Original Research Paper

Volume - 12 | Issue - 01 | January - 2022 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Clinical Science

EPIDEMIOLOGY AND CLINICAL FEATURES OF SNAKE BITE INDUCED ACUTE KIDNEY INJURY PATIENTS IN LAST DECADE AND ITS LONG-TERM OUTCOME – A SINGLE CENTER EXPERIENCE.

Rajdeb Banerjee	Department of Nephrology, Nil Ratan Sircar Medical College & Hospital. 138, AJC Bose Road, Kolkata-700014, West Bengal, India. Department of Physiology, University of Calcutta. 92, APC Road, Kolkata-700009, West Bengal, India.
Dr Piyali Banerjee*	MD(Anaesthesia), Burdwan Medical College, West Bengal, India. *Corresponding Author
Raghwendra Mishra	Department of Physiology, Ananda Mohan College. 102/1, Raja Ram Mohan Sarani, Kolkata-700009, West Bengal, India.
Roshnara Mishra	Department of Physiology, University of Calcutta. 92, APC Road, Kolkata-700009, West Bengal, India.
Pinaki Mukhopadhyay	Department of Nephrology, Nil Ratan Sircar Medical College & Hospital. 138, AJC Bose Road, Kolkata-700014, West Bengal, India.

ABSTRACT Snake envenomation and related clinical complication are of great relevance in tropical countries. The present study focuses on the epidemiological and clinicopathological profile of snake bite victims admitted or referred over the last decade to Nil Ratan Sircar Medical College and Hospital, a tertiary health care center located in eastern India. Acute kidney injury staging was done according to AKIN criteria. Snakebite patients were classified into acute kidney injury and non acute kidney injury group. A subset of these patients admitted during the last year of the study were included in a prospective longitudinal follow up for the evaluation of long term renal consequences after snakebite induced acute kidney injury. Oliguria, hematuria, cellulitis, inflammation were common in snake bite patient. All the plasma and urinary markers were significantly altered after renal injury ($p<0.05$). Inflammation and stress level were remain elevated over the follow up time period. In the follow up of 42 patients, 14 patients showed <90 ml/min/1.73m^2 estimated glomerular filtration rate, 18 patients showed higher urinary microprotein (>50mg/L), 14 patients showed elevated plasma creatinine (>1.2 mg/dl) and 16 patients showed hematuria at different follow up time periods up to 6 months. At the end of follow up, 15 patients (35.71%) showed signs of persistent renal insufficiency indicating long term renal impairments.

KEYWORDS : Snake envenomation, Acute kidney injury, eGFR, follow up.

INTRODUCTION

Snake bite is an important clinical emergency and a leading cause of morbidity and mortality in tropical countries(1). Snake envenomation is considered as a neglected tropical disease (2), affecting nearly 2.5 million people with about 100,000 death per year globally. In India alone, snakebite induced mortality rate is estimated in between 35,000-50,000 (3). Among the big four major venomous snake families, vipers are responsible for the substantial amount of bite incidents in India (1, 4). The major clinical features in snakebite are local pain, swelling and necrosis at the bite site, systemic involvement including hypotension, haemorrhage, conjunctival oedema, chemosis, central nervous system symptoms, myalgia, paralysis, abdominal pain and renal failure (5). Acute kidney injury (AKI) is the most common secondary complication in viper bites with rate ranging from 5% to 29% (3). Poteinuria, hematuria, disseminated intravascular coagulation (DIC), hemolysis, renal tubular necrosis are the most common signs of viper envenomation induced acute kidney injury (1, 5).

Previous reports showed that AKI of various origins can propagate towards chronic kidney disease (CKD) during any point of disease spectrum (6). Reports regarding the clinicopathological profiling of snake bite induced acute kidney injury (SAKI) and their follow is limited. In the present study, we evaluated the clinicopathological profile of snake envenomed patients admitted during April 2010 to May 2019 at Nil Ratan Sircar (NRS) Medical College and Hospital, a tertiary health care center located in Kolkata, West Bengal. Simultaneously, the long term renal consequences of a subset of snake venom induced acute kidney injury (SAKI) patients were also assessed.

MATERIAL AND METHOD

All the snake bite patients admitted to NRS Medical College & Hospital during April 2010 to May 2019 were included in the study. The snake was identified either by the victim, the attendants at the scene, dead snake brought by the patient party or by the photograph of the snake. Snakebite was confirmed by the presence of fang marks. A total number of 1012 snake bite patients were admitted during this period among which 673 patients, who required hemodialysis (HD), were grouped as snake bite induced AKI (SAKI) and rest of them who did not develop AKI were grouped as NSAKI (snakebite patient without AKI). Majority of the SAKI patients were viper bitten. AKI staging was classified according to AKIN criteria. Plasma biochemical parameters including creatinine, urea, estimated glomerular filtration rate (eGFR), sodium, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), creatinine phosphokinase (CPK), C-reactive protein (CRP) and urinary microprotein were measured using commercially available kits as per manufacturer's guideline. Plasma methylglyoxal (MG) concentration was estimated spectropho tometrically, following Ghosh *et al.* (2006) *and* AOPP was determined according to the method of Witko-Sarsat et al. (1996) (7, 8).

From June 2018 to May 2019, a prospective longitudinal follow up study was done. The SAKI patients (n = 56) during this time period were recalled at one month, three month and six month after bite and renal functional markers along with inflammatory and stress markers were reanalyzed. The follow up study plan was depicted in a flow chart (Fig 1).

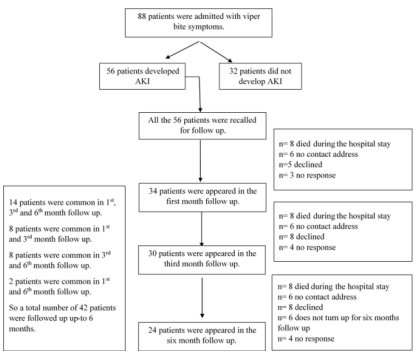


Fig 1: Flow chart depicting the prospective follow up events.

STATISTICALANALYSIS:

Data were represented as mean ± standard error of mean. Shapiro-Wilk test was performed to check the distribution of the data set. The data in one or more studied group were found to deviate from normal distribution pattern for all parameters hence, non-parametric analysis was conducted to assess any statistical significance. Kruskal-Wallis test were performed to check any statistical difference between the parameters of the studied groups. Mann Whitney U with Bonferroni correction was conducted to check the pairwise variation of the studied parameters. $p<0.05$ was considered as statistically significant. All calculations were carried out by statistical programme package SPSS version 16.

Observations

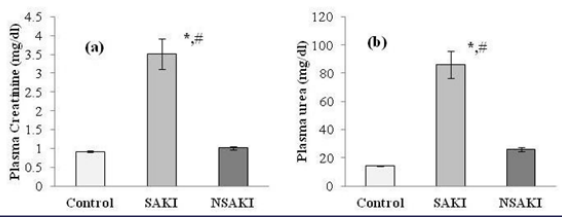
Most of the snake bite cases had occurred in rural areas. Among the 1012 snake bite patients, a total number of 673 were diagnosed with AKI as per AKIN criteia and required HD in the last 10 years. 87 SAKI patients were died during the hospital stay due to severe complications. The demographic details of the subjects were tabulated in Table 1. 72.06% of the SAKI patients were between 18 to 60 years and majority of the patients were male (73.99%). Lower limb was the most common site for snake bite (80.98%). Anuria, oliguria, hematuria and bleeding from the bite site were frequent manifestations after snake envenomation. Cellulitis and severe inflammation was present in 75.92% patients. Coagulation defect characterized by mild or moderate thrombocytopenia and low plasma fibrinogen level was noted in 29.27% patients. An average of 22.12 ± 1.13 vials of anti-snake venom serum (ASVS) was given during the treatment. Median number of HD required was 3 sessions. According to AKIN classification, 71.47% of the SAKI patients had severe AKI and classified as AKIN stage 3group.

Table 1: Demographic details of snake bite induced acute kidney injury patients. Data represented as Mean ± standard error of mean (SEM) and percentage

Characteristics	Snake bite patients with acute kidney injury (n=673)
Age <18 years 18-60 years >60years	42.96±14.39 years 125 (18.57%) 485 (72.06%) 63 (9.36%)
Sex Male Female	 498 (73.99%) 175 (26%)
Bite in lower limb	545 (80.98%)
Bite to blood taken time	1.6 days
Bleeding manifestation present	381 (56.61%)
Median HD (Among SAKI)	3 sessions
AKIN stage 1	88 (13.07%)
AKIN stage 2	104 (15.45%)
AKIN stage 3	481 (71.47%)
DIC Present	197 (29.27%)
Cellulitis and severe inflammation present	511 (75.92%)
Anuria present	117 (17.38%)
Oliguria present	302 (44.87%)
Hematuria present	254 (37.74%)
Anti-Snake Venom (1 vial= 10 ml)	22.12 ± 1.13 vials
Death during Hospital stay	87 (12.92%)

Biochemical Alterations:

The status of plasma and urinary biochemical parameters among SAKI, NSAKI, and healthy volunteer (control) groups is depicted in Figure 2 (Fig 2). Renal injury markers including plasma creatinine, urinary microprotein, plasma urea were significantly altered in the SAKI group ($p<0.05$). Inflammatory marker CRP, stress parameters including MG, AOPP were significantly increased in SAKI group than in NSAKI and control group ($p<0.05$).



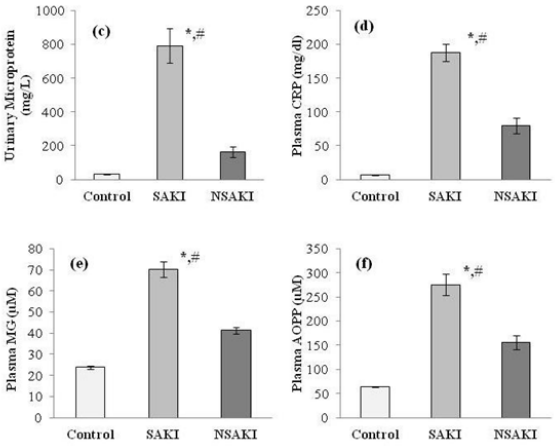


Fig 2: Bar diagram showing (a) plasma creatinine, (b) plasma urea, (c) urinary microprotein, (d) plasma CRP, (e) plasma MG, and (f) plasma AOPP concentration among the control, SAKI and NSAKI group. On Mann Whitney U analysis SAKI group showed significant (*p<0.05) alteration compared to control and NSAKI group (#p<0.05).

Follow up study

During June 2018-May 2019, a total number of 88 snake bite patients were admitted to NRSMCH, among which 56 developed SAKI and required HD of which 8 patients expired during hospital stay. The recovered patients (n=48) were recalled for follow up study. A first follow-up visit was scheduled at 1 month (1MFU) after bite. Subsequent follow-up visits were scheduled at 3 months (3MFU) and 6 months (6MFU) from the bite. Numbers of patient attended the first follow up, second follow up and third follow up were 34, 30, and 24 respectively. Some patients were dropped out due to several reasons. A total number of 42 patients responded in entire follow up study.

The clinical parameters for diagnosing SAKI, were re-evaluated at the end of each follow up. These parameters were tabulated in table 2 along with the control, SAKI and NSAKI group.

Table 2*:* Clinical and biochemical parameters among the control, SAKI, and NSAKI groups, and in the follow up groups. Data were represented as mean ± standard error of mean.

Biochemical parameters	Control (n=62)	SAKI (n=673)	NSAKI (n=339)	1MFU (n=34)	3MFU (n=30)	6MFU (n=24)	p value (Kruskal-Wallis ANOVA)
eGFR (ml/min/1.73m^2)	108.19±3.09	41.5±5.05	107.06±8.94	108.85±5.90	99.04±3.31	91.47±4.57	<0.001
Plasma creatinine (mg/dl)	0.92±0.019	3.51±0.40	1.01±0.04	1.06±0.04	1.03±0.02	1.14±0.04	<0.001
Plasma urea (mg/dl)	14.34±0.32	85.87±9.56	26.21±1.40	22.87±1.35	25.40±1.67	26.76±1.77	<0.001
Urinary microprotein (mg/L)	30.66±1.28	791.98±102.96	163.53±30.51	51.88±5.89	60.80±9.63	70.23±7.51	<0.001
Plasma CPK (U/L)	98.2±4.46	1061.96±242.98	294.1±69.32	127.06±16.66	177.6±25.25	161.37±19.67	<0.001
Plasma LDH (U/L)	381.8±17.86	758.37±75.58	468.69±48.22	449.42±32.9	456.26±19.41	458.5±39.09	<0.001
Plasma CRP (mg/dl)	7.08±0.46	188.07±12.52	80.17±11.48	24.98±6.18	42.69±9.58	38.18±7.56	<0.001
Plasma total protein (g/dl)	7.31±0.12	6.1±0.15	6.96±0.17	6.88±0.3	7.14±0.13	7.09±0.12	0.001
Plasma albumin (g/dl)	4.05±0.13	3.38±0.19	3.72±0.11	4.08±0.10	4.05±0.09	4.11±0.10	0.001

Plasma MG (µM)	23.88±0.72	70.28±3.68	41.43±1.55	29.07±1.78	31.31±3.88	50.11±6.86	<0.001
Plasma AOPP	63.36±1.09	275.36±21.67	156.36±14.43	230.33±15.13	177.73±12.59	185.26±26.28	<0.001

After discharge from the hospital, clinical markers were found to be restored towards the base level in the follow up time period. But in some parameters, there were significant alterations among the control and follow up groups. Plasma AOPP was significantly elevated from control at first (p<0.001), second (p<0.001), and third (p=0.001) follow up. Plasma urea (p=0.008), CRP (p=0.002) and urinary microprotein (p= 0.013) were still higher from the base level after second follow up (3MFU). At the end of 6month follow up there were significant elevation from the control group in plasma creatinine (p=0.034), urea (p=0.003), MG (p= 0.004), CRP (p=0.008), and urinary microprotein (p<0.001). So from this finding we might say that a fraction of patients were not fully recovered even after one, three or six months from the bite. At entire follow up schedule, 14 patients showed lower eGFR (<90ml/min/1.73m^2), 18 patients showed proteinuria (>50mg/L), 16 patients showed hematuria, and 14 patients showed elevated plasma creatinine (>1.2 mg/dl) (Table 3). 15 patients (35.71%) showed more than one renal adversity in each follow up consistently. At 6 months from the bite, 4 patients (16.66%) showed renal complications as indicated by lower eGFR, higher proteinuria, hematuria, and elevated plasma creatinine. One patient did not recover from the injury and needed regular HD even after 3 months. From the discharge time to 1MFU mean eGFR was recovered but beyond that it was found to decline again (Figure 3).

Table 3: Renal functional profile of the follow up patients. (*-present at each follow up time point).

Parameters	1MFU (n=34)	3MFU (n=30)	6MFU (n=24)
eGFR (<90ml/min/1.73m^2)	9	7	8 (*5)
Urinary Microprotein (>50 mg/L)	13	11	14 (*10)
Hematuria	11	8	5 (*4)
Plasma Creatinine (≥1.2 mg/dl)	8	6	8 (*4)
Did not recover from injury	1	1 (*1)	

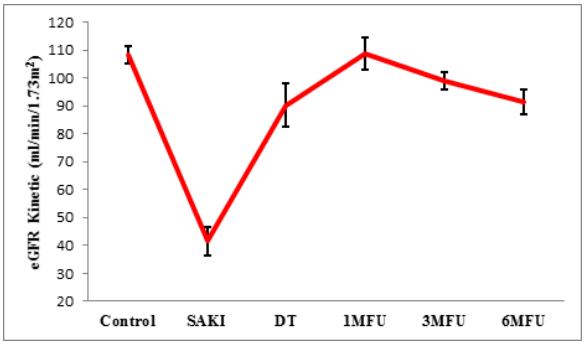


Fig 3: The mean eGFR (ml/min/1.73m2) kinetic of follow up patients at SAKI stage, Discharge time (DT), 1MFU, 3MFU and 6MFU.

DISCUSSION

Snake bite envenoming is an occupational health hazard, affecting mainly agricultural workers and considered to be one of the major causes of tropical AKI. Previous study reported that about 44% of patients with venomous snake bite developed AKI (9). Among the different snake species, viper bite is predominantly associated with AKI, characterized by proteinuria, oliguria, acute disseminated intravascular coagulation (DIC), thrombocytopenia, bleeding from the bite site, muscular pain etc (1). The type of snake venom and the injected amount of venom is responsible for the severity of the signs and symptoms in the envenomed patients (4). In the present study we have found that 66.5% of total snake bite patients admitted at or referred to our hospital developed AKI, which were majorly viper bitten. Bleeding manifestation, pain, oligoanuria, hematuria etc were the common clinical features present in SAKI patients.

Over the past decade, immune-inflammatory alterations, including cellular and soluble mediators, were shown to be associated with AKI and play an important role in the development and remission of AKI (10). Involvement of immune-inflammatory mediators were also reported in SAKI patients and in experimental studies of venom induced AKI (11, 12). In AKI due to snake bite, predominant renal infiltration of leucocytes with eosinophils, neutrophils and plasma cells were related with the development of interstitial inflammation via elevation of various cytokines, mediators and adhesion molecules, suggesting a pro-inflammatory dominance in SAKI (3). The inflammatory mediator CRP emerges as a promising marker of AKI development and is highly associated with mortality (13). In the present study, plasma CRP level was found to be significantly elevated after snake envenomation. We found a sharp increase in CRP level in SAKI group compared to NSAKI group.

During the initiation and progression of AKI of various origins, the involvement of oxidative stress is gaining momentum in recent times. Damaged and apoptotic cells release reactive oxygen species (ROS) (14) which can trigger the generation of reactive carbonyl species (RCO). RCO is formed by the oxidation of carbohydrates and lipids which may indirectly lead to advanced glycation or lipoxidation of proteins. Glyoxal, methylglyoxal, arabinose, and glycoaldehyde are generated from the autoxidation of carbohydrates. Oxidative stress associated with carbonyl stress is claimed to play important roles in both chronic and acute kidney diseases (15-17). Previous work by Mukhopadhyay et al., 2016 showed that carbonyl stress marker MG and oxidative stress marker AOPP were two independent predictors of SAKI (18) which is also reflected into the present study.

Simultaneously, to investigate the long term renal consequences of SAKI patients admitted during 2018-2019 in our hospital, we measured renal functional markers upto 6 months post snake bite.

The renal adversities were indicated by a persistent lower eGFR, hematuria, proteinuria, and high plasma creatinine individually at different follow-up time-points. Though 6 of survived SAKI patients had incomplete renal recovery at the time of discharge, 15 patients (35.71%) showed signs of persistent renal injury having more than one renal complication at each follow up time up to 6 months. From the study, we found 16.66% patients showed all renal adversities including lower eGFR, higher proteinuria, hematuria and high plasma creatinine even after 6 months from the bite. Plasma creatinine, urea, and urinary microprotein were found to be significantly elevated from the control at 6 months post snake bite. Previous research showed that proteinuria accelerates the progression of long term kidney disease through complement activation and tubular chemokines. The grade of proteinuria can be a responsible marker of chronic kidney disease and it can predict the loss of renal function (19). Hematuria is also strongly associated with chronic kidney diseases. Hematuria, resulting from renal functional injury, causes the presence of red blood cells into the urinary space; and promotes oxidative stress, inflammation, and structural damage to the kidney (20). Priyamvada et al. (2019) showed low eGFR, urinary albumin and hypertension can predict the adverse renal outcomes, which supports our findings (9). In association with renal injuries, we found significant elevation in stress levels and inflammatory marker in follow up groups. Previous studies reported that inflammation, oxidative and carbonyl stress are key players for AKI to CKD progression (6, 15-17) and this strengthens our results. We might say that elevated state of inflammation, stress level along with adverse renal functional markers can promote long term renal consequences.

In brief, this study highlights the epidemiological profile of viper bite patients admitted in NRS Medical College & Hospital, Kolkata, West Bengal over the last decade. There are significant alterations in clinicopathological spectrum among the SAKI and NSAKI groups. Our follow up study reveals that a fraction of the viper envenomed patients (35.71%) showed persistent clinical features describing the long term renal impairments.

CONCLUSION

In our hospital we have found that most of the admitted SAKI patients were viper bitten. SAKI group had significant renal functional deterioration than NSAKI. During the follow up of SAKI, several patients showed long term complications with either single or multiple renal insufiency markers including lower eGFR, high plasma creatinine, hematuria, and elevated urinary microprotein along with inflammation, oxidative and carbonyl stress over the period of 6 months.

REFERENCES

1. Chugh KS. Snake-bite-induced acute renal failure in India. Kidney international.

1989;35(3):891-907.
2. Chippaux JP. Snakebite envenomation turns again into a neglected tropical disease! The journal of venomous animals and toxins including tropical diseases. 2017;23:38.
3. Vikrant S, Jaryal A, Parashar A. Clinicopathological spectrum of snake bite-induced acute kidney injury from India. World journal of nephrology. 2017;6(3):150-61.
4. Kohli HS, Sakhuja V. Snake bites and acute renal failure. Saudi journal of kidney diseases and transplantation : an official publication of the Saudi Center for Organ Transplantation, Saudi Arabia. 2003;14(2):165-76.
5. Sitprija V. Snakebite nephropathy. Nephrology (Carlton, Vic). 2006;11(5):442-8.
6. Chawla LS, Kimmel PL. Acute kidney injury and chronic kidney disease: an integrated clinical syndrome. Kidney international. 2012;82(5):516-24.
7. Ghosh M, Talukdar D, Ghosh S, Bhattacharyya N, Ray M, Ray S. In vivo assessment of toxicity and pharmacokinetics of methylglyoxal. Augmentation of the curative effect of methylglyoxal on cancer-bearing mice by ascorbic acid and creatine. Toxicology and applied pharmacology. 2006;212(1):45-58.
8. Witko-Sarsat V, Friedlander M, Capeillère-Blandin C, Nguyen-Khoa T, Nguyen AT, Zingraff J, et al. Advanced oxidation protein products as a novel marker of oxidative stress in uremia. Kidney international. 1996;49(5):1304-13.
9. Priyamvada PS, Jaswanth C, Zachariah B, Haridasan S, Parameswaran S. Prognosis and long-term outcomes of acute kidney injury due to snake envenomation. Clinical kidney journal. 2020;13(4):564-70.
10. Kinsey GR, Li L, Okusa MD. Inflammation in Acute Kidney Injury. Nephron Experimental Nephrology. 2008;109(4):e102-e7.
11. Nasim F, Das S, Mishra R, Mishra R. Hematological alterations and splenic T lymphocyte polarization at the crest of snake venom induced acute kidney injury in adult male mice. Toxicon : official journal of the International Society on Toxinology. 2017;134:57-63.
12. Alves EC, Sachett JAG. Predicting acute renal failure in Bothrops snakebite patients in a tertiary reference center, Western Brazilian Amazon. PLoS One. 2018;13(8):e0202361.
13. Murashima M, Nishimoto M, Kokubu M, Hamano T, Matsui M, Eriguchi M. Inflammation as a predictor of acute kidney injury and mediator of higher mortality after acute kidney injury in non-cardiac surgery. Scientific reports. 2019;9(1):20260.
14. Tomsa AM, Alexa AL, Junie ML, Rachisan AL, Ciumarnean L. Oxidative stress as a potential target in acute kidney injury. PeerJ. 2019;7:e8046.
15. Miyata T, van Ypersele de Strihou C, Kurokawa K, Baynes JW. Alterations in nonenzymatic biochemistry in uremia: origin and significance of "carbonyl stress" in long-term uremic complications. Kidney international. 1999;55(2):389-99.
16. Mukhopadhyay S, Ghosh A, Kar M. Methylglyoxal increase in uremia with special reference to snakebite-mediated acute renal failure. Clinica chimica acta; international journal of clinical chemistry. 2008;391(1-2):13-7.
17. Miyata T, Kurokawa K, C VANYDS. Advanced glycation and lipoxidation end products: role of reactive carbonyl compounds generated during carbohydrate and lipid metabolism. Journal of the American Society of Nephrology : JASN. 2000;11(9):1744-52.
18. Mukhopadhyay P, Mishra R, Mukherjee D, Mishra R, Kar M. Snakebite mediated acute kidney injury, prognostic predictors, oxidative and carbonyl stress: A prospective study. Indian journal of nephrology. 2016;26(6):427-33.
19. Cravedi P, Remuzzi G. Pathophysiology of proteinuria and its value as an outcome measure in chronic kidney disease. British journal of clinical pharmacology. 2013;76(4):516-23.
20. Orlandi PF, Fujii N, Roy J, Chen HY, Lee Hamm L, Sondheimer JH, et al. Hematuria as a risk factor for progression of chronic kidney disease and death: findings from the Chronic Renal Insufficiency Cohort (CRIC) Study. BMC nephrology. 2018;19(1):150.