The impact of renal angiomyolipoma on estimated glomerular filtration rate in patients with tuberous sclerosis complex

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BACKGROUND: There is a growing concern that renal impairment may develop in patients with renal angiomyolipomas (AMLs) associated with tuberous sclerosis complex (TSC) as a consequence of the disease itself and/or the interventions to mitigate the risk of hemorrhage.

OBJECTIVE: To assess the estimated glomerular filtration rate (eGFR) in patients with bilateral renal AMLs and the impact of tumor burden and intervention on renal function.

DESIGN: Retrospective study.

SETTING: Urology department of a tertiary care hospital.

PATIENTS AND METHODS: All adult patients (≥18 years of age) with TSC-associated renal AMLs seen from October 1998 to June 2015. We included only patients with bilateral tumors or solitary kidneys at the last follow-up.

MAIN OUTCOME MEASURES: The eGFR, renal volume, and number and type of interventions.

RESULTS: We identified 12 patients (median age 27.6, interquartile range 23.7-39.9 years), a median follow-up period of 1266 days (33-3133), and a median renal size of 454.7 mL (interquartile range 344.7-1016.9 on the right side; 558.1 mL, interquartile range 253.7-1001.4 on the left). In 11 (91.7%) patients, the eGFR was >60 mL/min/1.73 m². Six patients had three total nephrectomies, one had a contralateral partial nephrectomy, and seven had selective arterial embolizations. Intervention was associated with a significantly reduced eGFR. The renal size did not correlate with the eGFR.

CONCLUSIONS: TSC-associated renal AMLs may attain a large size but normal renal function is maintained in 92% of patients. Interventions to mitigate the risk of hemorrhage are associated with decreased renal function.

LIMITATIONS: The renal size was used as a surrogate for tumor size. Other limitations were the limited number of patients and lack of split renal function testing.

A ngiomyolipomas (AMLs) are benign fat-containing tumors that affect the kidneys. AMLs associated with the tuberous sclerosis complex (TSC) are often larger, usually bilateral, and grow more rapidly than AMLs in sporadic cases.1,2 The greatest risk for patients with large lesions is life-threatening retroperitoneal hemorrhage. In a pooled analysis of renal AML cases, 44% of patients with TSC-associated AMLs presented with hemorrhages.1 In contemporary series, most patients required interventions to control symptoms of hemorrhage, including total or partial nephrectomy in 58% and embolization in 42%.3 Although prophylactic treatment to prevent hemorrhage and intervention to treat active bleeding are effective and safe,4 preservation of renal function emerges as an important target for novel therapeutic approaches.5 There is a growing concern that TSC-associated renal AMLs may cause renal impairment and failure.5,6 Although renal diseases are reported as the leading cause of death in TSC patients, the exact pattern by which the deterioration of renal function contributes to mortality and the underlying risk factors are not known.7 Factors that may affect the glomerular filtration rate (GFR) in those patients include tumor burden, as well as the nature and number
of interventions. Despite these concerns, we observed that some of our patients maintain a normal renal function in the presence of huge bilateral AMLs filling the entire abdomen. We conducted this study to identify how renal function is affected in TSC patients with large bilateral renal AMLs and the factors that may affect the estimated GFR (eGFR) in our tertiary care hospital.

**PATIENTS AND METHODS**

We conducted a retrospective study of all patients with TSC-associated renal AMLs who were referred to the urology department from October 1998 to June 2015. We included only those patients who met the clinical diagnostic criteria of TSC.\(^{10}\) Data were collected from paper and electronic records and included age, sex, weight, height, serum creatinine levels, and type and number of interventions. We excluded pediatric patients <18 years of age at the last follow-up and patients with a normal contralateral kidney or with a solitary lesion less than 4 cm in diameter. The serum creatinine level was determined using the Jaffe Reaction Method (Roche Diagnostics, Basel, Switzerland). The eGFR was calculated using three equations for adult patients: the Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), and Cockcroft-Gault (CockG) equations. The Schwartz equation was used for one pediatric patient at initial presentation.\(^{11-14}\) Renal size was calculated by using the ellipsoid formula. Renal volume was independently measured by 3-dimensional (3D) reconstruction of the same images using General Electric Advantage Windows 4.6 Volume software (GE Healthcare, Little Chalfont, United Kingdom). The kidney volume was measured through contiguous slices using free-hand outlining of the kidney. We compared data for patients who received any intervention to stop bleeding with those who did not need any intervention. We compared data for patients at their initial visit and last follow-up. We used the t test to compare continuous data and the chi-square or Fisher exact test (1-sided) for categorical data. Missing data were excluded from the analysis. We considered \(P<.05\) significant. We used IBM SPSS statistics 20 software (IBM Corporation, Armonk, New York, United States) for statistical analysis.

**RESULTS**

We excluded two adult patients because of contralateral kidneys with solitary lesions that had the largest diameter of <4 cm. We evaluated 12 eligible patients; all had bilateral renal AMLs and 9 of them were females. All patients had at least two major criteria for the clinical diagnosis of TSC (Table 1). At the last follow-up, the median 3D renal volume for female patients for the right side was 492.6 mL (232.7-1933.8; standard deviation [SD] 598.1, \(n=8\)) and for the left side, 638.3 mL (166.6-2403; SD 880.1, \(n=7\)) (Table 2). For the three male patients, the right median renal volume was 450.8 mL (259.7-1016.9) and the left, 510 mL (223.5-606.2). The patients had a median eGFR >60 mL/min/1.73 m\(^2\). There was a significant correlation between the GFR determined by using the three different methods: eGFR-MDRD correlated with eGFR-CKD-EPI (\(r=0.843, P=.001\)) and eGFR-CockG (\(r=0.632, P=.028\)), while eGFR-CKD-EPI correlated significantly with eGFR-CockG (\(r=0.76, P=.004\)). At the last follow-up, nine patients (75%) had an eGFR >90 mL/min/1.73 m\(^2\). Two patients (16.7%) had an eGFR 60-90 mL/min/1.73 m\(^2\) after two left total nephrectomies, one right partial nephrectomy, and two embolizations to control bleeding. One patient (8.3%) had an eGFR <60 mL/min/1.73 m\(^2\) after left total nephrectomy and embolization. The volume of the kidney as determined by the ellipsoid formula correlated significantly with the 3D reconstructed volume (\(r=0.972, P<.001\)). There was no significant correlation between the total renal volume and creatinine level or GFR (Table 3).

Six patients (50%) (five females and one male) received 11 interventions to stop bleeding during follow-up. There was no difference between sexes in exposure to interventions (\(P=.5\)). The patients had seven selective arterial embolizations, three had a total nephrectomy, and one had a partial nephrectomy. The eGFR was significantly lower for patients who un-

| Criteria                              | n   |
|--------------------------------------|-----|
| **Major**                            |     |
| Bilateral renal AML                  | 12  |
| Subependymal nodules                 | 11  |
| Facial angiofibroma                  | 10  |
| Cortical dysplasia                   | 2   |
| Lymphangioleiomyomatosis             | 1   |
| Subependymal giant cell astrocytoma  | 2   |
| **Minor**                            |     |
| Liver hamartoma                      | 5   |
| Retinal patch                        | 1   |

**Table 1. Criteria for clinical diagnosis of tuberous sclerosis complex.**
underwent an intervention compared with that for those who did not receive any intervention (Table 4). Renal volume data at the initial visit and last follow-up were available for eight patients. There was no difference between baseline and last follow-up renal volume, creatinine level, or eGFR (Table 5).

DISCUSSION

AML tumor burden and renal volume determination

We determined renal volume as an indicator of AML burden rather than measuring individual lesions, because in many cases it was difficult to distinguish between the numerous AML lesions that filled the kidneys and normal tissues (Figure 1A, B). The complexity of renal tumor burden significantly impairs individual tumor size measurement. A study of renal tumor burden by CT semiautomated volume determination of selected tumors showed high inter-observer and intra-observer variability that was even larger for the ellipsoid formula calculation. We determined the renal volume by two different methods, and two independent teams reviewed all the cases. The ellipsoid formula was calculated based on renal dimensions

Table 2. Patient characteristics at last follow-up.

|                         | n  | Median | SD  | Min  | Max  | Q1  | Q3  |
|-------------------------|----|--------|-----|------|------|-----|-----|
| Age (y)                 | 12 | 27.6   | 8.5 | 20.8 | 45.0 | 23.7| 39.9|
| Weight (kg)             | 12 | 56.3   | 19.8| 33.2 | 106.5| 46.5| 74.1|
| Height (cm)             | 12 | 159.0  | 7.6 | 149.0| 173.0| 151.3| 163.8|
| Serum creatinine (umol/L)| 12 | 62.0   | 26.8| 19.0 | 113.0| 43.3| 82.8|
| GFR (ml/min/1.77 m²)    | 12 | 122.8  | 94.2| 48.8 | 394.7| 86.2| 166.2|
| MDRD                    | 12 | 123.0  | 31.2| 52.0 | 165.0| 93.3| 136.0|
| CKD-EPI                 | 12 | 121.6  | 84.7| 47.2 | 314.3| 76.1| 174.3|

Kidney volume (cm³)

Ellipsoid formula

|                         | n  | Median | SD  | Min  | Max  | Q1  | Q3  |
|-------------------------|----|--------|-----|------|------|-----|-----|
| Right kidney            | 11 | 538.4  | 495.1| 256.6| 1880.1| 313.4| 776.7|
| Left kidney             | 10 | 540.0  | 966.6| 180.7| 2864.2| 267.9| 1213.1|
| Total renal volume      | 12 | 973.9  | 1185.4| 367.0| 4376.5| 583.8| 1812.1|

3D reconstruction

|                         | n  | Median | SD  | Min  | Max  | Q1  | Q3  |
|-------------------------|----|--------|-----|------|------|-----|-----|
| Right kidney            | 11 | 454.7  | 537.8| 232.7| 1933.8| 344.7| 1016.9|
| Left kidney             | 10 | 558.1  | 764.1| 166.6| 2403.0| 253.7| 1001.4|
| Total 3D renal volume   | 12 | 971.9  | 1112.6| 399.3| 4336.8| 495.0| 1897.5|

3D=3-dimensional; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration equation; CockG=Cockcroft-Gault equation; MDRD=Modification of Diet in Renal Disease equation; Q1=25 percentile; Q3=75 percentile.

Table 3. Correlation between renal volume and estimated glomerular filtration rate at last follow-up.

|                         | Cr   | MDRD | CKD EPI | CockG |
|-------------------------|------|------|---------|-------|
| Total kidney volume by ellipsoid formula | Pearson correlation | .029 | .074 | -0.034 | -.203 |
|                         | P value (2-tailed) | .930 | .820 | .916 | .527 |
| Total kidney volume by 3D reconstruction | Pearson correlation | -.150 | .199 | .145 | -.098 |
|                         | Sig. (2-tailed) | .642 | .535 | .653 | .761 |

CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration equation; CockG=Cockcroft-Gault equation; Cr=Serum creatinine; MDRD=Modification of Diet in Renal Disease equation.
Table 4. Comparison between patients who underwent any intervention to control bleeding versus no intervention.

|                               | No Intervention | Intervention to control bleeding |          |          |          |          |          |          |          |          |          |          |
|-------------------------------|-----------------|----------------------------------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
|                               | n   | Mean | Median | Min  | Max  | SD   | n  | Mean | Median | Min  | Max  | SD   |
| Age (yrs)                     | 6   | 26.9 | 25.8   | 20.8 | 35.3 | 5.3  | 6  | 33.9 | 34.4   | 21.3 | 45.0 | 10.2 |
| Weight (kg)                   | 6   | 68.1 | 68.5   | 33.2 | 106.5| 24.5 | 6  | 53.4 | 50.0   | 42.0 | 74.4 | 11.6 |
| Height (cm)                   | 6   | 158.7| 157.0  | 149.0| 173.0| 8.7  | 6  | 158.8| 160.1  | 150.0| 168.5| 7.1  |
| **Kidney volume (cm³)**      |      |      |        |      |      |      |    |      |        |      |      |      |
| Ellipsoid formula             |      |      |        |      |      |      |    |      |        |      |      |      |
| Right kidney                  | 6   | 600.0| 494.5  | 256.6| 1264.1| 373.7| 5  | 773.8| 557.8  | 289.6| 1880.1| 646.2 |
| Left kidney                   | 6   | 506.1| 540.0  | 180.7| 785.3| 238.1| 4  | 1479.8| 1434.4 | 186.1| 2864.2| 1396.5|
| 3D reconstruction             |      |      |        |      |      |      |    |      |        |      |      |      |
| Right kidney                  | 6   | 651.2| 448.1  | 232.7| 1416.5| 462.8| 5  | 788.0| 530.5  | 259.7| 1933.8| 665.2 |
| Left kidney                   | 6   | 516.5| 558.1  | 166.6| 672.2| 184.2| 4  | 1219.8| 1126.4 | 223.5| 2403.0| 1139.9|
| Serum creatinine (umol/L)     | 6   | 51.5 | 47.0   | 19.0 | 92.0 | 27.2 | 6  | 74.3 | 71.0   | 50.0 | 113.0 | 22.9  |
| GFR (ml/ min/1.77 m²)         |      |      |        |      |      |      |    |      |        |      |      |      |
| MDRD                          | 6   | 193.0| 150.6  | 90.5 | 394.7| 113.5| 6  | 96.2 | 94.0   | 48.8 | 136.1 | 31.7  |
| CKD-EPI                       | 6   | 133.8| 131.5  | 97.0 | 165.0| 24.8 | 6  | 99.0 | 101.5  | 52.0 | 127.0 | 28.3  |
| CockG                         | 6   | 192.6| 157.9  | 115.5| 314.3| 90.2 | 6  | 88.3 | 83.6   | 47.2 | 126.3 | 33.3  |

* t-test for comparison of means (2-tailed) Equal variances assumed.

3D=3-dimensional; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration equation; CockG=Cockcroft-Gault equation; MDRD=Modification of Diet in Renal Disease equation.
### Table 5. Change between first visit and last follow-up.

|                      | First visit |                      | Last follow-up visit |                      |     |
|----------------------|-------------|----------------------|----------------------|----------------------|-----|
|                      | n | Mean | Median | SD | Min | Max | n | Mean | Median | SD | Min | Max |     |
| Age (y)              | 8 | 25.8 | 24.8  | 8.9 | 10.6 | 41.7 | 8 | 30.9 | 26.5  | 10.2 | 20.8 | 45.0 | .031 |
| Weight (kg)          | 8 | 59.1 | 54.5  | 20.7 | 41.0 | 103.7 | 8 | 62.5 | 54.9  | 21.5 | 42.0 | 106.5 | .468 |
| Height (cm)          | 8 | 155.8| 158.0 | 9.4 | 138.0 | 168.5 | 8 | 157.6| 158.0 | 6.5  | 150.0 | 168.5 | .351 |
| Kidney volume (cm³)  |     |      |        |     |      |      |     |      |        |     |      |      |     |
| Ellipsoid formula    |     |      |        |     |      |      |     |      |        |     |      |      |     |
| Right kidney         | 7  | 586.4| 463.8 | 325.0| 232.0| 1135.2| 7  | 661.9| 450.6 | 562.6| 289.6| 1880.1| .544 |
| Left kidney          | 6  | 893.3| 606.3 | 795.3| 177.0| 2362.3| 6  | 1151.7| 534.1 | 1201.8| 186.1| 2864.2| .319 |
| Total kidney volume  | 8  | 1183.1| 921.3 | 729.2| 463.8| 2362.3| 8  | 1442.9| 853.3 | 1418.4| 367.0| 4376.5| .367 |
| 3D reconstruction    |     |      |        |     |      |      |     |      |        |     |      |      |     |
| Right kidney         | 7  | 594.6| 518.9 | 300.6| 276.3| 1090.1| 7  | 675.7| 454.7 | 576.7| 259.7| 1933.8| .571 |
| Left kidney          | 6  | 998.5| 739.7 | 823.7| 264.5| 2512.4| 6  | 1003.8| 571.9 | 945.1| 223.5| 2403.0| .982 |
| Total kidney volume  | 8  | 1269.1| 972.6 | 775.1| 415.5| 2512.4| 8  | 1344.1| 967.0 | 1306.7| 454.7| 4336.8| .794 |
| Serum creatinine (μmol/L) | 8  | 66.5 | 68.0  | 15.1 | 48.0 | 84.0  | 8  | 64.8 | 62.0  | 26.4 | 31.0 | 113.0 | .740 |
| GFR (ml/min/1.73 m²) |     |      |        |     |      |      |     |      |        |     |      |      |     |
| MDRD                 | 8  | 103.3| 109.9 | 25.7 | 72.7 | 140.5 | 8  | 125.3| 113.3 | 63.4 | 48.8 | 249.7 | .278 |
| CKD-EPI              | 8  | 106.5| 113.0 | 21.8 | 80.0 | 131.0 | 8  | 111.1| 118.0 | 33.1 | 52.0 | 156.0 | .587 |
| CockG                | 8  | 114.2| 97.0  | 60.5 | 62.1 | 251.6 | 8  | 142.0| 111.7 | 103.5| 47.2 | 314.3 | .298 |
| Duration (days)      | 8  | 1462.8| 1266.0| 1403.5| 33.0 | 3133.0| 8  | 1462.8| 1266.0| 1403.5| 33.0 | 3133.0|     |

*Paired samples t-test (2-tailed).

3D=3-dimensional; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration equation; CockG=Cockcroft-Gault equation; MDRD=Modification of Diet in Renal Disease equation.
Figure 1. An imaging study in 2013 of a 31-year-old female with bilateral large renal angiomyolipoma. She had selective arterial embolization for active bleeding twice on the right side (2005 and 2008) and once on the left side (2008). A. Coronal CT image shows the right kidney measuring 20.9x10.4 cm and left kidney 22.7x10.6 cm craniocaudally and transversely respectively. B. A transaxial CT image showing right kidney dimensions of 14.8x9.5 cm and left kidney dimensions of 18.3x10.5 cm. C. Technetium MAG3 diuretic renogram showing adequate perfusion and cortical uptake with slow transit and progressive accumulation of tracer in the dilated collecting system (delayed excretion showed good response to furosemide at 10 minutes). D. Static images of the renogram. Serum creatinine at the time of the study was 54 umol/L and eGFR >60 mL/min/1.77 m². MAG3=mercaptoacetyltriglycine.
of the few patients with small kidneys does not seem to have significantly affected the GFR results.

**Renal function determination**

We determined renal function using the eGFR formulas as an accepted alternative to the more accurate yet difficult to implement method of exogenous substance clearance.21 The results of the three formulas correlated significantly with each other. By definition, all patients are classified as having CKD stages 1-5 on the basis of kidney structural changes seen on imaging, regardless of the eGFR.21 CKD stages 1 and 2 according to this definition are associated with eGFR ≥90 mL/min/1.73 m² and ≥60 mL/min/1.73 m², respectively. Significant CKD (stages 3-5) is diagnosed when the eGFR is below 60 mL/min.21 Most of our patients (91.7%), according to this definition, had normal renal function at the last follow-up. The three patients with an eGFR <90 mL/min/1.73 m² had a total of three total nephrectomies, one contralateral partial nephrectomy, and three selective arterial embolizations. The reported eGFR reflects total renal function. It could be argued that the contralateral renal units contributed to normal renal function when the affected kidney was poorly functioning. In this series, several factors seem to refute this assumption. First, only 25% of renal units had a volume less than 254-345 ml. Second, all kidneys had numerous AML lesions. Third, three patients had a solitary kidney following total nephrectomy for bleeding. None had impaired renal function. However, a better way to emphasize our observations is to document split renal function using radioisotope scanning. Some patients underwent MAG3 scanning (Figure 1C, D). Even with huge bilateral AMLs, the scan shows increased blood flow due to high vascularity of the lesions and preserved renal function.

Another method to determine split renal function is to calculate the renal volume. Several studies showed that in normal kidneys, the relative renal tissue volume determined by CT correlated well with split renal function calculated from scintigraphy studies. The correlation was strong in healthy kidney donors,22 and in the case of chronically obstructed kidneys.23 It is not known whether this principle applies to kidneys with AMLs. In our series, there was no significant correlation between total renal volume and eGFR. This was probably because the increase in volume of AML-affected kidneys was due to the volume of the nonfunctioning tumor rather than an increase in healthy tissue volume. Another factor was the actual eGFR figures above 60, which though indicating normal renal function, may not correlate well with true GFR.

**Effect of AML on renal function**

Previous reports stressed that AMLs were associated with impaired renal function and contributed to mortality due to renal failure. Renal failure was labeled as the second cause of death in TSC patients after neurological complications.2 A survey of 260 dialysis units in France identified 65 patients with TSC and chronic renal failure.2 Eight patients died as a consequence of renal failure or its treatment. However, the authors estimated the prevalence of TSC and renal failure in France to be around 0.7 per million and 1% among patients with TSC. It is interesting that 41.5% of patients had a nephrectomy. Several case reports linked TSC AMLs with renal failure.24-29 These reports suggested that the mechanisms underlying renal failure included hyperfiltration injury leading to focal glomerulosclerosis and reduction of nephron mass by tumor invasion, cysts, and surgery. A more recent retrospective study reported more frequent CKD stages 3-5 in a TSC patient cohort treated in general practice than in another cohort at all ages; the frequency peaked at ages greater than 65 years (42% vs. 23%).30 In a retrospective, longitudinal cohort study of TSC patients treated at a specialty center in the Netherlands, 16% of patients younger than 70 years old reached CKD stage 3 or higher during follow-up.3 In contrast, in a reference population of non-TSC patients, only 3% had CKD stage 3 or higher.

On the other hand, other studies of large numbers of patients reported normal renal function despite numerous interventions to prevent or control bleeding.22 We observed that patients with huge bilateral AML such as that shown in Figure 1, still maintained normal renal function. It is interesting that the only situation when there was a significant deterioration of renal function in our series was in patients who underwent an intervention to stop bleeding. This is in agreement with the findings of the Dutch study, which showed that among other factors (age, AML size and number, female gender, and TSC2 gene mutation) significantly associated with advanced CKD stages, having undergone renal embolization was a likelihood.3 The embolization status for patients with CKD stages 1-5 was 25.4, 47.8, 59.3, 68.0, and 77.8%, respectively (P<.001).3 We speculate that AML burden itself does not impair renal function, but the intervention does. This is in agreement with data from several studies showing a significant number of nephrectomies,7 and embolizations7 in patients with renal impairment. We postulate that maintenance of normal renal function in such patients is attributable to the high vascularity supplying the kidney, lack of infiltration/replacement of AML lesions with normal func-
tioning renal tissue, and absence of compression exerted by these lesions on renal parenchyma. The lack of compression might be due to the free expansion of the lesions into the abdominal cavity, which is not confined by the renal capsule and the soft consistency of the fat-rich lesions.

In conclusion, TSC AML renal tumors may attain a large size and are subjected to numerous interventions. Potentially, some interventions can affect renal function. However, despite interventions in the vast majority of our patients, follow-up over several years did not show significant change in the eGFR, irrespective of tumor burden.

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REFERENCES
1. Nelson CP, Sanda MG. Contemporary diagnosis and management of renal angiomyolipoma. J Urol. 2002; 168(4 Pt 1): 1315.
2. Seyam RM, Bissada NK, Kattan SA, et al. Changing trends in presentation, diagnosis and management of renal angiomyolipoma: comparison of sporadic and tuberous sclerosis complex-associated forms. Urology. 2008; 72: 1077.
3. Koo KC, Kim WT, Ham WS, et al. Trends of presentation and clinical outcome of treated renal angiomyolipoma. Yonsei Med J. 2010; 51: 728.
4. Ewalt DH, Diamond N, Rees C, et al. Long-term outcome of transcatheter embolization of renal angiomyolipomas due to tuberous sclerosis complex. J Urol. 2005; 174: 1764.
5. Vekeman F, Magestro M, Karner P, et al. Kidney involvement in tuberous sclerosis complex: the impact on healthcare resource use and costs. J Med Econ. 2015; 18: 1060.
6. Wiedenholt WC, Gornicz MR, Kurland LT. Incidence and prevalence of tuberous sclerosis in Rochester, Minnesota, 1950 through 1982. Neurology. 1985; 35: 600.
7. Schilling R, Montagnac R. Chronic renal failure and its treatment in tuberous sclerosis. Nephron Dial Transplant. 2011; 118: e15.
8. Dixon BP, Hulbert JC, Bisler JJ. Tubero-sclerosis complex renal disease. Nephron Exp Nephrol. 2011; 118: e15.
9. Shepherd CW, Gornicz MR, Lie JT, et al. Causes of death in patients with tuberous sclerosis. Mayo Clin Proc. 1991; 66: 792.
10. Northrup H, Krueger DA; International Tuberous Sclerosis Complex Consensus Group. Tubero-sclerosis complex diagnostic criteria update: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol. 2013; 49: 243.
11. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999; 130: 461.
12. Levey AS, Stevens LA, Schmid CH, et al. CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009 May 5; 150(9):604-12. Erratum in: Ann Intern Med. 2011: 155: 408.
13. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976; 16: 31.
14. Schwartz GJ, Munofo A, Schneider MF, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol. 2009; 20: 629.
15. Rhode AM, Harrigel C, Friedman AC, et al. Comparison of the accuracy of CT volume calculated by circumscription to prolate ellipsoid volume (bidimensional measurement multiplied by coronal long axis). Acad Radiol. 2009; 16: 181.
16. Jones TB, Riddick LR, Harpen MD, et al. Ultrasoneographic determination of renal mass and renal volume. J Ultra sound Med. 1983; 2: 151.
17. Bakker J, Oliere M, Kaatee R, et al. In vivo measurement of kidney size: comparison of ultrasonography and MRI. Ultrasound Med Biol. 1998; 24: 683.
18. Breau RH, Clark E, Bruner B, et al. A simple method to estimate renal volume from computed tomography. Can Urol Assoc J. 2013; 7: 189.
19. Geraghty EM, Boone JM, McGahan JP, et al. Normal organ volume assessment from abdominal CT. Abdom Imaging. 2004; 29: 482.
20. Cheong B, Muthupilli R, Rubin MF, et al. Normal values for renal length and volume as measured by magnetic resonance imaging. Clin J Am Soc Nephrol. 2007; 2: 38.
21. Chapter 1: Definition and classification of CKD. Kidney Int Suppl (2011). 2013; 3: 19.
22. Soga S, Britz-Cunningham S, Kumamaru K, et al. Comprehensive comparative study of computed tomography-based estimates of split renal function for potential renal donors: modified ellipsoid method and other CT-based methods. J Comput Assist Tomogr. 2012; 36: 323.
23. Morrisroe SN, Su RR, Bae KT, et al. Differential renal function estimation using computerized tomography based renal parenchymal volume measurement. J Urol. 2010; 183: 2289.
24. Okada RD, Platt MA, Fleshman J. Chronic renal failure in patients with tubero-sclerosis. Association with renal cysts. Nephron. 1982; 30: 85.
25. Meyrier A, Rainfrey M, Roland J, et al. Tuberous sclerosis with chronic renal failure treated by hemodialysis and transplantation (author’s transl). Nephrologie. 1980; 1: 85.
26. Schilling R, Montagnac R, Grapin JL, et al. The kidney failure of Bourneville’s tubero-sclerosis: a new form of glomerular damage as a result of hyperfiltration? Nephrologie. 1985; 6: 219.
27. Svendsen F, Berg Schmidt E, Iversen G, et al. Uremia in a family with tuberous sclerosis. Scand J Urol Nephrol. 1987; 21: 79.
28. Yu DT, Sheth KJ. Cystic renal involvement in tuberous sclerosis. Clin Pediatr (Phila). 1985; 24: 36.
29. Brook-Carter PT, Peral B, Ward CJ, et al. Deletion of the TSC2 and PKD1 genes associated with severe infantile polycystic kidney disease—a contiguous gene syndrome. Nat Genet. 1994; 8: 328.
30. Kingswood C, Bolton P, Crawford P, et al. The clinical profile of tuberous sclerosis complex (TSC) in the United Kingdom: A retrospective cohort study in the Clinical Practice Research Datalink (CPRD). Eur J Paediatr Neurol. 2016; 20: 296.