Renal angiomylipomas are one of the most common renal manifestations in patients with tuberous sclerosis complex (TSC), with potentially life-threatening complications and a poor prognosis. Despite the considerable progress in understanding TSC-associated renal angiomylipomas, there are no large scale real-world data. The aim of our present study was to describe in detail the prevalence and outcome of renal angiomylipomas in patients with TSC, enrolled into the TuberOus SClerosis registry to increase disease Awareness (TOSCA) from 170 sites across 31 countries worldwide. We also sought to evaluate the relationship of TSC-associated renal angiomylipomas with age, gender...
and genotype. The potential risk factors for renal angiomyolipoma-related bleeding and chronic kidney disease (CKD) were studied in patients who participated in the TOSCA renal angiomyolipoma substudy. Of the 2,211 eligible patients, 1,062 (48%) reported a history of renal angiomyolipomas. The median age of TSC diagnosis for all subjects ($n = 2,211$) was 1 year. The median age of diagnosis of renal angiomyolipoma in the 1,062 patients was 13 years. Renal angiomyolipomas were significantly more prevalent in female patients ($p < 0.0001$). Rates of angiomyolipomas $> 3$ cm ($p = 0.0119$), growing lesions ($p = 0.0439$), and interventions for angiomyolipomas ($p = 0.0058$) were also higher in females than males. Pre-emptive intervention for renal angiomyolipomas with embolisation, surgery, or mammalian target of rapamycin (mTOR) inhibitor may have abolished the gender difference in impaired renal function, hypertension, and other complications. The rate of interventions for angiomyolipomas was less common in children than in adults, but interventions were reported in all age groups. In the substudy of 76 patients the complication rate was too low to be useful in predicting risk for more severe CKD. In addition, in this substudy no patient had a renal hemorrhage after commencing on an mTOR inhibitor. Our findings confirmed that renal angiomyolipomas in subjects with $TSC1$ mutations develop on average at the later age, are relatively smaller in size and less likely to be growing; however, by age 40 years, no difference was observed in the percentage of patients with $TSC1$ and $TSC2$ mutations needing intervention. The peak of appearance of new renal angiomyolipomas was observed in patients aged between 18 and 40 years, but, given that angiomyolipomas can occur later, lifelong surveillance is necessary. We found that pre-emptive intervention was dramatically successful in altering the outcome compared to historical controls; with high pre-emptive intervention rates but low rates of bleeding and other complications. This validates the policy of surveillance and pre-emptive intervention recommended by clinical guidelines.

**Keywords:** mTOR, registry, renal angiomyolipoma, TOSCA, tuberous sclerosis complex

**INTRODUCTION**

Tuberous sclerosis complex (TSC) is a rare, autosomal dominant genetic disorder characterized by hamartomatous lesions in multiple organs such as brain, kidneys, skin, lungs, eyes, and heart (1, 2). Renal manifestations are one of the most common causes of morbidity and were historically reported as the primary cause of death in adult TSC patients (3–5). The relative importance of mechanisms postulated to lead to impaired renal function are unknown (6) but a major risk factor may be intervention for renal angiomyolipomas (7).

Renal angiomyolipomas are the most common renal manifestations in patients with TSC, with an estimated prevalence ranging from 55 to 80% (8–11). They are usually multiple and bilateral, progress with age and cause more problems in females (12, 13). Angiomyolipomas $> 3$ cm in diameter have an increased risk of bleeding or invade adjacent normal renal parenchyma, potentially leading to kidney failure (10, 14). A retrospective cohort study showed that modifiable factors such as hypertension, proteinuria, and hyperfiltration occur frequently and early in patients with TSC and could play an important role in the development of chronic kidney disease (CKD) in these patients (15). Renal cysts, although asymptomatic in most patients, may be aggressive due to associated polycystic disease in a minority of patients and can even result in development of end stage renal disease in childhood or early adulthood (10, 16). Mutation studies have shown the occurrence and severity of TSC-associated renal angiomyolipomas and cysts to be higher among patients with TSC2 mutation than those with TSC1 mutation (8, 17).

Previously we have reported interim analysis data of the TOSCA (TuberOus SClerosis registry to increase disease Awareness) study, highlighting the burden of TSC-associated renal angiomyolipoma and showed that renal angiomyolipomas are initially asymptomatic, influenced by gender and genotype and can occur in younger patients (13). Here we present the final analysis data of the TOSCA registry with detailed overall characteristics of TSC-associated renal angiomyolipoma and its association with age, gender, and genotype. We have also analyzed possible risk factors for bleeding from renal angiomyolipomas and for CKD in patients with TSC from the TOSCA renal angiomyolipoma substudy.
MATERIALS AND METHODS

The study methodology has been published previously (18). In brief, TOSCA was a large-scale non-interventional study in patients with TSC. The study was designed with a core section and six ancillary substudies (research projects with more detailed focus on subependymal giant cell astrocytomas, renal angiomyolipoma, and lymphangioleiomyomatosis, genetics, TSC-associated neuropsychiatric disorder, epilepsy, and patient’s quality of life). Here we present findings from the core study and renal angiomyolipoma substudy. The TOSCA study was designed and conducted according to the Guidelines for Good Clinical Practice and ethical principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all patients, parents, or guardians prior to enrolment with prior endorsement by the local human research ethics committee.

Participants and Procedure

In the core study, patients of any age with TSC were enrolled from 170 sites across 31 countries and were followed for up to 5 years. Investigators from 18 sites across eight countries also agreed to participate in this renal angiomyolipoma substudy and enrolled a total of 76 patients, after receiving separate informed consent from the patients.

In the core study, patient data including demographics and clinical features of TSC across all organ systems, comorbidities, and rare manifestations, were collected at baseline and at regular visits scheduled at a maximum interval of 1 year. For the purpose of this manuscript, we presented data specific to renal

### TABLE 1 | Baseline patient demographics and clinical characteristics.

| Characteristic                                      | All patients (N = 2,211) | Patients with renal angiomyolipoma (N = 1,062) |
|-----------------------------------------------------|--------------------------|-----------------------------------------------|
| Patients by age at consent                          |                          |                                               |
| ≤2 years                                            | 282 (12.8)               | 25 (2.4)                                      |
| >2 to ≤5 years                                      | 301 (13.8)               | 76 (7.2)                                      |
| >5 to <9 years                                      | 334 (15.1)               | 133 (12.5)                                   |
| >9 to ≤14 years                                     | 307 (13.9)               | 164 (15.4)                                   |
| >14 to <18 years                                    | 138 (6.2)                | 79 (7.4)                                      |
| ≥18 to ≤40 years                                    | 625 (28.3)               | 411 (38.7)                                   |
| >40 years                                           | 224 (10.1)               | 174 (16.4)                                   |
| Median (range) age at diagnosis of TSC, a years     | 1.0 (<1–69)              | 1.0 (<1–67)                                  |
| Gender                                              |                          |                                               |
| Male                                                | 1,059 (47.9)             | 447 (42.1)                                   |
| Female                                              | 1,152 (52.1)             | 615 (57.9)                                   |
| Genetic molecular testing performed                 |                          |                                               |
| Total                                               | 1,011 (45.7)             | 525 (49.4)                                   |
| Genetic testing results b,c                          |                          |                                               |
| No mutation identified                              | 148 (14.8)               | 80 (15.2)                                    |
| TSC1 mutation                                       | 191 (18.9)               | 63 (12.0)                                    |
| TSC2 mutation                                       | 649 (64.2)               | 373 (71.0)                                   |
| Both TSC1 and TSC2 mutations                        | 5 (0.5)                  | 2 (0.4)                                      |
| Mutation variation type d                           |                          |                                               |
| Only pathogenic mutation                            | 663 (65.8)               | 343 (65.3)                                   |
| Only variant of unknown significance                | 43 (4.3)                 | 23 (4.4)                                     |
| Both                                                | 23 (2.3)                 | 5 (1.0)                                      |
| Time from TSC clinical diagnosis to molecular testing, months, mean (SD) | 81.8 (116.58) | 118.3 (133.4) |
| Patients with prenatal TSC diagnosis                | 154 (7.0)                | 53 (5.0)                                     |

SD, standard deviation; TSC, tuberous sclerosis complex.

Values are expressed as n (%) unless otherwise specified. a Data available for 2,174 patients (all patients) and 1,050 patients (cohort with renal angiomyolipoma at baseline).

b Genetic testing results were not available for 18 patients (all patients) and 7 patients (cohort with renal angiomyolipoma at baseline). c Percentages were calculated from number of patients with genetic molecular testing performed.

### TABLE 2 | Clinical characteristics of renal angiomyolipoma in overall population.

| Characteristic                                      | Baseline N = 2,211 | Follow-up 1 N = 2,099 | Follow-up 2 N = 1,935 | Follow-up 3 N = 1,664 |
|-----------------------------------------------------|--------------------|------------------------|------------------------|------------------------|
| Past history of renal angiomyolipoma               | 1,062 (48.0)       | –                      | –                      | –                      |
| Median (range) age at diagnosis of TSC, a years     | 13 (<1–67)         | –                      | –                      | –                      |
| Renal angiomyolipoma ongoing during the study b     | 1,024 (46.4)       | 1,024 (96.0)           | 1,002 (96.3)           | 909 (96.2)             |
| Renal angiomyolipoma symptoms and complications c   | None               | 840 (82.0)             | 894 (87.3)             | 885 (88.3)             | 816 (89.8) |
| Elevated blood pressure                            | 58 (5.7)           | 48 (4.7)               | 42 (4.2)               | 38 (4.2)               |
| Hematuria (blood in urine)                         | 43 (4.2)           | 31 (3.0)               | 22 (2.2)               | 20 (2.2)               |
| Hemorrhage                                         | 55 (5.4)           | 16 (1.6)               | 15 (1.5)               | 13 (1.4)               |
| Impaired renal function                            | 39 (3.8)           | 35 (3.4)               | 36 (3.6)               | 34 (3.7)               |
| Pain                                               | 63 (6.2)           | 37 (3.6)               | 27 (2.7)               | 17 (1.9)               |
| Other                                              | 30 (2.9)           | 13 (1.3)               | 16 (1.6)               | 12 (1.3)               |
| Patients received treatment for angiomyolipoma d    | 315 (29.7)         | 300 (28.1)             | 321 (30.8)             | 288 (30.5)             |

mTOR, mammalian target of rapamycin.

Values are expressed as n (%) unless otherwise specified. a Percentages calculated based on denominator of patients with history of renal angiomyolipoma. b Percentages calculated from number of patients with renal angiomyolipoma ongoing during the study. c The numbers include patients who experienced more than one symptoms simultaneously. d Treatment received as monotherapy or polytherapy.
angiomyolipoma including occurrence rate, annual incidence of newly diagnosed angiomyolipoma, maximum diameter on ultrasound or magnetic resonance imaging, clinical symptoms and complications, and management at baseline and during follow-up. The number of patients who completed follow-up 4 and follow-up 5 visits were low due to their late enrolment in the study, and hence follow-up data of only the first 3 years of the core study are reported here.

In the 76 patients in the renal substudy data was collected on; prevalence and size of renal angiomyolipomas and complication rates (including bleeding, hypertension, and CKD). We also present the effects of treatment with embolization or mammalian

![Graph showing patients with history of renal angiomyolipoma and intervention received across age groups at baseline.](image1)

| Age in years | Patients received intervention, n | Patients with a history of renal angiomyolipoma, n |
|--------------|----------------------------------|-----------------------------------------------|
| Overall      | 315                               | 1062                                          |
| ≥ 2          | 2                                 | 25                                            |
| > 2 to ≤ 5   | 2                                 | 76                                            |
| > 5 to ≤ 9   | 14                                | 133                                           |
| > 9 to ≤ 14  | 27                                | 164                                           |
| > 14 to ≤ 18 | 20                                | 79                                            |
| > 18 to ≤ 40 | 166                               | 411                                           |
| > 40         | 84                                | 174                                           |

**FIGURE 1** | Patients with history of renal angiomyolipoma and intervention received across age groups at baseline.

![Graph showing newly diagnosed renal angiomyolipoma after baseline visit.](image2)

**FIGURE 2** | Newly diagnosed renal angiomyolipoma after baseline visit.
target of rapamycin (mTOR) inhibitors on the risk of renal impairment. For the substudy, only the baseline data are reported here, as very few patients had follow-up visits due to their late enrolment in the study.

**Data Analyses**

All eligible patients enrolled in the TOSCA registry and renal angiomyolipoma substudy, without any major protocol deviations, were included in the analysis. Given that the study was observational in nature, results reported in this manuscript are primarily descriptive statistics. Continuous variables were evaluated quantitatively (e.g., frequency, mean, standard deviation, median, range), and categorical variables (e.g., presence/absence of a manifestation) were analysed in terms of frequency distribution at baseline and at follow-ups.

The Cochran–Mantel–Haenszel test was performed to evaluate the rates of renal angiomyolipomas stratified by age groups (<18 and ≥18 years), gender (male and female) and mutation (TSC1 and TSC2). The exact binomial test was used to evaluate the difference between proportion of patients with renal angiomyolipomas and those received treatment among both genders, regardless of age, and genetic mutation. Furthermore, we evaluated reported association of angiomyolipoma-related variables at baseline visit (rates of angiomyolipomas, angiomyolipomas with lesion >3 cm, growing angiomyolipomas, treatment of angiomyolipomas and symptoms) by age (<18 vs. ≥18 years), gender (male vs. female) and mutation (TSC1 vs. TSC2) using Chi-square test. Statistical significance was set at \( p < 0.05 \).

**RESULTS**

**Findings From the Core Study**

A total of 2,214 patients were enrolled from 170 sites across 31 countries. Of these, data of 2,211 eligible patients were analysed. Data of three patients were excluded due to major protocol deviations. Most patients were enrolled at sites where the principal investigators were pediatric neurologists (53%) or neurologists (17%).

Baseline demographics and clinical characteristics are summarized in Table 1. There were more females (52.1%) than males (47.9%), the majority of patients were under the age of 18 years (61.6%) and the median age at consent for the study was 13 years. The median age at first TSC diagnosis was 1 year (mean 6.9 years, range: <1–69 years). Molecular genetic testing was performed in 1,011 patients (45.7%). Of these, 64.2% had a TSC2 mutation and 18.9% TSC1 mutation. In 14.6% of patients, no mutation was identified. Of the 1,011 tested patients, 663 (65.6%) had pathogenic mutation, 43 (4.3%) had a variant of unknown significance and 23 patients (2.3%) had both a pathogenic mutation and variant of unknown significance. In 282 patients, the pathogenicity of the mutation was not recorded. Prenatal diagnosis of TSC was reported in 154 patients (7%). Parents of 1,036 of 2,211 patients (56.3%) were evaluated for TSC. Of these, 180 (17.4%) had mother, 126 (12.2) had fathers and 4 (0.4%) had both parents diagnosed with TSC. A considerable proportion of patients (23.6%) had relatives affected with TSC and patients with relatives also enrolled in TOSCA (10.6%).

**Clinical Characteristics of Renal Angiomyolipomas**

A history of renal angiomyolipomas was reported in 1,062 (48%) patients (Table 2, Figure 1). Baseline demographics of cohort with renal angiomyolipomas were similar to the overall cohort (Table 1). Of 1,024 patients (96.4%) with ongoing renal angiomyolipoma, 901 (88%) had multiple lesions, 859 (83.9%) had bilateral lesions, 342 (33.4%) had lesions >3 cm in size and 216 (21.1%) had growing lesions. The median age at diagnosis

![Figure 3](https://example.com/figure3.png)

**FIGURE 3** | Time since interventions prior to baseline. mTOR, mammalian target or rapamycin.
was 13 years (mean 17 years, range <1–67 years). Median
time from the previous scan to last assessment was 1 year
(range, <1–21).
Renal angiomyolipomas were asymptomatic in most patients
(840 of 1,024 patients, 82%). Very few patients experienced renal
angiomyolipoma-related symptoms or complications (Table 2).
After baseline visit, newly diagnosed renal angiomyolipomas
were reported in 22 (2.1%), 21 (2.0%), and 21 (2.2%) patients at
follow-up 1, follow-up 2, and follow-up 3, respectively (Figure 2).
A total of 315 patients (29.7%) had received treatment for renal
angiomyolipomas at baseline. In these patients, mTOR inhibit ors
(45.7%), embolization (44.8%), and nephrectomies (20%) were
the common treatment modalities. During the follow-ups,
more patients received treatment with mTOR inhibitors than
embolization (Table 2), and mTOR inhibitors appear to become
a predominant treatment in recent years (Figure 3). However,
the rate of nephrectomy was similar in each period prior
to baseline.

**Relationship of Renal Angiomyolipoma With Age**
The proportion of patients with angiomyolipomas increased with
age (from 8.9% in patients aged ≤2 years to 77.7% in patients aged
>40 years). Similarly, use of pre-emptive treatment increased with
age (Figure 1). Newly diagnosed renal angiomyolipomas were
more common in adults (Figure 2). There was an increased rate
of symptoms and complications with age (Table 3). Embolization

| Complication and symptom | Overall | Age at consent, years |
|--------------------------|---------|-----------------------|
|                          | (N = 2,211) | ≤2 | >2 to ≤5 | >5 to ≤9 | >9 to ≤14 | >14 to ≤18 | ≥18 to ≤40 | >40 |
| None                     | 840 (82.0) | 23 (100.0) | 74 (100.0) | 122 (96.1) | 147 (93.0) | 71 (92.2) | 298 (74.7) | 105 (63.3) |
| Elevated blood pressurea | 58 (5.7) | 0 (0) | 0 (0) | 0 (0) | 5 (3.2) | 5 (6.5) | 25 (6.3) | 23 (13.9) |
| Hemorrhageb              | 43 (4.2) | 0 (0) | 0 (0) | 0 (0) | 2 (1.3) | 1 (1.3) | 23 (5.8) | 17 (10.2) |
| Haematuriaa              | 55 (5.4) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 37 (9.3) | 18 (10.8) |
| Impaired renal functionb | 39 (3.8) | 0 (0) | 0 (0) | 1 (0.8) | 2 (1.3) | 0 (0) | 16 (4.0) | 20 (12.0) |
| Painb                    | 63 (6.2) | 0 (0) | 0 (0) | 1 (0.8) | 1 (0.6) | 1 (1.3) | 38 (9.5) | 22 (13.3) |
| Other                    | 30 (2.9) | 0 (0) | 0 (0) | 3 (2.4) | 2 (1.3) | 1 (1.3) | 17 (4.3) | 7 (4.2) |

All the values are expressed as n (%). aThe numbers include patients who experienced more than one symptom simultaneously.

![Figure 4](https://www.frontiersin.org) | Treatment modalities for renal angiomyolipomas by age groups. mTOR, mammalian target or rapamycin.
was more common in adults (54% vs. 9.2%), whereas children were mostly treated with mTOR inhibitors (73.8 vs. 38.4%), Figure 4).

### Relationship of Renal Angiomyolipoma With Gender

Of the 2,211 enrolled patients, 1,152 (52.1%) were female and 1,059 (47.9%) were male. A history of renal angiomyolipomas was reported at a significantly higher frequency in female than male patients (53.4 vs. 42.2%, \( p < 0.0001 \), Table 4). Newly diagnosed renal angiomyolipomas were also more common in female patients (2.3 vs. 1.8%). The gender difference (female vs. male) in the rates of renal angiomyolipomas remained statistically significant when stratified by age [<18 years [38.97 vs. 31.54%]; \( p < 0.0001 \) and \( \geq 18 \) years [71.35 vs. 65.18%]; \( p < 0.0001 \)].

The median age at diagnosis of renal angiomyolipomas in female patients was 14 years (mean 18.4 years, range <1–63 years), while it was 11 years (mean 15.1 years, range <1–67 years) in male patients. The difference in the age at diagnosis between male and female patients was not significant (\( p = 0.9891 \)). Five hundred and ninety females and 434 males had renal angiomyolipomas ongoing during the study. There was no significant differences between females and males in the occurrence of multiple lesions (88.8 vs. 86.9%, \( p = 0.3346 \)) and bilateral angiomyolipomas (85.1 vs. 82.3%, \( p = 0.1585 \)). Compared to males, females had significantly higher rates of lesions >3 cm in size (35.9 vs. 30.0%, \( p = 0.0119 \)) and growing lesions (22.9 vs. 18.7%, \( p = 0.0439 \)) at baseline. In both male and female patients, renal angiomyolipomas were asymptomatic in most patients at baseline (male: 86.2 vs. female: 79%). Most angiomyolipoma-related symptoms occurred equally in females and males. These include elevated blood pressure (5.3 vs. 6.2%, \( p = 0.5083 \)), haematuria (4.9 vs. 3.2%, \( p = 0.1829 \)) and impaired renal function (4.6 vs. 2.8%, \( p = 0.1345 \)). However, compared to males, females had significantly higher rates of hemorrhage (6.9 vs. 3.2%, \( p = 0.0090 \)) and pain (8.5 vs. 3%, \( p = 0.0003 \)). Overall, the rate of intervention at baseline were significantly higher among females than males (33 vs. 25.1%, \( p = 0.0058 \)). However, there was no significant gender difference (male vs. female) observed in the rates of specific interventions: embolization (50.9 vs. 41.4%; \( p = 0.0894 \)), mTOR inhibitors (46.8 vs. 43.8%; \( p = 0.6395 \)), nephrectomy (23.2 vs. 14.3%; \( p = 0.0629 \)), resection (7.9 vs. 4.5%; \( p = 0.2503 \)), and dialysis (1.5 vs. 0.9%; \( p = 0.6618 \)).

### Relationship of Renal Angiomyolipoma With Mutation Type

The prevalence of angiomyolipomas was significantly higher in patients with TSC2 vs. TSC1 mutations (57.5 vs. 33%, \( p < 0.0001 \); Table 5). The mean age at diagnosis of renal angiomyolipomas was 13.3 years (median, 9 years, range 1–63) in patients with a TSC2 mutations, while it was 22.5 years (median 21 years, range 1–60 years) in those with a TSC1 mutations. Patients with TSC2 mutations also had significantly higher rates of multiple angiomyolipomas (92.3 vs. 67.2%, \( p < 0.0001 \)), bilateral angiomyolipomas (87 vs. 47.5%, \( p < 0.0001 \)) angiomyolipoma lesions >3 cm (31.2 vs. 11.5%, \( p = 0.0013 \)) and growing angiomyolipomas (23.2 vs. 9.8%, \( p = 0.0150 \)).

Similar to the overall sample, renal angiomyolipomas were asymptomatic in most patients with TSC1 (90.2%) and TSC2 (83.1%) mutations. However, bleeding events were observed only in patients with TSC2 mutations (haematuria, 3.9% and hemorrhage, 5.2%). No significant difference in the rates of intervention of any sort was observed between those with TSC1 mutations and TSC2 mutations (\( p < 0.0801 \), Table 5).

### Other Renal Manifestations

The other renal features reported at baseline were multiple renal cysts (24.6%), polycystic kidney disease (proven TSC2/PKD1 mutation; 3.4%), renal malignancy (1.4%), and impaired renal function (non-angiomyolipoma-related; 1.9%) (Table 6). Compared with patients with a TSC1 mutation, those with TSC2 mutations had a higher occurrence of multiple

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**TABLE 4 |** Clinical characteristics of renal angiomyolipoma by gender.

| Characteristics                              | Female N=1,152 | Male N=1,059 | Odds ratio (95% CI) | P-value |
|----------------------------------------------|----------------|--------------|---------------------|---------|
| Past history of renal angiomyolipoma         | 615 (53.4)     | 447 (42.2)   | 1.6 (1.3, 1.9)      | <0.0001 |
| Median (range) age at angiomyolipoma diagnosis, years | 14 (<1–63) | 11 (<1–67) | – | 0.9891 |
| Renal angiomyolipoma ongoing during the study | 590 (56.9) | 434 (97.1) | – | 0.9891 |
| Multiple | 524 (86.1) | 357 (92.3) | 1.3 (0.9, 1.8) | 0.1585 |
| Bilateral | 212 (35.9) | 130 (30.0) | 1.4 (1.1, 1.9) | 0.0119 |
| Growsng | 135 (22.9) | 81 (18.7) | 1.4 (1.0, 1.9) | 0.0439 |
| Renal angiomyolipoma signs and symptoms | None | | | |
| Haematuria (blood in urine) | 29 (4.9) | 14 (3.2) | 1.6 (0.8, 3.0) | 0.1829 |
| Hemorrhage | 41 (6.9) | 12 (2.6) | 1.7 (0.8, 3.4) | 0.1345 |
| Impaired renal function | 27 (4.6) | 12 (2.6) | 1.2 (1.0, 1.4) | 0.0090 |
| Pain | 50 (8.5) | 13 (3.0) | 3.0 (1.6, 5.6) | 0.0003 |
| Others | 22 (3.7) | 8 (1.8) | 2.1 (0.9, 4.7) | 0.0771 |
| Treatment received for renal angiomyolipoma | | | | |
| mTOR inhibitor | 95 (46.8) | 49 (34.3) | 1.0 (0.7, 1.8) | 0.6395 |
| Embolization | 84 (41.4) | 57 (45.4) | 0.7 (0.4, 1.1) | 0.0894 |
| Nephrectomy | 47 (23.2) | 16 (14.3) | 1.8 (1.0, 3.4) | 0.0629 |
| Resection | 16 (7.9) | 5 (4.5) | 1.8 (0.6, 5.1) | 0.2503 |
| Dialysis | 3 (1.5) | 1 (0.9) | 1.7 (0.2, 16.1) | 0.6618 |
| Other | 10 (4.9) | 3 (2.7) | 1.9 (0.5, 6.9) | 0.3428 |

CI, confidence interval; mTOR, mammalian target of rapamycin. Values are expressed as n (%) unless otherwise specified. \( ^a \) Percentages calculated based on denominator of patients with history of renal angiomyolipoma. \( ^b \) Percentages calculated from number of patients with renal angiomyolipoma ongoing during the study. \( ^c \) The numbers include patients who experienced more than one symptom simultaneously. \( ^d \) Treatment received as monotherapy or polytherapy.
renal angiomyolipoma

Treatment received for

urine)

signs and symptoms

Renal angiomyolipoma

from number of patients with renal angiomyolipoma ongoing during the study.

ongoing during the study

Renal angiomyolipoma

in ongoing during the study

Renal angiomyolipoma

Renal angiomyolipoma diagnosis,

years

Renal angiomyolipoma

ongoing during the study

Renal angiomyolipoma

lesion

Growing

Renal angiomyolipoma

signs and symptoms

None

Elevated blood pressure

Haematuria (blood in

urine)

Hemorrhage

Impaired renal function

Pain

Other

Treatment received for

renal angiomyolipoma

mTOR inhibitor

Embolization

Nephrectomy

Resection

Dialysis

Other

study

Percentage calculated based

denominator of patients with history of renal angiomyolipoma.

Percentages calculated from number of patients with renal angiomyolipoma ongoing during the study.

Treatment received as monotherapy or polytherapy.

renal angiomyolipomas. There was no correlation between CKD stage and type of angiomyolipoma. Mean age at diagnosis of renal angiomyolipoma was 14.5 years for patients with grade 1 CKD, 26.4 years for patients with grade 2 CKD, 35 years for patients with grade 3a CKD, 22 years for patients with grade 3b CKD and 34 years for patients with grade 4 CKD. Size of renal angiomyolipomas were between 3 and 180 mm. Simple cysts were reported in 16 patients (38.1%) and polycystic kidney disease in two patients (4.8%). Of the three patients with CKD and cysts, but without renal angiomyolipoma at baseline, two had grade 1 CKD and one had grade 2 CKD.

Risk Factors of Chronic Kidney Disease

A total of 42 patients reported CKD at baseline. Of these, seven (16.7%) had grade 3a/3b CKD (GFR 30–59), and four (9.5%) had grade 4 CKD (GFR 15–29). Thirty-six of 42 CKD patients had typical renal angiomyolipomas, eight had atypical renal angiomyolipomas and two had other renal angiomyolipomas. There was no correlation between CKD stage and type of angiomyolipoma. Mean age at diagnosis of renal angiomyolipoma was 14.5 years for patients with grade 1 CKD, 26.4 years for patients with grade 2 CKD, 35 years for patients with grade 3a CKD, 22 years for patients with grade 3b CKD and 34 years for patients with grade 4 CKD. Size of renal angiomyolipomas were between 3 and 180 mm. Simple cysts were reported in 16 patients (38.1%) and polycystic kidney disease in two patients (4.8%). Of the three patients with CKD and cysts, but without renal angiomyolipoma at baseline, two had grade 1 CKD and one had grade 2 CKD.

Effect of Embolization or mTOR Inhibitor Treatment on CKD and Bleeding

Out of 76 patients enrolled, 47 patients received treatment; 20 were treated with mTOR inhibitors alone, four with embolization alone and five with both mTOR inhibitors and embolization at baseline. Among the 20 patients who were treated with mTOR inhibitors alone, eight (40%) had grade 2 CKD, four (20%) had grade 3a/3b CKD, and two had grade 4 CKD. No patient had unselected proteinuria while 7 patients (35%) had

renal cysts (33.6 vs. 13.3%) and polycystic kidney disease (4.7 vs. 0%).

Findings From the Angiomyolipoma Substudy

A total of 76 patients [24 (31.6%) male and 52 (68.4%) female] were enrolled into the substudy from eight countries [France (n = 25), United Kingdom (n= 15), Belgium and Japan (n = 11, each), Turkey (n = 6), Poland (n = 4), and Germany and Spain (n = 2, each)]. Most patients were Caucasians (57 patients, 75%). Hypertension was reported in 19 patients (25%). Pre-existing antihypertensive medication was reported in 12 patients (63.2%).

TABLE 6 | Rates of other renal manifestations at baseline in overall population and by mutational status.

| Characteristics | Overall | Patients with TSC1 mutation N = 196 | Patients with TSC2 mutation N = 654 |
|-----------------|---------|----------------------------------|----------------------------------|
| Renal manifestations in patients with angiomyolipomas | | |
| Multiple renal cysts | 544 (24.6) | 26 (13.3) | 220 (33.6) |
| Polycystic kidneys | Not applicable* | 0 | 31 (4.7) |
| Renal malignancy | 31 (1.4) | 4 (2.0) | 8 (1.2) |
| Renal manifestations in patients without angiomyolipoma | | |
| Impaired renal function | 43 (1.9) | 6 (3.1) | 18 (2.8) |

CI, confidence interval; mTOR, mammalian target of rapamycin; N/A, not applicable; TSC, tuberous sclerosis complex.

Values are expressed as n (%). *PKD was observed only in those with TSC2 mutations.

Risk Factors of Bleeding From Renal Angiomyolipomas

Of the 76 patients with renal angiomyolipomas, hemorrhage was reported in three patients at baseline, who were not taking mTOR inhibitors (patients aged 31, 34, and 43 years). All three of them were female and had TSC2 mutations, with largest angiomyolipoma diameter between 66 and 96 mm.

TABLE 5 | Clinical characteristics of renal angiomyolipoma by mutational status.

| Characteristics | Patients with TSC1 mutation N = 196 | Patients with TSC2 mutation N = 654 |
|-----------------|----------------------------------|----------------------------------|
| Past history of renal angiomyolipoma | 63 (33.0) | 373 (57.5) |
| Male | 28 (44.4) | 169 (45.3) |
| Female | 35 (55.6) | 204 (54.7) |
| Median (range) age at angiomyolipoma diagnosis, years | 21 (<1–60) | 9 (<1–59) |
| Renal angiomyolipoma ongoing during the study | 61 (93.8) | 362 (96.5) |
| Multiple | 41 (67.2) | 334 (92.3) |
| Bilateral | 29 (47.5) | 315 (87.0) |
| Lesion >3 cm | 7 (11.5) | 113 (31.2) |
| Growing | 7 (11.5) | 85 (23.5) |
| Renal angiomyolipoma signs and symptoms | | |
| None | 55 (90.2) | 301 (83.1) |
| Elevated blood pressure | 4 (6.6) | 23 (6.4) |
| Haematuria (blood in urine) | 0 | 14 (3.9) |
| Hemorrhage | 0 | 19 (5.2) |
| Impaired renal function | 1 (1.6) | 10 (2.8) |
| Pain | 2 (3.3) | 24 (6.6) |
| Other | 0 | 9 (2.5) |
| Treatment received for renal angiomyolipoma | 9 (13.8) | 103 (27.5) |
| mTOR inhibitor | 4 (44.4) | 56 (54.4) |
| Embolization | 2 (22.2) | 41 (39.8) |
| Nephrectomy | 3 (33.3) | 23 (22.3) |
| Resection | 1 (11.1) | 6 (5.8) |
| Dialysis | 0 | 1 (1.0) |
| Other | 0 | 3 (2.9) |

CI, confidence interval; mTOR, mammalian target of rapamycin; TSC, tuberous sclerosis complex.

Values are expressed as n (%) unless otherwise specified. Percentages calculated based on denominator of patients with history of renal angiomyolipoma. Percentages calculated from number of patients with renal angiomyolipoma ongoing during the study.

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renal angiomyolipomas (95% CI), Turkey (n = 6), Poland (n = 4), and Germany and Spain (n = 2, each)]. Most patients were Caucasians (57 patients, 75%). Hypertension was reported in 19 patients (25%). Pre-existing antihypertensive medication was reported in 12 patients (63.2%).

Risk Factors of Chronic Kidney Disease

A total of 42 patients reported CKD at baseline. Of these, seven (16.7%) had grade 3a/3b CKD (GFR 30–59), and four (9.5%) had grade 4 CKD (GFR 15–29). Thirty-six of 42 CKD patients had typical renal angiomyolipomas, eight had atypical renal angiomyolipomas and two had other renal angiomyolipomas. There was no correlation between CKD stage and type of angiomyolipoma. Mean age at diagnosis of renal angiomyolipoma was 14.5 years for patients with grade 1 CKD, 26.4 years for patients with grade 2 CKD, 35 years for patients with grade 3a CKD, 22 years for patients with grade 3b CKD and 34 years for patients with grade 4 CKD. Size of renal angiomyolipomas were between 3 and 180 mm. Simple cysts were reported in 16 patients (38.1%) and polycystic kidney disease in two patients (4.8%). Of the three patients with CKD and cysts, but without renal angiomyolipoma at baseline, two had grade 1 CKD and one had grade 2 CKD.

Effect of Embolization or mTOR Inhibitor Treatment on CKD and Bleeding

Out of 76 patients enrolled, 47 patients received treatment; 20 were treated with mTOR inhibitors alone, four with embolization alone and five with both mTOR inhibitors and embolization at baseline. Among the 20 patients who were treated with mTOR inhibitors alone, eight (40%) had grade 2 CKD, four (20%) had grade 3a/3b CKD, and two had grade 4 CKD. No patient had unselected proteinuria while 7 patients (35%) had

renal cysts (33.6 vs. 13.3%) and polycystic kidney disease (4.7 vs. 0%).
albuminuria grade 1. No patient on mTOR inhibitors alone had renal hemorrhage.

Among the four patients treated with embolization alone, one (25%) had grade 1 CKD, one (25%) had grade 2 CKD, and one (25%) had grade 4 CKD. Data was missing for one patient. One (25%) patient had proteinuria, while two (50%) had grade 1 albuminuria. No patient had renal hemorrhage.

DISCUSSION

The results from this final analysis have several novel observations. The prevalence of angiomyolipoma as well as rates of angiomyolipoma-related complications were higher in females than in male patients. This effect might be attributed to the presence of estrogen and progesterone receptors on the tumors (19). However, the mechanism of hormonal modulation on angiomyolipoma growth is not yet known. Female patients were also more likely to have bilateral, multiple and growing renal angiomyolipoma than male patients. This was in line with the other studies suggesting a higher propensity of angiomyolipoma growth in female patients (9, 20). Angiomyolipomas were diagnosed at a later age in females (median age 14 years) than in male patients (median age 11 years), but this difference was not statistically significant.

In our previous publication from the TOSCA core section interim analysis (13), we reported that the occurrence rate of renal angiomyolipomas was lower in the TOSCA cohort compared to other published literature (8, 9). Rates of haematuria and hypertension were also lower compared with those reported in TSC patients in other studies (6, 7, 21, 22), this may be a reflection of the age relatively young age of our subjects and possibly under-ascertainment. These lower rates of occurrence of renal angiomyolipomas and angiomyolipoma-related complications could be explained by a different (younger) age range of our population; however the current analysis shows that angiomyolipoma prevalence rose progressively with age, to 77.7% in those over 40 years of age, whereas complication rates remained much lower than in other studies. This suggests that active surveillance and a policy of pre-emptive treatment may have been successful in altering the natural history of renal TSC.

Patients with TSC2 mutations were reported to exhibit a higher incidence and severity of both renal angiomyolipoma and cysts than those with TSC1 mutations (8). In our study, the prevalence of angiomyolipoma was significantly higher in those with TSC2 mutations. This was in line with the previous other reports (7, 8, 17, 23). We also observed that patients with TSC2 mutations had angiomyolipoma at early age and experienced higher rates of bleeding complications (haematuria and hemorrhage). Rates of multiple angiomyolipomas, bilateral angiomyolipoma, renal angiomyolipoma lesions of >3 cm were significantly higher in those with TSC2 mutations than those with TSC1 mutations. Furthermore, more patients with TSC2 mutations received intervention for renal angiomyolipoma than those with TSC1 mutations.

As expected polycystic kidney disease was only found in those with TSC2 mutations because it is the result of a deletion stretching across the TSC2 and PKD1 genes on chromosome 16 (The "contiguous gene syndrome") (24).

The study showed that pre-emptive treatment was used increasingly commonly with age (Figure 1) and this was associated with a very low rate of bleeding and significant renal impairment. Figures 3, 4 show that mTOR inhibitors are now the most commonly used treatment.

Despite the fact that overall prevalence of hemorrhage and CKD was too low to accurately define risk factors, in our sub-study we observed that all the three patients who had hemorrhage had TSC2 mutation. Majority of the patients had grade 1/2 CKD (31 patients, 73.8%). Patients with CKD grade 2 or more were older but there was a clear trend for more advanced CKD stages.

Renal malignancy has been reported in about 2–4% of patients with TSC (25), which is much higher than that reported in a comparable age group in the general population (26). The occurrence rate of renal malignancy observed in this cohort was lower (1.4%) than that reported previously, in TSC (8, 25).

CONCLUSION

Renal angiomyolipomas are the major kidney risk for those with TSC; other renal complications are less common. We have shown a marked increase in the prevalence of intervention for renal angiomyolipomas, from <10% in those under 2 years of age to 48% in those over 40. The risk of needing an intervention was higher and begins earlier in those with a TSC2 mutation, but the difference disappears by age 40 years. Gender differences were much smaller, but in females the occurrence of angiomyolipomas was significantly greater, as were angiomyolipomas >3 cm and the need for intervention. However, there was no absolute cut-off between the differences in any of these categories which means lifelong surveillance is important in all patients. In the substudy of 76 subjects none had a renal hemorrhage after commencing on an mTOR inhibitor. The most encouraging finding was that pre-emptive intervention was dramatically successful in altering the outcome compared to historical controls; with high pre-emptive intervention rates but low rates of bleeding and other complications. This validates the policy of surveillance and pre-emptive intervention recommended by clinical guidelines.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

LIST OF ETHICS COMMITTEES

The study protocol and all amendments were reviewed and approved (if applicable) by independent ethics committee/institutional review board for each centre: National Hospital Organization Central Ethics Committee; Gazi University Clinical Research Ethics Committee; Independent
Multidisciplinary Committee on Ethical Review of Clinical Trials; Peking Union Medical College Hospital; Commissie Medische Ethiek UZ Brussel; CNIL (Commission National de l’Informatique et des Libertés); CCTIRS (Comité Consultatif sur le traitement de l’information en matière de recherche dans le domaine de la santé); Comité Ético Investigación Clínica de Euskadi (CEIC-E); Consejería de Salud y Bienestar Social, Dirección General de Calidad, Investigación, Desarrollo e Innovación, Comité Coordinador de Ética de la Investigación Biomédica de Andalucía; Research Ethics Committee of the University of Tartu (UT REC); Ethikkommission der Medizinischen Universität Graz; North Wales REC—West; Regionala Etikprövningsnämnden i Göteborg; REK—Regionale komitéer for medisinsk og helsefaglig forskningsetikk; Komisja Bioetyczna przy Instytucie Pomnik Centrum Zdrowia Dziecka; Ethikkommission bei der Ludwig-Maximilians-Universität München; Hokkaido University Hospital Independent clinical research Institutional Ethics Committee; Medical Juntendo University Institutional Ethics Committee; National Center for Chile Health and Development of IRB; Osaka University Hospital of IRB; Ethics Committee at Moscow Institute of Pediatrics and Pediatric Surgery; Peking University First Hospital; Sanbo Brain Hospital Capital Medical University; Tianjin Children’s Hospital; Children’s Hospital of Fudan University; Zhongshan Hospital Fudan University; Fudan University Shanghai Cancer Center; The Second Affiliated Hospital of Guangzhou Medical University; The First Affiliated Hospital, Sun Yan-sen University; The First Affiliated Hospital of Guangzhou Medical University; Shenzhen Children’s Hospital; West China Hospital, Sichuan University; Xijing Hospital; Children’s Hospital of Chongqing Medical University; Wuhan Children’s Hospital; The Second Affiliated Hospital of Xi’an Jiaotong university; Guangdong 999 Brain Hospital; Seoul National University Hospital Institutional Review Board; National Taiwan University Hospital (NTUH) Research Ethics Committee (REC); Institutional Review Board of the Taichung Veterans General Hospital; Institutional Review Board of Chung Shan Medical University Hospital; Institutional Review Board, Tungs’ Taichung MetroHarbor Hospital; Institutional Review Board of National Cheng Kung University Hospital; Metro South Human Research Ethics Committee; Sydney Children’s Hospital Network Human Research Ethics Committee; St Vincent’s Hospital Human Research Ethics Committee; Royal Melbourne Hospital Human Research Ethics Committee; Siriraj Institutional Review Board; The Institutional Review board, Faculty of Medicine, Chulalongkorn University, 3rd Floor, Ananathamahidol Building, King Chulalongkorn Memorial Hospital; The Committee on Human Rights Related to Research Involving Human Subjects; Institutional Review Board, Royal Thai Army Medical Department IRB RTA, 5th Floor, Phramongkutklaojevitya Building, Phramongkutklao College of Medicine; Research Ethics Committee, Faculty of Medicine, Chiang Mai University; Research and Development, Queen Sirikit National Institute of Child Health; Human Research Ethics Committee, Faculty of Health Sciences, University of Cape Town; Sheare Zedek Medical Center Helsinki Committee; Sheba Medical Center Helsinki Committee; Tel Aviv Sourasky Medical Center Helsinki Committee; General University Hospital of Patras Ethics Committee; Pendeli Children’s Hospital Ethics Committee; General University Hospital of Athens G. 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ETHICS STATEMENT

The studies involving human participants were reviewed and approved by all ethics committees involved in the TOSCA study (see list of ethics committees in article). Written informed consent to participate in this study was provided by the participants’ legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

JK, EB, MB, PC, MD, JF, MF, CH, SJ, JL, AM, RN, VS, RT, BZ, AJ, and MS designed the study, patient accrual, clinical care, data interpretation, drafted, revised, final review, and approval of the manuscript. TC, VC, GB, PV, CF, FO’C, JQ, YT, and SY designed the study, data interpretation, drafted, revised, final review, and approval of the manuscript. LD’A designed the study, trial management, data collection, data analysis, data interpretation, drafted, revised, final review, and approval of the manuscript. RM designed the study, data analysis, data interpretation, drafting, revised, final review, and approval of the manuscript. SS designed the study, trial statistician, data analysis, data interpretation, drafted, revising, final review, and approval of the manuscript. All authors contributed to the article and approved the submitted version.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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