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Original Investigation

Long-term Follow-up Assessing Renal Angiomyolipoma Treatment Patterns, Morbidity, and Mortality: An Observational Study in Tuberous Sclerosis Complex Patients in the Netherlands

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Background: Long-term data from patients with tuberous sclerosis complex (TSC)-associated renal angiomyolipoma (angiomyolipoma) are limited.

Study Design: Retrospective observational study.

Setting & Participants: Adult patients with TSC treated at the University Medical Center Utrecht (the Netherlands) from January 1990 through April 2012.

Predictors: Patient age and angiomyolipoma stage, based on computed tomography lesion count, size, and impact on renal anatomy, with higher stage representing higher angiomyolipoma burden. Patients in stages 3 or higher were considered at high risk for hemorrhage and candidates for selective arterial embolization.

Outcomes: Kidney-related outcomes included hypertension, anemia, decreased kidney function, dialysis, kidney transplantation, nephrectomy, kidney-related blood transfusions, and mortality. Observed mortality was compared to the Dutch National Bureau of Statistics using standardized mortality ratio.

Results: Median follow-up was 15.8 years, of which staging was available for 5.4 years. Of 351 patients with TSC, 244 (69.5%) had confirmed angiomyolipoma; 144 (59.0%) reached stage 3 or higher. Age and angiomyolipoma stage were positively correlated: median age in the none-detected stage was 36.8 years, increasing to 43.6 years for stage 6. Embolization was performed in 117 patients; 57 had 2 or more embolization procedures. Higher stage was associated with hypertension, anemia, decreased kidney function, and transfusion. Hypertension, anemia, and decreased kidney function were more common in patients who underwent selective arterial embolization. 7 patients required dialysis, 7 received a kidney transplant, and 16 underwent nephrectomy. 29 deaths were recorded, most commonly related to renal complications (n = 9 [31%]). Mortality was significantly higher in the study cohort versus the general population (standardized mortality ratio, 4.8; 95% CI, 3.4-6.9).

Limitations: Duration of follow-up with staging was too short to observe stage progression in most patients.

Conclusions: Despite the use of preventive selective arterial embolization, patients with TSC exhibit clinically significant kidney disease and excess mortality, largely because of kidney-related complications.

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INDEX WORDS: Renal angiomyolipoma; selective arterial embolization; kidney-related morbidity; hypertension; anemia; decreased kidney function; blood transfusion; renal hemorrhage; tuberous sclerosis complex (TSC); hamartoma; angiomyolipoma staging criteria; angiomyolipoma progression; mortality; morbidity.

Tuberous sclerosis complex (TSC) is a multisystem disorder characterized by growth of nonmalignant tumors (hamartomas) in various organs throughout the body, including the brain, kidney, lungs, and skin.[1,2] Most patients with TSC have mutations in the *TSC1* or *TSC2* genes, which encode the proteins hamartin and tuberin, respectively.[3] Together, hamartin and tuberin form a tumor suppressor complex that negatively regulates the activity of mammalian target of rapamycin complex 1 (mTORC1), a key regulator of protein synthesis, cell growth and proliferation, angiogenesis, cell metabolism, and cell orientation and migration.[1,3-6] When inhibition of mTORC1 is lost, increased activation of this pathway and formation of nonmalignant tumors characteristic of TSC occur. In the kidney, angiomyolipomas, which are

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composed of abnormal blood vessels, immature smooth muscle cells, and adipose tissue, occur in up to 75% of patients with TSC and are typically multiple in number and located bilaterally.[5] In addition to renal angiomyolipomas, other common renal manifestations of TSC include epithelial cysts (45%) and renal cell carcinoma (2%-3%).[5]

Renal angiomyolipoma is associated with significant morbidity and mortality. Adverse outcomes associated with renal angiomyolipoma can be acute, resulting from the hemorrhage of a lesion, or long term because progressive loss of normal renal parenchyma decreases kidney function and can lead to kidney failure.[1,7-9] Retroperitoneal hemorrhage, also referred to as Wunderlich syndrome, is an acute possibly severe event that can result in death.[7] A medical chart review revealed kidney disease in the form of angiomyolipomas, cysts, or both as the most common cause of death in patients with TSC.[10]

The vasculature of renal angiomyolipoma is characterized by thick-walled blood vessels that lack normal elastin, making them prone to rupture.[11] Yamakado et al[12] reported that aneurysm size was the most significant predictor of hemorrhage and that angiomyolipoma size and aneurysm size were positively correlated. Similarly, a UK renal registry analysis showed increased risk for hemorrhage in lesions demonstrating serial growth.[13]

Renal angiomyolipoma treatment goals focus on preventing acute events, preserving renal parenchyma, and maintaining long-term kidney function. At the time of this study, approved treatment options in the Netherlands included observation, nephron-sparing procedures (partial nephrectomy, cryotherapy, and radiofrequency ablation), and selective arterial embolization. Historically, embolization was reserved for symptomatic cases in which the angiomyolipoma caused bleeding.[14-16] In the early 2000s, practitioners began to use embolization on an elective basis in patients with large growing angiomyolipomas to prevent hemorrhage and preserve kidney function. This practice was added to the Dutch treatment guidelines in 2006.[17]

Although a number of studies describe the pathophysiology, epidemiology, and treatment of renal angiomyolipomas in patients with TSC, most have small patient samples and short periods of follow-up. The literature documenting long-term follow-up after elective embolization is limited. Consequently, most studies focus on reducing the number of acute events and are not able to report on long-term outcomes, including kidney function. This study was undertaken to evaluate renal angiomyolipoma characteristics, treatment patterns, and associated long-term outcomes in a large cohort of patients with TSC in the Netherlands.

METHODS

Participants

Inclusion criteria for this retrospective analysis were diagnosis of TSC according to the modified Gomez criteria (2 major or 1 major and 2 minor criteria)[18] and aged 18 years or older. From January 1990 through April 2012, patients were treated at the University Medical Center Utrecht (UMCU), where elective embolization is used in patients with TSC with at least one renal angiomyolipoma ≥ 3.5 cm (in longest diameter) that shows serial growth.

Patients or family caregivers could opt out of participation; as a result, data from 2 patients were omitted. This study was approved by UMCU's Institutional Review Board.

Data Sources and Measurement

Data were extracted from UMCU's electronic medical records system and combined with information from older paper-based records and medical charts. Computed tomographic (CT) scans were available from 2000 onward and were generally performed every 2 to 3 years as part of routine follow-up. (Magnetic resonance imaging was not widely available.) When possible, radiologic reports were used when original scans were unavailable. Angiomyolipoma and subependymal giant cell astrocytoma were identified by CT scan, epilepsy was measured by electroencephalography, and other manifestations were determined by clinical examination and history taking. Observations of the treating physician were used to determine the presence of skin lesions and assess cognitive function. Kidney function was measured by calculating estimated glomerular filtration rate using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine equation.[19] For this analysis, patients with estimated glomerular filtration rates < 60 mL/min/1.73 m^2 were considered to have decreased kidney function. Renal angiomyolipoma staging criteria developed at UMCU were used as part of the clinical assessment. The criteria (Table 1) are based on 3 factors: number of angiomyolipomas (both kidneys), size of angiomyolipomas, and gross radiologic anatomy of the kidney. Because angiomyolipomas can distort the gross appearance and architecture of the kidney, inspection of kidney anatomy is helpful in ascertaining the extent of disease. Embolization was performed using a combination of

Table 1. Renal Angiomyolipoma Staging Criteria Proposed by University Medical Center Utrecht

Stage	No. of Angiomyolipoma	Angiomyolipoma Size	Description of Kidney Anatomy
None detected[a]	None ≥ 1 cm in longest diameter	—	Normal
1	≤5	<3.5 cm	Normal
2	>5	<3.5 cm	Normal
3	≤5	At least 1 ≥3.5 cm	Kidney intact
4	>5	1-4 ≥3.5 cm	Kidney intact
5	>5	≥5 ≥3.5 cm	Kidney recognizable
6	>5	At least 1 ≥5.0 cm	Kidney not recognizable

[a]Angiomyolipoma not detectable or lesions < 1 cm unidentifiable as angiomyolipoma.

trisacryl gelatin microspheres (Embosphere; Merit Medical) and a mixture of polyvinyl alcohol particles, with no coiling. Dexamethasone and acetaminophen were used to avoid postembolization syndrome and manage pain.

Statistical Methods

Median age at first occurrence of angiomyolipoma and age at which renal angiomyolipomas became high risk for hemorrhage (renal angiomyolipoma stage $\geq$ 3, per Table 1) were estimated using parametric survival models with age from birth as the time axis. Weibull and log-normal distributions were fitted and the best-fitting model, based on the deviance, was chosen. Censoring was used to address: (1) patients who already had angiomyolipomas at the time of first observation (left censoring), (2) patients who were angiomyolipoma free at last follow-up (right censoring), and (3) patients who developed angiomyolipomas between 2 follow-up visits (interval censoring). These censoring patterns necessitated the use of a parametric model.

Descriptive statistics (number, percentage, mean, and standard deviation) were calculated for the highest observed angiomyolipoma stage and kidney-related outcomes (hypertension [systolic blood pressure $>$ 140 mm Hg and/or diastolic blood pressure $>$ 90 mm Hg], anemia [hemoglobin level $<$ 12.5 g/dL in women or $<$13.5 g/dL in men], decreased kidney function, dialysis, kidney transplantation, nephrectomy, kidney-related blood transfusions, and mortality). Correlations between the highest observed stage and kidney-related outcomes were analyzed by cross-tabulation and χ^2 tests for trend. Additionally, the correlation between hemoglobin level and log(estimated glomerular filtration rate) was assessed by Pearson correlation coefficient to better understand the underlying cause of anemia. The subgroup of patients with available CT scans was used for select analyses. In cases in which CT scans were not discernible, not taken, or otherwise unavailable, patients could not be categorized into an angiomyolipoma stage and were omitted from longitudinal models.

Descriptive statistics were used to report associations between the number of embolizations and kidney-related outcomes and mortality. Because 9 outcomes were analyzed separately, Bonferroni correction for multiple testing was applied to P values (ie, the critical P for significance was $0.05/9 = 0.0056$).

Time-dependent Cox proportional hazards models were used to analyze outcomes associated with elective embolization and nonelective embolization (which included cases in which it was not possible to confirm the embolization was done on an elective basis). The Cox model compares in a time-dependent fashion the risk of kidney-related outcomes and death from the time of the embolization procedure with patients of the same age who had not undergone embolization. Embolizations were classified as either elective or nonelective based on information in the patient's record. The first occurrence of each type of embolization was analyzed with adjustment for the highest observed angiomyolipoma stage. The time axis was age, with left truncation at the age of entry into the study and right-censoring for patients who had not reached the event of interest at last follow-up. Using this approach, the confounding effect of age was automatically accounted for.

Overall mortality was analyzed using the Kaplan-Meier method and compared with the expected survival curve based on age- and sex-matched mortality records for the population at risk, at each follow-up, from the Dutch National Bureau of Statistics. Differences between observed and expected survival curves were analyzed using the standardized mortality ratio with 95% confidence interval (CI) and P value based on the Poisson model.[20] The observed number of deaths in each combination of age, sex, and calendar year was used as the dependent variable, and the expected number of deaths for the same age-sex–calendar year combinations was used as an offset in the Poisson model. Additionally, a Cox regression analysis was used to explore the relationship between cognitive status and overall mortality. All analyses were performed using R statistical software package, version 3.02 (R Foundation for Statistical Computing). Standardized mortality ratio analysis was done with the R package survexp.fr.

RESULTS

Baseline Demographics

A total of 351 patients with TSC were identified at UMCU from January 1990 through April 2012. Baseline patient demographics and clinical characteristics are shown overall and separately for patients with and without renal angiomyolipomas (Table 2). Proportions of female and male patients were equal, and most were of European ancestry. Prevalent TSC manifestations were epilepsy, renal angiomyolipomas, angiofibromas, and subependymal nodules. More than half the patients had low to very low cognitive function (required semiconstant or constant oversight from a caregiver in a protective setting). Information was sufficient in 332 of 351 (94.6%) patients to assign a

Table 2. Baseline Patient Demographics and Clinical Characteristics for All Patients, and Stratified by Presence of Angiomyolipoma During Follow-up

	All (N = 351)	AML in F/U (n = 244)	No AML in F/U (n = 107)
Age at end of F/U, y	39.8 (18-89)	40.3 (18-79)	35.5 (18-89)
Sex			
Male	176 (50.1)	127 (52.0)	49 (45.8)
Female	175 (49.8)	117 (48.0)	58 (54.2)
Race			
White	345 (98.3)	239 (98.0)	106 (99.1)
Other	6 (1.7)	5 (2.0)	1 (0.9)
Diagnosis of TSC			
Confirmed	342 (97.4)	242 (99.2)	100 (93.5)
Suspected	9 (2.6)	2 (0.8)	7 (6.5)
Manifestations present			
SEGA	81 (23.1)	66 (27.0)	15 (14.0)
SEN	225 (64.1)	169 (69.3)	56 (52.3)
Rhabdomyomas	36 (10.3)	28 (11.5)	8 (7.5)
Lipomas	108 (30.8)	84 (34.4)	24 (22.4)
Angiofibromas	249 (70.9)	178 (73.0)	71 (66.4)
Hypomelanotic macules	138 (39.3)	87 (35.7)	51 (47.7)
LAM	40 (11.4)	35 (14.3)	5 (4.7)
Epilepsy	273 (77.8)	202 (82.8)	71 (66.4)
Autism/autism spectrum disorder	58 (16.5)	45 (18.4)	13 (12.1)
Low/very low cognitive function	195 (55.6)	155 (63.5)	40 (37.4)

Note: Values for categorical variables are given as number (percentage); for continuous variables, as median (range).

Abbreviations: AML, angiomyolipoma; F/U, follow-up; LAM, lymphangioleiomyomatosis; SEGA, subependymal giant cell astrocytoma; SEN, subependymal nodule; TSC, tuberous sclerosis complex.

renal angiomyolipoma stage (including 88 with "none detected"). Nineteen (7%) patients had evidence of angiomyolipoma but could not be staged because of missing or inadequate radiologic imaging. These patients were included in the none-detected group for analyses. Sex distribution of the 244 patients with angiomyolipomas (127 men and 117 women) was similar to patients without angiomyolipomas ($P = 0.3$). Mean age at the end of follow-up was 39.8 (range, 18-89) years. Overall mean duration of follow-up was 15.8 years. However, the mean duration of follow-up for which CT scans or reports were available was 5.4 years. Consequently, in most patients, changes of renal angiomyolipomas from one stage to another were not commonly observed.

Renal Angiomyolipoma Stage and Disease Progression

Of 244 patients with a renal angiomyolipoma, 144 (59%) had a highest observed stage of 3 or higher, at which point patients are considered at high risk for hemorrhage and are candidates for elective embolization per the UCMU treatment protocol. Nearly half the high-risk patients were women.

Age and renal angiomyolipoma stage were positively correlated: median age in the none-detected stage was 36.8 years, increasing to 43.6 years in stage 6. The Weibull model best fit this study's age versus angiomyolipoma stage distribution and was used to estimate median age at first renal angiomyolipoma occurrence, which was 8.6 (95% CI, 2.1-15.1) years. The median age at which renal angiomyolipomas became high risk for hemorrhage (stage $\geq$ 3), also estimated using a Weibull model, was 46.0 (95% CI, 37.9-54.0) years (Fig 1).

Embolization Profile by Highest Renal Angiomyolipoma Stage

A total of 117 patients had one or more embolization; 57 had at least 2. The number of embolization procedures per patient increased accordingly with angiomyolipoma stage for patients in stages 3 to 6. Patients in stages 0 to 2 typically were not treated with elective embolization. The mean number of embolizations per patient in stage 3 was 0.85, increasing to 2.06 in stage 6 (Table 3). Mean patient age at the time of the first embolization did not correlate with increasing angiomyolipoma stage. In general, the embolization rate (number of embolizations per year) increased as renal angiomyolipoma stage increased. For stage 3, the embolization rate was 0.09, compared with 0.14 for stage 6 ($P = 0.03$). Based on these embolization rates, patients in stage 3 require embolization approximately every 11 years, whereas patients in stage 6 require embolization every 7 years.

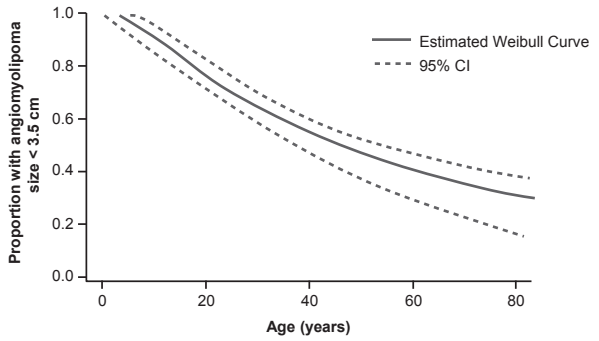

Figure 1. Time-to-event model of age of becoming high risk for hemorrhage (angiomyolipoma size $\geq$ 3.5 cm). Estimated Weibull curve (solid), with 95% confidence interval (CI; dotted). The median age is the age at which the solid curve passes through the 0.5 level.

Kidney-Related Outcomes

The occurrence of hypertension, anemia, decreased kidney function, and blood transfusion corresponded with increasing renal angiomyolipoma stage (P for trend < 0.001; Table 4). Anemia was a common occurrence overall (60.7%). A positive correlation between anemia (lowest hemoglobin level) and decreased kidney function was found ($r = 0.31$; $P < 0.001$). Seven patients required kidney dialysis, 7 underwent kidney transplantation, and 16 underwent nephrectomy. Of the 7 patients who underwent kidney transplantation, some never required dialysis. Bleeding complications from nephrectomy were not the cause of dialysis or transplantation in any patient in this study. The small number of transplantation and dialysis cases in the none-detected and stage-2 groups were likely the result of numerous relatively small (<1 cm) angiomyolipomas in both kidneys. In addition, due to the unknown angiomyolipoma stage of the 19 patients with missing or inadequate imaging who were classified in the none-detected angiomyolipoma group, we performed a sensitivity analysis to test whether removing these patients modified the results. The significance of the results was not affected.

Kidney outcomes are reported by number of embolization procedures in Table 5. Anemia was common regardless of the number of embolizations and occurred in 49.6%, 76.7%, 87.2%, and 94.4% of patients who had undergone 0, 1, 2, or 3 or more procedures, respectively. Hypertension and decreased kidney function were substantially more prevalent in patients who underwent embolization versus those who did not. Half (50.0%) the patients who underwent 3 or more embolizations had decreased kidney function. The occurrence of postembolization syndrome and need for a kidney transplant did not correspond with an increase in embolization procedures.

Risk for kidney outcomes is reported based on whether the first embolization was elective or nonelective (Table 6). When patients underwent elective

Table 3. Embolization Profile by Highest Angiomyolipoma Stage Attained During Follow-Up

Highest Angiomyolipoma Stage	No. of Patients	Embolizations Per Patient	Age at First Embolization, y	Embolization Rate[a]
Unknown[b]	19 (5.4)	NA	NA	NA
None detected[c]	88 (25.0)	NA	NA	NA
1	48 (13.7)	NA	NA	NA
2	52 (14.8)	NA	NA	NA
3	13 (3.7)	0.85 ± 0.90	41.7 ± 16.7	0.09 ± 0.10
4	69 (19.7)	1.06 ± 1.03	32.8 ± 11	0.08 ± 0.13
5	28 (8.0)	1.32 ± 1.12	39.4 ± 14.5	0.11 ± 0.11
6	34 (9.7)	2.06 ± 1.89	35.2 ± 12.4	0.14 ± 0.15

Note: Values are given as number (percentage) or mean ± standard deviation.
Abbreviation: NA, not applicable.
[a]Number of embolizations per year.
[b]Patients had angiomyolipomas but could not be classified due to a lack of computed tomographic scans.
[c]Angiomyolipoma not detectable or lesions < 1 cm unidentifiable as angiomyolipoma.

embolization (compared with those who did not undergo embolization), the hazard ratio (HR) for the first occurrence of hypertension was 3.04 ($P < 0.001$), and for the first occurrence of anemia was 3.92 ($P < 0.001$). When patients underwent nonelective embolization (compared with those who did not undergo embolization), the HR for the first occurrence of anemia was 3.83 ($P < 0.001$), and for the first occurrence of decreased kidney function was 2.88 ($P = 0.005$).

Mortality Analysis

Twenty-nine deaths were recorded during the observation period. Leading causes of death were renal complications (n = 9 [31%]), cancer (n = 5 [17%]), and epilepsy (n = 3 [10%]). Other causes were unknown or occurred in 2 or fewer patients. Renal complications leading to death included reduced kidney function in patients for whom hemodialysis was not appropriate (n = 4), complications following embolization (n = 3), angiomyolipoma hemorrhage (n = 1), and septicemia after spontaneous abscess in a renal angiomyolipoma (n = 1). One patient died of an infection after kidney transplantation. Of patients who died from renal complications, 7 had low or very low cognitive function. Overall, patients with low or very low cognitive function had an increased risk of all-cause mortality (HR, 2.97; $P = 0.02$, adjusted for angiomyolipomas stage).

Table 4. Observed Frequencies of Kidney-Related Outcomes According to Highest Renal Angiomyolipoma Stage

								Death	
Angiomyolipoma	HTN[a,b]	Anemia[b,c]	Decreased Kidney Function[b,d]	Dialysis	Kidney Tx	Nephrectomy	Transfusion[b,e]	All Cause	Renal Cause[f]
Unknown,[g] n = 19	3 (16)	8 (42)	3 (16)	1 (5)	2 (11)	1 (5)	1 (5)	2 (11)	0 (0)
None detected,[h] n = 88	10 (11)	34 (39)	4 (5)	1 (1)	1 (1)	2 (2)	1 (1)	2 (2)	1 (1)
Stage									
1, n = 48	8 (17)	27 (56)	5 (10)	0 (0)	0 (0)	1 (2)	3 (6)	6 (13)	1 (2)
2, n = 52	10 (19)	35 (67)	7 (14)	1 (2)	1 (2)	3 (6)	2 (4)	5 (10)	0 (0)
3, n = 13	6 (46)	6 (46)	2 (15)	0 (0)	0 (0)	1 (8)	0 (0)	0 (0)	0 (0)
4, n = 69	21 (30)	55 (80)	12 (17)	1 (1)	0 (0)	2 (3)	3 (4)	8 (12)	3 (4)
5, n = 28	13 (46)	19 (68)	9 (32)	1 (4)	1 (4)	2 (7)	2 (7)	0 (0)	0 (0)
6, n = 34	20 (59)	29 (85)	16 (47)	2 (6)	2 (6)	4 (12)	10 (29)	6 (18)	4 (12)
Total, n = 351	91 (25.9)	213 (60.7)	58 (16.5)	7 (2.0)	7 (2.0)	16 (4.6)	22 (6.3)	29 (8.3)	9 (2.6)

Note: Values are given as number (percentage). All percentages are calculated within their respective row.
Abbreviations: HTN, hypertension; Tx, transplantation.
[a]Defined as systolic blood pressure > 140 mm Hg and/or diastolic blood pressure > 90 mm Hg.
[b]$P < 0.001$.
[c]Defined as hemoglobin < 12.5 g/dL (women) or <13.5 g/dL (men).
[d]Defined as estimated glomerular filtration rate < 60 mL/min/1.73 m^2.
[e]Kidney related.
[f]$P < 0.05$ tests for trend.
[g]Patients had angiomyolipomas but could not be classified due to a lack of computed tomographic scans.
[h]Angiomyolipoma not detectable or lesions < 1 cm unidentifiable as angiomyolipoma.

Table 5. Observed Frequencies of Kidney-Related Outcomes, Postembolization Syndrome, and Mortality According to Number of Renal Embolizations

Embolization Procedures	HTN[a]	Anemia[b]	Decreased Kidney Function[c]	Dialysis	Kidney Tx	Nephrectomy	Postembolization Syndrome	Death	
								All Cause	Renal Cause
None, n = 234	44 (18.8)	116 (49.6)	24 (10.2)	4 (1.7)	5 (2.1)	9 (3.8)	—	18 (7.7)	3 (1.3)
1, n = 60	23 (38)	46 (77)	17 (28)	0 (0)	1 (2)	3 (5)	12 (12)	5 (8)	2 (3)
2, n = 39	17 (44)	34 (87)	8 (21)	0 (0)	1 (3)	1 (3)	4 (8)	4 (10)	2 (5)
≥3, n = 18	7 (39)	17 (94)	9 (50)	3 (17)	0 (0)	3 (17)	4 (11)	2 (11)	2 (11)
Total, n = 351	91 (25.9)	213 (60.7)	58 (16.5)	7 (2.0)	7 (2.0)	16 (4.6)	20 (10.5)	29 (8.3)	9 (2.6)

Note: Values are given as number (percentage). All percentages are calculated within their respective row.
Abbreviations: HTN, hypertension; Tx, transplantation.
[a]Defined as systolic blood pressure > 140 mm Hg and/or diastolic blood pressure > 90 mm Hg.
[b]Defined as hemoglobin < 12.5 g/dL (women) or <13.5 g/dL (men).
[c]Defined as estimated glomerular filtration rate < 60 mL/min/1.73 m^2.

The effect of elective and nonelective embolizations on risk for all-cause and kidney-related mortality were also assessed (Table 6). When patients underwent elective embolization, the HR for all-cause mortality compared with patients of the same age who did not undergo embolization was 0.49 ($P = 0.4$), and the HR for death as a result of renal complication was 0.53 ($P = 0.4$). When patients underwent nonelective embolization, HRs for all-cause mortality and death as a result of renal complications were 5.4 ($P = 0.007$) and 4.67 ($P = 0.02$), respectively (Table 6). Although these values are clinically meaningful, they were not statistically significant after Bonferroni correction for multiple testing.

The mortality rate in patients with TSC was significantly higher than in the Dutch general population (standardized mortality ratio, 4.8; 95% CI, 3.4-6.9; Fig 2), indicating that the 29 deaths observed in this study are almost 5 times higher than deaths of an age- and sex-matched group randomly selected from the Dutch general population over the same period.

DISCUSSION

Nearly three-quarters of the patients with TSC in this study had renal angiomyolipomas, and more than half were considered at high risk for hemorrhage based on the staging criteria described here. Patients with renal angiomyolipomas at higher stages were found to be at increased risk for many of the adverse kidney outcomes that were measured. Further, angiomyolipoma stage correlated with age, number of embolization procedures, and number of embolizations per year. These data suggest that angiomyolipoma staging criteria could serve as a diagnostic tool for evaluating disease burden at initial assessment and provide a scale for clinicians

Table 6. Effect of Elective and Nonelective Embolizations on Unadjusted Kidney-Related Outcomes and Mortality

Outcome	Elective[a]		Nonelective/Unknown[a]	
	HR (95% CI)	*P*	HR (95% CI)	*P*
First occurrence of				
Hypertension[b]	3.04 (1.71-5.41)[c]	<0.001[c]	0.43 (0.17-1.08)	0.07
Anemia[d]	3.92 (2.29-6.73)[c]	<0.001[c]	3.83 (2.15-6.80)[c]	<0.001[c]
Decreased kidney function[e]	1.41 (0.68-2.92)	0.4	2.88 (1.38-6.02)[c]	0.005[c]
Dialysis initiation	2.01 (0.14-27.99)	0.6	10.47 (0.91-121.18)	0.06
First nephrectomy	0.38 (0.05-3.13)	0.4	1.95 (0.47-8.00)	0.4
Death				
All cause	0.49 (0.11-2.26)	0.4	5.40 (1.59-18.40)	0.007
Renal complications	0.53 (0.11-2.47)	0.4	4.67 (1.30-16.78)	0.02

Note: Unknown refers to before 2000.
Abbreviations: CI, confidence interval; HR, hazard ratio.
[a]Effects on kidney-related outcomes of elective and nonelective embolization are time-dependent variables, from the age at which the embolization was performed onward.
[b]Defined as systolic blood pressure > 140 mm Hg and/or diastolic blood pressure > 90 mm Hg.
[c]Significant after Bonferroni correction for multiple testing.
[d]Defined as hemoglobin < 12.5 g/dL (women) or <13.5 g/dL (men).
[e]Defined as estimated glomerular filtration rate < 60 mL/min/1.73 m^2.

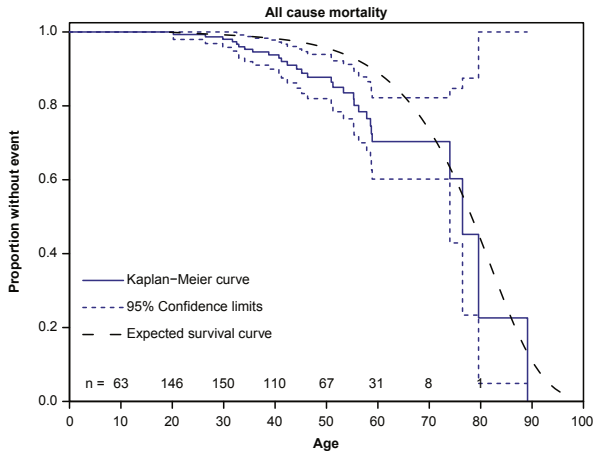

Figure 2. Survival curve of patients with angiomyolipomas compared with that expected from the general population in the Netherlands.

for tracking angiomyolipoma progression. Formal validation of the staging criteria is recommended so it can be used broadly in clinical practice.

Although the frequencies of most clinical features suggestive of or related to kidney disease (including hypertension, anemia, decreased kidney function, and blood transfusion) correspond with higher angiomyolipoma stage, anemia was common at all stages. One possible explanation for the high rate of anemia is that renal angiomyolipomas, irrespective of size, reduce the proportion of functional renal parenchyma, which ultimately affects erythropoietin secretion from peritubular interstitial cells in the renal cortex and outer medulla of the kidney.[21] A connection between anemia and renal tissue injury has previously been reported in acute and long-term settings.[21] Therefore, anemia may be an early surrogate marker for kidney damage in patients with TSC.

At the time of this study, embolization was the standard of care in the Netherlands for symptomatic (bleeding) angiomyolipomas and asymptomatic (nonhemorrhagic) large angiomyolipomas exhibiting serial growth. In symptomatic angiomyolipomas, embolization aims to stop bleeding by occluding aneurysmal blood vessels. Embolization was also believed to reduce angiomyolipoma size and potentially prevent additional growth due to the effect on afferent vessels, all while preserving kidney function. For these reasons, and the ability to preemptively reduce the risk for hemorrhage (when able to identify the aneurysm), embolization was considered a viable elective treatment approach.

One aim of this study was to assess the impact of elective embolization on patient outcomes in order to help clinicians evaluate treatment options. The number of acute clinically dangerous hemorrhages was low in our study group, likely as a result of the use of elective embolization. However, we observed that embolization was not always effective in cutting off the blood supply to the lesion, necessitating additional interventions. Given the number of kidney lesions often present in patients with TSC, it is difficult to differentiate between recurrence and growth of an adjacent angiomyolipoma.[22] Nevertheless, the embolization rate reported here suggests that patients with large growing asymptomatic angiomyolipomas will require an embolization every 7 to 11 years, something that may contribute to accelerated decline in kidney function.

With respect to kidney-related outcomes, we found similar adverse outcomes associated with elective and nonelective embolization. Regardless of the circumstances leading to embolization (elective or nonelective), patients who underwent the procedure were at a significantly higher risk for anemia. However, compared with having no embolization, the risk for developing hypertension was 3-fold greater following an elective procedure, and the risk for developing decreased kidney function was 3-fold greater following a nonelective procedure.

Recently published guidelines for the surveillance and monitoring of renal angiomyolipomas suggest a monitoring frequency of every 1 to 3 years throughout the patient's lifetime; however, the age at which monitoring should begin is not well defined.[23] Findings from this study estimate 8.6 years to be the median age of initial angiomyolipoma detection, consistent with findings from other studies.[4,24,25] Consequently, initiating monitoring no later than the age of 10 years would help ensure early detection.

As noted, the 5.4 years of follow-up in which radiologic imaging was available proved too short to broadly observe angiomyolipoma stage progression. However, based on a median age of 8.6 years at first detectable angiomyolipoma (stage 1) and a median age of 46.0 years for becoming high risk (stage $\geq$ 3), the average time between stages could be estimated at approximately 13 years (38.4 years for 3 transitions), assuming linear progression. It is important to note that there is age dependence to this observation and due to the exclusion of patients younger than 18 years, progression in children and adolescents has yet to be determined. Unfortunately, this study was unable to add insight into whether angiomyolipomas grow de novo in adults with TSC. When new-onset angiomyolipomas were documented, it was difficult to ascertain whether they appeared de novo or were previously present but undetectable. Similarly, in patients requiring repeat embolization, it was not captured whether those subsequent embolizations were on the same or new lesions.

Consistent with the findings reported by Shepherd et al[10] in 1991, kidney disease was the leading cause of death in patients with TSC in the current study despite the substantial advances in detection, monitoring, and treatment of angiomyolipomas, including elective embolization. Both studies also reported increased

mortality rates in patients with TSC compared with the general population in their respective countries.

The risk for mortality was significantly higher in patients with low or very low cognitive function, independent of the highest angiomyolipoma stage. Intellectual disability in patients with TSC, often associated with communication challenges and behavioral issues, can prove to be a barrier to diagnosis and optimal care. Additionally, in many cases, the guardians of these patients object to the more aggressive treatments, such as hemodialysis or peritoneal dialysis.

Renal angiomyolipoma associated with TSC clearly results in substantial morbidity and mortality. Proactive surveillance and monitoring of patients, beginning no later than the age of 10 years and continuing throughout life with increasing frequency with advancing age, are recommended for all patients with TSC.[23] Early detection and treatment are essential for the prevention of progressive damage to renal tissue and ultimately for improving patient outcomes. There is a high need for additional treatment options for patients with TSC.

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Contributions: Study conception/design: BZ, WvdW, SBvWvD-K, KCBR, CP, LR; data collection: BZ, LJR, WvdW; statistical analysis: MJCE, WvdW; review/interpretation of results: MJCE, WvdW, BZ, KCBR, LJR, SBvWvD-K, MM. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. BZ accepts responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

REFERENCES

1. Franz DN, Bissler JJ, McCormack FX. Tuberous sclerosis complex: neurological, renal and pulmonary manifestations. *Neuropediatrics*. 2010;41:199-208.

2. Borkowska J, Schwartz RA, Kotulska K, Jozwiak S. Tuberous sclerosis complex: tumors and tumorigenesis. *Int J Dermatol*. 2011;50:13-20.

3. Budde K, Gaedeke J. Tuberous sclerosis complex-associated angiomyolipomas: focus on mTOR inhibition. *Am J Kidney Dis*. 2012;59:276-283.

4. Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. *Lancet*. 2008;372:657-668.

5. Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. *N Engl J Med*. 2006;355:1345-1356.

6. Huang J, Manning BD. The TSC1-TSC2 complex: a molecular switchboard controlling cell growth. *Biochem J*. 2008;412:179-190.

7. Bissler JJ, Kingswood JC. Renal angiomyolipomata. *Kidney Int*. 2004;66:924-934.

8. Sarraf M, Masoumi A, Castro-Silva FJ, Myers JB, Wilson SS, Schrier RW. A case of tuberous sclerosis complex that progressed to end-stage renal disease. *Nat Clin Pract Nephrol*. 2009;5:172-176.

9. Clarke A, Hancock E, Kingswood C, Osborne JP. End-stage renal failure in adults with the tuberous sclerosis complex. *Nephrol Dial Transplant*. 1999;14:988-991.

10. Shepherd CW, Gomez MR, Lie JT, Crowson CS. Causes of death in patients with tuberous sclerosis. *Mayo Clin Proc*. 1991;66:792-796.

11. Eble JN. Angiomyolipoma of kidney. *Semin Diagn Pathol*. 1998;15:21-40.

12. Yamakado K, Tanaka N, Nakagawa T, Kobayashi S, Yanagawa M, Takeda K. Renal angiomyolipoma: relationships between tumor size, aneurysm formation, and rupture. *Radiology*. 2002;225:78-82.

13. Kingswood JC, Doyle T, Cox J, et al. The natural history of renal angiomyolipomata (AMLS) in tuberous sclerosis complex (TSC). Poster presented at: 49th ERA-EDTA Congress; May 24-27, 2012; Paris, France.

14. Nelson CP, Sanda MG. Contemporary diagnosis and management of renal angiomyolipoma. *J Urol*. 2002;168:1315-1325.

15. Fazeli-Matin S, Novick AC. Nephron-sparing surgery for renal angiomyolipoma. *Urology*. 1998;52:577-583.

16. Kwan KG, Matsumoto ED. Radiofrequency ablation and cryoablation of renal tumours. *Curr Oncol*. 2007;14:34-38.

17. Frohn-Mulder I, Halley DJJ, Hoff M, Lequin MH, Mulder J, Oranje AP. Guideline for the medical supervision of children with tuberous sclerosis complex. 2006. http://www.huidziekten.nl/richtlijnen/richtlijn-tubereuze-sclerose-bij-kinderen-2006.pdf. Accessed December 3, 2014.

18. Roach ES, Gomez MR, Northrup H. Tuberous sclerosis complex consensus conference: revised clinical diagnostic criteria. *J Child Neurol*. 1998;13:624-628.

19. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604-612.

20. Dutch National Bureau of Statistics. Statistics Netherlands web site. http://www.cbs.nl/nl-NL/menu/home/default.htm. Accessed February 6, 2014.

21. Nasri H. Renal cell protection of erythropoietin beyond correcting the anemia in chronic kidney disease patients. *Cell J*. 2014;15:378-380.

22. Sooriakumaran P, Gibbs P, Coughlin G, et al. Angiomyolipomata: challenges, solutions, and future prospects based on over 100 cases treated. *BJU Int*. 2010;105:101-106.

23. Krueger DA, Northrup H. Tuberous sclerosis complex surveillance and management: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. *Pediatr Neurol*. 2013;49:255-265.

24. Casper KA, Donnelly LF, Chen B, Bissler JJ. Tuberous sclerosis complex: renal imaging findings. *Radiology*. 2002;225:451-456.

25. Rakowski SK, Winterkorn EB, Paul E, Steele DJ, Halpern EF, Thiele EA. Renal manifestations of tuberous sclerosis complex: incidence, prognosis, and predictive factors. *Kidney Int*. 2006;70:1777-1782.