

From Tuberous Sclerosis Complex to end stage renal disease: Who are these patients?

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Abstract

In patients with tuberous sclerosis complex (TSC), renal complications are not limited to bleeding angiomyolipoma (AML); although rare, end-stage renal disease (ESRD) may occur. New treatments (e.g. mammalian target of rapamycin (m-Tor) inhibitors) for AML might influence the epidemiology of ESRD in patients with TSC. In France, 99 patients with TSC from the Renal Epidemiology and Information Network (REIN) registry and having undergone renal replacement therapy (RRT) between 2002 and 2016 were included in the present study. Additional data were collected from the patients' medical charts. The mean \pm standard deviation age at RRT initiation was 48.4 ± 16.4 and 73.8% had a neurologic impairment. Fifty-four patients underwent kidney transplantation after an average of 23 ± 12.3 months on dialysis. Among the 61 patients with additional data the most common renal lesion was AML: 26.2% of the patients had isolated AML, and 26.2% had AML and renal cysts, 65.6% of patients had undergone nephrectomy, and 16.4% had undergone at least one embolization. None of the patients had been treated with an m-Tor inhibitor before dialysis. The graft survival rate was 92.5% at 5 years and 70.2% at 10 years. The present cohort study is the first to have assessed TSC patients on RRT from a national registry. Nephrectomy or embolization due to AML was the leading cause of ESRD in our cohort. By reducing the size of the AML, m-tor inhibitors might lower the risk of complications and thus reduce the number of patients with TSC requiring RRT.

Introduction

Tuberous sclerosis complex (TSC) is a rare, autosomal-dominant genetic disorder with variable expressivity. Although TSC was first described in the 19th century, the affected genes : (*TSC1*, on 9q34) encoding hamartin, and (*TSC2*, on 16p13) encoding tuberin were only identified in 1997 ^{(1)(2) (3)}. The hamartin-tuberin complex inhibits the mammalian target of rapamycin (mTOR) pathway involved in cell proliferation and growth, thus causing a loss of control of cell division and a predisposition to tumorigenesis (albeit mostly benign) ⁽³⁾. Worldwide, the prevalence of TSC in the general population is 1:12500, and live birth rate is about 1:5800; about a million individual live with the disease ⁽⁴⁾⁽⁵⁾⁽⁶⁾.

The clinical presentation of TSC varies from an asymptomatic form to a disabling manifestation that can progress over time. Genetic diagnosis has totally changed the spectrum of clinical presentations, since many asymptomatic patients are now being identified. The neurologic presentation (i.e. epilepsy and mental retardation) was very important in the early diagnostic criteria but this criterion has also changed drastically. Typical skin lesions are often observed, such as hypomelanotic macules and unguis fibroma ⁽⁷⁾. Renal lesions include angiomyolipoma (AML), renal cysts, and (less frequently) renal cell carcinoma ⁽⁸⁾. Although these lesions can appear during childhood, related complications (such as hemorrhage) usually occur in adult patients and are the most common cause of TSC-associated death ⁽⁹⁾ ⁽¹⁰⁾. Angiomyolipoma is found in 38-80% of patients with TSC ⁽¹¹⁾⁽¹²⁾, and can be complicated by acute hemorrhage - the risk of which increases with the lesion's size and vascularity ⁽¹³⁾. In cases of acute hemorrhage, emergency embolization or even nephrectomy has to be performed. For many years, preventive embolization was the only treatment available for large AMLs ⁽¹⁴⁾. Accordingly, it has been reported 50% of patients having undergone three or more embolization procedures have worsened kidney function ⁽¹⁵⁾.

In 2012, the international Tuberous Sclerosis Complex Consensus Conference (TSCCC) updated the diagnostic criteria for TSC and thus modified the epidemiology of this disease. The presence of a pathogenic mutation in *TSC1* or *TSC2* is now sufficient for a definitive diagnosis of TSC. Ten to 25% of patients diagnosed with TSC do not have an identified mutation but present with two major features or with one major feature and at least two minor features. The presence of two or more AMLs is one of the eleven major criteria ⁽⁷⁾.

The TSCCC also revised the treatment strategy for TSC; treatment with an mTOR inhibitor was recommended as the first-line therapy for an asymptomatic, growing AML with a largest dimension >3 cm ⁽⁷⁾. The results of the Phase III EXIST-2 placebo-controlled trial suggested that treatment with the mTOR inhibitor everolimus was associated with a significant decrease in the size of AML ⁽¹⁶⁾.

This change in practice spares some patients from embolization or nephrectomy and might thus modify the pattern of renal outcomes in patients with TSC.

Few researchers have studied ESRD in patients with TSC. In 1996, Schillinger *et al.* ⁽¹⁷⁾ described a French retrospective cohort of 65 TSC patients on dialysis or having received a kidney transplant; the prevalence of ESRD was 1%. A few years later, Clarke *et al.* confirmed these results in a UK cohort of patients with TSC receiving renal replacement therapy (RRT). Clarke *et al.* also observed premature mortality along these patients but did not find any prognostic factors ⁽¹⁸⁾. In France, about 100 patients diagnosed with TSC were on RRT between 2002 and 2016 ⁽¹⁹⁾.

To the best of our knowledge, the characteristics and outcomes of patients with TSC on RRT (either dialysis or kidney transplantation) have not been described since Schillinger *et al.*'s report in 1996 ⁽¹⁷⁾, and an exhaustive cohort study has never been performed. Since 2001, the French nationwide Renal Epidemiology and Information Network (REIN) registry has collected information about all patients receiving RRT ⁽²⁰⁾.

In this context, the primary objective of the present French study was to use data from the REIN registry and medical records to describe the characteristics of incident and prevalent patients with TSC on RRT. The secondary objective was to describe outcomes and graft survival among TSC patients having undergone kidney transplantation.

Methods

Patient selection

In France, all patients requiring long-term dialysis are registered in the nationwide REIN registry. The registry was created in 2001 and had been deployed country-wide by 2011 ⁽²¹⁾. Nephrologists or clinical research associates in each dialysis or transplant center enter the registry data. The REIN registry contains information about patients with a kidney transplant (the CRISTAL database) and patients on dialysis (the DIADEM database). The presence or absence of a diagnosis of TSC does not appear in the CRISTAL database. Our use of the DIADEM database meant that we could not include patients having received a transplant before 2002 or those having received a transplant before dialysis in our cohort. Prevalent and incident patients with TSC were identified on the basis of primary nephropathy, secondary nephropathy or an associated diagnosis recorded in DIADEM. We included prevalent patients with TSC (i.e. alive patients who were already on dialysis when the REIN registry was extended to their region) and incident patients with TSC (i.e. those who started dialysis after the extension of the REIN registry to their region but before December 31st, 2016). Follow-up data was available through December 31st, 2017.

Data collection

1) The REIN registry

To describe the patients' characteristics and events of interest, data were extracted from the REIN registry: Demographic data: sex, age, Baseline data, Comorbidities (diabetes, chronic respiratory disease, cardiovascular disease, active malignancy, at least one disability, behavioral disorders, the level of walking disability and a requirement for ambulance transportation) and Information on medical follow-up: placement on the kidney transplant waiting list or the contraindication to transplantation, the date of kidney transplantation, and the date of death.

2) Medical records

In order to gather additional data from the patients' medical records, we completed standardized, anonymous questionnaire with the help of each patient's nephrologist. Firstly, the questionnaire and a study information sheet were mailed to the patient's dialysis center; if an answer had not been received two months later, a second letter was mailed out. If the center has not replied within a month, we e-mailed the nephrologist indicated in the patient's file. As a last resort, we phoned the dialysis center.

Statistical analysis

For descriptive analyses, categorical variables were quoted as the number (percentage), and continuous variables were quoted as the means \pm standard deviation (SD) or the median [interquartile range (IQR)]. Intergroup comparisons were performed using Student's test (or Wilcoxon's test, if necessary) for continuous variables and a chi-squared test (or Fisher's exact test, if necessary) for categorical variables. The threshold for statistical significance was set to $p < 0.05$. Graft survival was assessed from the date of transplantation until last follow-up (clinical outcome, return to dialysis, or death) and analyzed according to the Kaplan Meier method. Graft survival curves of patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD) without TSC and patients with IgA Nephropathy matched for class of age (5 years), sex and transplant era were added as a comparison. All analyses were performed using R-Studio, R Foundation for Statistical Computing, Vienna, Austria.

Ethics

Data collection by the REIN registry had been approved by the French national data protection commission (*Commission nationale de l'informatique et des libertés*, CNIL (Paris, France); reference: 903188). The present study was approved by the REIN registry's Scientific Advisory Board.

Results

Data collection

For the period between January 1st, 2002, and December 31st, 2016, we identified 99 patients in whom TSC was the primary or secondary cause of nephropathy (Figure 1). For 61 of the 99 patients, information from medical charts was provided by 50 dialysis or transplantation centers throughout France. Between 2002 and 2016, 65 incident patients with TSC initiated RRT and were thus registered in the REIN registry; they accounted for 0.56 % of the 115,920 incident patients on RRT in France during this period.

Characteristics of 99 TSC patients upon initiation of RRT

The characteristics of patients upon initiation of RRT are summarized in Table 1. Of the 99 patients, 34 were prevalent and 65 were incident. There were 58 females (58.6%), and the mean age upon initiation of RRT was 48.4. Seven patients were diagnosed with polycystic kidney disease (four primary diagnoses and three associated diagnoses). Thirty patients had at least one disability, and 16 of these cases

corresponded to a behavioral disorder. More than half (54.5%) of the patients in our population study had received a kidney transplant, and transplantation was medically contraindicated in around a third (31.3%), without further precision. The level of personal independence was quite high; 74.8% of the patients walked unassisted, and only 9.1% of them had to be taken to the dialysis center by ambulance.

Characteristics of the 61 patients with additional data from medical records.

The characteristics of the 61 patients with additional data from medical records (61.6%) are summarized in Table 2 and Figure 1. Thirty-nine of the patients (64%) were women. The mean age at TSC diagnosis was 25, and the mean age upon initiation of RRT was 45.68. Patients with additional data and those without did not differ significantly with regard to age upon initiation of RRT ($p=0.08$), the sex ratio ($p=0.38$), the proportion of incident patients ($p=0.08$), disability ($p=0.18$), and transplantation ($p=0.07$). About three quarters of the 61 patients had a skin lesion (72.1%), and 73.8% had neurologic damage. Psychiatric impairment was found in 34.4% of the patients, and lung lesions (mostly lymphangiomyomatosis, and all in women) were noted for 31.1% of the patients. Fourteen patients had undergone genetic screening: 9 had *TSC1* mutations and five had *TSC2* mutations. Seventeen patients had been diagnosed eventually with both TSC and polycystic syndrome even though for 10 of them it wasn't in the initial report of REIN registry. Forty-six patients (75.4%) had never received an mTOR inhibitor. Of the 13 patients who did receive an mTOR inhibitor, the drug was administered cutaneously in one case and as part of immunosuppressive therapy following a kidney transplant in the other 12 cases.

The diagnosis of TSC

Data on the diagnostic procedures are summarized in Figure 2. Most diagnoses of TSC in this specific population of patients on RRT (in 36.1% of patients) were prompted by the observation of renal damage. Neurologic impairment was the second most frequent revealing sign (34.4%), followed by a family history (11.5%), liver damage (11.5%) and skin lesions (4.9%). The mean age at diagnosis was significantly greater when TSC was revealed by renal damage (36.34 years) than when it was prompted by neurologic damage (14.17 years) ($p<0.001$). Furthermore, the mean age at diagnosis was also significantly greater when TSC was revealed by renal damage (36.34 years) than it was revealed by a skin lesion (17.76 years) ($p<0.001$).

Renal lesions

The most frequent renal lesion was AML; 26.2% of patients had isolated AML, and 26.2% had AML and renal cysts. Thirteen patients (21.3%) had renal cysts only, and 11.4% had carcinoma only. A great majority (65.6%) of patients had undergone nephrectomy (bilateral nephrectomy in 65% of these cases, unilateral nephrectomy in 30%, and partial nephrectomy in 5%). Ten patients had undergone embolization; only two of these patients did not subsequently undergo nephrectomy. Twenty-nine percent of patients did not undergo kidney surgery. Patients with renal cysts only and those with AML only did not differ with regard to age upon initiation of RRT (41.7 and 45.1 years of age, respectively; $p=0.49$). Similarly, the age upon initiation of RRT did not differ significantly when comparing patients with renal cysts (regardless of the presence of other lesions) and patients without (47.1 and 43.7, respectively; $p=0.40$), and when comparing patients diagnosed with TSC and polycystic kidney disease and patients with TSC only (44.3 and 45.6, respectively; $p=0.76$). It appears that patients with TSC and polycystic kidney disease (Table 3) but with only cyst as renal damage, reached end stage renal disease because of the progression of cysts. On the other hand, patients with cysts and AML or carcinoma needed RRT following nephrectomy.

Graft survival

Fifty-four patients with TSC (54.5%) underwent non-preemptive kidney transplantation; 37 of these (68%) were women. The mean \pm SD time interval between initiation of RRT and transplantation was 23 ± 12.3 months. Nine patients (16%) had a behavioral disorder, and 25 (46.3%) had a neurologic impairment. Sixteen patients (29%) had undergone bilateral nephrectomy, 5 (9%) had undergone unilateral nephrectomy, 2 (3.7%) had undergone partial nephrectomy, and 13 (24%) had not undergone kidney surgery. Of these 54 patients, 14 resumed dialysis, and 10 of the latter subsequently died. The median [IQR] follow-up for transplanted patients with TSC was 6.3 [2.97-10.6] years, with a maximum of 26.7 years. The graft survival rate among patients with TSC was 92.5% at five years and 70.2% at ten years (Figure 3).

Discussion

The present study is the first to have described a cohort of French TSC patients on RRT, as documented in a national registry. Our results emphasize the major value of registers for rare diseases such as TSC. The patients in our population started RRT earlier in life than patients in the REIN registry as a whole (respectively 48.6 vs. 67.5 years of age for women, and 48 vs. 68.3 for men); this was also true for patients with polycystic syndrome (48.4 years of age in our study vs. 59.7 for the REIN registry) ⁽²¹⁾.

Our study focused on patients with TSC on dialysis; this subgroup appeared to differ from patients with TSC in general. The first international registry of patients with TSC (the Tuberous Sclerosis Registry to Increase Disease Awareness, TOSCA) was created in 2012, in order to fill gaps in our knowledge of the natural history and management of this condition ⁽²²⁾. In the very large TOSCA cohort, epilepsy was recorded in 1748 patients (83.5% of the whole cohort), and 451 (54.9% of those documented) had intellectual disability. Furthermore, the presence or absence of TSC-associated neuropsychiatric disorders was not evaluated in 30% to 50% of patients, in view of the difficulty of this assessment. In fact, dialysis may be impossible in patients with major disability or serious behavioral problems because they are incapable of staying still during the dialysis session; hence, these patients do not appear in the REIN registry. This might constitute a major selection bias in estimation of the incidence and prevalence of stage 5 chronic kidney disease.

The mean age at diagnosis of TSC was 29.2 in Schillinger *et al.*'s cohort and 25 in our study; this reflects better screening thanks to genetic diagnosis. The mean age upon initiation of RRT was 39.1 in Schillinger *et al.*'s cohort and 48.4 in our study and; hence, it seems that (i) TSC is now being diagnosed earlier, and (ii) a more conservative approach to managing renal status has been adopted.

In the present study, patients in whom TSC was revealed by skin lesions or neurologic damages were diagnosed earlier in life than patients in whom TSC was revealed by renal damage; this is consistent with (i) the age-dependent expression of the clinical manifestations of TSC, and (ii) the fact that renal damage is usually asymptomatic ⁽⁸⁾. These results should also be considered with a degree of caution, since some of the diagnoses were made long ago, and the data in the patients' files may be incomplete.

Our results showed that 65.6 % of patients had undergone a nephrectomy, and that only transplanted patients had received an mTOR inhibitor. This is not surprising, since AML in TSC became an authorized indication for mTOR inhibitors in 2013, and our study was based on patients who started on RRT between 2002 and 2016. The latest guidelines ⁽⁹⁾ clearly specify that nephrectomy is to be avoided and that MRI of the abdomen every one to three years is required for the assessment of AML and renal cysts and then the initiation of an mTOR inhibitor if necessary. This approach should drastically lower the prevalence of ESRD among patients with TSC ⁽²³⁾. However, loss of renal function and proteinuria are adverse drug reactions for mTOR-Tor inhibitor, along with mouth ulcers ⁽²⁴⁾. This particular risk has been evaluated; it appears that renal function remains stable except when it is already severely

compromised prior to initiation. Hence, everolimus[®] is not considered to be nephrotoxic in closely monitored patients with AML and TSC⁽²⁵⁾. The TOSCA patients were enrolled between 2012 and 2014, i.e. after the latest recommendations on the treatment and follow-up of TSC. Among the patients with AML, 43.4% had been treated with mTOR inhibitor and only three patients were on dialysis⁽²⁶⁾. This suggests that in the near future, fewer patients with TSC will develop ESRD and require dialysis.

In the present study cohort, 21.3% of the patients had renal cysts only, and 26.2% had AML and renal cysts. Some researchers have suggested that given the potentially high growth rate of renal cysts, ESRD appears earlier for TSC patients with renal cysts than in TSC patients with other renal lesions⁽¹⁷⁾⁽²⁷⁾⁽²⁸⁾. In the present study, the mean age at RRT initiation did not differ significantly when comparing these two subgroups ($p=0.40$); this might be explained by the high frequency of nephrectomy (65.6%).

Lastly, our study of the largest yet cohort of transplanted patients with TSC evidenced good survival rates (92.5% at five years, vs. 80% in the general population of kidney transplant recipients between 2006 and 2008, and respectively 70.2% vs. 59.6% at ten years)⁽²¹⁾. Graft survival seems similar to that of patients with ADPKD without TSC. In view of the disease mechanism, patients with TSC as patients with polycystic kidney syndrome have few vascular impairments; this may contribute to the good observed graft survival rate. As mentioned above, the main limitation of the present study was its focus on TSC patients on dialysis. Although this may be considered as a source of selection bias, our focus enabled us to be exhaustive and to obtain a homogeneous patient population. The current extension of the REIN registry to stage 5 CKD patients not on RRT might enable us to gather further data and explore reasons for not initiating dialysis in this specific population.

Conclusion

Patients with TSC and ESRD are diagnosed earlier and start dialysis later than 20 years ago - presumably because of better care. Patients in whom TSC was revealed by skin lesions or neurologic damage were diagnosed earlier in life than patients in whom TSC was revealed by renal damage. The main cause of ESRD was nephrectomy. We hope that wider use of new treatments (such as mTOR inhibitors) will reduce the requirement for surgery and thus slow the move to RRT among patients with TSC. However, the graft survival rate among transplanted patients with TSC was good, and so transplantation should be considered as a treatment option in this situation.

The authors have no conflict of interest.

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Tables and Figures

Table 1: Characteristics of patients with TSC at the time of inclusion in the REIN registry.

Characteristic	Missing data	N=99 Mean (SD) or n (%)
Sex (male/female)	0	41/58 (41.4%/58.6%)
Cause of nephropathy	0	TSC: 90 (91%) Post-nephrectomy anephritis: 1 (1%) Chronic glomerulonephritis: 1 (1%) Membranoproliferative glomerulonephritis: 1 (1%) Benign nephrosclerosis: 1 (1%) Tubulopathy: 1 (1%) Polycystic kidney disease: 4 (4%)
Age upon initiation of RRT (years)	1	48.4 (16.4)
Albumin (g/L)	61	35.5 (7.4)
Hemoglobin (g/dL)	46	9.7 (2.0)
Emergency initiation of dialysis	38	15 (15.1%)
First dialysis with a catheter	39	22 (22.2%)
EPO treatment before starting dialysis	41	39 (39.4%)
Hemodialysis	0	94 (95%)
Peritoneal dialysis	0	5 (5%)
Arteriovenous fistula	22	55 (59%) (N=94)
BMI (kg/m ²)	21	24.2 (5)
Diabetes mellitus	3	0
High blood pressure	33	40 (40%)
Chronic respiratory disease	4	5 (5%)
Heart failure	4	5 (5%)
Active malignancy	4	9 (9.1%)
At least one disability	6	30 (30.3%)
Behavioral disorder	7	16 (16.2%)
On kidney transplant waiting list	0	27 (27.3%)
Not on the waiting list	0	72 (72.7%) Being screened: 20 (28%) Medical contraindication :31 (43%) Other contraindication: 7 (10%) Patient refusal: 2 (3%) Missing cause: 12 (16%)
Walking unassisted	19	74 (74.8%)
Ambulance transportation	23	9 (9.1%)
Deceased	0	25 (25.3%)
Living with a kidney transplant	0	54 (54.5%)

RRT: renal replacement therapy, N: total number, SD: standard deviation: BMI: Body Mass Index

Table 2: Characteristics of patients with TSC with additional clinical data from medical records (n=61)

Characteristics	Missing data	N=61 Mean (SD) or number (%)
Sex (male/female)	0	21/39 (36%/64%)
Age upon diagnosis of TSC (years)	12	25.04 (16.8)
Age upon initiation of RRT	0	45.68 (16.35)
Skin lesion	0	44 (72.1%)
Neurologic damage	0	45 (73.8%)
Psychiatric impairment	0	21 (34.4%)
Lung lesion	0	19 (31.1%)
Other lesion	0	23 (37.7%)
Genetic screening	10	14 (22.9%) <i>TSC1</i> = 9 (64.3%) <i>TSC2</i> = 5 (35.7%)
Creatinine level upon diagnosis of TSC (μmol/L)	30	221 (127.2)
Polycystic kidney disease	1	17 (27.9%)
Nephrotoxic treatment	1	4 (6.6%)
Family history of ESRD	4	13 (21.3%)
AML only	1	16 (26.2%)
Renal cysts only	1	13 (21.3%)
Carcinoma only	1	7 (11.4%)
AML + cysts	1	16 (26.2%)
Carcinoma + other lesions	1	5 (8.2%)
Nephrectomy	1	40 (65.6%) unilateral: 12 (30%) bilateral: 26 (65%) partial: 2 (5%)
Embolization (yes/no)	2	10 (16.4%) 1: 6 (60%) 2: 3 (30%) >2: 1 (10%)
mTOR inhibitor	2	No: 46 (75.4%) Yes: 13 (21.3%) after transplantation: 12 (92.3%) cutaneous application: 1 (7.7%)

AML: angiomyolipoma, mTOR: mammalian target of rapamycin, RRT: renal replacement therapy

Figure 1. Flow chart

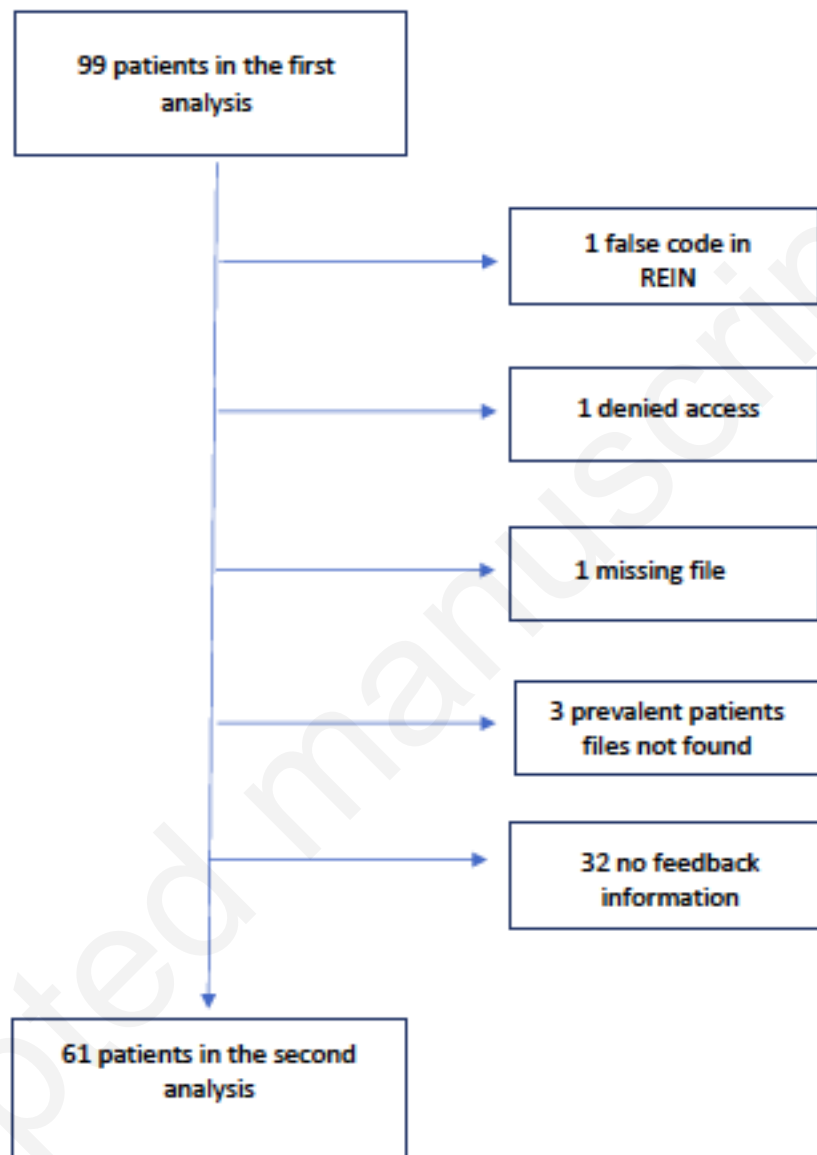


Figure 2: Signs prompting the diagnosis of TSC

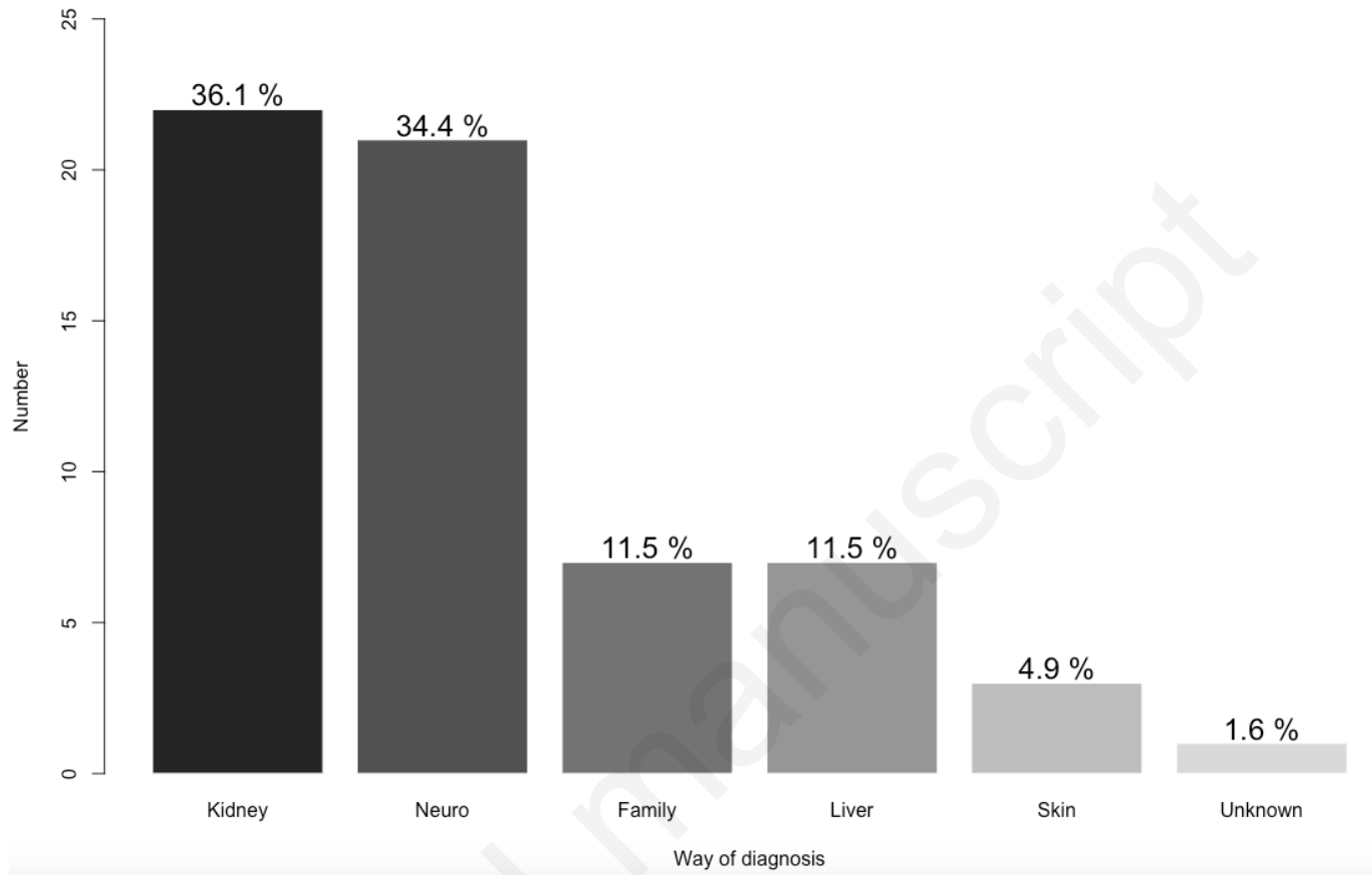
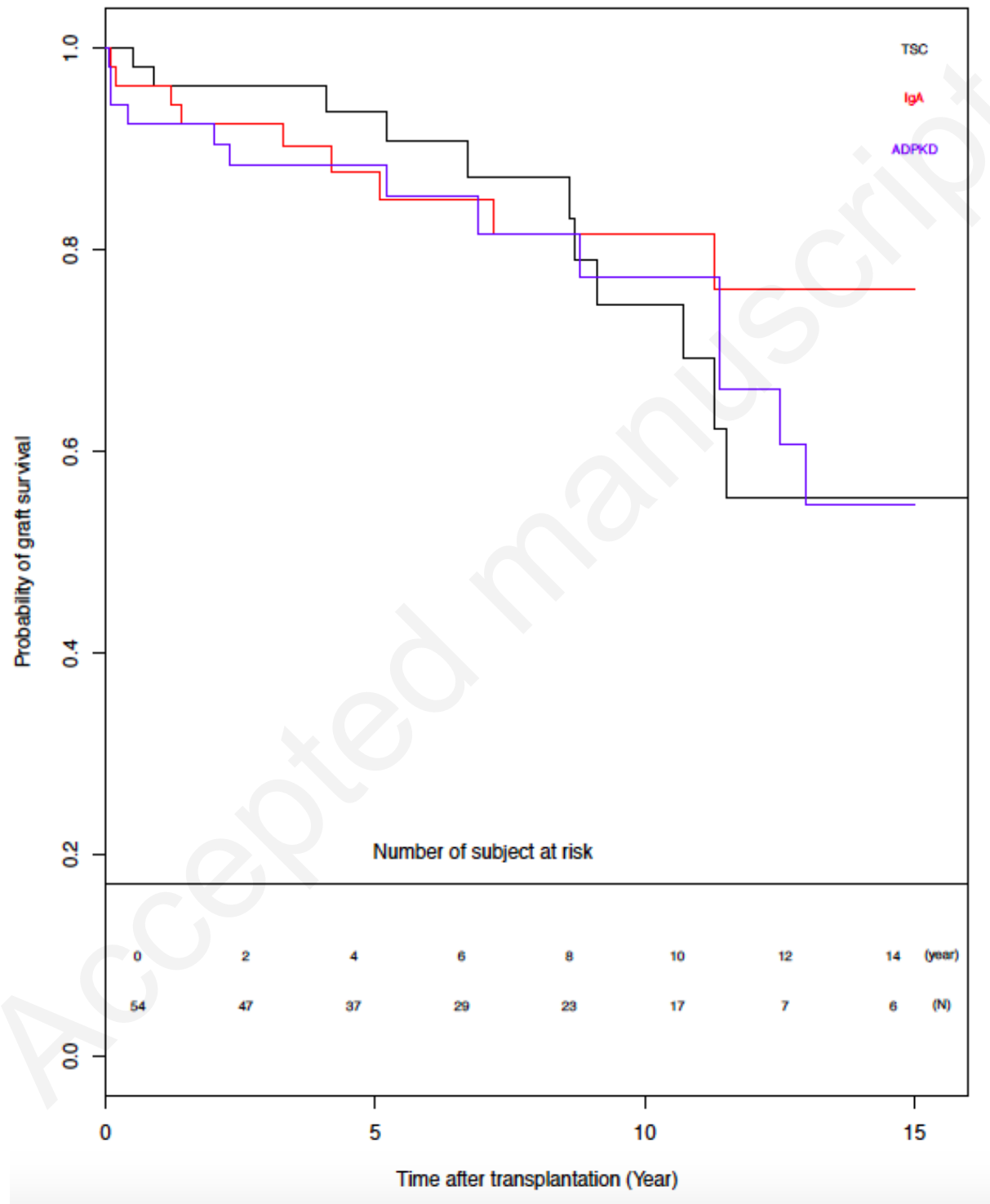


Table 3: Description of renal lesions in patients with TSC and polycystic renal disease (N=17)

Patient	Cyst	AML	Carcinoma	Treatment
1	+	-	+	None
2	+	-	-	None
3	+	+	-	Nephrectomy
4	+	-	-	None
5	+	+	-	Nephrectomy
6	+	-	-	None
7	+	+	-	Nephrectomy
8	+	+	-	Embolization and Nephrectomy
9	+	+	-	None
10	+	-	+	Nephrectomy
11	+	-	-	None
12	+	+	-	Nephrectomy
13	+	-	+	Nephrectomy
14	+	+	+	Nephrectomy
15	+	+	-	None
16	+	-	-	None
17	+	+	-	Nephrectomy

Figure 3: Kaplan Meier curve for graft survival of TSC patients and matched patients (age class, gender and transplant era) with Autosomal dominant PKD (ADPKD) or IgA nephropathy.



TSC : Patients Tuberous sclerosis complex; IgA : patients with IgA nephropathy; ADPKD : patients with autosomal Dominant polycystic Kidney Disease. Number of subject at risk for TSC patients only.