Original Article

Use and outcomes of kidneys from donors with renal angiomyolipoma: A systematic review

Desiree Garcia Anton, Karthik Kovvuru, Swetha R Kanduri, Narothama Reddy Aeddula[1], Tarun Bathini[2], Charat Thongprayoon[3], Wisit Kaewput[4], Karn Wijarnpreecha[5], Kanramon Watthanasuntorn[6], Sohail Abdul Salim, Praise Matemavi[7], Pradeep Vaitla, Franco Cabeza Rivera, Wisit Cheungpasitporn

Department of Internal Medicine, Division of Nephrology, University of Mississippi Medical Center, [7]Department of Transplant and Hepatobiliary Surgery, University of Mississippi Medical Center, Jackson, Mississippi, [1]Department of Medicine, Division of Nephrology, Deaconess Health System, Evansville, IN, [2]Department of Internal Medicine, University of Arizona, Tucson, AZ, [3]Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, [5]Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, Mayo Clinic, Jacksonville, Florida, [6]Department of Internal Medicine, Bassett Medical Center, Cooperstown, New York, USA, [4]Department of Military and Community Medicine, Phramongkutklao College of Medicine, Bangkok, Thailand

Abstract

Background: Renal angiomyolipoma (AML) is the most frequent mesenchymal tumor of the kidney. Although there is a rare possibility of malignant transformation of AML, this risk has not been studied in immunosuppressed patients. The safety of donors with AML and their kidney transplant recipients has not been well established.

Methods: A literature search was conducted utilizing MEDLINE, EMBASE, and Cochrane databases from inception through May 15, 2018 (updated on October 2019). We included studies that reported the outcomes of kidney donors with AML or recipients of donor with AML. The protocol for this meta-analysis is registered with PROSPERO (International Prospective Register of Systematic Reviews; no. CRD42018095157).

Results: Fourteen studies with a total of 16 donors with AML were identified. None of the donors had a diagnosis of tuberous sclerosis complex (TSC), pulmonary lymphangioleiomyomatosis (LAM), or epithelioid variant of AML. Donor age ranged from 35 to 77 years, and recipient age ranged from 27 to 62 years. Ninety-two percent of the donors were female. Only 8% were deceased donor renal transplant. The majority underwent *ex vivo* resection (65%) before transplantation, followed by no resection (18%), and the remaining had *in vivo* resection. Tumor size varied from 0.4 cm to 7 cm, and the majority (87%) were localized in the right kidney. Follow-up time ranged from 1 to 107 months. Donor creatinine prenephrectomy ranged 0.89–1.1 mg/dL and postnephrectomy creatinine 1.0–1.17 mg/dL. In those who did not have resection of the AML, tumor size remained stable. None of the donors with AML had end-stage renal disease or died at last follow-up. None of the recipients had malignant transformation of AML.

Conclusion: These findings are reassuring for the safety of donors with AML (without TSC or LAM) as well as their recipients without evidence of malignant transformation of AML. As such, this can also positively impact the donor pool by increasing the number of available kidneys.

Keywords: Donor, kidney transplant, renal angiomyolipoma, renal transplantation, transplantation

Address for correspondence: Dr. Wisit Cheungpasitporn, Department of Internal Medicine, Division of Nephrology, University of Mississippi Medical Center, Jackson, Mississippi, USA 39216.
E-mail: wcheungpasitporn@gmail.com
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INTRODUCTION

Kidney transplantation (KTx) is the modality of choice for patients with end-stage renal disease (ESRD) as it improves the quality of life and the survival.[1,2] Kidney transplant recipients have an increased life expectancy by 3–15 years compared to people on renal replacement therapies.[3] Even though the number of kidney transplants are steadily increasing every year, they are not able to exceed wait-listed ESRD patients. Efforts to expand the donor pool by accepting donors with marginal criteria could help mitigate the shortage. There is still a scarcity of available donors more so in the regions of the world where there is a lack of established living and deceased donor programs.[4] One feasible solution to expand the living donor pool is to include the donors with renal lesions which are amenable for transplant with less potential long-term risk to the immunocompromised recipients.[5]

Renal angiomyolipoma (AML) is the most frequent mesenchymal tumor of the kidney.[6] Although first referenced in 1900,[7] its histopathology was originally described by Fischer in 1911.[8] Renal AML is a heterogeneous, triphasic tumor with varying elements of smooth muscle, adipose tissue, and vascular elements.[9] Renal AML can occur sporadically with an incidence ranging from 55% to 80%[10] or in association with the tuberous sclerosis complex (TSC) in about 20%–30% and very rarely as sporadic lymphangioleiomyomatosis (LAM).[11,12] The sporadic forms of AML are typically small, solitary, unilateral, and predominantly seen middle-aged women.[13,14] The diagnosis of the AML is commonly asymptomatic and could be detected incidentally on imaging in more than 80% of the cases. However, in tumors >4 cm in size, they could present with clinical manifestations of left flank pain, tender mass, hematuria, and fatigue.[15-17] Less than 15% manifests as hemorrhage at the presentation (Wunderlich syndrome), a potential emergency needing immediate intervention, whereas less than 10% of them appear with hypovolemic shock.[18]

Renal AML is usually benign and a true malignant AML is rare.[6] Risk factors for malignant AML include size >7 cm, tumor necrosis, and epithelioid carcinoma-like pattern.[19] The historical criteria for active intervention of renal AML are symptomatic lesions >4 cm with risk of rupture, intolerable pain, hemorrhagic hypovolemic shock, suspected malignancy, especially in renal AML associated with TSC, and females of childbearing age.[20] Although there is a rare possibility of malignant transformation of the AML, the risk is not studied in immunosuppressed patients such as kidney transplant recipients.

The first report of a direct live donor KTx after *ex vivo* excision of the AML is reported in 1993.[21] Since then, multiple cases and single-center series of successful live and cadaveric donor transplantations were reported after *ex vivo* and *ex vitro* incisions.[22-24] There is still a dearth of knowledge of the safety of donors with AML and their kidney transplant recipients. In this context, we have conducted a systematic review to use and the outcomes of kidneys from donors with renal AML.

METHODS

Search strategy

The protocol for this meta-analysis is registered with PROSPERO (International Prospective Register of Systematic Reviews; no. CRD42018095157). The Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement[25] was followed in conducting this systematic review. Ovid MEDLINE, EMBASE, and the Cochrane databases were systemically searched from database inceptions through May 15, 2018, and updated on October 2019. We conducted a literature search to identify all potential studies that reported the outcomes of kidney donors with AML or recipients of donor with AML. Two investigators (D. G. A. and C. T.) performed an independent literature search using the search terms of "angiomyolipoma" AND ("donor" AND "renal" OR "kidney"). Language restriction was not applied. Potentially related studies are manually reviewed using the references.

Study selection

Observational studies, clinical trials, case series, or case reports providing data on the use of kidneys from donors with renal AML were included in the systematic review. Two investigators (D. G. A. and C. T.) independently reviewed retrieved articles for eligibility. A third reviewer (W. C.) solved inconsistencies by collective agreement.

Data collection

The following data were collected from individual studies: title, name of authors, year of the study, publication year, country where the study was conducted, recipient characteristics, donor characteristics, age and sex of donor and recipient, cause of ESRD, and tumor size and outcomes.

RESULTS

A total of 84 potentially eligible articles were identified with our search approach. After excluding 52 articles based on title and abstract for clearly not fulfilling inclusion criteria on the basis of the type of article, patient population, animal studies, or duplicates, 32 articles remained for full-length

article review. Eighteen articles did not report the outcomes of kidney donors with AML or recipients of donor with AML. Therefore, 14 studies[15,21-23,26-35] with a total of 16 donors with AML were identified. The systematic review of the literature flowchart is demonstrated in Figure 1.

None of the donors had a diagnosis of TSC, pulmonary LAM, or epithelioid variant of AML. Donor age ranged from 35 to 77 years, and recipient age ranged from 27 to 62 years. Ninety-two percent of the donors were female. Only 8% were deceased donor renal transplant [Figure 2]. The majority underwent *ex vivo* resection (65%) before transplantation, followed by no resection (18%), and the remaining had *in vivo* resection. Donor age ranged from 35 to 77 years, and recipient age ranged from 27 to 62 years. Ninety-two percent of the donors were female. Only 8% were deceased donor renal transplant.

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Donor creatinine prenephrectomy ranged 0.89–1.1 mg/dL and postnephrectomy creatinine 1.0–1.17 mg/dL. In those who did not have resection of the AML, tumor size remained stable. None of the donors with AML had ESRD or died at last follow-up. None of the recipients had malignant transformation of AML.

DISCUSSION

Renal AML and renal cysts are common renal lesions of TSC complex. A two-hit hypothesis has been proposed to explain the pathophysiology. TSC has autosomal dominant inheritance with mutations in TS1 and TS2 genes encoding for hamartin and tuberin proteins, respectively. The second hit could be a superadded viral/bacterial infection, smoking, or other etiologies which could potentiate a

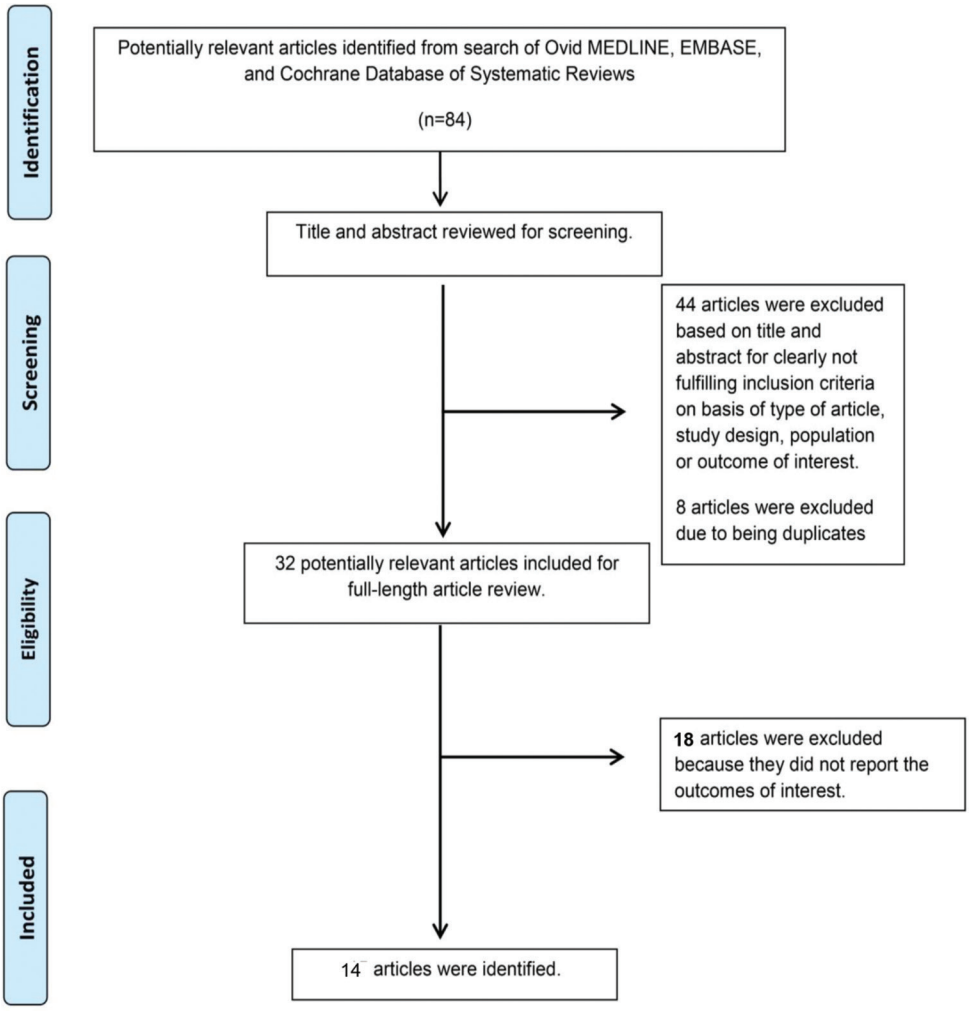

Figure 1: The flowchart for the systematic review

Recipient age	Recipient sex	Preemptive	ESRD cause	Donor age	Donor sex	Living	Donor type
27	female	no	not reported	55	female	yes	mother
39	male	no	MPGN	59	female	yes	mother
54	male	yes	PCKD	47	female	yes	wife
44	female	no (2nd txp)	GN	43	female	yes	sister
not reported	not reported	not reported	not reported	55	female	yes	sister in law
62	male	no	undetermined	60	female	yes	wife
not reported	not reported	not reported	not reported	not reported	not reported	not reported	not reported
29	male	no	IgA	35	female	yes	wife
60	male	not reportd	ATN	67	female	no	unrelated
not reported	not reported	not reportd	not reported	not reported	not reported	yes	not reported
not reported	male	not reportd	PCKD	56	female	yes	wife
56	female	no, 2nd txp	not reported	77	female	yes	not reported
47	male	no, 3rd txp	not reported	50	male	yes	not reported
not reported	not reported	not reportd	not reported	62	female	yes	not reported
58		no	FSGS	not reported	not reported	yes	not reported
61		no	HTN and PVD	not reported	not reported	yes	not reported

Figure 2: Characteristics of recipients of donor with angiomyolipoma and kidney donors with angiomyolipoma. Abbreviations: ESRD: End-stage renal disease, MPGN: Membranoproliferative glomerulonephritis, PCKD: Polycystic kidney disease, GN: Glomerulonephritis, IgA: Immunoglobulin A, ATN: Acute tubular necrosis, FSGS: Focal segmental glomerulosclerosis, HTN: Hypertension, PVD: Peripheral vascular disease, TXP: Transplant

Size tumor	F/U	Cr at end of F/U	Resection Tumor	TSC-Donor	IS recipient	Tumor size at F/U
15mmx10mm	5 yrs	1	no	no	CNI based	same at end f/u
1 cm	18 months	1.6	no	no	not reported	same at 18 m
7cm	36 months	1.7	yes ex vivo	no	CNI based	n/a
3 cm	2 months	1.1	yes ex vivo	not reported	not reported	n/a
2.6 cm Left	24 m	1.5	yes ex vivo	no	not reported	n/a
7 cm	not reported	1.8	yes in vivo	not reported	not reported	n/a
not reported	18 months	2.4	not reported	not reported	not reported	not reported
7 mm	24 m	1.4	yes ex vivo	no	not reported	n/a
4mm	5 yrs	1.9	no	not reported	CNI based	stable
2.2 cm	1 yr	1.2	yes ex vivo	no	not reported	n/a
4.2 cm x 2.5 cm	not reported	1.6	yes in vivo	no	not reported	n/a
3.5 cm	107 m	graft loss-rejection	yes ex vivo	not reported	not reported	n/a
not reported	16 m	not reported	yes ex vivo	not reported	not reported	n/a
not reported	1 m	not reported	yes ex vivo	not reported	not reported	not reported
1.1 cm	15 m	CrCl 72	yes ex vivo	not reported	CNI based	n/a
2.3 cm	12 m	CrCl 39	yes ex vivo	not reported	CNI based	n/a

Figure 3: Tumor size and outcomes of recipients of donor with angiomyolipoma. Abbreviations: F/U: Follow-up, Cr: Creatinine, TSC: Tuberous sclerosis complex, IS: Immunosuppression, CNI: Calcineurin inhibitor, m: Month, yr: Year, cm: Centimeters, CrCl: Creatinine clearance

plethora of the symptoms. Hamartin and tuberin proteins form a complex which would further downregulate the activity of mammalian target of rapamycin (mTOR) activity. Mutation is these proteins might potentiate further cell growth, proliferation, and increased vascular endothelial growth factor activation leading to renal cyst formation.[36-39] With tumors >4 cm and potential vascular aneurysm, compression of renal parenchyma further contributes to chronic kidney disease with worsening renal failure, urinary concentration defects, and essential hypertension.

Diagnosis of AML is commonly based on imaging characteristics as clinical features are rarely seen. Ultrasound, computed tomography (CT) abdomen, and magnetic resonance imaging (MRI) are frequent modalities in practice. Ultrasound is simple, most available, affordable modality, however, it is neither sensitive nor specific in diagnosing AML lesions. Hyperechoic lesion with acoustic shadowing is typically seen on a fat-rich lesion on ultrasound.[10] This pattern could be seen with most other renal malignancies, and hence, ultrasound is not very reliable. Unenhanced CT abdomen is a commonly used diagnostic modality of choice. Based on fat quantification, renal AML is classified as fat-rich, fat-poor, and fat-invisible AMLs. Fat poor and fat invisible are not clearly differentiated by abdominal CT. MRI abdomen is very sensitive in diagnosing and distinguishing fat-poor AML lesions from renal malignancies.[40,41] Renal biopsy can provide an accurate diagnosis of AML, however, it is rarely performed considering the risk of tumor rupture and hemorrhage.[42]

There have been no prospective randomized trials comparing surveillance and treatment for AML. 2012 consensus guidelines recommend mTOR inhibitors (everolimus) as modality of choice treatment for asymptomatic renal AML associated with TSC larger than 3 cm in size.[43,44] The goal of treatment is to pursue a regression of the size of the tumor. Treatment with mTOR inhibitors is not approved for idiopathic renal AML. There are multiple case reports highlighting the effects of everolimus in reducing the tumor size of hamartomas of greater than 20 cm.[44] Side effect profile, especially after KTx, includes impaired wound healing, proteinuria, renal dysfunction, hyperlipidemia, stomatitis, and acne-like symptoms.[23,45,46]

With tumors >4 cm, the risk of vascular complications and retroperitoneal hemorrhage is high. Nephron-sparing techniques are first-line treatment to reduce the risk of chronic kidney disease and eventual ESRD. They include radiofrequency ablation microwave ablation techniques, selective arterial embolization, and partial nephrectomy.[47] However, given an increased risk of recurrence up to 40%, close surveillance and monitoring is recommended.[48] Total nephrectomies are reserved for larger lesions with suspicion for malignancies and as emergent life-saving procedures.[49,50]

There has been no specific protocol for surveillance for asymptomatic patients with renal AML.[47] However, an expert panel recommends physical examination and imaging studies done at 6 months and annually, especially for patients with high risk of spontaneous rupture and bleeding.[51,52] Ultrasound can be used for follow-up once the diagnosis is made. Checking glomerular filtration

rate, urine analysis, serum creatinine, and blood pressure monitoring are indicated in assessing renal functions periodically. A team approach including urologist, general surgeon, nephrologist, and radiologist might together help navigate the donor with AML and help to increase the organ pool with benign kidney lesions.[22]

There has been a plethora of growing literature with case reports of successful renal transplantation after excision of AML. Postoperative 5-year follow-up did not demonstrate a significant increase in size of the tumor despite immunosuppression. Although it might not solve the global problem of kidney transplant shortage, it could certainly pave the way for the recipients whose only available donors have benign renal AML. Hence, patients with small, sporadic, asymptomatic renal AML can be included in donor pool with favorable donor and recipient outcomes.

CONCLUSION

In summary, these findings of our systematic review are reassuring for the safety of donors with AML (without TSC or LAM) as well as their recipients without evidence of malignant transformation of AML. As such, this can also positively impact the donor pool by increasing the number of available kidneys.

Authors' contributions

All authors had access to the data and a role in writing the manuscript.

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Conflicts of interest

There are no conflicts of interest.

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