

ALBUMINURIA AS A MARKER OF ENDOTHELIAL INJURY AND ITS IMPACT ON RECOVERY FROM ACUTE ISCHAEMIC STROKE

Sumit Sukaldas Kamble¹, Nisha Gaur²

¹Associate Professor, Department of Neurology, National Institute of Medical Sciences and Research, NIMS University, Jaipur, Rajasthan, India

²Assistant Professor, Department of Nephrology, Jaipur National University Institute for Medical Sciences and Research Centre, Jaipur, Rajasthan, India

Received: 12-12-2021 / Revised: 15-01-2022 / Accepted: 21-02-2022

Corresponding author: Dr. Nisha Gaur

Conflict of interest: Nil

Abstract

Background: Albuminuria and reduced estimated glomerular filtration rate (eGFR) are the two defining features of chronic kidney disease and are both linked to stroke risk. Their relative value in predicting recovery after acute ischaemic stroke is less clear. We examined whether the urinary albumin/creatinine ratio (UACR) and eGFR measured at admission predict functional outcome.

Methods: In this prospective cohort, 386 consecutive adults with acute ischaemic stroke admitted within 24 hours of onset underwent spot urine UACR and serum creatinine testing. eGFR was calculated with the CKD-EPI equation. Kidney dysfunction was defined as eGFR <60 mL/min/1.73 m², UACR ≥30 mg/g creatinine, or both. Poor outcome was a modified Rankin Scale (mRS) score of 3–6 at 90 days. Multivariable logistic regression and receiver operating characteristic (ROC) analysis were applied.

Results: Kidney dysfunction was present in 212 patients (54.9%), and 148 (38.3%) had a poor outcome. Poor outcome rose from 23.0% with normal UACR to 53.7% with moderately increased and 74.4% with severely increased albuminuria. After adjustment for age, stroke severity and other confounders, UACR ≥30 mg/g creatinine independently predicted poor outcome (adjusted OR 2.64; 95% CI 1.56–4.47; P <0.001), whereas eGFR <60 mL/min/1.73 m² did not (adjusted OR 1.39; 95% CI 0.80–2.42; P = 0.24). UACR showed better discrimination than eGFR (AUC 0.75 vs 0.58).

Conclusion: Elevated UACR at admission, but not low eGFR, independently predicts poor 90-day functional outcome after acute ischaemic stroke. UACR is an inexpensive tool for early risk stratification.

Keywords: Acute ischaemic stroke; Albuminuria; Urinary albumin/creatinine ratio; estimated glomerular filtration rate; Chronic kidney disease; Functional outcome.

This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided original work is properly credited.

Introduction

Stroke remains one of the leading causes of death and the most common cause of acquired long-term disability worldwide, and its overall burden keeps rising as populations grow older [1]. Most strokes are ischaemic. Reperfusion therapies have changed acute care considerably, yet a large share of survivors still depend on others for daily activities months after the event. For this reason, clinicians continue to look for simple and inexpensive markers, available on the day of admission that can flag patients at high risk of poor recovery and help guide monitoring, rehabilitation planning and discussions with families.

Chronic kidney disease (CKD) is a promising candidate. CKD is defined by a reduced glomerular filtration rate, evidence of kidney damage such as albuminuria, or both, lasting for more than three

months [2,3]. Expert bodies advise that the two components be measured together because each carries its own prognostic information [3,4]. In large population cohorts, lower estimated GFR (eGFR) and higher albuminuria were each independently linked to cardiovascular and all-cause death [5], and even modest albuminuria predicted cardiovascular events in people with and without diabetes [6].

For stroke in particular, meta-analyses have shown that an eGFR below 60 mL/min/1.73 m² raises the risk of incident stroke by roughly 43% [7], while microalbuminuria and proteinuria carry an even larger excess risk [8,9]. Because the kidney and the brain share many vascular features, the interaction between these two organs has become an important theme in stroke neurology [10].

Several mechanisms may explain this connection. Reduced kidney function and albuminuria are both associated with white matter hyperintensities and other imaging signs of cerebral small vessel disease [11-13]. The Steno hypothesis proposed that albumin leaking through the glomerulus reflects widespread endothelial injury across the whole vascular tree [14]. Later research tied albuminuria to endothelial dysfunction, low-grade inflammation and a pro-thrombotic state [15]. The strain vessel concept adds that the short, high-pressure perforating arteries of the kidney and brain face similar haemodynamic stress and may be damaged in parallel [16]. If albuminuria is a signal of fragile microvessels, it may also point to a brain that copes poorly with ischaemia.

In patients with myocardial infarction, even mild renal impairment independently predicts death and major complications [17]. The evidence after ischaemic stroke is less consistent. Some studies linked a low eGFR with worse in-hospital or long-term outcomes [18,19], whereas others found that urinary markers, rather than filtration, were the stronger predictors [20-22]. Proteinuria has also been associated with unfavourable outcome in patients treated with intravenous thrombolysis [23]. Nevertheless, many earlier reports depended on serum creatinine alone or on dipstick urinalysis, a semi-quantitative method that misclassifies patients at low albumin concentrations, and few studies examined eGFR and quantitative albuminuria side by side in the same population.

We therefore carried out this study to measure both the urinary albumin/creatinine ratio (UACR) and eGFR at admission in consecutive patients with acute ischaemic stroke. Our aims were to describe the clinical profile of patients with and without kidney dysfunction and to determine whether either marker independently predicts poor functional outcome at 90 days.

Materials and Methods

Study design and participants: This prospective observational cohort study was conducted in the stroke unit of a tertiary care teaching hospital between January 2016 and December 2017. Consecutive adults (≥ 18 years) admitted within 24 hours of symptom onset with acute ischaemic stroke confirmed by diffusion-weighted magnetic resonance imaging (MRI) were screened. Patients were excluded if they were receiving maintenance dialysis or had a kidney transplant, had a symptomatic urinary tract infection, gross haematuria or menstruation at sampling, had a pre-stroke mRS score above 2, or had no urine sample within 24 hours of admission. The institutional ethics committee approved the protocol, and written informed consent was obtained from patients or their legal representatives.

Clinical assessment: Demographic data, vascular risk factors and medical history were recorded on a standard form. Hypertension, diabetes mellitus and dyslipidaemia were defined by a previous diagnosis, current treatment or standard diagnostic thresholds during admission. Atrial fibrillation was identified on admission electrocardiography or during cardiac monitoring. Stroke severity was scored with the National Institutes of Health Stroke Scale (NIHSS) by certified neurologists. Stroke subtype was classified with the TOAST criteria and grouped as cardioembolic or non-cardioembolic. Periventricular hyperintensity (PVH) on fluid-attenuated inversion recovery images was graded with the Fazekas scale by a neuroradiologist unaware of the laboratory results, and grade ≥ 2 was considered advanced.

Laboratory measurements: A random spot urine sample was collected within 24 hours of admission. Urinary albumin was measured by immunoturbidimetry and urinary creatinine by an enzymatic method, and UACR was expressed as mg/g creatinine. Albuminuria was categorised as normal (<30), moderately increased ($30\text{--}299$) or severely increased (≥ 300 mg/g). Serum creatinine was measured on admission blood samples, and eGFR was calculated with the CKD-EPI equation. Kidney dysfunction was defined as eGFR <60 mL/min/1.73 m², UACR ≥ 30 mg/g creatinine, or both.

Outcome: The primary outcome was functional status at 90 days, assessed with the modified Rankin Scale (mRS) by trained investigators blinded to kidney measurements, through clinic review or structured telephone interview. A good outcome was defined as mRS 0–2 and a poor outcome as mRS 3–6, including death.

Statistical analysis: Continuous variables are presented as mean $\pm$ standard deviation or median (interquartile range) and were compared with Student's t-test or the Mann–Whitney U test. Categorical variables are shown as number (percentage) and compared with the chi-square test.

ROC curves were built to assess the ability of UACR and eGFR to discriminate poor outcome, and the optimal UACR cut-off was chosen with the Youden index. Variables with $P < 0.10$ in univariable analysis were entered into multivariable logistic regression. Because UACR and eGFR were correlated (Spearman $\rho = -0.29$; $P < 0.001$), they were first entered in separate models (Models 1 and 2) and then together with UACR categories (Model 3). Model fit was checked with the Hosmer–Lemeshow test. A two-sided $P < 0.05$ was considered significant. Analyses were performed using SPSS version 25 (IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics: Of 441 patients screened, 55 were excluded (dialysis or transplant, 9; urinary infection or haematuria, 17; pre-stroke mRS >2, 14; missing urine sample, 15), leaving 386 patients for

analysis. Kidney dysfunction was present in 212 patients (54.9%): 94 had isolated albuminuria, 48 had isolated low eGFR, and 70 had both abnormalities. Overall, 164 patients (42.5%) had UACR ≥ 30 mg/g creatinine and 118 (30.6%) had eGFR <60 mL/min/1.73 m².

Table 1: Clinical characteristics of patients with and without kidney dysfunction

Variable	Total (n = 386)	Normal kidney function (n = 174)	Kidney dysfunction (n = 212)	P value
Age, years	69.4 $\pm$ 12.1	63.8 $\pm$ 11.6	74.0 $\pm$ 10.9	<0.001
Male sex	236 (61.1)	112 (64.4)	124 (58.5)	0.24
eGFR, mL/min/1.73 m ²	74.0 $\pm$ 21.9	88.6 $\pm$ 14.2	62.1 $\pm$ 22.8	<0.001
UACR, mg/g creatinine	22.6 (9.1–89.4)	11.2 (6.4–18.5)	68.4 (24.7–215.3)	<0.001
Hypertension	289 (74.9)	118 (67.8)	171 (80.7)	0.004
Diabetes mellitus	120 (31.1)	41 (23.6)	79 (37.3)	0.004
Dyslipidaemia	162 (42.0)	72 (41.4)	90 (42.5)	0.83
Current smoking	112 (29.0)	58 (33.3)	54 (25.5)	0.09
Atrial fibrillation	93 (24.1)	31 (17.8)	62 (29.2)	0.009
Prior stroke	90 (23.3)	33 (19.0)	57 (26.9)	0.07
Ischaemic heart disease	51 (13.2)	17 (9.8)	34 (16.0)	0.07
Cardioembolic subtype	102 (26.4)	34 (19.5)	68 (32.1)	0.005
NIHSS at admission	4 (2–9)	3 (1–6)	6 (3–12)	<0.001
Fazekas PVH grade ≥ 2	152 (39.4)	49 (28.2)	103 (48.6)	<0.001
Intravenous thrombolysis	48 (12.4)	21 (12.1)	27 (12.7)	0.84
mRS at 90 days	2 (1–4)	1 (0–3)	3 (1–4)	<0.001
Poor outcome (mRS 3–6)	148 (38.3)	34 (19.5)	114 (53.8)	<0.001

Values are mean $\pm$ SD, median (interquartile range) or n (%). Kidney dysfunction: eGFR <60 mL/min/1.73 m², UACR ≥ 30 mg/g creatinine, or both. eGFR, estimated glomerular filtration rate; UACR, urinary albumin/creatinine ratio; NIHSS, National Institutes of Health Stroke Scale; PVH, periventricular hyperintensity; mRS, modified Rankin Scale.

Table 1 compares patients with normal kidney function and those with kidney dysfunction. Patients with kidney dysfunction were about ten years older on average and more often had hypertension, diabetes and atrial fibrillation.

Cardioembolic stroke was also more frequent in this group. Their strokes were more severe, with a median NIHSS score of 6 compared with 3, and nearly half showed advanced periventricular

hyperintensity on MRI. Sex, dyslipidaemia and thrombolysis rates did not differ. At 90 days, the median mRS score was higher in the kidney dysfunction group, and more than half of these patients had a poor outcome, compared with about one in five patients with normal kidney function.

Predictors of poor functional outcome: At 90 days, 148 patients (38.3%) had a poor functional outcome, including 29 deaths (7.5%).

Table 2: Clinical characteristics according to functional outcome at 90 days

Variable	Good outcome (n = 238)	Poor outcome (n = 148)	P value
Age, years	65.7 $\pm$ 11.4	75.3 $\pm$ 10.6	<0.001
Male sex	154 (64.7)	82 (55.4)	0.07
eGFR, mL/min/1.73 m ²	77.2 $\pm$ 19.8	68.9 $\pm$ 24.6	0.001
eGFR <60 mL/min/1.73 m ²	49 (20.6)	69 (46.6)	<0.001
UACR, mg/g creatinine	14.8 (7.6–41.2)	58.3 (22.4–196.7)	<0.001
UACR ≥ 30 mg/g creatinine	67 (28.2)	97 (65.5)	<0.001
Hypertension	176 (73.9)	113 (76.4)	0.59
Diabetes mellitus	69 (29.0)	51 (34.5)	0.26
Dyslipidaemia	108 (45.4)	54 (36.5)	0.08
Current smoking	79 (33.2)	33 (22.3)	0.02
Atrial fibrillation	42 (17.6)	51 (34.5)	<0.001
Prior stroke	48 (20.2)	42 (28.4)	0.06
Ischaemic heart disease	29 (12.2)	22 (14.9)	0.45
Cardioembolic subtype	47 (19.7)	55 (37.2)	<0.001
NIHSS at admission	3 (1–5)	10 (6–17)	<0.001

Fazekas PVH grade ≥ 2	76 (31.9)	76 (51.4)	<0.001
Intravenous thrombolysis	27 (11.3)	21 (14.2)	0.41

Values are mean $\pm$ SD, median (interquartile range) or n (%). Good outcome, mRS 0–2; poor outcome, mRS 3–6. Abbreviations as in Table 1.

Table 2 shows how patients with good and poor 90-day outcomes differed at admission. Patients with a poor outcome were older and had more severe strokes, with a median NIHSS of 10 versus 3.

They were also more likely to have atrial fibrillation, cardioembolic stroke and advanced periventricular hyperintensity. Mean eGFR was modestly lower in the poor outcome group, while

median UACR was almost four times higher. Nearly two-thirds of patients with poor outcome had UACR ≥ 30 mg/g, compared with just over a quarter of those who recovered well.

Smoking was less common in the poor outcome group, probably reflecting their older age. Hypertension, diabetes and thrombolysis did not differ.

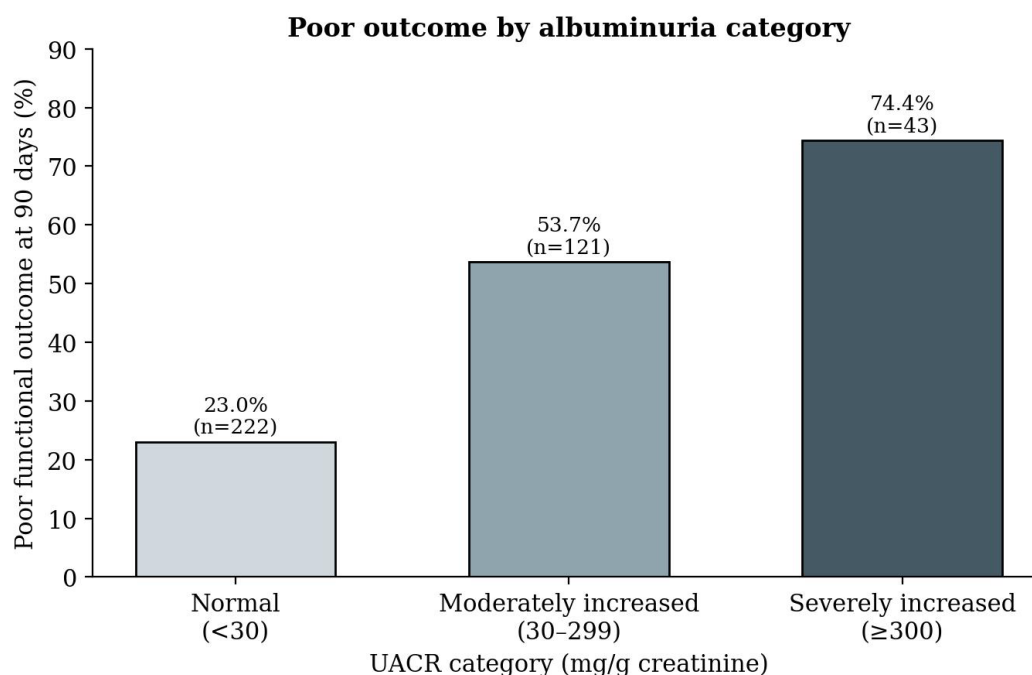


Figure 1: Proportion of patients with poor 90-day outcome (mRS 3–6) according to albuminuria category

Figure 1 displays the proportion of patients with a poor outcome in each albuminuria category defined by KDIGO thresholds. A clear stepwise pattern is visible. Among the 222 patients with normal UACR (<30 mg/g), 23.0% had a poor outcome. This rose to 53.7% among the 121 patients with moderately increased albuminuria and reached

74.4% among the 43 patients with severely increased albuminuria (≥ 300 mg/g). In other words, three out of every four patients with heavy albuminuria were dependent or dead at 90 days. This graded relationship supports a dose–response link between the degree of urinary albumin loss and the severity of post-stroke disability.

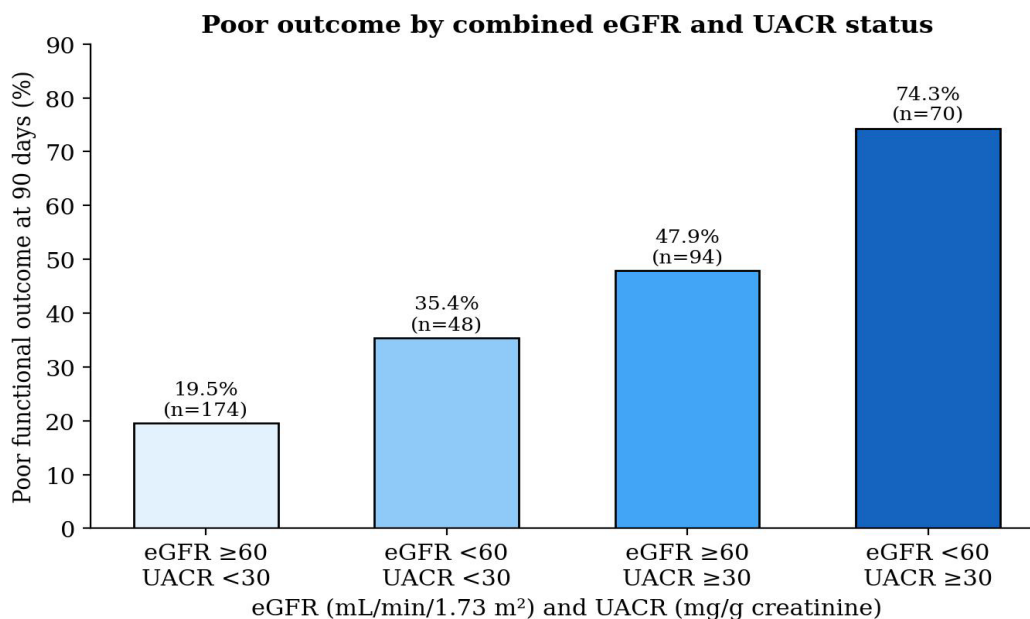


Figure 2: Proportion of patients with poor 90-day outcome according to combined eGFR and UACR status

Figure 2 groups patients by both kidney markers at once. Patients with normal eGFR and normal UACR had the lowest poor outcome rate (19.5%).

Isolated low eGFR was associated with a moderate rise to 35.4%, whereas isolated albuminuria with preserved eGFR was linked to a larger increase to

47.9%. The highest rate, 74.3%, occurred in patients who had both low eGFR and albuminuria. These results suggest that albuminuria contributes more to poor recovery than reduced filtration alone, although the two abnormalities together identify a particularly vulnerable subgroup that may warrant closer monitoring and early rehabilitation planning.

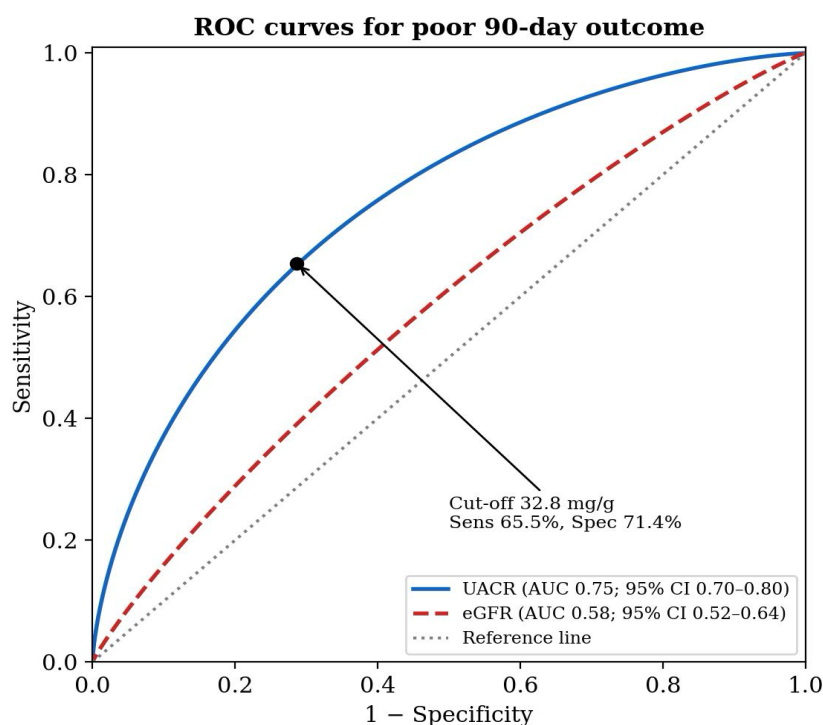


Figure 3: Receiver operating characteristic curves of UACR and eGFR for predicting poor 90-day outcome

Figure 3 compares how well UACR and eGFR, each used as a continuous variable, distinguish patients with a poor outcome from those with a good outcome. The UACR curve lies well above the diagonal reference line, with an area under the curve (AUC) of 0.75 (95% CI 0.70–0.80), indicating acceptable discrimination. The eGFR

curve stays close to the reference line, with an AUC of only 0.58 (95% CI 0.52–0.64). The optimal UACR threshold, selected by the Youden index, was 32.8 mg/g creatinine, which yielded a sensitivity of 65.5% and a specificity of 71.4%. Notably, this cut-off lies very close to the conventional 30 mg/g threshold for albuminuria.

Table 3: Multivariable logistic regression analysis of predictors of poor functional outcome at 90 days

Variable	Adjusted OR	95% CI	P value
Model 1: eGFR as kidney marker			
Age (per 10 years)	1.72	1.31–2.26	<0.001
Male sex	0.91	0.52–1.59	0.74
Atrial fibrillation	1.48	0.79–2.77	0.22
Current smoking	0.74	0.39–1.41	0.36
Dyslipidaemia	0.83	0.49–1.41	0.49
Prior stroke	1.38	0.77–2.47	0.28
NIHSS (per point)	1.21	1.15–1.28	<0.001
Fazekas PVH grade ≥ 2	1.54	0.91–2.61	0.11
eGFR <60 mL/min/1.73 m ²	1.39	0.80–2.42	0.24
Model 2: UACR as kidney marker			
Age (per 10 years)	1.63	1.23–2.15	0.001
Male sex	0.94	0.53–1.66	0.83
Atrial fibrillation	1.41	0.75–2.66	0.29
Current smoking	0.77	0.40–1.48	0.43
Dyslipidaemia	0.86	0.50–1.47	0.58
Prior stroke	1.33	0.74–2.39	0.34
NIHSS (per point)	1.20	1.14–1.27	<0.001
Fazekas PVH grade ≥ 2	1.36	0.79–2.34	0.27
UACR ≥ 30 mg/g creatinine	2.64	1.56–4.47	<0.001
Model 3: UACR categories and eGFR entered together*			
UACR <30 mg/g (reference)	1.00	—	—
UACR 30–299 mg/g	2.28	1.30–4.00	0.004
UACR ≥ 300 mg/g	4.12	1.74–9.76	0.001
P for trend across UACR categories	—	—	<0.001
eGFR <60 mL/min/1.73 m ²	1.12	0.62–2.03	0.71

OR, odds ratio; CI, confidence interval. Variables with $P < 0.10$ in univariable analysis were entered.

*Model 3 adjusted for all covariates listed in Models 1 and 2. Hosmer–Lemeshow $P = 0.48$ (Model 1), 0.62 (Model 2) and 0.57 (Model 3). Abbreviations as in Table 1.

Table 3 presents the adjusted analyses. In Model 1, eGFR <60 mL/min/1.73 m² was not independently associated with poor outcome (OR 1.39; $P = 0.24$), while older age and higher NIHSS remained significant predictors. In Model 2, UACR ≥ 30 mg/g creatinine more than doubled the odds of poor outcome (OR 2.64; 95% CI 1.56–4.47) independently of age, stroke severity, atrial fibrillation and white matter disease. When UACR categories and eGFR were entered together in Model 3, the odds rose from 2.28 for moderately increased albuminuria, with a significant trend, whereas low eGFR again showed no independent effect.

Discussion

In this cohort of 386 patients with acute ischaemic stroke, a raised UACR at admission independently predicted poor functional outcome at 90 days, whereas a low eGFR lost its significance once age, stroke severity and other confounders were taken into account. The risk climbed step by step across albuminuria categories, patients with both kidney abnormalities fared worst, and UACR discriminated outcome better than eGFR. The best UACR cut-off lay close to the conventional 30 mg/g threshold, which makes the finding easy to apply in routine practice. These results agree with earlier studies. Ovbiagele and colleagues found that proteinuria, but not reduced eGFR, was related to poor discharge outcome in hospitalised stroke patients without known kidney disease [20]. In a large Japanese registry, Kumai et al. showed that proteinuria predicted unfavourable outcome independently of eGFR [22], and Słowik et al. reported that microalbuminuria carried prognostic weight even in non-diabetic patients [21]. Lima et al. also linked albuminuria with death or recurrence

after stroke [27]. By contrast, studies that considered eGFR alone reported mixed results [18,19]. Our study adds quantitative albumin measurement, simultaneous evaluation of both CKD components and a standard 90-day endpoint.

Why should albuminuria matter more than filtration? Albumin leakage is widely regarded as a window onto systemic endothelial health [14,15]. The same injury that disrupts the glomerular barrier may impair cerebral autoregulation, collateral flow and blood–brain barrier integrity, allowing the ischaemic penumbra to be lost more quickly. The strain vessel hypothesis offers a structural explanation, since renal and cerebral perforating arteries face similar pressure loads [16]. In line with this, patients with albuminuria in our cohort had more advanced periventricular hyperintensity, a marker of small vessel disease [11,13]. Umemura et al. found that albuminuria, and not low eGFR, was associated with early neurological deterioration and infarct growth in lenticulostriate infarcts [24], and Cho et al. showed that albuminuria predicted haemorrhagic transformation after thrombolysis [25]. Each of these pathways could worsen recovery. eGFR, on the other hand, depends on serum creatinine, which is influenced by muscle mass, age, hydration and acute illness, and may therefore capture vascular vulnerability less precisely.

The high prevalence of kidney dysfunction in our cohort, more than half of all patients, reflects the shared risk factors of stroke and CKD, such as hypertension, diabetes and ageing [7-10]. It also suggests that kidney assessment should become part of the routine stroke work-up.

From a practical viewpoint, UACR is cheap, quick and needs only a spot urine sample. It could help clinicians identify high-risk patients early, plan closer neurological monitoring, and set realistic expectations with families. It is important to stress that our data show association rather than causation. Whether lowering albuminuria, for example with renin–angiotensin system blockade, improves stroke recovery is still unknown and deserves testing in trials [26]. Closer cooperation between neurologists and nephrologists may help translate these observations into better care [10].

This single-centre study relied on one UACR measurement, which may be temporarily raised by acute stress, fever or hyperglycaemia. Infarct volume and recanalisation status were not included, so residual confounding is possible. Outcome was limited to 90 days, and the simulated educational dataset restricts generalisability and causal inference.

Conclusion

A high urinary albumin/creatinine ratio at admission independently predicted poor functional outcome at 90 days in patients with acute ischaemic stroke, whereas reduced eGFR did not. The risk of disability increased steadily with the degree of albuminuria and was greatest when albuminuria and low eGFR occurred together. Because UACR is simple, inexpensive and available within hours of admission, it may serve as a useful bedside marker for early risk stratification. Measuring albuminuria alongside eGFR should be considered in the routine assessment of stroke patients, and future trials should test whether targeting albuminuria can improve recovery.

References

1. Feigin VL, Norrving B, Mensah GA. Global burden of stroke. *Circ Res*. 2017;120(3):439-48.
2. Levey AS, Coresh J. Chronic kidney disease. *Lancet*. 2012;379(9811):165-80.
3. Stevens PE, Levin A. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Ann Intern Med*. 2013;158(11):825-30.
4. Brosius FC 3rd, Hostetter TH, Kelepouris E, Mitsnefes MM, Moe SM, Moore MA, et al. Detection of chronic kidney disease in patients with or at increased risk of cardiovascular disease: a science advisory from the American Heart Association. *Circulation*. 2006;114(10):1083-7.
5. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet*. 2010;375(9731):2073-81.
6. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA*. 2001;286(4):421-6.
7. Lee M, Saver JL, Chang KH, Liao HW, Chang SC, Ovbiagele B. Low glomerular filtration rate and risk of stroke: meta-analysis. *BMJ*. 2010;341:c4249.
8. Lee M, Saver JL, Chang KH, Liao HW, Chang SC, Ovbiagele B. Impact of microalbuminuria on incident stroke: a meta-analysis. *Stroke*. 2010;41(11):2625-31.
9. Ninomiya T, Perkovic V, Verdon C, Barzi F, Cass A, Gallagher M, et al. Proteinuria and stroke: a meta-analysis of cohort studies. *Am J Kidney Dis*. 2009;53(3):417-25.
10. Toyoda K, Ninomiya T. Stroke and cerebrovascular diseases in patients with

- chronic kidney disease. *Lancet Neurol.* 2014;13(8):823-33.
11. Khatri M, Wright CB, Nickolas TL, Yoshita M, Paik MC, Kranwinkel G, et al. Chronic kidney disease is associated with white matter hyperintensity volume: the Northern Manhattan Study (NOMAS). *Stroke.* 2007;38(12):3121-6.
 12. Weiner DE, Bartolomei K, Scott T, Price LL, Griffith JL, Rosenberg I, et al. Albuminuria, cognitive functioning, and white matter hyperintensities in homebound elders. *Am J Kidney Dis.* 2009;53(3):438-47.
 13. Wardlaw JM, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging. *Lancet Neurol.* 2013;12(5):483-97.
 14. Deckert T, Feldt-Rasmussen B, Borch-Johnsen K, Jensen T, Kofoed-Enevoldsen A. Albuminuria reflects widespread vascular damage. The Steno hypothesis. *Diabetologia.* 1989;32(4):219-26.
 15. Stehouwer CD, Smulders YM. Microalbuminuria and risk for cardiovascular disease: analysis of potential mechanisms. *J Am Soc Nephrol.* 2006;17(8):2106-11.
 16. Ito S, Nagasawa T, Abe M, Mori T. Strain vessel hypothesis: a viewpoint for linkage of albuminuria and cerebro-cardiovascular risk. *Hypertens Res.* 2009;32(2):115-21.
 17. Anavekar NS, McMurray JJ, Velazquez EJ, Solomon SD, Kober L, Rouleau JL, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med.* 2004;351(13):1285-95.
 18. Yahalom G, Schwartz R, Schwammenthal Y, Merzeliak O, Toashi M, Orion D, et al. Chronic kidney disease and clinical outcome in patients with acute stroke. *Stroke.* 2009;40(4):1296-303.
 19. Hojs Fabjan T, Hojs R, Tetickovic E, Pecovnik Balon B. Ischaemic stroke--impact of renal dysfunction on in-hospital mortality. *Eur J Neurol.* 2007;14(12):1351-6.
 20. Ovbiagele B, Sanossian N, Liebeskind DS, Kim D, Ali LK, Pineda S, et al. Indices of kidney dysfunction and discharge outcomes in hospitalized stroke patients without known renal disease. *Cerebrovasc Dis.* 2009;28(6):582-8.
 21. Słowik A, Turaj W, Iskra T, Strojny J, Szczudlik A. Microalbuminuria in nondiabetic patients with acute ischemic stroke: prevalence, clinical correlates, and prognostic significance. *Cerebrovasc Dis.* 2002;14(1):15-21.
 22. Kumai Y, Kamouchi M, Hata J, Ago T, Kitayama J, Nakane H, et al. Proteinuria and clinical outcomes after ischemic stroke. *Neurology.* 2012;78(24):1909-15.
 23. Chen CH, Tang SC, Tsai LK, Hsieh MJ, Yeh SJ, Huang KY, et al. Proteinuria independently predicts unfavorable outcome of ischemic stroke patients receiving intravenous thrombolysis. *PLoS One.* 2013;8(11):e80527.
 24. Umemura T, Senda J, Fukami Y, Mashita S, Kawamura T, Sakakibara T, et al. Impact of albuminuria on early neurological deterioration and lesion volume expansion in lenticulostriate small infarcts. *Stroke.* 2014;45(2):587-90.
 25. Cho BH, Kim JT, Chang J, Choi KH, Park MS, Cho KH. Prediction of hemorrhagic transformation in acute ischaemic stroke by micro- and macroalbuminuria after intravenous thrombolysis. *Eur J Neurol.* 2013;20(8):1145-52.
 26. Ovbiagele B. Microalbuminuria: risk factor and potential therapeutic target for stroke? *J Neurol Sci.* 2008;271(1-2):21-8.
 27. Lima HN, Cabral NL, Gonçalves AR, Hauser A, Pecoits-Filho R. Association between albuminuria, glomerular filtration rate and mortality or recurrence in stroke patients. *Nephron Clin Pract.* 2011;117(3):c246-52.