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
INTRODUCTION

The presence of cysts in the kidney is recognized as an abnormal sac formation derived from the renal tubule and filled with urinary-like fluid. Renal cystic disease may arise from a variety of etiologies (e.g., 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, childhood, or adulthood 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. 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, proteinuria, decreased estimated glomerular filtration rate, and increased albuminuria, hypertension, and hyperfiltration. Moreover, simple cysts can potentially reduce allograft function in transplant recipients 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. Because of this, transgenic mini-pig models for polycystic kidney disease were developed as an alternative to rodents. Furthermore, transplant models are of particular interest, and genetic alterations have brought about the distinct possibility of xenotransplantation.

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 polycystic kidney disease is hereditary and results in a variable number of cysts within the cortex and medulla. In swine where breeding is often limited, renal cysts may be an early determinant of kidney disease, these underlying 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). However, preexisting renal dysfunction has been associated with an increased risk of subsequent AKI. 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.

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 H₂O, and respiration rate of 8-10 breaths/min. End-tidal PCO₂ 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 Iovue-370 (BIPSO GmbH, Singen, Germany; generic name: iodipamidol; 755 mg/mL; contains sodium 0.053 mg, organically bound iodine 370 mg/mL) was injected into a cathetered lateral auricular vein. All CT scans were performed using a Toshiba Aquilion 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 (Bayer 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
The significance was set at \( P = 0.05 \).

Data were presented as mean \pm standard error of the mean (SEM). More dense cysts (> 20 HU) were much smaller in size (0.63 \pm 0.23 mL) when compared with less dense cysts (3.94 \pm 1.22 mL; \( P = 0.028 \)).

The average kidney volume was comparable between animals without (113.40 \pm 2.26 mL) and with renal cysts (117.50 \pm 2.55 mL; \( P = 0.24 \)). 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 \pm 2.48 HU. All cysts were grouped into density of water. More dense cysts (> 20 HU) were found in right kidneys and 19 cysts were found in left kidneys. 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 \pm 1.3 mL vs 1.6 \pm 0.4 mL, \( P = 0.27 \)) or density (22.3 \pm 2.5 HU vs 20.5 \pm 1.7 HU, \( P = 0.57 \)) between left and right kidneys.

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### 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.
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.

### 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.

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 ≥ .24). 

| Kidney | BUN mg/dL | Creatinine mg/dL | Albumin g/dL | TP g/dL | Glucose mg/dL | WBC 10e3/µL |
|--------|-----------|------------------|--------------|---------|---------------|--------------|
| 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.
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) 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. The cyst incidence in this study is similar to a single herd of livestock swine which were found in 47.5% of the animals. 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. 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. 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
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 developed a set of criteria based on 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 IIIF 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 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 $\pm$ 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 ($R = 0.175; P = 0.013$). Cysts that had less than 20 HU were significantly larger (3.94 $\pm$ 1.22 mL) than those that were greater than 20 HU (0.63 $\pm$ 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. Urea nitrogen, sodium, potassium, uric acid, amylase, protein, glucose, and creatinine were all within normal physiological parameters for urine.

### TABLE 3

| 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).
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. Importantly, only one breed, age group, and gender were examined. In humans, the incidence of cyst are more common in men; 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 investigation, approval was obtained from the institutional Care and Use Committee (IACUC), US Army Institute of Surgical Research.

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

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