NE	<0.001
SBP at admission, mm Hg	159 ± 28	158 ± 28	154 ± 31	159 ± 31	<0.001
DBP at admission, mm Hg	90 ± 18	88 ± 19	84 ± 20	84 ± 21	<0.001
Initial NIHSS score	3 (1–7)	3 (1–9)	4 (2–13)	4 (2–8)	<0.001
MRI in acute phase	5,836 (95)	2,322 (94)	1,691 (93)	173 (92)	<0.001
Alteplase treatment	531 (9)	258 (11)	182 (10)	13 (7)	0.062
Endovascular treatment	487 (8)	187 (8)	162 (9)	12 (6)	0.356
Duration of hospitalization	14 (9–24)	15 (9–26)	17 (10–29)	18 (11–33)	<0.001
mRS at discharge	2 (1–4)	2 (1–4)	3 (1–4)	3 (1–4)	<0.001
mRS 3–6 at discharge	2,233 (37)	1,053 (43)	983 (55)	99 (54)	<0.001
In-hospital death	161 (3)	89 (4)	132 (7)	7 (4)	<0.001

Abbreviations: DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HD = hemodialysis; mRS = modified Rankin scale; NE = not evaluable; NIHSS = National Institutes of Health Stroke Scale; SBP = systolic blood pressure.
Values are presented as frequency (%), mean ± SD, or median (interquartile range), as appropriate.

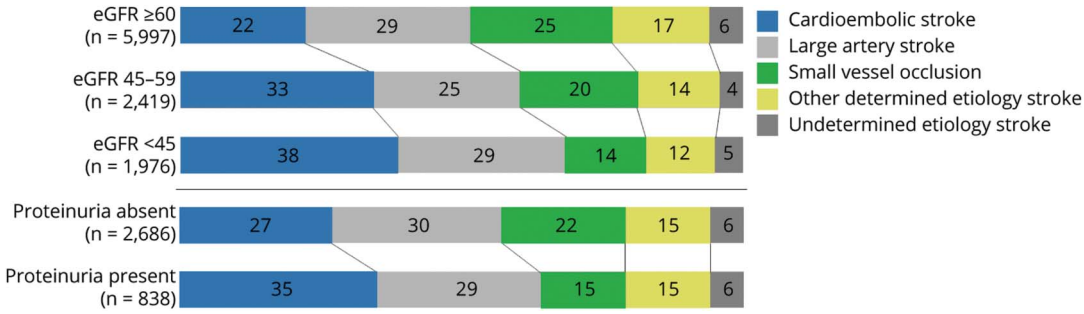
≥60 mL/min/1.73 m^2 without proteinuria (eFigure 3, links.lww.com/WNL/B860).

Association Between Renal Impairment and Unfavorable Functional Outcome

Figure 4 demonstrates the proportions of unfavorable functional outcomes in each ischemic stroke subtype. An inverse linear trend was observed between unfavorable outcomes and eGFR strata in all subtypes except for undetermined etiology stroke. In contrast, unfavorable outcomes were more common in patients with proteinuria than in those without proteinuria in all ischemic stroke subtypes.

In multivariate analysis, as compared to patients with eGFR ≥60 mL/min/1.73 m^2, patients with eGFR <45 mL/min/1.73 m^2 had a higher risk of unfavorable outcomes in cardioembolic stroke and small vessel occlusion (Figure 5). Proteinuria was also associated with a higher risk of unfavorable outcomes in these 2 subtypes (Figure 5). There was no significant heterogeneity of unfavorable outcome across the following variables: age, sex, hypertension, history of stroke, premorbid mRS, or initial NIHSS (eTables 1 and 2, links.lww.com/WNL/B860). Significant heterogeneity was observed for previous statin use in cardioembolic stroke and for diabetes or previous antiplatelet use in small vessel occlusion ($p_{interaction}$ <0.05) (eTables 1 and 2). In sensitivity analyses for patients not receiving hemodialysis, patients with eGFR <45 mL/min/1.73 m^2 showed a trend toward higher risk of unfavorable outcome in cardioembolic stroke (eFigure 4). Proteinuria remained significantly associated

Figure 1 Percentages of Ischemic Stroke Subtypes by Renal Impairment



The distributions of ischemic stroke subtypes according to estimated glomerular filtration rate (eGFR) strata and proteinuria.

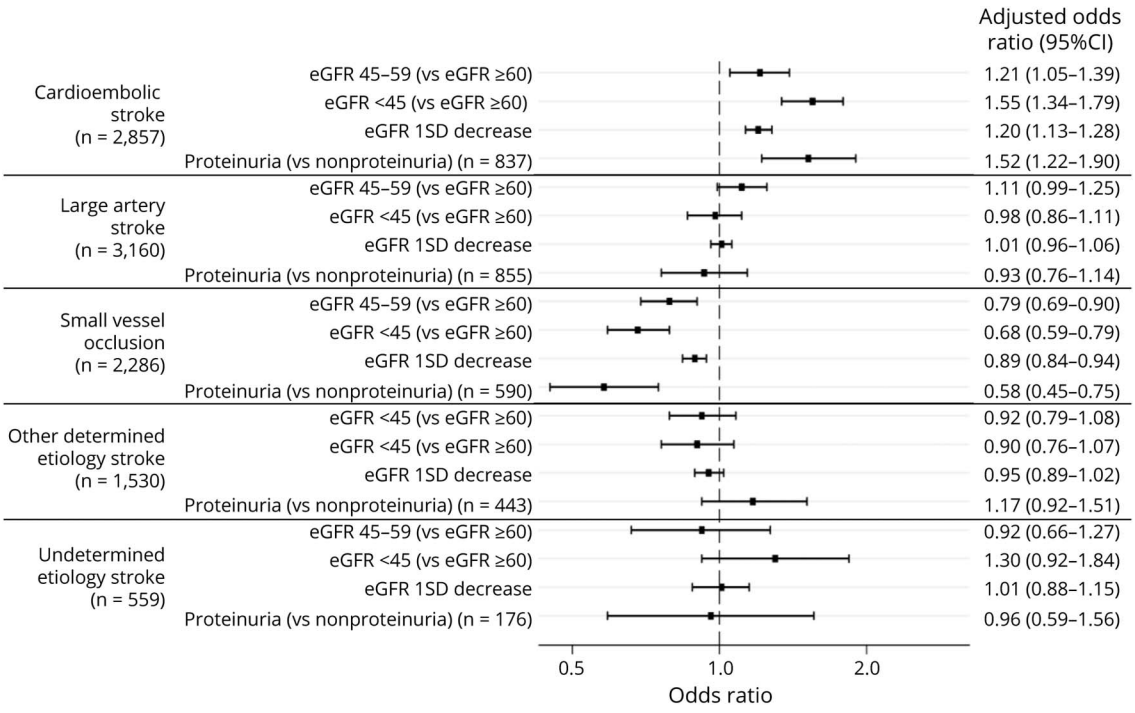
with unfavorable outcomes in patients with cardioembolic stroke (eFigure 4). In the adjusted restricted cubic spline analysis, a U-shaped association with a higher risk of unfavorable outcome at eGFR <30 and eGFR >60 mL/min/1.73 m^2 was observed for cardioembolic stroke (Figure 6 and eFigure 5). Lower levels at eGFR <40 mL/min/1.73 m^2 were also associated with a higher risk of unfavorable outcomes in patients with small vessel occlusion (Figure 6 and eFigure 5).

Compared with a joint reference category of eGFR ≥60 mL/min/1.73 m^2 without proteinuria, eGFR ≥60/<60 mL/min/1.73 m^2 with proteinuria was associated with a higher risk of unfavorable outcomes in cardioembolic stroke (eFigure 6, links.lww.com/WNL/B860).

Association Between Renal Impairment and In-Hospital Mortality

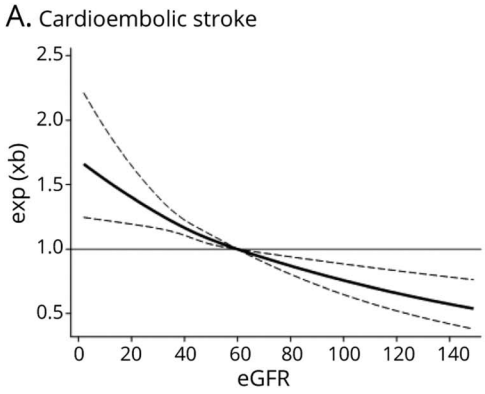
An inverse linear trend was observed between in-hospital death and eGFR strata in all subtypes except for undetermined etiology stroke (eFigure 7, links.lww.com/WNL/B860). In multivariate analysis, as compared to patients with eGFR ≥60 mL/min/1.73 m^2, patients with eGFR <45 mL/min/1.73 m^2 had a higher risk of in-hospital death in cardioembolic stroke and

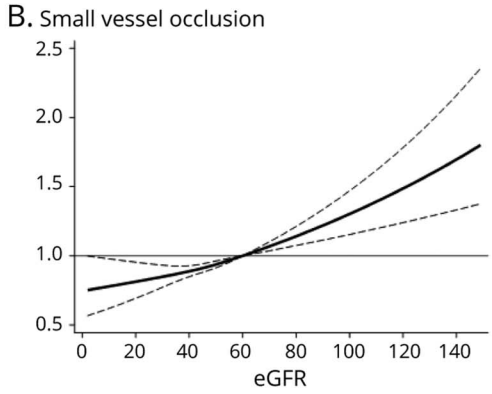
Figure 2 Associations Between Renal Impairment and Ischemic Stroke Subtypes



Odds ratio of renal impairment (estimated glomerular filtration rate [eGFR] 45–59 mL/min/1.73 m^2, eGFR <45 mL/min/1.73 m^2, decreases in eGFR, or proteinuria) vs eGFR ≥60 mL/min/1.73 m^2 or no proteinuria for the proportion of ischemic stroke subtypes. Risk estimates were adjusted for age, sex, hypertension, diabetes, previous statin use, and atrial fibrillation.

Figure 3 Associations Between All eGFR Levels and Ischemic Stroke Subtypes (Cardioembolic Stroke and Small Vessel Occlusion)





Odds ratios (ORs) for the proportion of (A) cardioembolic stroke and (B) small vessel occlusion by estimated glomerular filtration rate (eGFR) (per mL/min/1.73 m^2) using restricted cubic splines. Risk estimates were adjusted for age, sex, hypertension, diabetes, previous statin use, and atrial fibrillation. Solid lines represent the OR and dashed lines represent 95% CI. Knots were placed at 30, 45, and 60 mL/min/1.73 m^2 of eGFR. An eGFR of 60 mL/min/1.73 m^2 was used as a reference.

small vessel occlusion. Proteinuria was significantly associated with in-hospital death in other determined etiology stroke (eFigure 8).

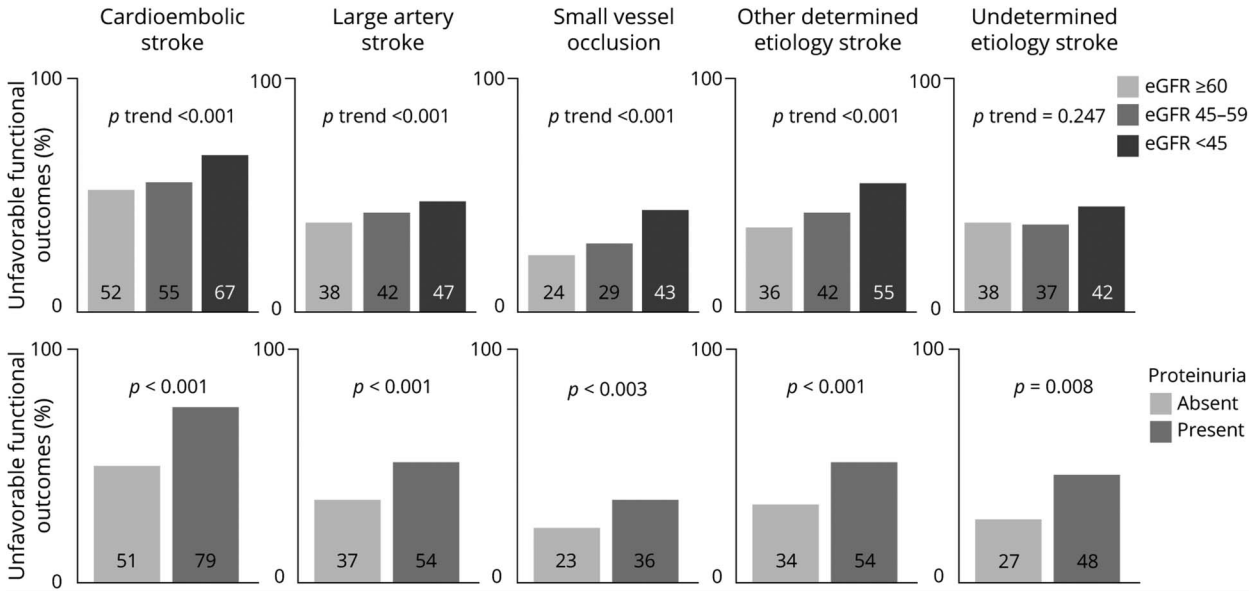
Associations of Hemodialysis With Ischemic Stroke Subtypes and Outcomes

In multivariate analysis, as compared to patients with eGFR ≥60 mL/min/1.73 m^2, patients receiving hemodialysis were significantly associated with a higher proportion of cardioembolic stroke and a lower proportion of large artery stroke, and had a higher risk of unfavorable outcomes in cardioembolic stroke (eTable 3, links.lww.com/WNL/B860).

Discussion

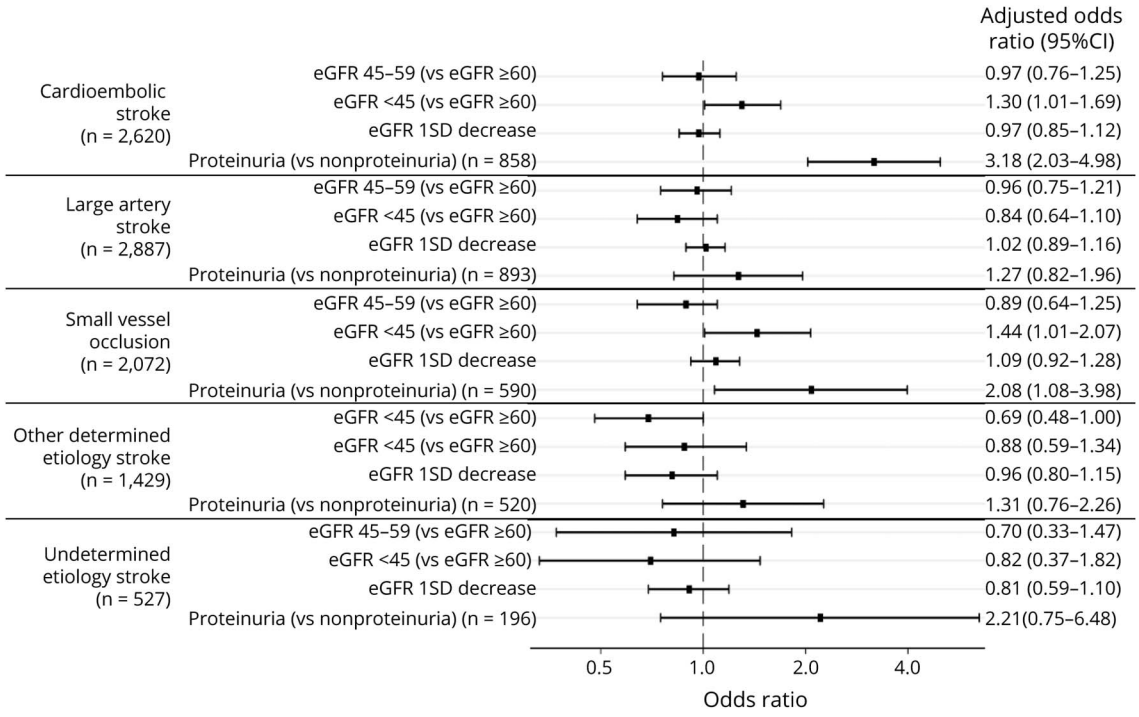
In this large, multicenter, prospective registry-based study, we identified a potential association between renal impairment, ischemic stroke subtypes, and subtype-specific functional outcomes. Renal impairment (decreased eGFR or proteinuria) was independently associated with a higher proportion of cardioembolic stroke and a lower proportion of small vessel occlusion. In categorical models with a comparison of eGFR ≥60 mL/min/1.73 m^2, eGFR < 45 mL/min/1.73 m^2 showed a significant association with unfavorable outcomes after cardioembolic stroke and small vessel occlusion. Lower eGFR <40 mL/min/1.73 m^2 was consistently

Figure 4 Proportions of Unfavorable Functional Outcomes in Ischemic Stroke Subtypes According to the eGFR Categories (≥60, 45–59, <45 mL/min/1.73 m2) or Proteinuria



Distribution of unfavorable functional outcomes in ischemic stroke subtypes according to estimated glomerular filtration rate (eGFR) strata and proteinuria.

Figure 5 Associations Between Renal Impairment and Unfavorable Functional Outcomes in Ischemic Stroke Subtypes

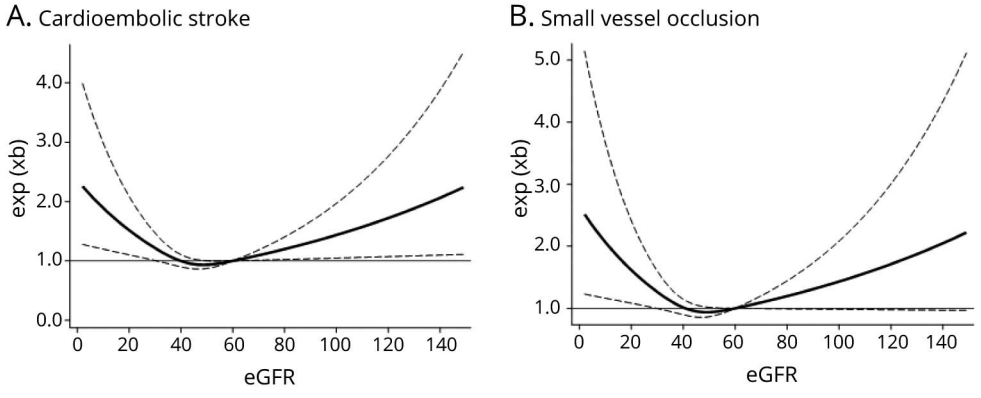


Odds ratio of renal impairment (estimated glomerular filtration rate [eGFR] 45–59 mL/min/1.73 m^2, eGFR <45 mL/min/1.73 m^2, decreases in eGFR, or proteinuria) vs eGFR ≥60 mL/min/1.73 m^2 or no proteinuria for unfavorable functional outcomes in ischemic stroke subtypes. Risk estimates were adjusted for age, sex, hypertension, diabetes, history of stroke, previous statin use, previous antiplatelet use, alteplase or endovascular treatment, premorbid modified Rankin Scale score, and initial National Institutes of Health Stroke Scale score.

significant for unfavorable outcomes in small vessel occlusion and cardioembolic stroke, while higher eGFR was slightly significant for unfavorable outcomes in cardioembolic stroke in spline models. Proteinuria was independently associated with unfavorable outcomes in patients with cardioembolic stroke and small vessel occlusion. There was no clear association between renal impairment and proportions/short term outcome in the other stroke subtypes (large vessel atherosclerosis and unknown/other causes).

CKD is associated with an increase in stroke risk via a combination of shared traditional vascular risk factors and secondary consequences of renal dysfunction such as chronic inflammation, oxidative stress, mineral bone disease, cerebral hypoperfusion, anemia, and systemic conditions.[5-7] CKD increases endothelial dysfunction, arterial media stiffness, intimal plaque atherosclerosis, and vascular calcification.[7,21] Furthermore, renal impairment causes alterations in hemostatic

Figure 6 Associations Between eGFR Levels and Unfavorable Functional Outcomes in Ischemic Stroke Subtypes (Cardioembolic Stroke and Small Vessel Occlusion)



Odds ratios (ORs) for unfavorable functional outcomes after (A) cardioembolic stroke and (B) small vessel occlusion by estimated glomerular filtration rate (eGFR) (per mL/min/1.73 m^2) using restricted cubic splines. Risk estimates were adjusted for age, sex, hypertension, diabetes, history of stroke, previous statin use, previous antiplatelet use, alteplase or endovascular treatment, premorbid modified Rankin Scale score, and initial National Institutes of Health Stroke Scale score. Solid lines represent the OR and dashed lines represent 95% CI. Knots were placed at 30, 45, and 60 mL/min/1.73 m^2 of eGFR. An eGFR of 60 mL/min/1.73 m^2 was used as a reference.

systems that may result in a prothrombotic state.[22,23] In patients with CKD, all of these factors could contribute to worsened initial neurologic severity and subsequent disability and mortality following both cardioembolic and noncardiogenic ischemic strokes.[5] Despite the underpinning pleiotropic mechanisms, there are few studies regarding the relative contribution of ischemic stroke subtypes in patients with CKD. The largest study with 3,178 patients from the OXVASC cohort showed a 10% increase in the proportion of cardioembolic stroke to all ischemic stroke in patients with CKD, as compared to those with normal renal function.[8] Although the increase was statistically significant after adjustment for sex and age, it was no longer significant after further adjustment for hypertension. The difference in the final statistical result between the OXVASC study and ours seemed to be due to the 3 times larger sample size of our study.[8] A small single-center study involving 451 patients also demonstrated an insignificant 10% increase in the proportion of cardioembolic stroke to all ischemic stroke in patients with vs without CKD.[24]

Our analyses consistently found that cardioembolic stroke accounted for the largest proportion of ischemic stroke subtypes in patients with renal impairment. A monotonic decrease in eGFR linearly increased the proportion of cardioembolic stroke. The consistency in both continuous and categorical models for eGFR showed that the association may be robust. Atrial fibrillation is highly common in the CKD population. In those patients on long-term maintenance hemodialysis, the incidence of atrial fibrillation is 2- to 3-fold higher than in the general population.[25,26] A number of mechanisms, such as concomitant vascular risk factors, heart failure, left atrial enlargement, diastolic dysfunction, myocardial fibrosis, activation of the renin-angiotensin-aldosterone system, and chronically elevated inflammatory status, have been proposed to cumulatively result in the development of atrial fibrillation in the CKD population and consequently enhance the risk of incident stroke.[22] A Danish registry study of >132,000 patients with atrial fibrillation reported that those with CKD had a 49% higher risk of stroke. Those on maintenance dialysis had an 83% higher risk of stroke than those without CKD after controlling for the CHA_2DS_2-VASc score and antithrombotic treatment.[27] Thus, advanced CKD is an independent risk factor for stroke in patients with atrial fibrillation.

Our study uniquely observed an inverse association between renal impairment and the proportion of small vessel occlusion. The OXVASC cohort reported that CKD was associated with a lower risk of small vessel disease in the crude model. However, these associations were no longer significant after adjustment for age, sex, and hypertension.[8] A plausible explanation for the lower proportion of small vessel occlusion with renal impairment may be attributable to a focus on symptomatic lacunar stroke, which was not entirely encompassed in the burden of accompanying cerebral small vessel disease.[28] A recent large genome-wide association study was conducted that consisted of patients with only European ancestry. It revealed a shared genetic susceptibility between renal impairment and specific stroke subtypes. This was particularly evident in large-artery stroke, small vessel occlusion, and intracerebral hemorrhage.[29] Nevertheless, the discrepancy might be explained by differences in the study design, methodology, and ethnicity. The nature of the current study could not infer the causal relationship.

To our knowledge, this is the first study to determine the association between renal impairment and clinical outcomes after specific ischemic stroke subtypes. Our new finding was that eGFR <45 mL/min/1.73 m^2 has a significant association with poststroke disability after small vessel occlusion and cardioembolic stroke. This suggests a potential predictive value of eGFR for these subtypes. Moreover, the monotonic increase in risk with a threshold eGFR begins to increase at <40 mL/min/1.73 m^2 in continuous models. This is largely consistent with the risk of eGFR <45 strata in categorical models. We also found that a high eGFR was slightly significant for functional outcomes after cardioembolic stroke, indicating a U-shaped association between eGFR levels and unfavorable outcomes after cardioembolic stroke. The U-shaped association with continuous eGFR levels has been demonstrated for all-cause mortality or cardiovascular mortality in meta-analyses of population-based studies.[30,31] A plausible explanation might be attributable to the potential presence of residual confounding variables despite a high eGFR, such as frailty due to reduced muscle mass.

This is also the first study to determine the association between proteinuria and specific ischemic stroke subtypes, especially cardioembolic stroke and small vessel occlusion. The association of proteinuria with ischemic stroke subtypes has rarely been examined. Two population-based longitudinal studies, both with few stroke events, showed a positive association between proteinuria and lacunar stroke, but not with cardioembolic stroke.[32,33] The current results, together with the results of eGFR and functional outcomes, suggest that lower eGFR or proteinuria manifest as the following: increased aging, advanced shared vascular risk factors, systemic diseases, and a cardioembolic milieu as compared to patients with a higher eGFR or without proteinuria. Moreover, we replicated previous reports of an association between albuminuria and unfavorable functional outcomes after overall ischemic stroke: proteinuria is more robust to clinical effect than eGFR levels.[14,34] The consistent effect of proteinuria on disability and mortality supports that increased proteinuria can reflect an integrated marker of endothelial damage at the glomerular level as well as of systemic microvascular injury including the brain,[35] suggesting compromises in blood–brain barrier integrity, which in turn could impede recovery after ischemic stroke.[36,37]

There was no significant association between renal impairment and the proportion of large artery stroke in this cohort. Although CKD might be associated with cerebral large artery disease via arterial medial calcification and stiffening of large arteries, it might be more strongly associated with the above-stated increased risks of atrial fibrillation and other etiologies

of cardioembolic stroke. Note that the nature of this study was the proportion, not the incidence, of each ischemic stroke subtype in patients with renal impairment. Prior studies also reported lack of association of renal impairment with proportions of large vessel stroke in overall cohorts.[7,23,38]

The lack of association between renal function and other determined etiology stroke could be due to the underlying heterogeneity of stroke cause. The recent pooled analysis also denied meaningful associations of renal impairment with recurrence and mortality after embolic stroke of undetermined source.[39]

A strength of this study was the much larger number of patients compared to previous studies with the same theme.[8] The large availability of neuroimaging and diagnosis to classify all cases of stroke by specialists also strengthened the study.

There are also inherent limitations. First, eGFR and proteinuria were based on single assessments at baseline, and they were affected by acute stroke. Accurate diagnosis for CKD was difficult because multiple data before stroke onset or at the chronic stage of stroke were not available. The lack of preadmission or repeated measurements of renal function could limit accurately identifying the clinical effect of renal impairment on stroke outcome. The renovascular dynamic data could provide crucial insights into the role of renal function for poststroke outcomes. Second, direct measurement of GFR, cystatin C–based method for calculating eGFR, or markers other than eGFR and proteinuria was not available in all cohorts. Third, we used only qualitative measurements using a dipstick test. However, a positive dipstick test is useful for risk stratification, despite being a less precise measure of albuminuria. Fourth, the mRS scores were only assessed at hospital discharge for all patients. Therefore, we cannot exclude the possibility that recovery continued to occur beyond hospital discharge. Finally, our data were restricted to Japanese individuals. This could limit the generalizability of our findings to other ethnicities.

Our study demonstrates the differential proportions and substantial clinical effects of low eGFR or proteinuria on ischemic stroke subtypes. Decreased eGFR and proteinuria conferred a higher proportion of cardioembolic stroke using real-world data. Severe renal impairment and proteinuria are independent risk factors for certain ischemic stroke subtypes and for an associated worse prognosis within these subtypes. The mechanisms underlying these associations should be explored in further studies.

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Disclosure

K. Toyoda reports personal fees from Daiichi-Sankyo, Bayer Yakuhin, Bristol-Myers-Squibb, Takeda, and Nippon Boehringer-Ingelheim, outside the submitted work. The remaining authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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Appendix 1 Authors

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Masatoshi Koga, MD, PhD	National Cerebral and Cardiovascular Center, Suita, Japan	Execution of JSDB, revised the manuscript for intellectual content
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Appendix 2 Coinvestigators

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