East African Medical Journal Vol. 91 No. 3 March 2014
ESTIMATED GLOMERULAR FILTRATION RATE AND RISK OF SURVIVAL IN ACUTE STROKE
E. I. Okaka, MBBS, FWACP, F. A. Imarhiagbe, MBChB, FMCP, F. E. Odiase, MBBS, FMCP, O. C. A. Okoye, MBBS, FWACP,
Department of Medicine, University of Benin Teaching Hospital, Benin City, Nigeria

Request for reprints to: F. A. Imarhiagbe, P.O. Box 7184, GPO Benin City, Nigeria, email: dnimei@yahoo.com

ESTIMATED GLOMERULAR FILTRATION RATE AND RISK OF SURVIVAL IN ACUTE STROKE

E. I. OKAKA, F. A. IMARHIAGBE, F. E. ODIASE and O. C. A. OKOYE

ABSTRACT

***Objective*: To assess the risk of survival in acute stroke using the MDRD equation derived estimated glomerular filtration rate.**
***Design*: A prospective observational cross-sectional study.**
***Setting*: Medical wards of a tertiary care hospital.**
***Subjects:* Eighty three acute stroke patients had GFR calculated within 48 hours of admission after basic data were captured.**
***Outcome measures:* Stroke outcome was defined as either discharged or still-in-care (survived) or all cause in-hospital death. GFR was estimated by the MDRD equation, stroke severity was assessed by the Canadian Neurological Scale (CNS). Data were compared between the GFR groups of < 60ml/min and ≥ 60ml/min. Relative risks (RR) and odds ratios (OR) for stroke outcomes (survival and death) were estimated between the GFR groups and the homogeneity of the odds ratios among the different layers of stroke severity (CNS < 6.5 and ≥ 6.5) was determined by Breslow-Day and Tarone's test. Matanel Hazensel and Cochran's tests were used to determine conditional independence and the common odds ratio with stroke severity as a layering variable.**
***Results*: No significant differences were found between the age and sex distribution of the two GFR groups. Serum urea and creatinine and CNS were significantly different between the GFR groups (p<0.001, <0.001, <0.001). RR of survival and death for the GFR groups-less than 60ml/min and above or equal to 60ml/min were (0.425 and 1.204) and (2.360 and 0.830). The OR of survival for GFR below 60ml/min compared to GFR above or equal to 60ml/min was 0.353. There was homogeneity across the two layers of stroke severity (CNS score less than 6.5 and above or equal to 6.5), p=0.612 and 0.612.**
***Conclusion*: Independent of stroke severity, GFR is a surrogate in the assessment of the risk of survival in acute stroke**

INTRODUCTION

Stroke is independently associated with impairment in the structure and function of the glomerulus. (1). Estimated Glomerular Filtration Rate (GFR) as determined by the four-item Modification of diet in renal disease (MDRD) equation is a fairly reliable way of estimating renal filtration function albeit with some drawbacks and GFR below 60 ml/min per 1.73 metres squared of body surface area over a period of at least three months defines chronic kidney disease(CKD) (2-6).

Normal renal function is primordial to the maintenance of homeostatsis and conversely, impaired renal function indirectly influences the outcome of acute and chronic diseases of other organ systems as have been amply demonstrated in cardiovascular diseases including strokes in related studies (7,8).

Acute stroke outcome is generally influenced among other things by the severity of the stroke, presence of co-morbidities like poor renal function, age of the patient and the quality of care received (9). Poor renal function as measured by the GFR influences acute stroke outcome negatively both in terms of survival and functional disability (7,8).

This study prospectively investigated the risk of survival in a cohort of acute stroke patients without previously known renal disease, using admission GFR in a tertiary care hospital in sub- Saharan Africa.

MATERIALS AND METHODS

Eighty three acute stroke patients, without previously known renal disease, that were consecutively admitted into the general medical wards of a tertiary care hospital out of an estimated ninety patients over a three month period, had GFR calculated within

forty eight hours of admission after basic data of age, sex, Glasgow Coma Scale (GCS), stroke severity, stroke sub-type, blood sugar, serum creatinine, serum urea and urine protein were captured with the study pro forma. History of hypertension, diabetes mellitus, alcohol consumption and tobacco smoking were also obtained. All patients were followed up prospectively for outcome in ninety (90) days from the day of admission into the wards . Stroke outcome was defined as either discharged or still-in-care (survived) or all cause in-hospital death.

Serum creatinine was tested for by using the alkaline picric acid method described by Jaffe and GFR was estimated by the 4-item MDRD equation, GFR in ml/min/1.73m2 of body surface area = 186 x creatinine-1.154 x Age-0.203 x 0.742 (if female) x 1.21 (if black). Stroke severity was assessed by the Canadian Neurological Scale (CNS), and stroke pathologic type was characterised by cranial computed tomography or magnetic resonance imaging (MRI) as either cerebral infarct or intra-cerebral haemorrhage. Biochemical parameters were obtained from the hospital's main laboratory. Patients with acute kidney injury and known CKD were excluded. Study was approved by the institutional review board (ethics committee).

Basic data were described as means (standard deviation) and percentages and were compared between the GFR groups of above or equal to 60ml/min and below 60ml/min. Means were compared to the independent t-test and categorical or discrete variables were compared with chi-square for any significant difference(s).

Relative risks and odds ratios for stroke outcomes (survival and death) were determined between the GFR groups on a crosstab and the homogeneity of the odds ratios among the different layers of stroke severity (CNS score less than 6.5 and above or equal to 6.5) was determined by Breslow-Day and Tarone's test of homogeneity. Matanel Hazensel and Cochran's tests were used to determine conditional independence and the common odds ratio with stroke severity as a layering variable. Analysis was done with SPSS version 17 and P-value of less than 0.05 was taken as significant for all tests.

RESULT

A total of 83 patients were seen with a mean age of 63.28 ± 15.27 years (median 65 years, range 21-94) comprising 30 (36.1%) females and 53 (63.9%) males and no significant differences were found between the age and sex of patients of both GFR groups (p=0.245 and 0.167). Urea, creatinine, GCS and CNS score were significantly different between the eGFR groups, p<0.001, <0.001, <0.001, <0.001 respectively (Table 1). Proteinuria, stroke outcome and sub-type, history of hypertension and diabetes mellitus, history of alcohol consumption and tobacco smoking were however not significantly different between the GFR groups (p=0.923, 0.179, 0.378, 0.068, 0.179, 0.548,0.415 respectively) Table 1.

Table 1
Comparing basic characteristics of the study groups

Parameter	eGFR<60ml/hr	eGFR≥60ml/hr	P	Total
Mean Age (sd)- yrs	67.00(13.38)	62.25(15.59)	0.245	-
Sex(f/m)	9/9	21/44	0.167	30/53
History of hypertension(yes/no)	11/7	53/12	0.068	-
History of diabetes(yes/no)	7/11	15/50	0.179	-
History of alcohol(yes/no)	2/16	11/54	0.548	-
History of smoking(yes/no)	1/17	8/57	0.415	-
Proteinuria (n) -nil/1+/2+/3+	7/ 4 / 4/ 3	22/18/12/9	0.923	-
Stroke subtype(ich/ci)	9/9	25/40	0.378	-
Outcome (survived/dead)	2/16	17/48	0.179	-
Mean urea(sd)- mg/dl	116.61(71.73)	44.29(20.96)	<0.001	-
Mean creatinine(sd)- mg/dl	2.17(1.18)	0.971(0.16)	<0.001	-
GCS(<8/ ≥8)	10/7	13/33	<0.001	-
CNS(<6.5/≥6.5)	2.70(3.00)	7.36(4.49)	<0.001	-
N	18	65	-	83

eGFR –estimated glomerular filtration rate
sd-standard deviation
ci-cerebral infarct
ich-intracerebral haemorrhage

Relative risk of survival and death for GFR below 60ml/min was 0.425 and 1.204 respectively (95% confidence) and for GFR above or equal to 60ml/min, the relative risk of survival and death were 2.360 and 0.830 (Table 2). The odds ratio for survival for eGFR below 60ml/min compared to eGFR above or equal to 60ml/min was 0.353, that is GFR below 60ml/min was 0.353 times likely to survive compared to GFR above or equal to 60ml/min (Table 2).

Table 2

Showing the risk estimates of survival and death of GFR 0-59ml/min compared to 60ml/min and above

	Value	95% CI
OR of GFR 0-59ml/min compared to 60ml/min and above for survival	0.353	0.073-1.698
RR of survival for cohort GFR (0-59ml/min)	0.425	0.108-1.670
RR of death for cohort GFR (0 -59ml/min)	1.204	0.968-1.497
N	83	

OR= odds ratio
RR= relative risk
CI=confidence interval

There was homogeneity across the two layers of stroke severity (CNS score less than 6.5 and above or equal to 6.5), p=0.612 and 0.612 respectively (Table 3).

Table 3

Showing tests of homogeneity of odds ratio across layers of stroke severity(CNS of below 6.5 and 6.5 and above)

	chi-square	p
Breslow-Day	0.258	0.612
Tarone's	0.258	0.612

CNS=Canadian Neurological Scale

Tests of conditional independence between the GFR and stroke outcome was not significant, p=0.210 and 0.377, and the common odds ratio was 0.358, consistent with the odds ratio calculated from the cross tab above. (Tables 4 and 5 respectively).

Table 4

Showing tests of conditional independence between eGFR and stroke outcome after adjusting for stroke severity

	chi-squared	p
Cochran's	1.574	0.210
Mantel-Haenszel	0.780	0.377

Table 5

Showing tests of common odds ratio estimate

Estimate	p	95% CI
0.358	0.223	0.069-1.866

CI = Confidence interval

DISCUSSION

Estimated GFR as determined by the MDRD equation is a reliable assessment of glomerular filtration rate, which is a measure of renal excretory function (3). Declining renal function takes its toll on homeostasis and exacts negatively on the outcomes of diseases of other organ systems (10-13).

In this study, the mean age and sex of study subjects were not significantly different between the GFR groups but the higher mean age of the group with GFR below 60ml/min is noted. Declining GFR is clearly associated with advancing age, male sex, hypertension, diabetes mellitus and tobacco smoking but less clearly with alcohol consumption (7,8,14-16). The presence of proteinuria in declining GFR is however known to further improve the risk stratification for adverse cardiovascular outcomes (17,18).The absence of significant differences between the GFR groups in proteinuria, history of hypertension, diabetes, alcohol consumption and smoking in this study attenuates the contributions of these conditions to the declining renal function in the group with GFR below 60ml/min.

The significantly higher mean serum creatinine and urea in the lower GFR group are expected findings in comparison with the group with the higher GFR as they are both measures of renal excretory function. (19). GCS and CNS were also significantly lower in the group with GFR below 60ml/min, findings consistent with earlier related studies (20). Stroke severity as measured by the CNS and indirectly by the GCS is a reliable predictor of acute stroke outcome (9).

There were more in-hospital deaths in the group with GFR below 60ml/min as shown in similar studies, the difference was however not significant (21). Stroke sub-types were also not significantly different between the groups, though there was a comparatively higher percentage of intra-cerebral haemorrhage in the lower GFRgroup as in related studies and this may largely derive from the higher blood pressure associated with this sub-type of stroke as well as the altered haemostasis in declining renal function (16,22,23).

Remarkably the risk of survival was worse in the group with GFR below 60ml/min and the event odds (survival or death) were not significantly influenced by the severity of the stroke as shown in the homogeneity of the odds ratio across the stroke severity groups (13, 23). This last point becomes relevant when viewed in the light of the fact that stroke severity was significantly worse in the group with GFR below 60 ml/min. It is noteworthy also that the independence of the relationship between the risk of survival and GFR was not obscured by stroke severity and the consistency shown between the initial and common odds ratio is corroborative. We can safely conclude that GFR, determined by the MDRD equation, is a reliable surrogate for the assessment of the risk of outcome in acute stroke independent of the severity of the stroke in the population studied as shown in other climes (25-27). The small sample size and the estimation of GFR on admission when clinical stability might not be safely guaranteed are limitations of this study. Larger studies would probably better clarify the issues raised.

REFERENCES

1. Ovbiagele B. Imapairment in glomerular filtration rate or glomerular filtration barrier and occurrence of stroke. *Arch Neurol* 2008; **65**: 934-938
2. Matsushita K,Mahmoodi BK, Woodward M, Emberson JR, Jafar TH, Jee SH *et al.* Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. *JAMA*. 2012; **307**: 1941-1951.
3. Madero M, Sarnak MJ. Creatinine-based formulae for estimating glomerular filtration rate: is it time to change to chronic kidney disease epidemiology collaboration equation? *Curr Opin Nephrol Hyperetns*. 2011; **20**: 622-630
4. Soares AA, Eyff TF, Compani RB, Ritter L, Camargo JL, Silveiro SP. Glomerular filtration rate measurement and prediction equations. *Clin Chem Lab Med*. 2009; **47**: 1023-1032.
5. Hojs R, Berc S, Ekart R, Gorenjak M, Puklarec L. Serum cystatin C-based equation compared to serum creatinine-based equations for estimation of glomerular filtration rate in patients with chronic kidney disease. *Clin Nephrol*. 2008; **70**: 10-17
6. Herget-Rosenthal S, Bokenkamp A, Hofmann W. How to estimate GFR- serum creatinine, serum cystatin C or equations? *Clin Biochem*. 2007; **40**: 153-161.
7. Rahman M, Ford CE, Cutler JA, Davis BR, Piller LB, Whelton PK *et al*. Long term renal and cardiovascular outcomes in Antihypertensive and Lipid –Lowering Treatment to Prevent Hearat Attack Trial(ALLHAT) participants by baseline estimated GFR. *Clin J Am Soc Nephrol*. 2012; **7**: 989-1002.
8. Losito A, Pittavin L, Ferri C, De Angelus L. Reduced Kidney function and outcome in acute ischemic stroke: relationship to arterial hypertension and diabetes. *Nephrol Dial Transplant*. 2012; **27**:1054-1058
9. Obiako OR, Oparah SK, Ogunniyi A. Prognosis and outcome of acute stroke in the University College Hospital Ibadan, Nigeria. *Niger J Clin Pract*. 2011; **14**: 359-362
10. 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**: 1296-1303
11. Lee M, Ovbiagele B. Reno-cerebrovascular disease: linking the nephron and neuron. *Expert Rev Neurother*. 2011; **11**: 241-249
12. Naganuma M, Koga M, Shiokawa Y, Nakagawara J, Furui E, Kimura K *et al*. Reduced estimated glomerular filtration rate is associated with stroke outcome after inmtravenous rt -PA: the stroke Acute Management with Urgent Risk-Factor Assessment and Improvement(SAMURAI) rt-PA registry. *Cerebrovasc Dis* 2011; **31**:123-9

13. Hao Z, Wu B, Lin S, Kong FY, Tao WD, Wang DR et al. Association between renal function and clinical outcome in patients with acute stroke. *Eur Neurol.* 2010; **63**: 237-242
14. De Cosmo S, Lamacchia O, Rauseo A, Viti R, Gesualdo L, Pilotti A *et al*. Cigarette smoking is associated with glomerular rate in male patients with type 2 diabetes. *Diabetes Care*. 2006; **29**:2467-2470
15. Funakoshi Y, Omon H, Onoue A, Mihara S, Ogata Y, Katoh T. Association between frequency of drinking alcohol and chronic kidney disease in men. E*nviron Health Prev Med*. 2012; **17**: 199-204
16. Schabitz WR, Reinecke H. Chronic kidney disease and alcohol consumption. *Stroke* 2011; **42**: 2385-2386
17. Tonelli M, Klarenbach SW, Lloyd AM, James MT, Manns BJ, Hemmelgam BR. Higher estimated glomerular filtration rates may be associated with increased risk of of adverse outcomes, especially with concomitant proteinuria. *Kidney Int.* 2011; **80**: 1306-1314
18. Bello AK, Hemmelgam B, Lloyd A, James MT, Manns BJ, Klarenbach S *et al*. Associations among estimated glomerular filtration rate, proteinuria, and adverse cardiovascular outcomes. *Clin J Am Soc Nephrol*. 2011;**6**: 1418-1426
19. Bagshaw SM, Gibney RT. Conventional markers of kidney function. *Crit Care Med*. 2008; **36**: S152-158
20. Lee M, Saver JL, Chang KH, Liao HW, Chang SC, Ovbiagele B. Low glomerular filtratuion rate and risk of stroke: meta-analysis. *BMJ* 2010; **341**:c4249
22. Tsagalis G, Akrivos T, Alevizaki M, Manios E, Stamatellopoulos K, Laggaouranis A *et al*.Renal Dysfunction in acute stroke: an independent predictor of long-term all combined vascular e*vents and overall mortality.* Nephrol Dial Transplant 2009; **24**:194-200
23. Cutting S, Castro C, Lee VH, Prabhakaran S. Impaired renal function is not associated with increased volume of intracerebral hemorrhage. *J Stroke Cerebrovasc Dis*. 2012;**23**:86-90.
24. Rhoney DH, Parker D Jr, Millis SR, Whittaker P. Kidney dysfunction at the time of intracerebral hemorrhage is associated with increased in-hospital mortality: a retrospective observational cohort study. *Neurol Res*. 2012; **34**: 518-521
25. Agaba EI, Wigwe CM, Agaba PA, Tzamaloukas AH.. Performance of the Cockcroft-Gault and MDRD equation in adult Nigerians with chronic kidney disease. *Int Urol Nephrol* 2009;**41**:635-642
26. Abefe SA, Abiola AF, Olubunmi AA, Adewale A. Utility of predicted creatinine clearance using MDRD formula compared with other predicted formulae in Nigerian patients. *Saudi J Kidney Dis Transpl* 2009; **20**:86-90
27. Froissart M, Rossert J, Jacquort C, Pailard M, Houllier P. Predictive Performance of the modification of diet in renal disease and Cockcroft-Gault equation for estimation of renal function. *J Am Nephrol* 2005;**16**:763-773