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ORIGINAL ARTICLE

A 30% incidence of renal cysts with varying sizes and densities in biomedical research swine is not associated with renal dysfunction

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Abstract

Background: Renal cystic disease arising from various etiologies results in fluid-filled cavities within the kidneys. Moreover, preexisting renal dysfunction has been shown to exacerbate multiple pathologies. While swine bred for biomedical research are often clinically inspected for illness/parasites, more advanced diagnostics may aid in uncovering underlying renal abnormalities.

Methods: Computed tomography was performed in 54 female prepubertal Yorkshire swine to characterize renal cysts; urine and blood chemistry, and histology of cysts were also performed.

Results: Digital reconstruction of right and left kidneys demonstrated that roughly one-third of the animals (17/54; 31%) had one or more renal cyst. Circulating biomarkers of renal function were not different between animals that had cysts and those that did not. Alternatively, urinary glucose ($P = .03$) was higher and sodium ($P = .07$) tended to be lower in animals with cysts compared to animals without, with no differences in protein ($P = .14$) or potassium ($P = .20$). Aspiration of cystic fluid was feasible in two animals, which revealed that the cystic fluid urea nitrogen (97.6 ± 28.7 vs 911.3 ± 468.2 mg/dL), potassium (29.8 ± 14.4 vs 148.2 ± 24.85 mmol/L), uric acid (2.55 ± 1.35 vs 11.4 ± 5.65 mg/dL), and creatinine (60.34 ± 17.26 vs 268.99 ± 95.79 mg/dL) were much lower than in the urine. Histology demonstrated a cyst that markedly compresses the adjacent cortex and is lined by a single layer of flattened epithelium, bounded by fibrous connective tissue which extends into the parenchyma. There is tubular atrophy and loss in these areas.

Conclusion: This study provides valuable insight for future studies focusing on kidney function in swine bred for biomedical research.

KEYWORDS

computed tomography, cyst, kidney, renal dysfunction, swine

The corresponding address is the author's current affiliation but not where the work was performed.
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1 | INTRODUCTION

The presence of cysts in the kidney is recognized as an abnormal sac formation derived from the renal tubule and filled with urine-like fluid. Renal cystic disease may arise from a variety of etiologies (eg, congenital, acquired, hereditary) that result in one or more cysts ranging in size from a few microns to centimeters. Cysts may be formed during embryonic development,[1] childhood,[2,3] or adulthood,[4-6] and in some instances, develop further into benign or malignant tissue. As a result of their etiology and development, classifying cyst types based on characteristics such as genetic mutations, morphology, size, and quantity has advanced.[7,8]

Although many genetic diseases are recognized for the formation of cysts, in the majority of cases cyst development is sporadic and not necessarily associated with a disease. In serious progression of the disease, some patients may experience complete kidney failure if not properly treated. Regardless of etiology, the presence of simple renal cysts is associated with reduced creatinine clearance,[9] proteinuria, decreased estimated glomerular filtration rate,[10] and increased albuminuria, hypertension, and hyperfiltration.[11] Moreover, simple cysts can potentially reduce allograft function in transplant recipients,[12] and therefore consideration of donors should be performed with caution.

Animal models are used to study the etiology of kidney cystic disease, especially for underlying mechanisms and potential treatment targets. For the kidney, swine are often used due to anatomical similarities with humans such as a multilobular and multipapillary structure, as well as parallels in intrarenal arteries and the collecting system.[13] Because of this, transgenic mini-pig models for polycystic kidney disease were developed as an alternative to rodents.[14] Furthermore, transplant models are of particular interest, and genetic alterations have brought about the distinct possibility of xenotransplantation.[15]

Unfortunately, even with careful breeding practices animals may present with existing underlying pathologies and the incidence of cysts has been discovered in a variety of animal species. For example, feline autosomal dominant poly cystic kidney disease is hereditary and results in a variable number of cysts within the cortex and medulla.[16] In the abattoir, the incidence of renal cysts in cattle was reported as 26%[17] and in swine it was 47%.[18] In swine where breeding is often limited by a few sires, inherited renal cysts were identified postmortem in over 50% of the progeny.[19] These underlying diseases or abnormalities may often go unnoticed unless intentionally tested for.

In our institute, Yorkshire swine are commonly used to study the effects of trauma (i.e., ischemia, burn) on the development of acute kidney injury (AKI).[20] However, preexisting renal dysfunction has been associated with an increased risk of subsequent AKI.[21,22] While sonography, magnetic resonance imaging, or computed tomography (CT) are valuable tests to identify these types of organ abnormalities, they are not routinely performed. Given that the presence of renal cysts may be an early determinant of kidney disease, these underlying abnormalities may induce variability, adversely impacting interpretation of data. The objective of this study was to identify the incidence and size of renal cysts in research swine and determine whether their presence was associated with renal dysfunction.

2 | METHODS

Research was conducted in compliance with the Animal Welfare Act, the implementing Animal Welfare Regulations, and the principles of the Guide for the Care and Use of Laboratory Animals, National Research Council. The facility's Institutional Animal Care and Use Committee approved all research conducted in this study. The facility where this research was conducted is fully accredited by AAALAC International.

Fifty-four female biomedical research-bred domestic Yorkshire swine weighing 41.4 ± 0.6 kg, free of parasites and infection were included in this retrospective case series design study. Animals were purchased from Midwest™ Research Swine (Gibbon, MN) which is licensed by the US Department of Agriculture under the Animal Welfare Act, and are classified as high health status herd pigs. Animals had a minimum 7-day acclimation period during which they were singly housed with ad libitum access to water, and were fed a commercial laboratory pelleted diet formulated for pigs.

2.1 | Computed tomographic angiographies

Following the acclimation period, contrast-enhanced angiographies were performed under anesthesia. Briefly, animals were fasted overnight and anesthetized with an IM injection of tiletamine-zolazepam (Telazol, 6 mg/kg), intubated, and placed on a ventilator with an initial tidal volume of 10 mL/kg, a peak inspiratory pressure of 20 cm H_2O, and respiration rate of 8-10 breaths/min. End-tidal PCO_2 of 40 ± 5 mm Hg was maintained on the ventilator with 1%-3% isoflurane for anesthesia. Animals were positioned prone, and 40 mL of contrast agent Isovue-370 (BIPSO GmbH, Singen, Germany; generic name: Iopamidol; 755 mg/mL; contains sodium 0.053 mg, organically bound iodine 370 mg/mL) was injected into a catherized lateral auricular vein. All CT scans were performed using a Toshiba Aquillion Prime (Irvine, CA USA) and helical acquisition (helical pitch factor 0.813) multislice detector (80 rows of 0.5 mm, rotation time 0.5 s, 120 kV, 300 mA) system. The rate of contrast delivery was 4 mL/s via the MEDRAD Stellant CT Injector System (Beyer Medical Care Inc 1 Bayer Dr Indianol, PA, USA). A region of interest (ROI) was placed on the descending aorta between T13 and T14, and using Toshiba Sure start technique imaging, acquisition was initiated when the ROI reached a Hounsfield unit (HU) reading of 150. A body scan from thoracic vertebra T3 to lumbar vertebra L3 was performed in all animals. Images were reconstructed using soft tissue filter (FC08).

2.2 | Tissue collection and analysis

Venous blood samples were collected into K2 EDTA containing tubes and centrifuged at 4300× *g* for 10 minutes. Urine was collected while the CT was performed via placement of a Foley catheter. Serum, urine, and cyst aspirate were analyzed on a Siemens

Dimension Xp (Malvern, PA) and Plus Clinical Chemistry System (Thermo Fisher Scientific; Lafayette, CO). All images were evaluated digitally by a bioscience specialist (JSL) and a physiologist (BIG), and were aware that animals may have cysts. The right and left kidneys were reconstructed for quantification of volume and perfusion (HU) using VitreaAdvanced Version 6.7.4 (Vital Image Inc, Minnetonka, MN). Similarly, all cysts identified were reconstructed for quantification of volume. For image analysis, the window level was set at 80 and the window width at 150. The following CT parameters were recorded per animal: number of cysts, volume of cysts, volume of kidneys, and HU of cysts and kidneys.

Animals were killed with 10 mL of Fatal Plus (Vortech Pharmaceuticals, Dearborn, MI). On necropsy, kidneys were macroscopically examined for any gross abnormalities and photographed (Canon Rebel T5i EOS 700D; Tokyo, Japan). Harvested kidneys were weighed, and when possible, cystic fluid was collected via a 16-gauge needle, with subsequent excision of the cyst cavity for histological analysis.

Renal tissue including cysts were preserved in 10% neutral-buffered formalin for a minimum of 48 hours, embedded in paraffin wax, and sectioned into 4 μm slices. Hematoxylin and eosin (H&E), Masson's Trichrome staining, and terminal deoxynucleotidyl transferase (TdT) dUTP Nick-End Labeling (TUNEL) staining were performed according to the manufacturer's instructions (Sigma Life Science, St. Louis, MI), and cover-slipped with mounting media containing DAPI (Vector Labs, Burlingame, CA). Images were acquired using a Carl Zeiss Observer D1 microscope (Carl Zeiss, Thornwood, NY).

2.3 | Statistical analysis

GraphPad Prism was used for statistical analysis and graphical representation of data. Serum and urine chemistry data were tested for normality with D'Agostino and Person normality tests. Data were compared between animals with and without cysts via a two-tailed, unpaired Student's *t* test, or Mann-Whitney test, as appropriate. All data were presented as mean ± standard error of the mean (SEM). The significance was set at $P < .05$.

3 | RESULTS

3.1 | Computed tomography angiography detection of renal cysts

Coronal and axial slices of CT scans as well as 3D reconstruction of kidneys without (A-C) and with cysts (D-I) are shown in Figure 1. Of the 54 animals, 17 had at least 1 cyst (range 1-6) that was identified using CT angiography (31% prevalence). Each of the 17 animals is represented in Table S1, which includes cyst frequency and volume. Of these animals, a total of seven pigs had more than one cyst present in either kidney. Of note, there was no tendency for kidneys from either side to contain cysts more often, as five animals had cysts in both kidneys, seven animals had cysts in the left kidney, and five had cysts in the right kidney. Moreover, a total of 16 cysts were found in right kidneys and 19 cysts were found in left kidneys. There was also no difference in size (3.2 ± 1.3 mL vs 1.6 ± 0.4 mL, $P = .27$) or density (22.3 ± 2.5 HU vs 20.5 ± 1.7 HU, $P = .57$) between left and right kidneys.

The average kidney volume was comparable between animals without (113.40 ± 2.26 mL) and with renal cysts (117.50 ± 2.55 mL; $P = .24$). The volume of the cysts was variable and ranged from 0.09 to 21.02 mL, with the 0.09 mL cyst visualized in the superior portion of the left kidney in Figure 1I. The average percentage of kidney volume taken up by cysts was 2%, with the smallest percent detected was 0.11% and the highest 8.32%. Average Hounsfield units (HU) of kidneys was 113.30 ± 2.06 in animals without cysts and 111.09 ± 2.23 HU in animals with cysts ($P = .48$). Additionally, the HU of all cysts averaged 21.48 ± 1.57 HU. All cysts were grouped into <20 HU or >HU according to the density of water. More dense cysts (> 20 HU) were much smaller in size (0.63 ± 0.23 mL) when compared with less dense cysts (3.94 ± 1.22 mL; $P = .028$).

3.2 | Macroscopic morphological abnormalities of the kidneys

The majority of kidneys without cysts appeared normal in shape and color. Alternatively, 2 of the 17 (11%) animals whose kidneys had cyst demonstrated abnormal morphology of the kidneys macroscopically. In both cases, the right kidney weighed more than the left kidney (93 vs 84 g and 150 vs 126 g). More notable was the irregular shape, wherein the superior end of individual animals' right kidney showed an abnormal lack of elongation and blunting of the end (Figure 2A and C, B and D). In the majority of animals with at least one cyst, no apparent abnormalities were noted (Figure 3A) at necropsy and, if not for CT (Figure 3B) or bilateral dissection (Figure 3C), the cyst may otherwise not have been identified. However, in some instances, the wall of the cyst was easily visible near the entrance of the renal artery (Figure 3D; right kidney dorsal side). In this animal, CT demonstrated a single large cyst (Figure 3E) which was easily located upon dissection (Figure 3F).

3.3 | Renal function biochemistry data

Serum (Table 1) and urine (Table 2) were collected immediately after CT was performed for quantification of renal function. Values of blood urea nitrogen, creatinine, albumin, total protein, glucose, and WBCs in the blood were not different between animals with cyst(s) and those without, and all values were within normal range

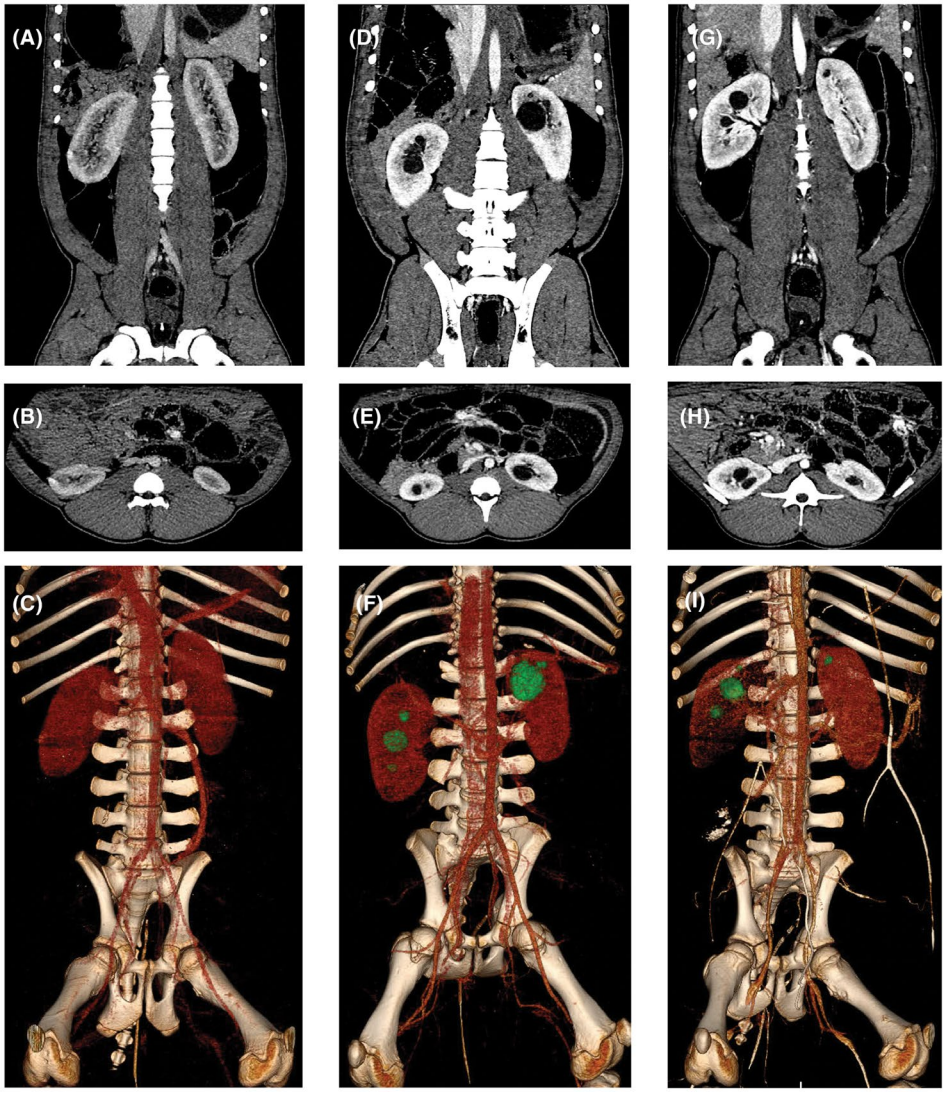

FIGURE 1 Axial (A) and coronal (B) CT scans in an animal without cysts in the kidney. (C) 3D reconstruction of bone, vasculature, and kidneys in the same animal. (D-F) Axial, coronal, and 3D scans views in animal #1 showing five of the six total cysts. (G-I) Animal #2, axial, coronal and 3D scans showing all four cysts

($P \geq .24$). In the urine, differences between animals with cysts and those without were only detected for glucose ($P = .032$). However, there was a tendency for sodium ($P = .071$) to be higher, and urea nitrogen ($P = .102$) to be less in animals with cysts than those without. Alternatively, uric acid ($P = .493$), potassium ($P = .195$), protein ($P = .144$), or creatinine ($P = .283$) were not different.

3.4 | Cystic fluid biochemical data

Values of urea nitrogen, sodium, potassium, uric acid, amylase, protein, glucose, and creatinine in the cystic fluid aspirated from two large cysts were all within normal physiological parameters (Table 3). One animal had a fluid/serum sodium ratio of 0.39 and the second had 0.12, categorizing both as a distal/gradient cyst based on the <0.4 cystic fluid/serum sodium ratio.[23]

3.5 | Histopathological analysis

Microscopic characterization was performed with H&E and Masson's Trichrome. Figure 4A demonstrates a cyst that markedly compresses the adjacent cortex. The cyst is lined by a single layer of flattened epithelium, bounded by fibrous connective tissue which often extends into the parenchyma. In these areas, there is tubular atrophy and degeneration (Figure 4B). In addition, the parenchyma is infiltrated by variable numbers of lymphocytes and plasma cells. Figure 4C demonstrates staining of the fibrous connective tissue surrounding the cyst and replacing the existing parenchyma. TUNEL staining reveals that some, but not all, epithelial cells undergo an appreciable measure of apoptosis shown in different magnifications (ie, 200x (Figure 5D-F) and 1000x (Figure 5G-I). This was not apparent in adjacent tubules not associated with a cyst from the same animal (Figure 5A-C).

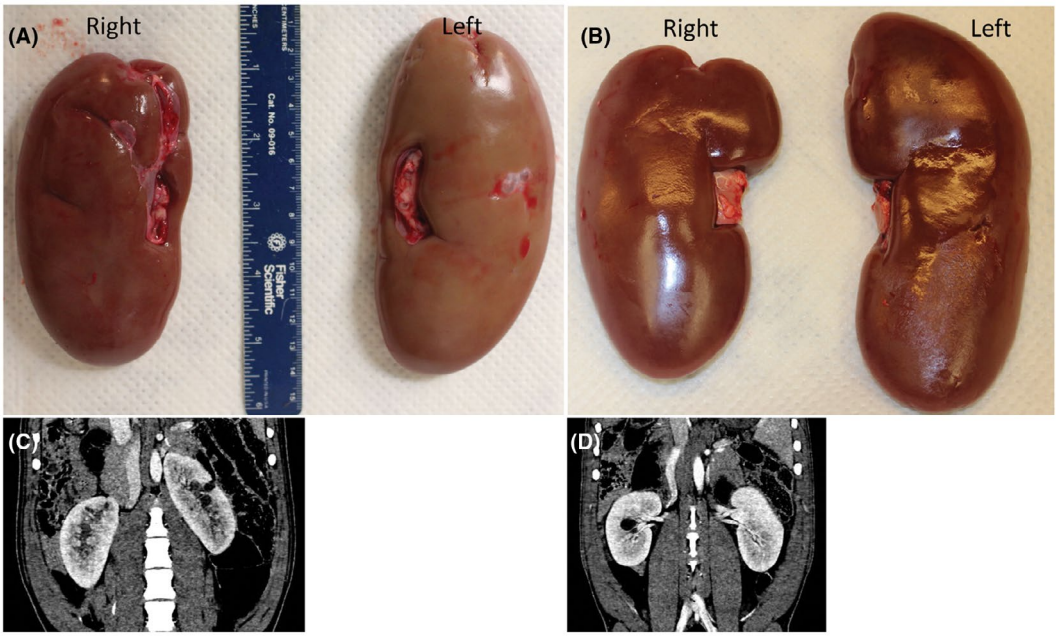

FIGURE 2 A and B, Kidneys are irregular in shape, wherein the superior end of individual animals' right kidney showed an abnormal lack of elongation and blunting. C and D, Coronal scans of demonstrating location of cysts within kidney that are not visible at a macroscopic level

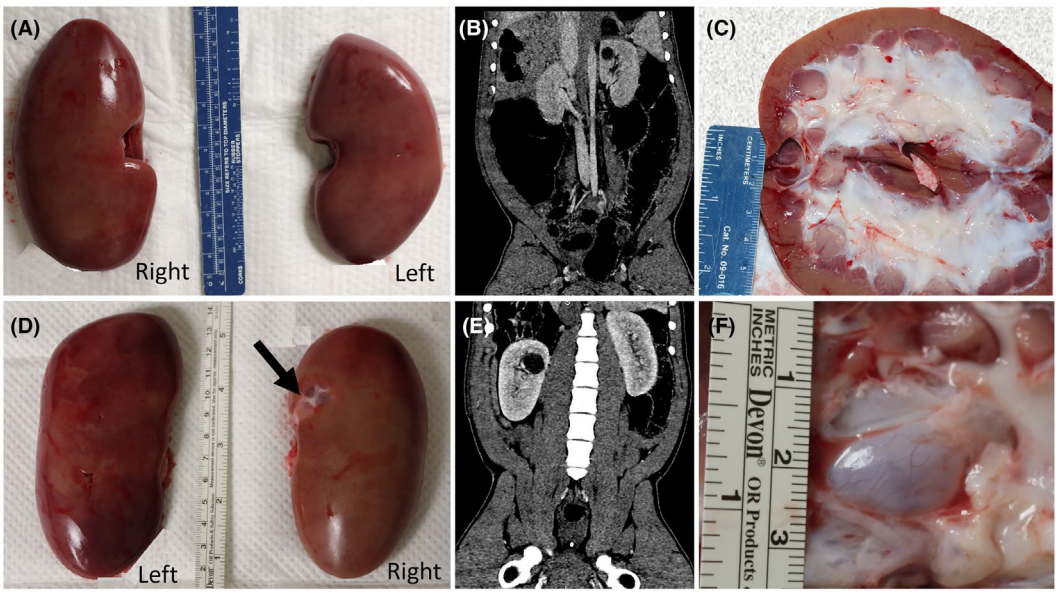

FIGURE 3 (A) Excised kidneys of animal with no visual abnormalities, but coronal CT (B) and dissection (C) indicate presence of a cyst. (D) Cyst wall is visible on right kidney, and (E) coronal scan aligns with location of cyst. (F) Dissection of the right kidney to expose cyst wall

TABLE 1 Serum Biochemistry Differences in Animals with and without Cysts. Serum was collected immediately after CT. Values of blood urea nitrogen, creatinine, albumin, total protein, glucose, and WBCs in the blood were not different between animals with cysts and those without (normal) and all values were within normal range ($P \geq .24$)

Kidney	BUN mg/dL	Creatinine mg/dL	Albumin g/dL	TP g/dL	Glucose mg/dL	WBC $10e^3/\mu L$
Normal	8.11 ± 0.43	1.25 ± 0.03	1.05 ± 0.04	5.54 ± 0.08	65.15 ± 3.20	17.88 ± 0.50
Cystic	8.82 ± 0.59	1.31 ± 0.05	1.01 ± 0.06	5.38 ± 0.12	66.38 ± 4.64	17.19 ± 0.81
P value	.33	.30	.58	.24	.83	.45

Abbreviations: BUN, blood urea nitrogen, TP, total protein, WBC, white blood cells.

TABLE 2 Urine Biochemistry Differences in Animals with and without Cysts. Urine was collected via a Foley catheter during CT procedure. Differences between animals with cysts and those without (normal) were detected in some urinary biochemical markers

Kidney	UN mg/dL	Na mmol/L	K mmol/L	URCA mg/dL	Amylase U/L	Protein mg/dL	Glucose mg/dL	Creatinine mg/dL
Normal	277.7 ± 27.09	42.00 ± 4.77	55.93 ± 4.39	3.466 ± 0.41	260.3 ± 56.28	17.06 ± 2.49	15.66 ± 1.85	83.42 ± 9.36
Cystic	400.8 ± 64.23	28.44 ± 4.34	76.12 ± 11.82	3.667 ± 0.49	270.1 ± 72.19	19.17 ± 2.603	25.02 ± 4.24	100.8 ± 12.94
P value	.10	.07	.20	.49	.67	.14	.03	.28

Abbreviations: K, potassium; Na, sodium; UN, urea nitrogen; URCA, uric acid.

4 | DISCUSSION

Yorkshire swine are often used for various research models including xenotransplantation, hemorrhage, and burn. At the United States Army Institute of Surgical Research, trauma studies often examine organ dysfunction (including acute kidney injury)[24] and animals frequently undergo postmortem evaluation of organs following a research study. Anecdotally, renal cysts have been reported, with not much information on how they may affect kidney function. The objective of this study was to identify how often the presence of cysts occurs in this animal population. The salient findings of the current report are that renal cysts occur in approximately one-third of swine kidneys from a single research breeder. Moreover, while these cysts vary in size and perfusion, they do not seem to adversely affect kidney function.

Renal function biomarkers (i.e., creatinine, BUN) quantified in the serum did not demonstrate differences in the presence of cysts. However to unequivocally measure renal function, diagnostic tests to measure glomerular filtration rate must be performed, which was not feasible for this study. Reportedly, the frequent observation in pigs is single or few unilocular, bilateral cortical cysts, with an approximate size of 1-2 cm in diameter.[25] The cyst incidence in this study is similar to a single herd of livestock swine which were found in 47.5% of the animals.[19] However, there was notable variability in animals in terms of the number and volume of cysts, while there was no difference in cyst incidence or size in left or right kidneys.

It is possible that the variability in severity of cyst development in these animals may reflect separate etiologies that include varying degrees of genetic or environmental influences. Unfortunately, the lack of genetic testing and breeding records on the animals in this study (as well as their dams and sires) prevents diagnosing the kidney cysts as a hereditary disease. Therefore, if renal cystic disease identified in these animals is due to an autosomal dominant trait as seen in humans' remains to be supported. However, if these animals presented with something analogous to autosomal recessive polycystic kidney disease in humans, this would most likely be associated with renal failure. While we did not identify renal dysfunction, it is not known whether this condition would progress to renal failure, as is seen in human cystic disease.

Age of these animals is also a consideration, and whether formation of cysts developed in utero or after birth is unknown. The animals' young age (<6 months) and the large size of some cysts (up to 14.5 mL) would suggest that formation may have started in utero; however, in human patients, cyst size progression occurs more rapidly in younger patients.[26] These lesions may be inherited as an autosomal dominant trait, and polygenic inheritance may influence the total number of cysts in animals with the dominant gene, which may also increase in number with increasing age.[25] If these swine were allowed to reach adulthood, it is likely that cyst development and fibrosis would progress, which could negatively affect kidney function. Additionally, it is difficult to diagnose if the condition would remain simple, if multiple cysts would arise, or if there would be development into a more serious abnormality later in life. Although it may be speculated that the

TABLE 3 Individual biochemical values of the cystic fluid aspirated from two large cysts at necropsy. Urea nitrogen, sodium, potassium, uric acid, amylase, protein, glucose, and creatinine were all within normal physiological parameters for urine

Animal ID	UN mg/dL	Na mmol/L	K mmol/L	URCA mg/dL	Amylase U/L	Protein mg/dL	Glucose mg/dL	Creatinine mg/dL
9	126.3	56	15.4	1.2	387	24.1	5	43.08
14	68.9	27	44.2	3.9	128	18.6	21	77.6

Abbreviations: K, potassium; Na, sodium; UN, urea nitrogen; URCA, uric acid.

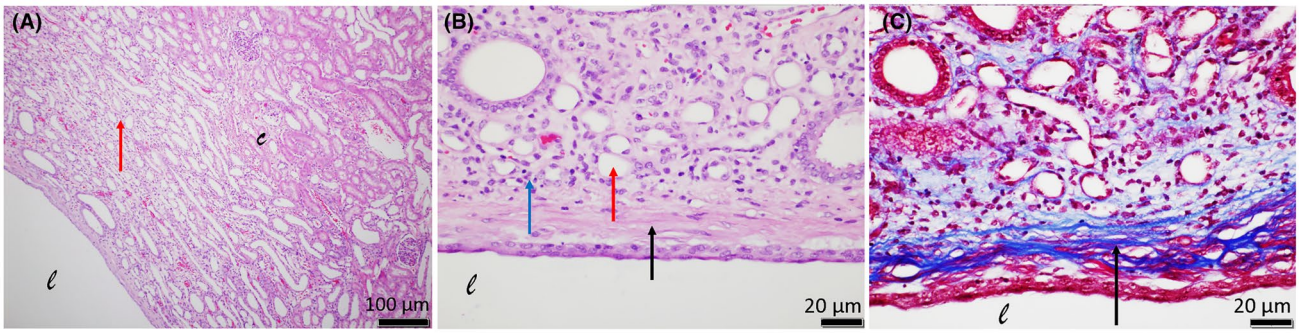

FIGURE 4 A, Female Yorkshire pig renal cyst H&E stain at low magnification shows that the cyst markedly compresses the adjacent cortex (*c*). Note the atrophic tubules (red arrow) in the cortex. Cyst lumen (*l*). B, H&E and (C) Masson's Trichome shows an epithelial lined cyst bounded by fibrous connective tissue (black arrow) which extends into the parenchyma. Note the atrophic tubules (red arrows) and lymphoplasmacytic inflammation (blue arrow)

occurrence of kidney cysts in swine may be hereditary, it is important to recognize all underlying predispositions for the formation of renal cysts early in adolescence.

The use of CT also allows for a detailed image of bone, soft tissues, and (with contrast) blood vessels so that animals can further be tested for appropriateness for use in research studies. Although less cost-effective than ultrasonography, the use of CT also allows for a noninvasive method of gathering detailed kidney morphology. The identification and characterization of renal cysts in swine is advantageous to classify if the animal is suitable for studying AKI. The current practice for classification of common renal cystic lesions by radiologists and urologists requires soft-tissue imaging methods. In 1986, Bosniak[7] developed a set of a criteria based off of CT imaging to classify renal cysts into one of five categories. According to the Bosniak classification, all of the cysts identified in this study would fall into category I as they were round in shape, and simple with no imperceptible wall. Additionally, cysts identified in this study lacked calcification. Category II includes cysts that are septated, minimally calcified, infected, or are high density. Although one cyst whose wall was visualized from the outside of the intact kidney possibly appeared to be partitioned by a septum (Figure 3D), this was not visualized on CT (Figure 3E). Therefore, none of the cysts in the swine demonstrated any of the category II attributes according to their CT angiography. Category IIF cysts are subjectively difficult to differentiate from II, but have been crucial for treatment regimes. Category III includes lesions that contain a thickened wall with or without fibrosis and septations with the possibility of calcification.

Furthermore, the criteria for diagnosis of a cyst using CT according to Bosniak[7] requires density of the fluid to be homogenous throughout in the absence of contrast. However, all animals in this study received contrast before imaging, and thus the average HU of all renal cysts identified was 21.48 ± 1.57 HU (i.e., higher than water). Additionally, since there was not a pre-contrast scan it is unknown if there was a slight enhancement of density following administration of the contrast dye. There was, however, a size association wherein the larger the cyst, the lower the HU ($R = 0.175$; $P = .013$). Cysts that had less than 20 HU were significantly larger (3.94 ± 1.22 mL) than those that were greater than 20 HU (0.63 ± 0.23 mL; data not shown). Since the lesions are round and fluid-filled, this would suggest the regions are cystic and not a renal carcinoma. As mentioned previously, whether this condition would progress with increasing age of the animal remains unknown.

Researchers have put effort into characterizing the composition of the cystic fluid within kidneys.[27,28] Urea nitrogen, sodium, potassium, uric acid, amylase, protein, glucose, and creatinine levels were quantified in the cystic fluid, which were within normal physiologic ranges. The sodium content within the cyst would indicate the location of the cyst would be categorized as distal/gradient.[28] Therefore, the cells surrounding the cyst wall would be functioning similar to those in distal nephrons which, on examination of its location, were found in the cortex (Figure 3C). Additionally, glucose values of the cystic fluid are lower than what was collected in the urine suggesting there is no concentrating of fluid within the cyst, and decent exchange of fluid.

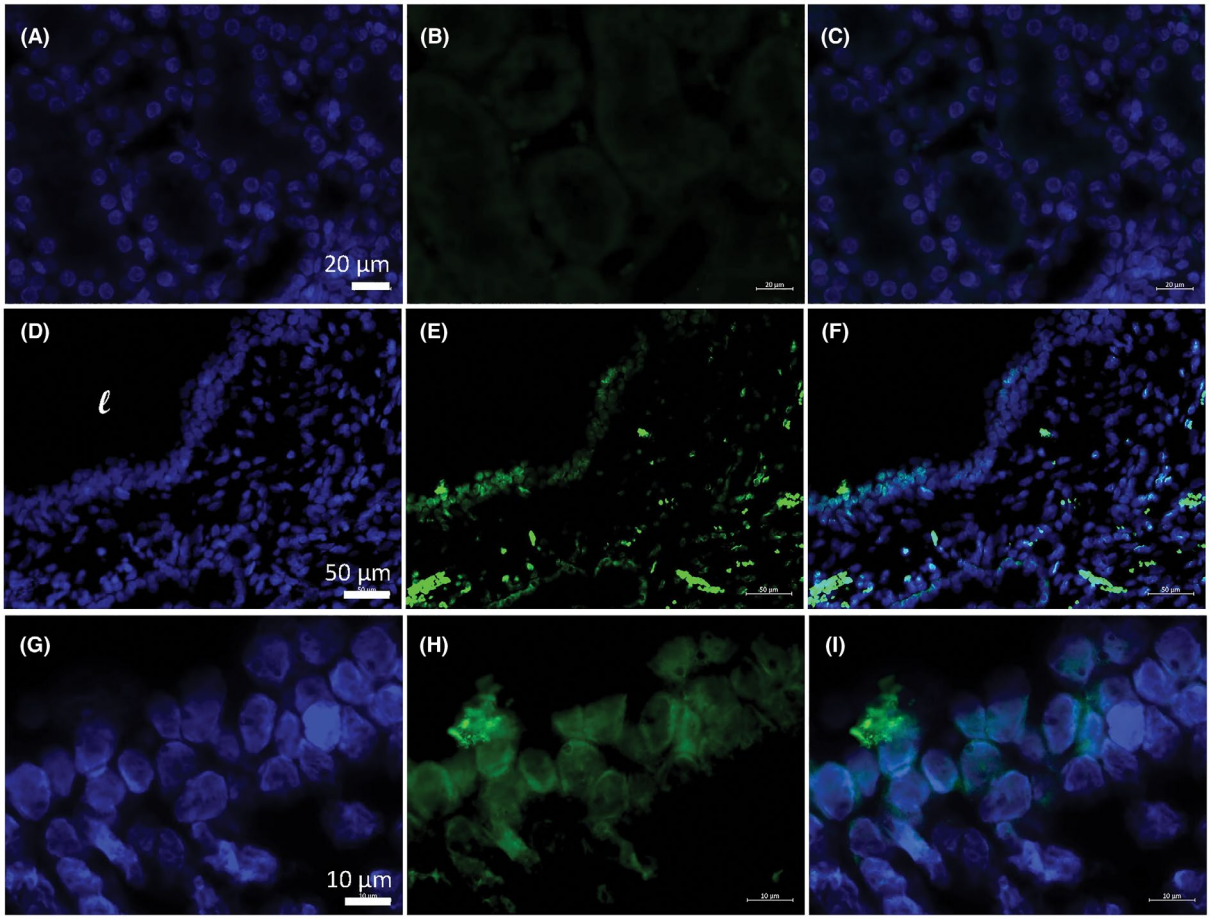

FIGURE 5 TUNEL and DAPI staining was performed to identify apoptotic cells in the renal cyst of a female Yorkshire pig. A 400x image of adjacent renal tubules not associated with the cyst has been provided as an internal negative control (A-C). (D) DAPI, (E) TUNEL, and (F) merge of an epithelial layer containing apoptotic cells. Higher magnification images of this epithelium is shown in (G-I). (*l*) indicates the lumen

There are certain limitations to this study that need mentioning. First, diet before arrival at our institute was not available, which may contribute to undesirable formation of cysts. For example, ingestion of diphenylamine, a pesticide by the pregnant dam, has been shown to cause polycystic syndrome in newborn rats.[29] Importantly, only one breed, age group, and gender were examined. In humans, the incidence of cyst are more common in men[11,26]; therefore, if this holds true in male Yorkshire swine remains unknown. Also, due to cyst size and blind dissections, cystic fluid was not able to be aspirated from a large number of cysts. Finally, due to cost considerations, these animals and the progression of renal cysts were not followed across time.

5 | CONCLUSION

The past and current research demonstrate swine are a viable model for investigation of kidney disease and injury. Previous necropsy of swine within the institute suggested kidney abnormalities that warranted further controlled investigation of incoming animals. Data presented here describe the incidence of kidney cysts in a relevant biomedical research animal population; CT detected renal cysts in 31% of swine. Since preexisting renal dysfunction can confound outcomes after certain insults, the lack of association between cysts and kidney function is encouraging. However, because of the association between renal cyst and abnormalities of renal function, researchers should be aware of the potential variability that may be introduced, especially when renal function is an outcome.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

BIG and DMB conceived and designed the research. BIG, JSL, AJL, and DMB performed the experiments. BIG, JSL, and AJL analyzed the data. BIG, IJS, and DMB interpreted results of the experiments.

BIG, AJL, and DMB prepared the figures. BIG drafted the manuscript. All authors edited, revised, and approved the final version of manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Prior to the commencement of this investigations, approval was obtained from the institutional Care and Use Committee (IACUC), US Army Institute of Surgical Research.

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REFERENCES

1. Zerres K, Mucher G, Becker J, et al. Prenatal diagnosis of autosomal recessive polycystic kidney disease (ARPKD): molecular genetics, clinical experience, and fetal morphology. *Am J Med Genet*. 1998;76(2):137-144.
2. McHugh K, Stringer DA, Hebert D, Babiak CA. Simple renal cysts in children: diagnosis and follow-up with US. *Radiology*. 1991;178(2):383-385.
3. Fick GM, Duley IT, Johnson AM, Strain JD, Manco-Johnson ML, Gabow PA. The spectrum of autosomal dominant polycystic kidney disease in children. *J Am Soc Nephrol*. 1994;4(9):1654-1660.
4. Gabow PA, Chapman AB, Johnson AM, et al. Renal structure and hypertension in autosomal dominant polycystic kidney disease. *Kidney Int*. 1990;38(6):1177-1180.
5. Baert L, Steg A. On the pathogenesis of simple renal cysts in the adult. A microdissection study. *Urol Res*. 1977;5(3):103-108.
6. Laucks SP Jr, McLachlan MS. Aging and simple cysts of the kidney. *Br J Radiol*. 1981;54(637):12-14.
7. Bosniak MA. The current radiological approach to renal cysts. *Radiology*. 1986;158(1):1-10.
8. Parfrey PS, Bear JC, Morgan J, et al. The diagnosis and prognosis of autosomal dominant polycystic kidney disease. *N Engl J Med*. 1990;323(16):1085-1090.
9. Al-Said J, Brumback MA, Moghazi S, Baumgarten DA, O'Neill WC. Reduced renal function in patients with simple renal cysts. *Kidney Int*. 2004;65(6):2303-2308.
10. Kong X, Ma X, Zhang C, Su H, Gong X, Xu D. Increased risk of kidney damage among Chinese adults with simple renal cyst. *Int Urol Nephrol*. 2018;50(9):1687-1694.
11. Rule AD, Sasiwimonphan K, Lieske JC, Keddis MT, Torres VE, Vrtiska TJ. Characteristics of renal cystic and solid lesions based on contrast-enhanced computed tomography of potential kidney donors. *Am J Kidney Dis*. 2012;59(5):611-618.
12. Qiu W, Jiang Y, Wu J, et al. Simple cysts in donor kidney contribute to reduced allograft function. *Am J Nephrol*. 2017;45(1):82-88.
13. Giraud S, Favreau F, Chatauret N, Thuillier R, Maiga S, Hauet T. Contribution of large pig for renal ischemia-reperfusion and transplantation studies: the preclinical model. *J Biomed Biotechnol*. 2011;2011:532127.
14. He J, Ye J, Li Q, et al. Construction of a transgenic pig model overexpressing polycystic kidney disease 2 (PKD2) gene. *Transgenic Res*. 2013;22(4):861-867.
15. Waltz E. When pig organs will fly. *Nat Biotechnol*. 2017;35(12):1133-1138.
16. Eaton KA, Biller DS, DiBartola SP, Radin MJ, Wellman ML. Autosomal dominant polycystic kidney disease in persian and persian-cross cats. *Vet Pathol*. 1997;34(2):117-126.
17. Monaghan ML, Hannan J. Abattoir survey of bovine kidney disease. *Vet Rec*. 1983;113(3):55-57.
18. Wells GA, Hebert CN, Robins BC. Renal cysts in pigs: prevalence and pathology in slaughtered pigs from a single herd. *Vet Rec*. 1980;106(25):532-535.
19. Wijeratne WV, Wells GA. Inherited renal cysts in pigs: results of breeding experiments. *Vet Rec*. 1980;107(21):484-488.
20. Gomez BI, McIntyre MK, Gurney JM, et al. Enteral resuscitation with oral rehydration solution to reduce acute kidney injury in burn victims: Evidence from a porcine model. *PLoS One*. 2018;13(5):e0195615.
21. Hajjar K, Bou Chebl R, Kanso M, Abou DG. Autosomal dominant polycystic kidney disease and minimal trauma: medical review and case report. *BMC Emerg Med*. 2018;18(1):38.
22. Hsu CY, Ordoñez JD, Chertow GM, Fan D, McCulloch CE, Go AS. The risk of acute renal failure in patients with chronic kidney disease. *Kidney Int*. 2008;74(1):101-107.
23. Sullivan LP, Wallace DP, Grantham JJ. Chloride and fluid secretion in polycystic kidney disease. *JAm Soc Nephrol*. 1998;9(5):903-916.
24. Burmeister DM, Gomez BI, Dubick MA. Molecular mechanisms of trauma-induced acute kidney injury: Inflammatory and metabolic insights from animal models. *Biochim Biophys Acta (BBA) Mol Basis Dis*. 2017;1863(10 Pt B):2661-2671.
25. Cianciolo RE, Mohr CF, In: Maxie MG, Urinary System. ed. *Jubb, Kennedy, and Palmer's pathology of domestic animals*. Vol 2. 6th ed. Philadelphia, PA: Elsevier; 2016:376-464.
26. Terada N, Ichioka K, Matsuta Y, Okubo K, Yoshimura K, Arai Y. The natural history of simple renal cysts. *J Urol*. 2002;167(1):21-23.
27. Bricker NS, Patton JF. Cystic disease of the kidneys; a study of dynamics and chemical composition of cyst fluid. *Am J Med*. 1955;18(2):207-219.
28. Gardner KD Jr. Composition of fluid in twelve cysts of a polycystic kidney. *N Engl J Med*. 1969;281(18):985-988.
29. Crocker JF, Brown DM, Borch RF, Vernier RL. Renal cystic disease induced in newborn rats by diphenylamine derivatives. *Am J Pathol*. 1972;66(2):343-350.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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