Nephrol Dial Transplant (2018) 33: 1176–1180
doi: 10.1093/ndt/gfx244
Advance Access publication 9 August 2017

ORIGINAL ARTICLE

Measured (and estimated) glomerular filtration rate: reference values in West Africa

Eric Yayo[1], Mireille Ayé[2], Carine Yao[1], Appolinaire Gnionsahé[3], Marie-Laure Attoungbré[1], Etienne Cavalier[4], Hans Pottel[5], Dagui Monnet[1,*] and Pierre Delanaye[6,*]

[1]Département de Biochimie, UFR sciences pharmaceutiques et Biologiques, University Felix Houphouet Boigny, Abidjan, Côte D'Ivoire, [2]Département d'Hématologie, UFR sciences pharmaceutiques et Biologiques, University Felix Houphouet Boigny, Abidjan, Côte D'Ivoire, [3]Département de Néphrologie, UFR sciences Médicales, University Felix Houphouet Boigny, Abidjan, Côte D'Ivoire, [4]Department of Clinical Chemistry, University of Liège, CHU Sart Tilman, Liège, Belgium, [5]Department of Public Health and Primary Care at Kulak, KU Leuven Kulak, Kortrijk, Belgium and [6]Department of Nephrology Dialysis Transplantation, University of Liège, CHU Sart Tilman, Liège, Belgium

Correspondence and offprint requests to: Pierre Delanaye; E-mail: pierre_delanaye@yahoo.fr
*These authors contributed equally to this work as last senior authors.

ABSTRACT

Background. Establishment of normal reference values for glomerular filtration rate (GFR) is mandatory in nephrology. However, no data are available for measured GFR (mGFR) in Africa.

Methods. GFR was measured in 237 healthy adult subjects (103 women and 134 men, mean age 34 ± 10 years) by iohexol plasma clearance.

Results. The mean mGFR was 103 ± 17 mL/min/1.73 m^2 and the median value was 103 mL/min/1.73 m^2 (2.5th and 97.5th percentiles are 76 and 137 mL/min/1.73 m^2, respectively). No significant difference in mGFR results was observed in patients < 40 years of age, whereas a significant decline in mGFR was observed after 40 years of age. There was no significant difference between mGFR in men and women.

Conclusions. Normal GFR values and descriptions of percentiles are now available for West Africa. As in Caucasians, no significant difference was observed between men and women. Moreover, the same age-associated decline in mGFR is also observed after 40 years of age, as in Caucasians.

Keywords: CKD, GFR, elderly, ethnicity, guidelines

INTRODUCTION

The establishment of normal reference values is a mandatory but difficult task in medicine. Regarding renal function, glomerular filtration rate (GFR) measured by exogenous markers remains the reference [1, 2]. The vast majority of available data with measured GFR (mGFR) in healthy populations concerns Caucasians [3, 4]. Some publications in Asian populations suggest a lower mGFR normal range compared with Caucasians [5–7]. However, only limited data are available for people of African ancestry. These data concern African Americans (AAs) and suggest that mGFR is similar to that of Caucasians and decreases with age [3, 8, 9]. The lack of data is obvious for African populations, where early diagnosis is important, as several countries (especially sub-Saharan) have only limited access to renal care systems [10]. Moreover, lifestyle and diet are very different in Africa and the USA (with less protein-rich meals in West Africa), which could theoretically lead to potential differences in normal GFR values. The goal of the current study is to establish normal reference values for mGFR [and estimated GFR (eGFR)] in West Africa.

MATERIALS AND METHODS

Only healthy adults were considered in this analysis and patients were recruited from blood donors in Abidjan, the most populous city of Ivory Coast (West Africa). Healthy status was confirmed by interview and clinical evaluation to exclude hypertension and diabetes and subjects all had normal blood results (normal haemoglobin, thrombocyte and leucocyte counts, negative serology for HIV, hepatitis B and C and absence of significant proteinuria). The protocol was approved by the Ethics Committee of Côte d'Ivoire (Comité national d'éthique et de la recherche de Côte d'Ivoire, authorization no. 039/MSLS/CNER-dkn). All patients signed informed consent. GFR was measured by iohexol plasma clearance, as previously described [11]. Briefly, 5 mL of iohexol (Omnipaque 240, GE Healthcare, Diegem, Belgium) was intravenously administrated and flushed with 10 mL of normal saline. Blood samples were obtained using the contralateral arm at 120, 180, 240 and 300 min after injection and GFR was calculated according to

the Brochner–Mortensen equation [12]. Results were then indexed for body surface area (BSA) with the Du Bois formula [13]. Collected blood samples were centrifuged and stored at −20°C. Then, samples were shipped for iohexol measurement at the university laboratory of Liège, Belgium with validated high-performance liquid chromatography, as previously described [11]. To ensure the quality of iohexol measurements, the laboratory is accredited for the ISO 15189 standard and also participates in the interlaboratory quality test for iohexol performed by Equalis, Uppsala, Sweden [12]. Serum creatinine samples were drawn, stored, shipped and measured in the same conditions and in the same laboratory with an isotope dilution mass spectrometry traceable enzymatic assay (Cobas 6000, Roche Diagnostic) [14]. The following eGFR equations were considered: the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [15] and full-age spectrum (FAS) equations [16]. For the CKD-EPI equations, several publications have suggested that the ethnic factor proposed for AAs should not be used in both normal GFR levels [17, 18] and in Africans (or European African) [19, 20]. So analyses were repeated with and without the ethnic factor. For the FAS equations, the Q values were calculated in the current cohort and were 0.79 and 1.02 for women and men, respectively. mGFR (and eGFR) values were normally distributed and the reported summary statistics include mean, median and 2.5th and 97.5th percentiles [3]. For mGFR, percentile lines were obtained using PROC QUANTREG in SAS 9.4 (SAS Institute, Cary, NC, USA) using a simple quadratic regression line of the form $A + B \times Age^2$. All other statistical analyses were performed using SAS 9.4 .

RESULTS

GFR was measured in 237 adult subjects (103 women and 134 men). The mean age was 34 ± 10 years (range 18–67) and mean body mass index and BSA were 24 ± 5 kg/m^2 (range 16.4–48.2) and 1.78 ± 0.17 m^2 (range 1.39–2.45), respectively. GFR was normally distributed (Figure 1). The mean non-indexed mGFR was 106 ± 19 mL/min/1.73 m^2 (range 60-179 mL/min) and the median value was 104 mL/min (2.5th and 97.5th percentiles are 75 and 151 respectively). The mean mGFR was 103 ± 17 mL/min/1.73 m^2 (range: 63–169 mL/min/1.73 m^2) and the median value was 103 mL/min/1.73 m^2 (2.5th and 97.5th percentiles are 76 and 137, respectively) (Figure 1). No significant difference in mGFR results was observed in patients < 40 years of age, whereas a significantly lower mGFR value was observed after 40 years of age (Table 1 and Figure 2). Regarding the whole population, there was no significant difference between mGFR in men and women when indexed (103 mL/min/1.73 m^2 in both genders) or non-indexed results are considered (104 in women and 107 in men). Detailed results of mGFR for men and women are given in Table 2. Comparing mGFR between men and women in the three age categories, no significant differences were observed after Bonferroni correction for multiple testing. We compared percentiles of mGFR with percentiles in Caucasians determined from a meta-analysis [4, 21] with data from living kidney donors. The percentiles of healthy African subjects perfectly fit with Caucasians (Figure 2).

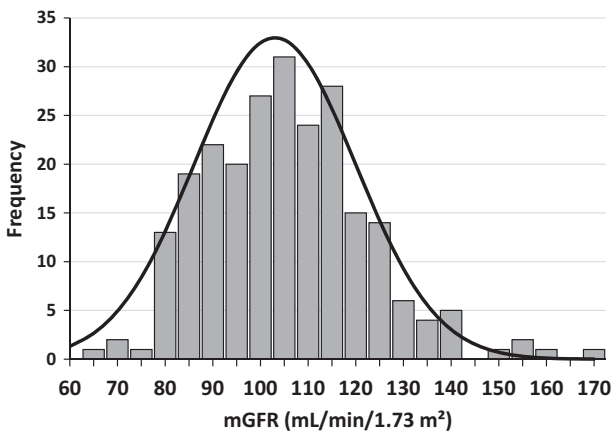

FIGURE 1: Normal distribution of mGFR results in 237 healthy people.

eGFR

Figure 3 shows the results of mGFR according to age (and 2.5th, 50th and 97.5th percentile curves) in the same healthy population overlaid with 2.5th, 50th and 97.5th percentile curves (of the form Percentile = $A + B \times Age^2$) for the CKD-EPI without ethnic factor (CKD-EPI) or with ethnic factor equation (CKD-EPIe) (Figure 3A without ethnic factor and Figure 3B with ethnic factor) and the full age spectrum equation (Figure 3C). For both eGFR predictions, the B-coefficient of the

Table 1. Mean GFR values according to age categories

Age category (years)	*n*	Mean mGFR	95% CI	P-values
<30	88	107.3	104.2–110.3	
30–40	90	103.6	99.9–107.4	0.1360
>40	59	95.8	91.4–100.1	0.0081

P-values indicate the difference in mGFR compared with the previous age group.

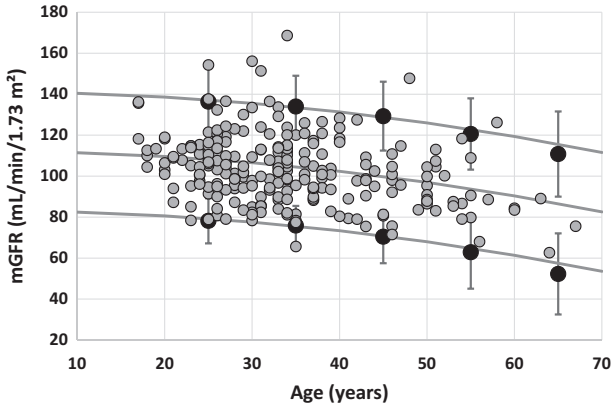

FIGURE 2: mGFR percentiles according to age. The solid grey circles are mGFR results and solid grey lines are 2.5th, 50th and 97.5th percentiles for mGFR in the current African population. The solid black circles with error bars are upper and lower reference limits obtained from the meta-analysis study including 633 Caucasian potential living kidney donors.

quantile regression lines were only significantly different from zero for the median quantile curve and therefore this coefficient was also used for the 2.5th and 97.5th percentile curves. The B-coefficient for the eGFR median quantiles were not significantly different from the B-coefficient of the mGFR median quantile curve. On the other hand, the intercept (A-coefficient) of the eGFR quantile curves was mostly significantly different from the intercept of the mGFR quantile curves, except for the 97.5th percentile curve for CKD-EPI ($P = 0.139$) and FAS ($P = 0.096$). A-coefficients of the 2.5th percentile curves for the eGFR models were significantly different from the A-coefficient of the mGFR 2.5th percentile curve. Finally, only the FAS ($P = 0.203$) median quantile curves had an A-coefficient that was not significantly different from the A-coefficient of the mGFR median quantile line. These statistical results confirm the visual comparisons in Figure 3: agreement between eGFR and mGFR percentiles is better for the CKD-EPI than for CKD-EPIe. Also, the agreement with mGFR is better for the FAS equation than for the CKD-EPI equation.

Table 2. Mean mGFR according to gender in different age groups

Age group (years)	Mean age, years	*n*	Mean mGFR (SD)	95% CI
Males				
<30	24.8	49	104.3 (13.5)	100.4–108.2
30–40	34.0	56	103.6 (17.4)	98.9–108.3
>40	46.5	29	98.4 (17.0)	92.0–104.9
Females				
<30	24.5	39	111.0 (14.5)	106.3–115.7
30–40	34.1	34	103.7 (19.1)	97.0–110.4
>40	51.1	30	93.2 (16.5)	87.0–99.3

DISCUSSION

For the first time, normal reference values for mGFR have been established in a healthy population living in Africa. Prior data only included AAs. In 1946, Shock [8] published mGFR results in 29 AAs with mGFR by renal inulin clearances. He found mean mGFRs of 128 ± 14, 88 ± 13 and 71 ± 8 mL/min/1.73 m^2 for subjects 18–41, 60–69 and 70–80 years old, respectively. The higher mGFR values observed by Shock are also found when data obtained in the 1950s are compared with recent publications in non-AA populations [3, 4]. In 2009, Poggio *et al.* [3] studied a cohort of living kidney donors including both Caucasians ($n = 901$) and AAs ($n = 117$). In this cohort, mGFR by renal clearance of iothalamate showed no significant difference according to ethnicity (mean mGFR 109 ± 15 versus 107 ± 17 mL/min/1.73 m^2 in AAs and Caucasians, respectively), although AAs were slightly younger than Caucasians (36.1 ± 9.1 versus 38.8 ± 10.5 years old, respectively). The mean mGFR observed in men in our cohort is very similar to the results observed by Poggio *et al.* [3] in AA men. However, Poggio *et al.* found higher mean mGFRs in AA women compared with to AA men. In the current young African population, no significant difference can be found in mGFR values between genders, as suggested by most of published data in Caucasians [3, 4]. Further research seems necessary to explain this discrepancy between healthy AA women and men.

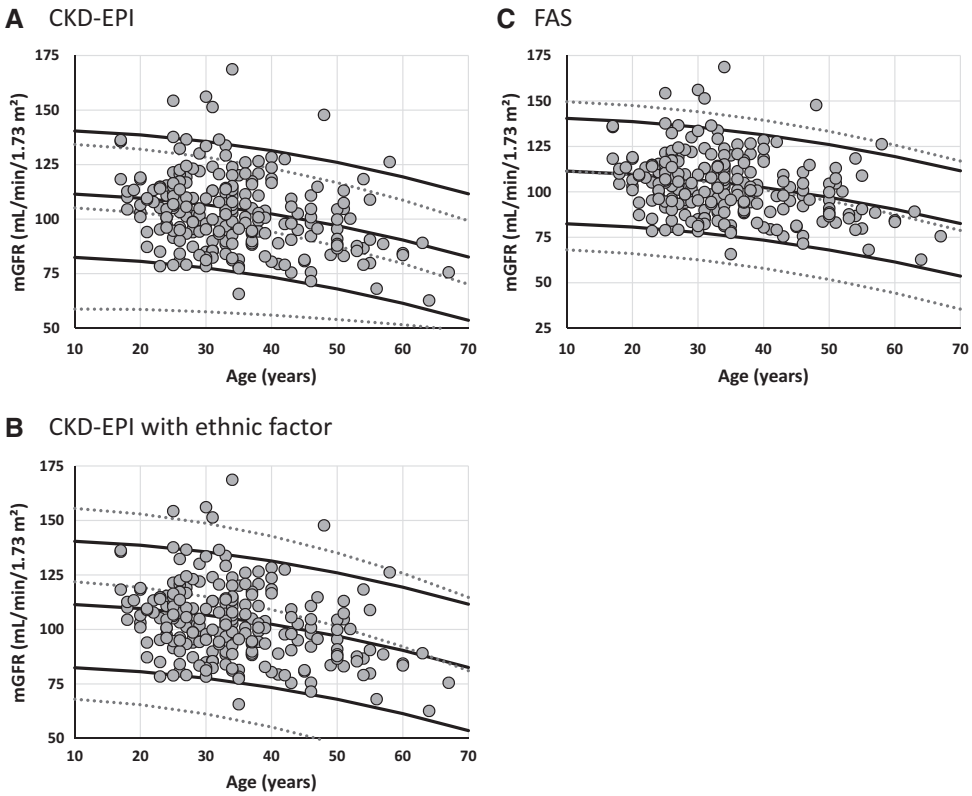

FIGURE 3: mGFR percentiles according to age. Circles represent mGFR versus age for the African population. Solid black lines represent the 2.5th, 50th and 97.5th percentiles for mGFR. Dotted lines represent the 2.5th, 50th and 97.5th percentiles for the (**A**) CKD-EPI equation without the ethnic factor, (**B**) CKD-EPI equation with the ethnic factor and (**C**) FAS equation.

Recently, results from the Multi-Ethnic Study of Atherosclerosis (MESA) have been published with mGFR by iohexol plasma clearance in subjects free from cardiovascular disease but not strictly healthy (139 AAs and 155 Caucasians) [9]. The authors described a similar mGFR value in both AAs and Caucasians (74 ± 20 and 71 ± 17 mL/min/1.73 m^2, respectively). Together with MESA, Poggio *et al.* [3] and recent meta-analyses [4, 9], we suggest that normal GFR values are similar in AA, Caucasian and West African populations. The overall mean mGFR was lower in the MESA cohort, but these patients were also much older (70.7 ± 8.6 years) [9]. In our African cohort, only eight subjects were > 55 years of age, reflecting the low mean age in the Ivory Coast population (in 2010, the median age of the population was 19.6 years while only 3.8% of the population was > 65 years old). The current results can also be compared with a recent meta-analysis including studies with mGFR in healthy Caucasian populations and published after 2000 [4]. In this analysis, 107 mL/min/1.73 m^2 could be considered, in both genders, as the mean normal GFR value until 40 years of age, and normal GFR decreases after 40 years of age [4]. This observation is confirmed in the current cohort from Africa. Indeed, in Table 2, the value 107 mL/min/1.73 m^2 is in the 95% CI for all mGFR results for subjects < 40 years of age, with the same trend of decreasing mGFR values after 40 years of age (Figure 2). Eventually the percentiles observed in the current healthy African population perfectly fit with percentiles calculated in a recent analysis including 633 Caucasian living kidney donors [21].

Regarding eGFR equations, our results showed the best concordance with mGFR for the FAS creatinine equation, confirming the results in Caucasian cohorts but using the Q values adapted for Africans [16, 22]. Regarding the CKD-EPI equation, recognized to be useful in the normal GFR range, a better fit with mGFR percentiles is observed when the ethnic coefficient is not used, confirming prior data in Africans, European Africans and even AAs [17–20].

There are some limitations to this work. First, as already discussed, few patients > 65 years of age have been included. Second, our data are purely transversal, as all other publications with mGFR use other ethnicities [3–5]. Third, GFR was measured with plasma clearance, a technique that could be considered less physiological than urinary clearance. However, iohexol plasma clearance is accepted as a reference method for GFR measurement [12, 23], is free of all non-GFR determinants that are major limitations for serum creatinine or plasma cystatin [12, 24] and has recently been considered as the best balance between physiology and feasibility [12, 25]. Finally, our results are from West Africa and need to be confirmed in other African regions with other anthropometric characteristics (such as in Maghreb or East Africa). However, anthropometric differences between people in West Africa and Caucasians are more important than between people from Maghreb and Caucasians.

In the current work we described for the first time the normal reference value of mGFR in Africa. These values are similar in men and women, as in Caucasians [3, 26]. The percentiles do not seem fundamentally different from results observed in Caucasians and AAs. As in these other ethnic groups [4], normal GFR values are significantly lower after 40 years of age.

ACKNOWLEDGEMENTS

We thank the data nurses who performed the iohexol procedure in Abidjan: Ella Brou and Floriana Abaké. We thank the technicians who contributed to iohexol measurement in Liège: Anne-Catherine Bekaert and Eric Brevers.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Stevens LA, Levey AS. Measured GFR as a confirmatory test for estimated GFR. *J Am Soc Nephrol* 2009; 20: 2305–2313
2. Delanaye P, Mariat C. The applicability of eGFR equations to different populations. *Nat Rev Nephrol* 2013; 9: 513–522
3. Poggio ED, Rule AD, Tanchanco R *et al.* Demographic and clinical characteristics associated with glomerular filtration rates in living kidney donors. *Kidney Int* 2009; 75: 1079–1087
4. Pottel H, Hoste L, Delanaye P. Glomerular filtration rate in healthy living potential kidney donors: a meta-analysis. *Nephron* 2017; 135: 105–119
5. Ma YC, Zuo L, Chen L *et al.* Distribution of measured GFR in apparently healthy Chinese adults. *Am J Kidney Dis* 2010; 56: 420–421
6. Jafar TH, Islam M, Jessani S *et al.* Level and determinants of kidney function in a South Asian population in Pakistan. *Am J Kidney Dis* 2011; 58: 764–772
7. Barai S, Bandopadhayaya GP, Patel CD *et al.* Do healthy potential kidney donors in india have an average glomerular filtration rate of 81.4 ml/min? *Nephron Physiol* 2005; 101: 21–26
8. Shock NW. Kidney function tests in aged males. *Geriatrics* 1946; 1: 232–239
9. Inker LA, Shafi T, Okparavero A *et al.* Effects of race and sex on measured GFR: the Multi-Ethnic Study of Atherosclerosis. *Am J Kidney Dis* 2016; 68: 743–751
10. Ashuntantang G, Osafo C, Olowu WA *et al.* Outcomes in adults and children with end-stage kidney disease requiring dialysis in sub-Saharan Africa: a systematic review. *Lancet Glob Health* 2017; 5: e408–e417
11. Delanaye P, Jouret F, Le Goff C, Cavalier E. Concordance between iothalamate and iohexol plasma clearance. *Am J Kidney Dis* 2016; 68: 329–330
12. Delanaye P, Ebert N, Melsom T *et al.* Iohexol plasma clearance for measuring glomerular filtration rate in clinical practice and research: a review. Part 1: how to measure glomerular filtration rate with iohexol? *Clin Kidney J* 2016; 9: 682–699
13. Du Bois D, Du Bois EF. A formula to estimate the approximative surface area if height and weight be known. *Arch Intern Med* 1916; 17: 863–871
14. Piéroni L, Delanaye P, Boutten A *et al.* A multicentric evaluation of IDMS-traceable creatinine enzymatic assays. *Clin Chim Acta* 2011; 412: 2070–2075
15. Levey AS, Stevens LA, Schmid CH *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; 150: 604–612
16. Pottel H, Hoste L, Dubourg L *et al.* A new estimating glomerular filtration rate equation for the full age spectrum. *Nephrol Dial Transplant* 2016; 31: 798–806
17. Delanaye P, Mariat C, Maillard N *et al.* Are the creatinine-based equations accurate to estimate glomerular filtration rate in African American populations? *Clin J Am Soc Nephrol* 2011; 6: 906–912
18. Anker N, Scherzer R, Peralta C *et al.* Racial disparities in creatinine-based kidney function estimates among HIV-infected adults. *Ethn Dis* 2016; 26: 213–220
19. Flamant M, Vidal-Petiot E, Metzger M *et al.* Performance of GFR estimating equations in African Europeans: basis for a lower race-ethnicity factor than in African Americans. *Am J Kidney Dis* 2013; 62: 182–184
20. van Deventer HE, George JA, Paiker JE *et al.* Estimating glomerular filtration rate in black South Africans by use of the modification of diet in renal disease and Cockcroft-Gault equations. *Clin Chem* 2008; 54: 1197–1202
21. Pottel H, Delanaye P, Weekers L *et al.* Age-dependent reference intervals for estimated and measured glomerular filtration rate. *Clin Kidney J* 2017; 1–7. doi: 10.1093/ckj/sfx026
22. Pottel H, Hoste L, Delanaye P *et al.* Demystifying ethnic/sex differences in kidney function: is the difference in (estimating) glomerular filtration rate or in serum creatinine concentration? *Clin Chim Acta* 2012; 413: 1612–1617

23. Soveri I, Berg UB, Björk J *et al.* Measuring GFR: a systematic review. *Am J Kidney Dis* 2014; 64: 411–424
24. Schei J, Stefansson VTN, Mathisen UD *et al.* Residual associations of inflammatory markers with eGFR after accounting for measured GFR in a community-based cohort without CKD. *Clin J Am Soc Nephrol* 2016; 11: 280–286
25. Delanaye P, Melsom T, Ebert N *et al.* Iohexol plasma clearance for measuring glomerular filtration rate in clinical practice and research: a review. Part 2: Why to measure glomerular filtration rate with iohexol? *Clin Kidney J* 2016; 9: 700–704
26. Eriksen BO, Melsom T, Mathisen UD *et al.* GFR normalized to total body water allows comparisons across genders and body sizes. *J Am Soc Nephrol* 2011; 22: 1517–1525

Received: 22.5.2017; Editorial decision: 20.6.2017

Nephrol Dial Transplant (2018) 33: 1180–1188
doi: 10.1093/ndt/gfx247
Advance Access publication 17 August 2017

ORIGINAL ARTICLE

Etiology and renal outcomes of acute tubulointerstitial nephritis: a single-center prospective cohort study in China

Tao Su[1,2,3,*], Yanghui Gu[1,2,3,4,*], Pingping Sun[1,2,3], Jiawei Tang[1,2,3], Suxia Wang[1,2,3,5], Gang Liu[1,2,3], Xiaomei Li[1,2,3] and Li Yang[1,2,3]

[1]Renal Division, Department of Medicine, Peking University First Hospital, Beijing, P.R. China, [2]Peking University Institute of Nephrology, Beijing, P.R. China, [3]Key Laboratory of Renal Disease, Ministry of Health of China, Beijing, P.R. China, [4]Renal Division, Department of Medicine, Second Clinical Medical College, Guangzhou University of Traditional Chinese Medicine, Guangzhou, P.R. China and [5]Laboratory of Electron Microscopy, Pathological Centre, Peking University First Hospital, Beijing, P.R. China

Correspondence and offprint requests to: Li Yang; E-mail: li.yang@bjmu.edu.cn
*These two authors contributed equally to this work.

ABSTRACT

Background. The aim of this study was to explore the etiology, long-term renal outcomes and affecting factors of acute tubulointerstitial nephritis (ATIN).

Methods. Patients with biopsy-proven ATIN from 1 January 2005 to 31 December 2013 at Peking University First Hospital were enrolled in the study and received scheduled follow-up for at least 24 months. The causes of ATIN were defined at biopsy and reclassified during follow-up. Factors affecting renal recovery at 6 months post-biopsy and estimated glomerular filtration rate (eGFR) at 12 months post-biopsy and at the end of follow-up were analyzed.

Results. A total of 157 ATIN patients were enrolled, with an average follow-up of 48 months (range 24–108 months). A modified etiology spectrum was identified, with a decreased proportion of drug-induced ATIN (D-ATIN, 64% at biopsy to 50% after follow-up) and an increase in autoimmune-related ATIN (22–41%) with late-onset systemic manifestations in patients who had been classified as D-ATIN or ATIN of unknown cause. Recurrent kidney injury was observed in 51% of the patients with tubulointerstitial nephritis and uveitis syndrome (TINU), 53% of those with an autoimmune disease and 8% of those with D-ATIN, resulting in prolonged immunosuppressive treatment. By 12 months, decreased eGFR (<60 mL/min/1.73 m^2) was observed in 47% of the patients with D-ATIN, 74% of those with TINU and 57% of those with other autoimmune diseases. In multivariable analysis, female sex, older age, presence of hypertension and recurrent kidney injury were independent risk factors for worse renal outcomes.

Conclusions. Our data demonstrate that autoimmune-related ATIN may present with systemic manifestations after kidney injury and is, therefore, commonly misdiagnosed. Repeated kidney injury is not uncommon in patients with ATIN. Scheduled follow-up is, therefore, critical for defining the exact etiology and proper management of ATIN.

Keywords: acute kidney injury, acute tubulointerstitial nephritis, etiology, outcome, treatment

INTRODUCTION

Acute tubulointerstitial nephritis (ATIN) represents a significant cause of renal parenchymal acute kidney injury (AKI) [1–5], which clinically features prominent tubular dysfunction and acutely decreased glomerular filtration. It is histopathologically characterized by inflammation and edema of the renal interstitium and tubulitis, sparing the glomeruli and the vasculature. ATIN accounts for 1–3% of all renal biopsies [5–9] and occurs in 10–27% of patients who undergo biopsy