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Urinary Albumin/Creatinine Ratio (UACR) Vsegfr as Predictors of Functional Outcome in Patients with Acute Ischemic Stroke Who Hasn't Received Intravenous Thrombolysis

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ABSTRACT:
BACKGROUND/AIM
Albuminuria and a low estimated glomerular filtration rate (eGFR) are widely recognised indices of kidney dysfunction and have been linked to cardiovascular events, including stroke. We evaluated albuminuria, measured using the urinary albumin/creatinine ratio (UACR), and the eGFR in the acute phase of ischemic stroke, and investigated the clinical characteristics of ischemic stroke patients with and those without kidney dysfunction. these have not been evaluated simultaneously.
METHODOLOGY
In this prospective observational study, 100 patients with acute ischemic stroke were evaluated. Kidney dysfunction was defined as eGFR(<60 ml/min/1.73m^2), UACR(>30mg/g). Neurological severity and functional outcome were assessed using National Institutes of Health Stroke Scale (NIHSS) at admission and modified Rankin scale (mRS) at discharge respectively. mRS score 3-5 or death was defined as poor outcome. The impacts of eGFR and UACR on outcome at discharge were analysed.
RESULTS
Out of 100 patients 65 were male and 56% had kidney dysfunction. Mean age was significantly higher in kidney dysfunction group (75.7vs62.3). Mean NIHSS score on admission and mRS in kidney dysfunction group were 6 and 3 respectively, which were significantly (P<0.001) higher than in normal kidney function group (3,1 respectively).The poor outcome rates were 60.8% for low eGFR and high UACR, 19.3% for normal eGFR and UACR. Multivariate analysis performed after adjusting confounding factors showed that UACR not eGFR, independently associated with poor outcome.

CONCLUSION
High UACR at admission predicts poor outcome at discharge in patients with acute ischemic stroke

KEYWORDS: Acute ischemic stroke, albuminuriaurinary albumin/creatinine ratio, estimated glomerular filtration rate, prognosis

I. INTRODUCTION

Stroke is the major cause of long-term disability in adults, and the second leading cause of death worldwide. Thirty-day mortality rate of ischemic stroke has been estimated at around 15% in high-income countries and several factors are known to increase stroke mortality.

Kidney dysfunction, defined as a low glomerular filtration rate (GFR) or albuminuria, is an important global health problem[1]. Meta-analyses of cohort studies and trials have indicated that albuminuria/proteinuria increases the risk of stroke by 71–92% and an estimated GFR (eGFR) of <60 mL/min/1.73 m2 increases the risk by 43%. Recent reports have suggested that low eGFR and/or proteinuria may be associated with subclinical brain abnormalities, including white matter changes, micro-bleeds, mild cognitive disorders, and intima-media thickening of the carotid arteries, and particular attention has been focused on the cerebro-renal interaction.

Even minimal kidney dysfunction has shown to be independently associated with poor outcomes in coronary artery disease[2]. But, the association between kidney dysfunction and clinical characteristics in patients with acute ischaemic stroke remains unclear. Previous studies have used unreliable renal function measures, such as serum creatinine levels, and have evaluated only impaired kidney function (i.e., low eGFR) or only abnormal filtration barrier (i.e., albuminuria)[3-5]; however, these have not been evaluated simultaneously as recommended by experts. Moreover, the associations of eGFR and albuminuria with clinical characteristics at admission and outcome in patients with acute stroke have not been appropriately evaluated. Recent studies showed that proteinuria is independently associated with unfavourable

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outcomes in ischemic stroke patients[6-8]; however, the urine protein level was evaluated using dipstick testing, which is semi-quantitative and is associated with frequent false-positive and false-negative results. In the present study[9,10], we evaluavated albuminuria, measured using the urinary albumin/creatinine ratio (UACR), and the eGFR in the acute phase of ischemic stroke, investigated the clinical characteristics of ischemic stroke patients with and those without kidney dysfunction.

AIMS AND OBJECTIVES OF THE STUDY

1.To assess the levels of urinary albumin/creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR) in patients of acute ischemic stroke.

2. To study the relationship of measured urinary albumin/creatinine ratio (UACR), and the eGFR in the acute phase of ischemic stroke, with functional outcome at discharge

STUDY DESIGN: - Observational, prospective inter group comparative study

SAMPLE SIZE- 100

II. METHODOLOGY

• After institutional Ethical committee clearance informed consent was taken from all patients meeting inclusion criteria and /or from their family members.

• Brain computed tomography was done in all patients to rule out cerebral and subarachnoid hemorrhage, and fresh infarcts were confirmed using diffusion-weighted imaging.

• Based on the neurological signs, risk factors, ECG, 2DECHO and brain magnetic resonance imaging (MRI) and magnetic resonance angiography findings at admission, we classified ischemic stroke into cardio-embolic and non-cardio embolic subtypes.

• Neurological severity and functional outcome were assessed using National Institutes of Health Stroke Scale (NIHSS) at admission and using the modified Rankin scale (mRS) at discharge respectively.

• Good outcomemRS score of 0–2 and poor outcome - (3–5 or death (mRS score of 6)

• Urine samples were collected at admission for UACR and eGFR was calculated using formula of MDRD formula of GFR (mL/min/1.73 m^2) = 175 × (Scr)-1.154 × (Age)-0.203 × (0.742 if female)

• The risk factors will be assessed included age, hypertension, diabetes, atrial fibrillation, hyperlipidemia, smoking habits, and a history of ischemic stroke or ischemic heart disease.

• The data so obtained was entered in a standard proforma and analyzed using SPSS v23.0.

INCLUSION CRITERIA

1. Patients admitting with imaging proven acute ischemic stroke
2. Patients admitting with in 24 hrs of onset dysfunction
3. Age more than 18 yrs

EXCLUSION CRITERIA

1. Patients with acute ischemic stroke who have received intravenous thrombolysis
2. Patients with hemorrhagic stroke, transient ischemic attacks, todd's palsy, hypoglycemia and other stroke mimickers

III. STATISTICAL ANALYSIS

Initially we compared the clinical characteristics between patients with and those without kidney dysfunction at admission. We then compared these characteristics between the good and poor outcome groups. The significance of intergroup differences was assessed using the chi-square test. Potential variables with a $P < 0.10$ in univariate analysis were entered into a multivariate logistic regression model to identify the variables independently associated with a poor outcome. We used separate multiple logistic regression analyses for the eGFR and UACR. Further multiple logistic regression analyses using clinically relevant thresholds of eGFR 60 mL/min/1.73 m 2 and UACR >30 mg/g creatinine. All statistical analyses were performed using SPSS v23.0. A P-value of <0.05 was considered statistically significant.

IV. RESULTS

Out of 100 patients 65 were male and 56% had kidney dysfunction. Mean age was significantly higher in kidney dysfunction group (75.7vs62.3) ($p<0.05$). Additionally, the incidences of hypertension and cardio-embolic stroke were higher among patients with kidney dysfunction group($P = 0.02$ and $P < 0.02$, respectively).

Mean NIHSS score on admission and mRS in kidney dysfunction group were 6 and 3 respectively, which were significantly ($P<0.05$) higher than in normal kidney function group (3,1 respectively).

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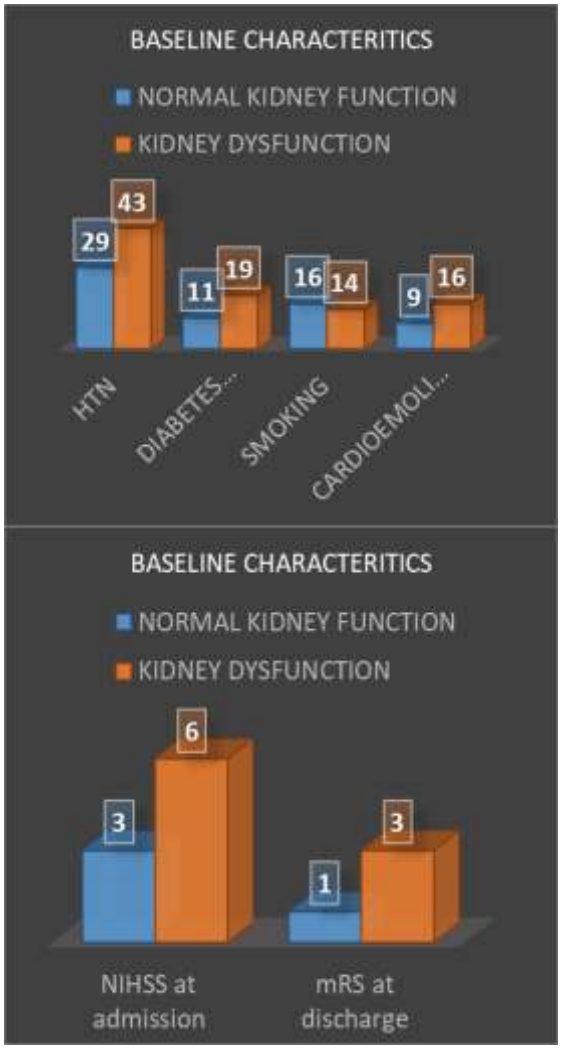

Figure 1,2 Bar graphs showing Baseline Characteristics of patients with normal kidney function and kidney dysfunction

40% met the criteria for a poor outcome. The association between baseline characteristics of the patients and a poor functional outcome are presented in Table 1 .The mean age ,cardioembolic stroke and NIHSS score were significantly greater among patients with a poor outcome than among those with a good outcome ($P < 0.05$). The poor outcome rates were 60.8% for low eGFR and high UACR, 19.3% for normal eGFR and UACR. Multivariate analysis performed after adjusting confounding factors showed that UACR not eGFR, independently associated with poor outcome, UACR ≥30.0 mg/g creatinine (OR, 2.53; 95% CI, 1.49–4.35; P = 0.0006) was independently associated with a poor outcome, while eGFR<60 mL/min/1.73 m2 (OR, 1.24; 95% CI, 0.70–2.18; P = 0.46) was not associated with a poor functional outcome

	GOOD OUTCOME (n 60)	POOR OUTCOME (n 40)
AGE	65.4	73.6
MALE	40	22
HTN	45	28
DM2	18	12
SMOKING	18	8
CARDIOEMOLIC STROKE	13	16
NIHSS	2	10
eGFR	72.6	66.9
UACR	180.5	430.6

Table 1 Base line characteristics of good outcome Vs poor outcome groups

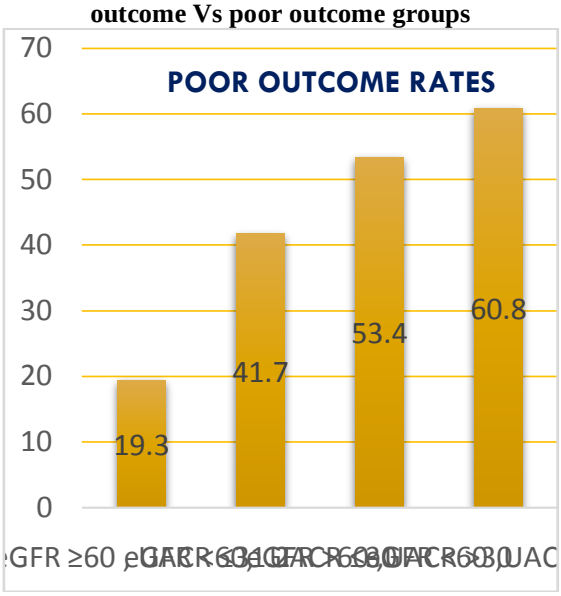

Figure 3 Poor outcome rates according to the eGFR and UACR

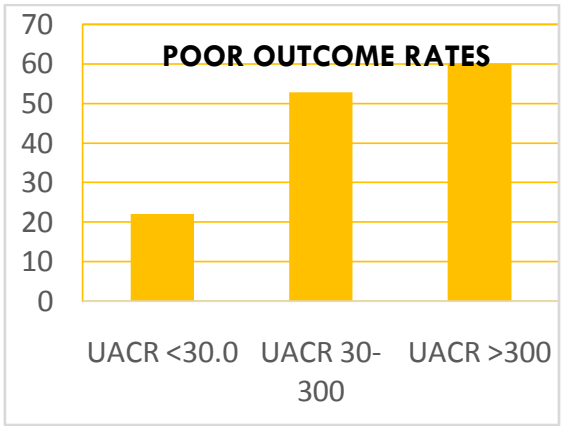

Figure 4 : Poor outcome rates according to the UACR.

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V. DISCUSSION

Our study analysed the UACR and eGFR in acute ischemic stroke patients. We found that the UACR at admission was independently associated with poor outcome at discharge, where as low eGFR was not an independent predictor of poor outcome. The independent predictability of UACR is statistically significant after adjusting for confounding factors. Also our study showed with increase in UACR levels the poor outcome rates increased. Morbidity and mortality are higher with stroke than with other cardiac disease, and stroke patients need long-term rehabilitation and care leading to high family burden and medical costs. Previous studies showed, several factors, such as old age, a high NIHSS score at admission, prior stroke, and high blood glucose levels, were consistently associated with a poor outcome after acute ischemic stroke. In those studies kidney dysfunction was rarely discussed. To understand the factors contributing to recovery, identification of predictors of outcome plays crucial role. Our study found that old age, hypertension, cardio-embolic stroke, a high NIHSS score at admission, and a high mRS score at discharge were significantly associated with the presence of kidney dysfunction. These findings were similar to previous studies.17, 21, 28 Kidney dysfunction was diagnosed in 56%, which was higher than that in normal population. In our study kidney dysfunction patients had severe neurological symptoms and the poor functional outcome even after hospitalization.

We observed that the presence of albuminuria, evaluated using the UACR, was independently associated with severe neurological deficits at stroke onset and a poor functional outcome at discharge in the multivariate analyses after adjusting for confounding factors. Two recent studies reported that proteinuria, not a low eGFR, was independently associated with a poor functional outcome in patients with acute ischemic stroke; however, in these studies, the urine protein level was evaluated using dipstick testing, which is semiquantitative. Dipstick testing is useful only for estimating urinary protein levels between 300 and 500 mg/day, which may result in frequent false-positive and false-negative results. Moreover, ROC analysis demonstrated that an UACR cut-off of 31.2 mg/g creatinine was required to predict a poor outcome; interestingly, this is similar to the definition of microalbuminuria. In contrast, we did not find an association between a low eGFR and a poor functional outcome.

Albuminuria is a marker of CKD progression and is an indicator of systemic endovascular damage via non-traditional vascular risk factors, including endothelial dysfunction, maladaptive carotid arterial remodelling, homocysteinaemia, impaired endothelial release of tissue plasminogen activator, extravascular coagulation, high levels of inflammatory cytokines, and oxidative stress. As endovascular injury, an atherosclerotic state, inflammation, and a coagulation state may be detrimental to ischemic brain damage, the outcome may be more strongly affected by albuminuria than by a low eGFR via these factors. A previous study reported that albuminuria was associated with hemorrhagic transformation after ischemic stroke treated with tissue plasminogen activator, contributing to poor outcome.in our study we hadn't included IV thrombolysed patients to eliminate this confounding factor. Kumai et al. reported that fibrinogen, high-sensitivity C-reactive protein, thrombin-antithrombin complex, and D-dimer levels had a tendency to increase in the presence of proteinuria in patients with acute ischemic stroke. Moreover, Umemura et al. reported that albuminuria, not a low eGFR, was independently associated with early neurological deterioration and infarct volume expansion in patients with small subcortical infarcts.

VI. CONCLUSION

- Stroke outcome is multifactorial and is only partially predictable based on the clinical, laboratory, and imaging.
- However, the presence of albuminuria at admission might be an index of possible severe clinical symptoms at admission and a poor functional outcome at discharge in patients with acute ischemic stroke.
- Evaluation of albuminuria might be of high clinical utility owing to the ease and low cost of the assessment.

VII. LIMITATIONS

UACR was measured only on admission, albuminuria can sometimes occur during acute stress, dehydration, or infection; thus, the possibility that the UACR was affected by acute stroke cannot be excluded.

mRS score at the time of hospital discharge does not necessarily reflect the long-term prognosis

VIII. DISCLOSURES

The authors declare no conflict of interest. Ethical Approval for this study was taken from the institutional ethical committee in December 2020.

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