Title
Predictors of Progression to Liver Transplantation Among Post-Renal Transplants Patients with Autosomal Recessive Polycystic Kidney Disease (ARPKD) and Congenital Hepatic Fibrosis (CHP)

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Author
Mangahas, Micheal F

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Predictors of Progression to Liver Transplantation Among Post-Renal Transplants Patients with Autosomal Recessive Polycystic Kidney Disease (ARPKD) and Congenital Hepatic Fibrosis (CHF)

By

Michael Francis Mangahas

A thesis submitted in partial satisfaction of the requirements for the degree of

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In

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In the

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Of the

University of California, Berkeley

Committee in charge:

Professor John S. Swartzberg M.D.
Professor John Balmes M.D.
Professor Doug Jutte M.D.

Spring 2013
To my wonderful research team at UCSF: Emily Perito Rothbaum, MD and Sue Rhee, MD – for introducing me to the world of rare kidney and liver disorders, for pushing me to pursue research in unknown territories, and for your expertise and encouragement. To David L. Thomas, for the invaluable help in locating archived medical charts, deep in the dark recesses of UCSF Medical Storage and Archives. To my thesis committee, John E. Swartzberg, MD; John Balmes, MD; and Doug Jutte, MD, for all of their mentorship and guidance in seeing this to completion. And last but not least, this thesis is dedicated to my family: to my mother and brother – who knew that this insatiable curiosity and refusal to accept the easy answers would serve me well one day. Thank you for challenging me to be the best I can be, to never settle for anything less, and to work hard and work honestly.
Glossary of Terms:

1. ARPKD – abbreviation of **autosomal-recessive polycystic kidney disease**.

2. CHF – abbreviation of **congenital hepatic fibrosis**: a developmental disorder of the liver marked by formation of irregular broad bands of fibrous tissue containing multiple cysts formed by disordered terminal bile ducts, resulting in vascular constriction and portal hypertension.

3. Cholangitis: inflammation of one or more bile ducts—also called “angiocholitis”.

4. Cholestasis: stoppage or suppression of bile flow, having intrahepatic or extrahepatic causes.

5. Sepsis: a systemic response typically to an infection (as of the abdomen or lungs) usually of bacterial origin that is usually marked by abnormal body temperature and white blood cell count, tachycardia, tachypnea, and hypotension. Specifically: systemic inflammatory response syndrome induced by a documented infection.

6. Varix (plural: varices): an abnormally dilated and lengthened vein, artery, or lymph vessel. Varices are at risk of rupturing and causing severe acute blood loss.

7. Ductal Plate: An embryonic precursor to the hepatic portal triad. The ductal plate is comprised of mesenchymal cells that will differentiate into the portal vein/venules, the hepatic arteries, and a bile duct/ductile.

8. Portal Hypertension: an increased venous pressure in the portal circulation caused by compression or occlusion in the portal or hepatic vascular system. It results in splenomegaly, large collateral veins, ascites, and, in severe cases, esophageal varices. Portal hypertension is frequently associated with cirrhosis.

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2 Source: Dorland's Medical Dictionary for Health Consumers. © 2007 by Saunders
3 Source: http://www.merriam-webster.com/medical/cholangitis
4 Source: Dorland's Medical Dictionary for Health Consumers. © 2007 by Saunders, an imprint of Elsevier, Inc
5 Source: http://www.merriam-webster.com/medical/sepsis
7 Leonis and Balistreri, “Evaluation and Management of End-Stage Liver Disease in Children..”
8 Desmet, “Ludwig Symposium on Biliary Disorders--Part I. Pathogenesis of Ductal Plate Abnormalities..”
9. Hypoplasia\textsuperscript{10}: a condition of arrested development in which an organ or part remains below the normal size or in an immature state.

10. Splenomegaly\textsuperscript{11}: abnormal enlargement of the spleen

11. Hepatomegaly\textsuperscript{12}: enlargement of the liver

12. Hepatosplenomegaly\textsuperscript{13}: coincident enlargement of the liver and spleen

13. Thrombocytopenia\textsuperscript{14}: decrease in number of platelets in circulating blood

14. Hypersplenism\textsuperscript{15}: a condition marked by excessive destruction of one or more kinds of blood cells in the spleen

15. ESRD: abbreviation – \textit{end-stage renal disease}

16. ESLD: abbreviation – \textit{end-stage liver disease}

17. Ectasia\textsuperscript{16}: the expansion of a hollow or tubular organ

18. Dysgenesis\textsuperscript{17}: defective development especially of the gonads (as in Klinefelter’s syndrome or Turner’s syndrome) – in this literature review, it is used in relation to biliary dysgenesis, or defective development of the biliary system.

19. ECM – Extracellular matrix\textsuperscript{18}: any substance produced by cells and excreted to the extracellular space within the tissues, serving as a scaffolding to hold tissues together and helping to determine their characteristics.

20. HSPG - heparan sulfate\textsuperscript{19}: a glycosaminoglycan occurring in the cell membrane of most cells, consisting of a repeating disaccharide unit of glucosamine and uronic acid residues, which may be acetylated and sulfated;

\textsuperscript{10} Source: http://www.merriam-webster.com/medical/hypoplasia
\textsuperscript{11} Source: Dorland’s Medical Dictionary for Health Consumers. © 2007 by Saunders, an imprint of Elsevier, Inc
\textsuperscript{12} Source: Dorland’s Medical Dictionary for Health Consumers. © 2007 by Saunders, an imprint of Elsevier, Inc
\textsuperscript{13} Source: Dorland’s Medical Dictionary for Health Consumers. © 2007 by Saunders, an imprint of Elsevier, Inc
\textsuperscript{14} Source: Dorland’s Medical Dictionary for Health Consumers. © 2007 by Saunders, an imprint of Elsevier, Inc
\textsuperscript{15} Source: http://www.merriam-webster.com/medical/hypersplenism
\textsuperscript{16} Source: http://www.merriam-webster.com/medical/ectasia
\textsuperscript{17} Source: http://www.merriam-webster.com/medical/dysgenesis
\textsuperscript{18} Source: Dorland’s Medical Dictionary for Health Consumers. © 2007 by Saunders, an imprint of Elsevier, Inc
\textsuperscript{19} Source: http://encyclopedia.thefreedictionary.com/Heparin+sulfate
it accumulates in several mucopolysaccharidoses. HSPG is the proteoglycan formed from heparin sulfate.

21. HSCs – Hepatic Stellate cells\(^{20}\): also known as Ito cells, lipocytes, or fat-storing cells, are pericytes found in the perisinusoidal space (a small area between the sinusoids and hepatocytes) of the liver. The stellate cell is the major cell type involved in liver fibrosis, which is the formation of scar tissue in response to liver damage.

22. LDLT – abbreviation of **living donor liver transplantation**: In this procedure a health person (usually a family member, friend, or co-worker) donates a portion of their liver to the transplant patient. One of the two lobes of the donor’s liver is removed. The recipient’s damaged liver is also removed. The healthy liver lobe is then attached in the place from which the recipient’s liver was removed. There it begins rapidly to regenerate healthy liver tissue. The donor’s liver also quickly regenerates and continues to function normally\(^{21}\).

23. DDLT – abbreviation of **deceased donor liver transplantation**: In this procedure either the whole liver or a lobe of the liver is removed from a deceased patient and transplanted in a living patient. The recipient’s damaged liver may be removed and the healthy liver transplanted in the place from which the recipient’s liver was removed. In pediatric patients, livers from adult cadaver donors can be reduced in size to fit a pediatric patient\(^{22}\).

24. Pulmonary Hypoplasia\(^{23}\) – Underdevelopment of the lungs. In APRKD, fetal kidneys fail to function properly and lead to a decrease in fetal urine output. Fetal urine output is important in regulating the level of amniotic fluid during gestation. Decrease urine output leads to decreased amniotic fluid levels inside the uterus, this condition is also known as **oligohydramnios**. Amniotic fluid contains important growth factors necessary for organ maturation, and it is also the movement of amniotic fluid in and out of the fetal lungs that allows the fetal lungs to grow and mature. Thus decreased fluid levels can lead to underdevelopment of the fetal lungs. It is hypothesized that oligohydramnios can lead to pulmonary hypoplasia by causing fetal lung compression, altering fetal lung movement, and/or decreasing perfusion and development of the lung tissue and potential airspaces themselves. This can cause significant mortality and morbidity in the neonate with ARPKD as the underdeveloped lungs lead to respiratory distress. Neonates with pulmonary hypoplasia often require mechanical


\(^{22}\) Source: [http://encyclopedia.thefreedictionary.com/Liver+transplantation](http://encyclopedia.thefreedictionary.com/Liver+transplantation)

ventilation. Respiratory insufficiency/distress secondary to pulmonary hypoplasia is a common cause of mortality within the neonatal period of life in ARPKD patients.
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      ii. Normal Development of the Biliary System – The Ductal Plate
      iii. Normal Cholangiocyte Physiology and Cellular Dysfunction in ARPKD/CHF
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Part 3: References
I. Introduction – What is ARPKD?:
Autosomal Recessive Polycystic Kidney Disease (ARPKD) is a rare genetic disorder that causes the formation of cysts within the collecting tubules of the kidney and the larger intrahepatic bile ducts in the liver. It is estimated to have a prevalence of 1:20,000-40,000 live births. Early signs are predominantly related to renal dysfunction, such as fluid overload and systemic hypertension. ARPKD carries high rates of neonatal morbidity as decreased fetal urine production leads to oligohydramnios (insufficient amniotic fluid) with resulting respiratory hypoplasia. ARPKD also has a significant neonatal mortality rate (death within the first month of life) that is estimated to be about 30-50%. The most common cause of neonatal mortality in ARPKD/CHF is respiratory insufficiency or failure. Those that survive usually require renal transplant as the cystic disease is progressive and eventually leads to kidney failure.

Complications due to liver disease become the dominant clinical feature in older children, adolescents, and adults with ARPKD as they either have milder renal disease or have undergone renal transplant. Liver manifestations of ARPKD are due to an associated disease called congenital hepatic fibrosis (CHF). CHF causes fibrosis and scarring around the peri-biliary and in the peri-portal areas of the liver thus leading to portal hypertension and associated morbidities. Liver manifestations in ARPKD/CHF are also related to an irregular development of the biliary system, or

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1 Guay-Woodford and Desmond, “Autosomal Recessive Polycystic Kidney Disease: the Clinical Experience in North America.”
3 Cole, Conley, and Stapleton, “Polycystic Kidney Disease in the First Year of Life.”
5 In utero, fetal kidneys begin to excrete urine in the second trimester. Fetal urine output accounts for about 70 – 80% of the amniotic fluid volume. Amniotic fluid is essential for the normal development of the fetal lungs, thus when fetal urine output is decreased oligohydramnios develops and can lead to underdevelopment of the fetal lungs.
6 Zerres et al., “Prenatal Diagnosis of Autosomal Recessive Polycystic Kidney Disease (ARPKD): Molecular Genetics, Clinical Experience, and Fetal Morphology.”
7 Guay-Woodford and Desmond, “Autosomal Recessive Polycystic Kidney Disease: the Clinical Experience in North America.”
10 Area surrounding the smaller bile ducts in the liver.
11 Area surrounding the portal veins and venules in the liver.
biliary dysgenesis, which leads to enlarged and immature biliary vessels that compromise bile formation and flow through the liver.\textsuperscript{12}

Biliary dysgenesis in general can be classified by the location and size of biliary vessels involved. Caroli’s Disease refers to the pattern of intrahepatic dilation of the large radicles of the biliary tree with or without findings of ARPKD/CHF.\textsuperscript{13,14} Caroli initially described two variant forms of this biliary Dysgenesis: one with CHF (Caroli’s Syndrome) and one without CHF (Caroli’s Disease).\textsuperscript{15} However, Caroli’s Disease rarely occurs in the absence of CHF.\textsuperscript{16} Thus, for the purposes of this paper, the three terms: ARPKD/CHF, Caroli’s Disease, and Caroli’s Syndrome will be used interchangeably to refer to the same disease syndrome involving ARPKD, the associated congenital hepatic fibrosis (CHF) and the associated biliary Dysgenesis (Caroli’s Disease/Caroli’s Syndrome).

Congenital hepatic fibrosis (CHF) refers to the associated and specific pattern of scarring and fibrosis seen in ARPKD/CHF, but is also associated with biliary dilation of the smaller intrahepatic and intralobular biliary ducts. While CHF has been demonstrated to exist in all patients with ARPKD, it is not understood why some patients remain asymptomatic while others develop serious complications, nor the timing for the development of symptoms, or which patients will develop morbidity from liver disease. CHF includes a spectrum of pathologies with varying degrees of severity and morbidity that range from mild fibrosis of the liver to end-stage liver disease with severe portal hypertension. As a result, management of hepatobiliary disease in patients with ARPKD remains complicated and individualized.\textsuperscript{17}

In this literature review, I will focus on the pathophysiology and prognosis of patients who have predominant liver disease manifestations. I will first review normal genetics; cellular biology and physiology of the biliary system to better understand how the genetic mutation associated with ARPKD/CHF leads to the disease manifestations. I will then review the gaps in existing knowledge on the development, pathophysiology, and progression of CHF in ARPKD with a special focus on portal hypertension and associated complications such as variceal formation and bleeding. While hepatic manifestations of disease in ARPKD/CHF can also be cured with liver transplantation, to date it is not clear when liver transplants

\textsuperscript{12} Sweeney and Avner, “Diagnosis and Management of Childhood Polycystic Kidney Disease.;” Onori et al, “Polycystic Liver Diseases.;”
\textsuperscript{13} Sato, Ren, and Nakanuma, “Caroli’s Disease: Current Knowledge of Its Biliary Pathogenesis Obtained From an Orthologous Rat Model.;”
\textsuperscript{14} Sung et al, “Caroli’s Disease and Congenital Hepatic Fibrosis Associated with Polycystic Kidney Disease. a Case Presenting with Acute Focal Bacterial Nephritis.;” De Kerckhove et al, “The Place of Liver Transplantation in Caroli’s Disease and Syndrome.;” Wen, “Congenital Hepatic Fibrosis in Autosomal Recessive Polycystic Kidney Disease.”
\textsuperscript{15} Sato, Ren, and Nakanuma, “Caroli’s Disease: Current Knowledge of Its Biliary Pathogenesis Obtained From an Orthologous Rat Model.”
\textsuperscript{16} ibid.
\textsuperscript{17} Beaunoyer et al., “Optimizing Outcomes for Neonatal ARPKD.”
are indicated. This is partly because liver disease does not typically become symptomatic until later in life.

In addition, because the long-term prognosis for patients with liver disease is unknown, I will also review ten studies with retrospective and/or prospective patient data on ARPKD outcomes and mortality (Table 1). Four studies were retrospective chart reviews, one study was prospective, and five studies were mixed retrospective chart review and prospective review of patients with ARPKD. The median study follow-up time was 13 years (range: 6 - 43 years). The median sample size was 47 patients (range: 17 – 186 patients). Thus, the patient populations in all reviewed studies are relatively small given the rarity of this disease that carries a high rate of neonatal mortality. While available literature did provide good information on long-term outcomes of ARPKD (especially focused on renal functioning and improvement of systemic hypertension) information about long-term hepatic complications with ARPKD remains scant. Lastly, no studies in the reviewed literature looked at the indications for when liver transplantation may be indicated to treat liver disease in ARPKD/CHF, and no studies to date have looked at what factors may affect the progression of fibrosis in ARPKD/CHF.

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Table 1: Summary of Studies looking at ARPKD and Liver Disease (continued on next page)

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<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Sample Size</strong></td>
<td>17</td>
<td>73 (n=18 for analysis)</td>
<td>42</td>
<td>115</td>
<td>52</td>
</tr>
<tr>
<td><strong>Type of Study</strong></td>
<td>Retrospective</td>
<td>Retrospective</td>
<td>Mixed</td>
<td>Prospective</td>
<td>Mixed</td>
</tr>
<tr>
<td><strong>Age of Diagnosis</strong></td>
<td>Range: 0 – 1yr 100% &lt;1yr (inclusion criteria)</td>
<td>Range: 0 – 9yrs 78% &lt;1yr 22%&gt;1yr</td>
<td>Range: 0-14yrs 72% &lt;1yr 34% - &gt;1yr</td>
<td>Range: 0 - 21.8 yrs 74% - &lt;1yr 26% &gt;1yr</td>
<td>Range: No Data 85% &lt;1yr 15% &gt;1yr</td>
</tr>
<tr>
<td><strong>Signs of Liver Disease</strong></td>
<td>35.3% Hepatomegaly 23.5% Splenomegaly</td>
<td>No Data</td>
<td>2.4% hepatomegaly</td>
<td>5.8% hepatosplenomegaly</td>
<td>83% hepatomegaly 60% splenomegaly 23% esophageal varices 20% hypersplenism</td>
</tr>
<tr>
<td><strong>Evidence of Portal Hypertension ‡</strong></td>
<td>35%</td>
<td>11%</td>
<td>No Data</td>
<td>46%</td>
<td>23%</td>
</tr>
<tr>
<td><strong>Cause of Death</strong></td>
<td>No Data</td>
<td>No Data</td>
<td>Sepsis: 2</td>
<td>Sepsis: 3</td>
<td>Renal Failure: 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Resp. Failure: 4</td>
<td>ERSD: 1</td>
<td>Resp. Failure: 7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Renal Failure: 1</td>
<td>Other: 7</td>
<td>Variceal Bleeding: 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other: 6</td>
<td></td>
<td>Sepsis: 1</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Other: 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lost to follow-up: 5</td>
</tr>
<tr>
<td><strong>Survival Rate</strong></td>
<td>88% @1yr</td>
<td>87% @1yr</td>
<td>76% @ 1yrs</td>
<td>94% M @ 1yr</td>
<td>77% @ 1yr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>73% @ 5yrs</td>
<td>82% F @ 1yr</td>
<td>71% @ 5 yrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>94% M @ 3yrs</td>
<td>60% @ 15 yr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>79% F @ 3yrs</td>
<td></td>
</tr>
</tbody>
</table>

Resp. Failure = respiratory failure; ERSD = end-stage renal disease; M = male sex; F = female sex; yr = year; yrs = years
* Analysis of 166 patients born after January 1990
‡ Based on either: hepatomegaly, splenomegaly, directional reversal of portal venous flow on Doppler ultrasound, or presence of esophageal varices
Table 1: Summary of Studies looking at ARPKD and Liver Disease

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Sample Size</strong></td>
<td>14</td>
<td>31</td>
<td>209 (n=166 for analysis)*</td>
<td>186</td>
<td>10</td>
</tr>
<tr>
<td><strong>Type of Study</strong></td>
<td>Retrospective</td>
<td>Retrospective</td>
<td>Mixed</td>
<td>Mixed</td>
<td>Retrospective</td>
</tr>
<tr>
<td><strong>Age of Diagnosis</strong></td>
<td>Range: 0 – 7.7yrs 92.8% &lt;1yr</td>
<td>Range: 0-14 yrs 74% &lt;1yr 26% &gt;1yr</td>
<td>Range: No Data 84% &lt;1yr 16% &gt;1yr</td>
<td>Range: No Data 70% &lt;1yr 30% &gt;1yr</td>
<td>Range: 0 – 33mos 60% prenatal</td>
</tr>
<tr>
<td><strong>Signs of Liver Disease</strong></td>
<td>88% splenomegaly 67% hypersplenism 77% varices 40% GI bleeding 14% cholangitis</td>
<td>52% hepatomegaly 36% splenomegaly 44% Caroli’s disease (of 27 patients) 37% esophageal varices 6.5% liver transplant</td>
<td>3.6% cholangitis 6% variceal bleeding 4.2% liver transplant 16.2% Caroli’s disease 22.9% portal hypertension</td>
<td>21% hepatosplenomegaly 5% esophageal varices</td>
<td>30% cholangitis 60% Caroli’s disease 10% liver transplant</td>
</tr>
<tr>
<td><strong>Evidence of Portal Hypertension ‡</strong></td>
<td>50% w/in 1st year 78% of all cases at end of follow up 63% of survivors of KTX w/o liver transplantation</td>
<td>37%</td>
<td>35% of older population 15% in pts. Born after 1990</td>
<td>44%</td>
<td>60%</td>
</tr>
<tr>
<td><strong>Cause of Death</strong></td>
<td>Sepsis: 3 Liver failure: 1 Other: 1</td>
<td>Resp. failure: 4 Sepsis: 1 Lost to follow-up: 1</td>
<td>Resp. Failure: 19 Sepsis: 8 Renal Failure: 4 Other: 5</td>
<td>No Data</td>
<td>Sepsis: 1</td>
</tr>
<tr>
<td><strong>Survival Rate</strong></td>
<td>92.9% @1yr 84.8% @5yrs</td>
<td>87% @1yr 80% @9yrs</td>
<td>79% @1yr 75% @5yrs</td>
<td>85% @1yr 84% @5 yrs 82% @10yrs</td>
<td>9/10 alive at mean follow up time of 8.2 ± 5.9 yrs.</td>
</tr>
</tbody>
</table>

Resp. Failure = respiratory failure; ERSD = end-stage renal disease; M = male sex; F = female sex; yr = year; yrs = years
* Analysis of 166 patients born after January 1990
‡ Based on either: hepatomegaly, splenomegaly, directional reversal of portal venous flow on Doppler ultrasound, or presence of esophageal varices.
I.a. Liver Disease in ARPKD/CHF:
While most studies focus on renal manifestations of ARPKD because they present earlier and more dramatically, scant research has focused on the liver manifestations of the disease. Little is known about when liver manifestations first appear as well as risk factors for the most common complications of liver disease in ARPKD/CHF. There is no consensus on how to best treat and manage CHF and its complications in these patients. This research project aims to first review the existing literature on liver disease in ARPKD with a specific focus on CHF and its complications. More specifically, I will address: “Who develops portal hypertension, and at what age?” and “What are the early signs and risk factors for common complications that arise from the development of portal hypertension in ARPKD?”

I.b. Genetics and Cellular Biology of ARPKD:
In ARPKD, mutations in the polycystic kidney hepatic disease 1 gene, or PKHD1, leads to formation of abnormally functioning fibrocystin—which disrupts primary cilia functioning. PKHD1 is found on chromosome 6, at locus: 6p12.2. It is a 472 kb long gene with 67 exons that is transcribed into an mRNA strand 16,235 base pairs long. This mRNA strand is translated into a transmembrane protein of 4074 amino acids called fibrocystin. PKHD1 is highly expressed in the epithelial cells of the kidney, pancreas, and liver bile ducts. In these cells, fibrocystin is located on the apical side of the cells where it is associated with the primary cilium, basal bodies, and in small 100 nm diameter membrane-bound particles called PKD exosome-like vesicles (PKD-ELV’s). Fibrocystin is thought to play a role in normal cell signal transduction pathways that lead to regulation of proliferation of epithelial cells. Most relevant to ARPKD and CHF is the key role PKHD1 plays in the development of abnormally functioning fibrocystin.

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3 Bakeberg et al., “Epitope-Tagged Pkhd1 Tracks the Processing, Secretion, and Localization of Fibrocystin.”
5 Ward et al., “Cellular and Subcellular Localization of the ARPKD Protein; Fibrocystin Is Expressed on Primary Cilia.” Bakeberg et al., “Epitope-Tagged Pkhd1 Tracks the Processing, Secretion, and Localization of Fibrocystin.”
6 Ward et al., “Cellular and Subcellular Localization of the ARPKD Protein; Fibrocystin Is Expressed on Primary Cilia.”
7 Bakeberg et al., “Epitope-Tagged Pkhd1 Tracks the Processing, Secretion, and Localization of Fibrocystin.”
and embryogenesis of normal kidney and liver tubule formation. This occurs in the collecting ducts of the kidney and the precursor to mature bile ducts: the ductal plates of the liver.

I.b.i. Genetic Mutations and Genotype/Phenotype Correlations:
Several studies in this literature review conducted genetic testing and genotype analysis, but only one study correlated these findings to clinical outcomes, morbidity, and mortality. Bergman et al. proposed that there are two main types of mutations that lead to disease: missense mutations in the PKHD1 gene, and truncating mutations that insert a stop codon into an exon region of the PKHD1 gene. This study found that patients who were homozygous for a mutation that inserted a stop codon anywhere along the gene for PKHD1 died during the perinatal period and were thought to have severe renal disease involvement. In contrast, patients who survived the neonatal period, and/or had milder disease severity had at least one missense mutation but not two truncating stop codon mutations. Only about 10-20% of the many possible mutations are shared amongst non-consanguineous patients with ARPKD, with most mutations being unique to a single familial line.

This study also tried to compare mutations found in patients with near normal renal functioning and more severe liver related disease (n=15) versus patients who did not have significant hepatobiliary manifestations of disease (n=17) and found that missense mutations were comparatively distributed between the two groups (70% vs. 78%) However, the authors concluded that given the small sample size it was not possible to detect any significant findings. Currently 252 expected mutations linked to the development of ARPKD exist, but in this study only 76.6 percent of these mutations were actually detected by current methods in patients who survive the neonatal period, suggesting that mutation detection rates still are low with the current methodologies. This suggests that future research is still needed to understand the clinical manifestations of the multiple genotype variants of ARPKD.

The most prevalent single mutation identified in this study was a substitution of a cytosine to thymine (c.107C>T), which codes for a missense codon. This mutation

8 Bergmann, Senderek, Windelen, Küpper, Middendorf, Schneider, Dornia, Rudnik-Schöneborn, Konrad, Schmitt, Seeman, Neuhaus, Vester, Kürfel, Büttner, Zerres, APN (Arbeitsgemeinschaft für Pädiatrische Nephrologie), “Clinical Consequences of PKHD1 Mutations in 164 Patients with Autosomal-Recessive Polycystic Kidney Disease (ARPKD).”
9 ibid.
10 ibid.
11 ibid.; Halvorson, Bremmer, and Jacobs, “Polycystic Kidney Disease: Inheritance, Pathophysiology, Prognosis, and Treatment.”
12 Bergmann, Senderek, Windelen, Küpper, Middendorf, Schneider, Dornia, Rudnik-Schöneborn, Konrad, Schmitt, Seeman, Neuhaus, Vester, Kürfel, Büttner, Zerres, APN (Arbeitsgemeinschaft für Pädiatrische Nephrologie), “Clinical Consequences of PKHD1 Mutations in 164 Patients with Autosomal-Recessive Polycystic Kidney Disease (ARPKD).”
13 ibid.
14 ibid.
accounts for about 15-20% of mutations detected in patients with ARPKD\textsuperscript{15}. It is still not understood why certain mutations lead to more predominant renal disease manifestations, while others lead to disease with minimal renal involvement and more liver disease manifestations.

\textsuperscript{15}ibid.
Figure 1. Summary of the genes, proteins, described mutations, and genotype/phenotype correlations associated with ADPKD, ARPKD, and MKS (only the MKS3 gene and protein are shown). Details of the mutations come from the ADPKD Mutation Database18 (ADPKD), ARPKD Mutation Database24 (ARPKD), and various articles describing MKS mutations.

Figure 1: Summary of cystic liver disease genes, proteins, and described mutations. ARPKD is seen in the middle column. 16.

16 Harris, “2008 Homer W. Smith Award: Insights Into the Pathogenesis of Polycystic Kidney Disease From Gene Discovery.”
Figure 2: This image shows the proposed molecular structure of the Fibrocystin protein and its location in primary cilia on the apical side of cells in the collecting ducts of the kidneys, and in the cells lining the bile ducts in the liver 17.

17 Turkbey et al., “Autosomal Recessive Polycystic Kidney Disease and Congenital Hepatic Fibrosis (ARPKD/CHF).”
I.b.ii. Normal Development of the Biliary System - The Ductal plate:
To understand how liver disease is manifested in ARPKD, it is important to understand the normal development and physiology of the biliary system, how dysfunction in normal cell signaling leads to cystogenesis of the biliary ducts, and how intrahepatic cysts lead to the symptoms of liver disease seen in ARPKD: cholangitis, sepsis, and portal hypertension.

Bile ducts first develop from a primitive embryonic structure called the ductal plate. In the first 7 weeks of gestation, the primitive liver is comprised of primary precursor cells called "hepatoblasts". These cells are bipotential and can differentiate into either hepatocytes or cholangiocytes. Hepatoblasts are arranged in cords, already representative of the mature liver architecture with cells in hexagonal plates with alternating sinusoids. At this point however, there is still no central portal vein, nor any functional bile ducts. Development of intrahepatic bile ducts begins at about the 8th gestational week. At about this time, the hepatoblast, in contact with the mesenchyme around a central portal vein differentiate into smaller cells and form a "sleeve" of epithelial biliary-type cells around a developing central portal vein. This structure is referred to as the ductal plate. The ductal plates become duplicated with a second layer of similar cells along its perimeter dividing the ductal plate into two surfaces: the layer in contact with the portal vein and the mesenchyme, and a layer in contact with the surrounding primitive liver parenchyma. In between the two layers of cells is a thin slit-like lumen. Cells in contact with the mesenchyme and peri-portal surface of the ductal plate will further differentiate into cholangiocytes. The cells on the outer surface of the ductal plate, in contact with the surrounding liver parenchyma, will differentiate into hepatocytes.

At about the 12th gestational week, the ductal plate undergoes progressive remodeling in which segments of the double-layered ductal plate dilates and forms longitudinal cuboidal or tubular segments. These eventually develop into mature portal biliary tracts. Through continual development and apoptosis of various precursor cells, the ductal plate remodels into mature peri-portal bile ducts. Mature bile ducts extend in between the hepatocytes through bile canaliculi that drain towards the peri-portal bile ducts.

Ductal plate maturation progresses centrally from larger diameter branches of the biliary tree distally to smaller branches in the periphery of the liver. Histological

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evidence from neonatal liver biopsies reveals the presence of immature biliary ductal plates suggesting that maturation of the biliary system continues throughout the neonatal period. In ARPKD, mutations of the PKHD1 gene and of fibrocystin lead to abnormally functioning and developing cholangiocytes.

I.b.iii. Normal Cholangiocyte Physiology and Cellular Dysfunction in ARPKD/CHF:
Cholangiocytes are bile duct epithelial cells. Bile is synthesized in the hepatocytes, but bile becomes modified as it moves through the bile ducts. Cholangiocytes help to regulate the composition of bile primarily through regulation of chloride and bicarbonate anion balance. Cholangiocytes are ciliated cells that contain non-motile, primary cilia on their luminal sides. Cholangiocytes are the only ciliated cells in the liver. As described above, primary cilia on cholangiocytes form complexes with multiple other intracellular and transmembrane proteins including fibrocystin. In normally functioning cholangiocytes, primary cilia respond to the flow and the chemical composition of bile. They initiate signal cascades that regulate cholangiocyte secretion and cellular proliferation during organogenesis and throughout life. Cholangiocytes have additional functions besides regulation of bile composition. They are also important receptors for pro-inflammatory chemokines and cytokines, as well as cells that actively participate in initiating inflammatory responses. Lastly, cholangiocytes can serve as precursor cells in the regeneration of hepatocytes and other liver mesenchymal cells.

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25 Ward et al., "Cellular and Subcellular Localization of the ARPKD Protein; Fibrocystin Is Expressed on Primary Cilia;" LaRusso and Masyuk, "The Role of Cilia in the Regulation of Bile Flow."

26 ibid.; Ward et al., "Cellular and Subcellular Localization of the ARPKD Protein; Fibrocystin Is Expressed on Primary Cilia;" ibid.

27 Strazzabosco, Fabris, and Spirli, "Pathophysiology of Cholangiopathies."

28 ibid.
Interestingly, cholangiocytes have localized actions based on where they are located along the biliary tree. Also, cholangiopathies, or diseases of the biliary tree, also seem to be localized to specific regions of the biliary tree depending on the nature of the cholangiocyte dysfunction or injury. The smallest division of the biliary tree is that of the canals of Herring, then progress to larger cholangioles, and then to bile ductules, then to bile ducts. Inflammation and cholangiopathy in ARPKD/CHF is often seen at the level of the terminal cholangioles and medium sized bile ductules. However, as stated before, large intrahepatic bile ducts may also be involved in the setting of Caroli’s Syndrome. Cholangiocytes located in the terminal cholangioles can become activated into “reactive cholangiocytes” and lead to the progression of inflammation and fibrosis.

I.c. Pathogenesis of biliary disease in ARPKD/CHF:
It is hypothesized that abnormal fibrocystin leads to decreased apoptosis of cholangiocytes. Malformations in the primary cilia protein complex can lead to decreased intracellular Ca$^{2+}$ signaling with resultant increased cAMP production. This lack of properly regulated cell signaling also leads to increased proliferation of cholangiocytes and resulting dilation of biliary ducts during ductal plate remodeling with abnormal branching.

Primary cilia are also hypothesized to play a role in the polar orientation of cholangiocytes, or which side will face the lumen of the bile duct and which side will not. It is important for cholangiocytes undergoing mitosis to be able to align their mitotic spindles with the axis of the tubule they are a part of such that when then the daughter cells are formed, they contribute to elongating the bile duct rather than increasing the diameter of the bile duct lumen. This is also important because ion...
transporters are differentially expressed between the apical (luminal) and basolateral sides of the cholangiocytes. In rodent models with low expression of PKHD1, mitotic spindle orientation is distorted leading to tubule enlargement, and may be implicated in bile duct ectasia in ARPKD/CHF, but has not yet been demonstrated in humans 37.

These irregular ducts often present in an interrupted ring around the periphery of a central portal tract that is lacking a central bile duct 38. As these abnormal bile ducts develop, peri-ductal spaces become infiltrated with collagenous and fibrotic tissue that eventually forms intra-portal bridges that is the characteristic pathological finding of CHF 39.

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37 Lecchi, Cholangiocyte Biology as Relevant to Cystic Liver Diseases.
Figure 3: This image shows the malformations of the ductal plate in ARPKD/CHF leading to biliary Dysgenesis during organ development in utero.

Turkbey et al., "Autosomal Recessive Polycystic Kidney Disease and Congenital Hepatic Fibrosis (ARPKD/CHF)"."
I.d. Pathogenesis of Fibrosis in ARPKD/CHF
The pathogenesis of fibrosis in ARPKD/CHF remains a mystery: in chronic liver diseases other than ARPKD/CHF, hepatic stellate cells become activated in response to liver injury or inflammation and migrate to and proliferate in the area of injury. Once activated, HSCs are able to produce extracellular matrix (ECM) proteins and secrete a wide milieu of pro-inflammatory cytokines and chemokines. The main pro-inflammatory chemokine released by activated HSCs is tissue growth factor β1 (TGF-β1). TGF-β1 triggers the activation of multiple other inflammatory and immune cells, as well as the release of chemokines/cytokines. The end result is the deposition of collagen and other ECM components to make fibrotic tissue at the site of injury.

In the setting of ARPKD/CHF associated fibrosis, scant activated HSCs can be seen in the fibrotic areas suggesting that some other cell must be the key mediator of fibrogenesis in this disease. It is thought that other myofibroblast precursor cells, such as periductal fibroblasts (also known as portal fibroblasts; PFs) may be involved in the development of persistent injury and fibrosis in ARPKD/CHF. In a study by Wen et al. PFs have been shown to undergo cell differentiation into myofibroblasts and collagen deposition in fibrosis. Ozaki et al. also demonstrated that immunohistochemical staining of fibrotic tissue in ARPKD/CHF reveals high levels of heparin sulfate proteoglycan (HSPG, a component of ECM) which is not seen in other chronic liver fibrotic diseases, suggesting a unique pathology of fibrosis in ARPKD/CHF. It is thought that HSPG acts as a reservoir for pro-inflammatory chemokines/cytokines helping to maintain a chronic state of persistent inflammation and fibrosis. A cycle of fibrosis and ECM deposition by some unknown myofibroblast cells, and ECM remodeling leading to reactivation and recirculation of pro-inflammatory chemokines/cytokines located within HSPG and the ECM, ultimately leads to chronic and progressive peri-portal fibrosis.

However, these studies are still in their infancy, and more research is needed to confirm a model for the pathogenesis of fibrosis in ARPKD/CHF. In addition, why there seems to be a wide range in the severity and rate of progression of fibrosis in ARPKD/CHF also remains unknown. In the next section, I will discuss some of the

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41 Friedman, "Mechanisms of Hepatic Fibrogenesis.;" Ozaki, Sato, Yasoshima, Harada, and Nakanuma, "Diffuse Expression of Heparan Sulfate Proteoglycan and Connective Tissue Growth Factor in Fibrous Septa with Many Mast Cells Relate to Unresolving Hepatic Fibrosis of Congenital Hepatic Fibrosis..."
42 ibid.
43 ibid.
44 ibid.
45 ibid.
46 Dranoff and Wells, "Portal Fibroblasts: Underappreciated Mediators of Biliary Fibrosis.;" Lecchi, Cholangiocyte Biology as Relevant to Cystic Liver Diseases.
47 Wen, "Congenital Hepatic Fibrosis in Autosomal Recessive Polycystic Kidney Disease."
48 Ozaki, Sato, Yasoshima, Harada, and Nakanuma, "Diffuse Expression of Heparan Sulfate Proteoglycan and Connective Tissue Growth Factor in Fibrous Septa with Many Mast Cells Relate to Unresolving Hepatic Fibrosis of Congenital Hepatic Fibrosis..."
49 ibid.
common manifestations of liver disease as a result of either the biliary dysfunction/dysgenesis or due to the progressive congenital hepatic fibrosis associated with ARPKD.

ARPKD is typically diagnosed prenatally typically at the beginning of the third trimester. In the next section I will review how ARPKD is diagnosed, when, and how the disease presents from birth throughout the first year of life.

II. Diagnosis and Disease Progression:
Diagnosis of ARPKD was made in utero or within the first month of life in a majority of the study population in all 10 studies: median percentage of prenatal diagnosis and diagnosis ≤1month was 55% of cases (range: 47% - 100%, including one study in which diagnosis <1year was an inclusion criteria). The diagnosis of ARPKD was made within 1 year was made in a median of 74% of diagnoses (range: 60% - 100%). Also, while prenatal genetic testing has been available since 1994 the majority of patients in the reviewed literature were diagnosed by ultrasonography and/or clinical examination at birth. It is unclear if there is any advantage to genetic testing over ultrasound detection in terms of management or treatment, but may offer parents a diagnosis of ARPKD sooner if they are considering terminating the pregnancy.

II.a. Initial Presentation of ARPKD and Morbidity Within the First Year of Life:
Initial clinical presentation and symptoms were documented in nine studies in this literature review. Seven of the nine studies listed palpable abdominal masses as the major initial presentation of ARPKD. Palpable masses were most frequently

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50 Cole, Conley, and Stapleton, “Polycystic Kidney Disease in the First Year of Life.”
51 ibid.
52 Zerres et al., “Prenatal Diagnosis of Autosomal Recessive Polycystic Kidney Disease (ARPKD): Molecular Genetics, Clinical Experience, and Fetal Morphology.”
due to nephromegaly, and were found in a median of 68% of patients (range: 26% - 100% of patients)\textsuperscript{55}. Hepatomegaly was observed less frequently on initial presentation (median: 18.55% of patients, range: 7.7% - 50%) and was described in eight studies \textsuperscript{56}.

The second most common initial presentation of ARPKD was respiratory disease. It was described in five studies \textsuperscript{57} and incidences ranged from 4.3% – 90% of patients. Respiratory distress was found in 9/10 patients (90%) in a small study by Beaunoyer et al. in patients undergoing nephrectomy and/or kidney transport, and was also a common finding in other studies as well (range: 9% – 70% of patients)\textsuperscript{58}.


\textsuperscript{58} Roy, Dillon, Trompeter, and Barratt, “Autosomal Recessive Polycystic Kidney Disease: Long-Term Outcome of Neonatal Survivors;” Beaunoyer et al., “Optimizing Outcomes for Neonatal ARPKD;”
The most frequent etiologies of pulmonary diseases in infants with ARPKD were pneumothorax (range: 9.6% - 60% of patients) 59. Hypertension as an initial presentation of ARPKD was reported in three studies with a median of 19.4% of patients (range: 17.6% - 55% of patients 60).

Systemic hypertension as an initial presentation of ARPKD was not as common as renal enlargement or respiratory distress, but it was a common comorbidity of ARPKD 61. Systemic hypertension was documented in eight of ten studies (range: 17.6% - 100%, * The range is reported due to the diverse study populations and number of patients in each study 62). One study by Roy et al cited that 39% of patients developed systemic hypertension within the first year of life, 54% by 5 years, and 60% by 15 years of observation 63. These studies were consistent with the rest of the literature reviewed in this paper, suggesting that the three major manifestations of ARPKD at initial presentation are: nephromegaly, respiratory distress secondary to pulmonary hypoplasia and systemic hypertension.

Morbidity in ARPKD infants surviving the first year of life is initially related to renal dysfunction. The enlarged cystic kidneys, with the abnormally functioning primary
cilia located on the luminal surfaces of the collecting tubule epithelium are unable to effectively regulate solute and ion excretion/reabsorption. With the loss of regulated solute and ion excretion/reabsorption, the kidneys become unable to effectively excrete urine. As a result, intravascular volume increases leading to systemic hypertension. For infants, the renal disease may be stabilized with dialysis and/or medications, or cured with renal transplantation. Among those surviving the first month, prognosis is good; systemic hypertension and creatinine clearance rates seem to stabilize or even improve with increasing age. Furthermore, there is no increased risk of transplantation failure or transplant-related death amongst patients with ARPKD versus patients who do not have ARPKD. Now that renal transplantation surgery has improved greatly and children with ARPKD are living into adolescence and adulthood, liver disease has become more critical consideration in the long-term management and treatment of ARPKD.

Death due to liver disease-related complications in ARPKD is rare, and was only reported in four of the reviewed studies. In one study by Roy et al., four deaths were attributed to refractory bleeding from esophageal varices. Some studies...
have demonstrated cholangiocarcinoma in association with ARPKD and CHF, but more studies are needed to demonstrate its association \(^{71, 72, 73}\).

II.b. Signs of Liver Disease in ARPKD:
As discussed above, there are two main etiologies of liver disease in ARPKD/CHF: hepatobiliary disease that arises from the abnormal proliferation and dilation of bile ducts, and from complications of the associated congenital hepatic fibrosis.

II.b.i. Complications of Biliary Dysgenesis in ARPKD/CHF:
While both fibrosis and biliary tubule dysgenesis are always present in ARPKD/CHF \(^{74}\), the severity, degree, and size of bile ducts affected by the associated biliary dysgenesis were highly variable in the reviewed literature. Ectasia of larger diameter intrahepatic biliary ducts in patients with ARPKD/CHF (consistent with Caroli’s Syndrome) was reported in three studies, with incidences that ranged from 16.2% - 60% of patients as seen either on ultrasonography or radiography \(^{75}\). One study by Capisonda et al. found 26% of patients had Caroli’s Syndrome on initial clinical presentation. At the end of this study’s observation period (1990 – 2000), 44% of the surviving 27 patients were found to have Caroli’s Syndrome \(^{76}\). However, this study did not state if other patients developed evidence of Caroli’s Syndrome later in life after the study observation period, nor the age of onset for Caroli’s Syndrome in any patients. This study supports the hypothesis that initially, biliary dysgenesis starts microscopically with smaller diameter bile ducts, and then progresses to macroscopic enlargement of larger bile ducts.

As the disease progresses, hepatomegaly often develops. Hepatomegaly can be detected either by ultrasonography, radiography, or clinically by palpation, and was reported in six studies (mean: 35.7% range: 2.4% -83%; \(^{77}\)). The wide range in the

\(^{71}\) Goilav et al., “Predominant Extrahepatic Biliary Disease in Autosomal Recessive Polycystic Kidney Disease: a New Association..”

\(^{72}\) Fonck et al., “Autosomal Recessive Polycystic Kidney Disease in Adulthood..”


\(^{74}\) Cole, Conley, and Stapleton, “Polycystic Kidney Disease in the First Year of Life..”


\(^{76}\) Capisonda et al., “Autosomal Recessive Polycystic Kidney Disease: Outcomes From a Single-Center Experience..”

rates of hepatomegaly was probably due to the significant variability in the study populations in terms of age at presentation and sample size. For example, in one study by Roy et al., hepatomegaly was found in 83% of 35 patients who were all older than 1 year of age. This study initially had 52 patients but 12 died under the age of five and 5 were untraceable at the time of follow up. Thus, this specific study's patient population most likely represents older patients with milder renal disease. The median age in which patients were diagnosed with ARPKD due to clinical findings of hepatomegaly was reported in only one study by Deget et al. and was found to be 12 years (range 1-20 years). This supports the hypothesis that hepatomegaly or clinical signs of liver involvement as the initial presentation of ARPKD is usually found in patients older than 1 year, or in cases where renal involvement was mild and a diagnosis of ARPKD was made later in life.

Biliary cyst formation and impaired biliary flow can also lead to both acute and chronically recurrent cholangitis with or without sepsis. Sludging and stasis of bile can provide a fertile ground for bacteria to breed. Cholangitis was reported in three studies with a median incidence of 14%, and ranged from 3.6 – 30% of patients. In a study by Guay-Woodford et al., cholangitis was reported in eight cases (out of 166): six were reported from the cohort born after January 1990, and two in the cohort born before January 1990. Khan et al. proposed that cholangitis occurs much less frequently than portal hypertension in ARPKD/CHF with an estimated prevalence of cholangitis is 6-12% of patients. However, mortality can occur from cholangitis, and in the study by Khan et al. was attributed to sepsis in three patients. Furthermore, a study by Kashtan et al. suggests that patients with ARPKD may develop frequent episodes of recurrent

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Roy, Dillon, Trompeter, and Barratt, “Autosomal Recessive Polycystic Kidney Disease: Long-Term Outcome of Neonatal Survivors.”


Shorbagi and Bayraktar, “Experience of a Single Center with Congenital Hepatic Fibrosis: a Review of the Literature.”

Davis et al., “Survival of Childhood Polycystic Kidney Disease Following Renal Transplantation: the Impact of Advanced Hepatobiliary Disease.”

Khan, Schwarzenberg, Sharp, Matas, and Chavers, “Morbidity From Congenital Hepatic Fibrosis After Renal Transplantation for Autosomal Recessive Polycystic Kidney Disease.”

Guay-Woodford and Desmond, “Autosomal Recessive Polycystic Kidney Disease: the Clinical Experience in North America.”

Guay-Woodford and Desmond, “Autosomal Recessive Polycystic Kidney Disease: the Clinical Experience in North America.”

Khan, Schwarzenberg, Sharp, Matas, and Chavers, “Morbidity From Congenital Hepatic Fibrosis After Renal Transplantation for Autosomal Recessive Polycystic Kidney Disease.”

ibid.
bacteremia containing enteric organisms before and after renal transplantation. In six patients, “typical” clinical features of cholangitis were absent but were proven to be due to cholangitis upon either laboratory and/or liver biopsy. This suggests that the prevalence of cholangitis in ARPKD/CHF may be underestimated and may be associated with death due to septicemia. This also suggests that while cholangitis may be a rare complication of ARPKD/CHF, it should be treated seriously as it may be fatal. No studies looked at the impact immunosuppressive drugs may play in increasing the risk of episodes of cholangitis in post-renal transplanted patients. While liver transplantation has been shown effective in curing and preventing further episodes of cholangitis in patients with ARPKD/CHF, it is still unclear if all patients with recurrent cholangitis should be given a liver transplant as no studies have looked at the benefits of such treatment.

II.b.ii. Complications of Fibrosis in ARPKD/CHF:
Signs and symptoms of CHF are nonspecific and are not typically seen until later in life, in later childhood or even adulthood. One complication from progressive CHF that is responsible for serious morbidity is portal hypertension. Portal hypertension develops when the fibrotic liver prevents normal venous return of blood through the liver. The pathogenesis of portal hypertension, while better understood in other chronic liver diseases, is poorly understood in the setting of ARPKD/CHF.

There are two current theories for the pathogenesis of portal hypertension in ARPKD/CHF; one theory is that the abnormal biliary ducts lead to secondary compression of intra-hepatic portal veins, which leads to increased pressures proximal to the compression. In addition, the fibrosis associated with ARPKD exacerbates the compression and rigidity of the portal venous system, leading to increased pressures. The second theory is that, the mutations associated with ARPKD lead to portal venous hypoplasia in addition to abnormal bile ducts. In this model, the portal veins do not develop normally for similar reasons elucidated in the

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87 ibid.; Kashtan et al., “Recurrent Bacteremia with Enteric Pathogens in Recessive Polycystic Kidney Disease.”
88 “Typical” symptoms and signs of ascending bacterial cholangitis include fever, right upper abdominal pain and tenderness, jaundice, and elevated transaminase levels. In this study by Kashtan et al. only one patient experienced recurrent fevers and right upper abdominal pain and tenderness associated with recurrent bouts of cholangitis. Laboratory cultures and histological evidence of bacterial cholangitis with gram-negative enteric bacteria was confirmed in 6 patients without any of the above mentioned signs or symptoms.
92 ibid.
93 ibid.
The pathogenesis of the bile ducts. Smaller, slit-like vessels are less compliant, and are narrow and transmit a higher pressure gradient throughout the portal venous system.

Formally, portal hypertension is defined as a portal vein pressure greater than 5 mmHg, or a portal vein to hepatic vein gradient greater than 10 mmHg. However, because it is often difficult to measure portal vein and hepatic vein pressures non-invasively, the diagnosis of portal hypertension is often made using clinical evidence. A diagnosis of portal hypertension can be made based on various pieces of clinical evidence. In this review, portal hypertension is defined as clinical and/or sonographic evidence of hepatomegaly, splenomegaly; directional reversal of portal venous flow on Doppler ultrasound; endoscopic and/or radiographic evidence of esophageal varices. Table 1 summarizes the findings from the 10 studies reviewed in this literature review (See Table 1: Summary of Studies looking at ARPKD and Liver Disease).

In the studies reviewed, portal hypertension was found in a median of 35% of patients, and an average of 34% of patients in nine studies. The range of incidence of portal hypertension ranged from 11% to 60%. The age of patients diagnosed

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94 ibid.
with portal hypertension was only provided in the study by Guay-Woodford et al., and was reported as median ages and age ranges (2.8 years (0.9 – 4.7 years)\textsuperscript{98}.

In one study, patients were stratified into patients born before January 1\textsuperscript{st}, 1990 and those born after January 1\textsuperscript{st} 1990 to include historical retrospective chart data with mixed prospective-retrospective chart data \textsuperscript{99}. In this study, portal hypertension was documented more frequently in the patient population born before 1990 (35\% versus 15\%) \textsuperscript{100}. The patient population born before 1990 contained 26 individuals, and only 2 of these 26 patients were diagnosed prenatally. Since some of these patients were born before ultrasound was used to diagnosis ARPKD, this population may represent patients who have milder kidney involvement as peers with more severe renal involvement may have died without a diagnosis of ARPKD and thus not included in this study \textsuperscript{101}. This same study by Guay-Woodford et al. also found that as age increases, so does the incidence of portal hypertension \textsuperscript{102}. The patients in the study by Guay-Woodford et al. were found to have differing average age for presentation of portal hypertension; the cohort born before 1990 was found to have a median age of 8.2 years when diagnosed with portal hypertension, whereas the cohort born after 1990 was found to have a median age of 2.8 years (range: 0.9 to 4.7 years) \textsuperscript{103}.

Initially, portal hypertension may be asymptomatic, or may only present with clinical signs such as splenomegaly. Splenomegaly was noted in four studies \textsuperscript{104}. It was less common than hepatomegaly (mean: 27.8\%, range: 23\% - 37\%) \textsuperscript{105}. In two studies, hepatosplenomegaly was observed—with 5.8\% of patients in the study by Zerres et al., and 21\% in the study by Bergmann et al \textsuperscript{106}. The study by Zerres et al.

\textsuperscript{98} Guay-Woodford and Desmond, “Autosomal Recessive Polycystic Kidney Disease: the Clinical Experience in North America..”
\textsuperscript{99} ibid.
\textsuperscript{100} ibid.
\textsuperscript{101} ibid.
\textsuperscript{102} ibid.
\textsuperscript{103} ibid.
had 103 patients for analysis whereas the study by Bergmann et al. had only 10 patients. Thus, the prevalence by Zerres et al. may be more representative of the population at large. However, ages of onset were not consistently listed for patients with hepatomegaly, splenomegaly, or hepatosplenomegaly.

As portal hypertension worsens, there is a risk of developing of varices. Varices are dilated, tortuous veins under high pressure that, when close to the luminal surface of the gastrointestinal tract, can rupture and cause profuse bleeding. In response to chronically increased portal venous pressure, collateral blood vessels develop as pressure outlets for high-pressure portal veins. These varices approach and expand into the surface of the intestine around the esophagus, stomach, retroperitoneum, umbilicus and rectum. These aberrant collateral blood vessels are under high pressure due to the backup in the portal venous circulation and are at high risk of rupturing with resultant bleeding. Variceal bleeding is associated with a high mortality rate and requires emergent, intensive management. Risk of variceal bleeding increases as the portal venous pressure increases and the risk of death with an acute variceal bleed can be as high as 30%. It is clear that portal hypertension causes significant morbidity and reduction in the quality of life in patients with ARPKD.

Medical treatment of varices includes the use of beta blockers such as propranolol to prevent rupture of varices, endoscopic variceal banding and ligation to minimize varices, sclerotherapy to cauterize ruptured and bleeding varices. However, neither endoscopic banding nor sclerotherapy act to reduce the high pressure gradient between the liver and the portal vein. Thus while banding and sclerotherapy can effectively treat acute variceal bleeding, they do not prevent the recurrence of bleeding. For recurrent bleeding or acute bleeds that do not respond to medical or endoscopic treatment, portosystemic shunts may be used.

Portosystemic shunts work by creating low-pressure channels to divert blood from the high-pressure portal vein into collateral veins such as the hepatic vein. A

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108 ibid.
111 Groszmann et al., "Beta-Blockers to Prevent Gastroesophageal Varices in Patients with Cirrhosis."
112 Beta blockers help to treat portal hypertension by decreasing cardiac output via β1 adrenergic receptor antagonism, and causing vasoconstriction of splanchic vessels via β2 adrenergic receptor antagonism (source: Groszmann et al., "Beta-Blockers to Prevent Gastroesophageal Varices in Patients with Cirrhosis.").
113 ibid.
114 ibid.
transjugular intrahepatic portosystemic shunt\textsuperscript{117} or, “TIPS” shunt, is one type of a portosystemic shunt that is used to treat complications of portal hypertension (ascites and variceal bleeding). A TIPS shunt creates a low-resistance channel between a branch of the portal vein and the hepatic vein inside the liver through the deployment of a metal shunt. This allows blood to bypass the smaller venules of the portal vein and drain directly into the hepatic veins. The advantage of this type of procedure is it can be done with minimally invasive techniques without the use of general anesthesia. It is typically performed using a catheter inserted into the jugular vein and then guided towards the hepatic vein inside the liver using angiographic techniques. Typically TIPS shunts are used in patients with recurrent variceal bleeding or variceal bleeding that cannot be adequately controlled with medical therapy, endoscopic banding, or sclerotherapy\textsuperscript{118}. However, this procedure is not commonly performed in pediatric patients, as there is concern about the risks involved with this procedure such as the development of hepatic encephalopathy\textsuperscript{119}.

In the study by Guay-Woodford et al., esophageal variceal bleeding was reported in 10 patients: six in the younger cohort and four from the older cohort\textsuperscript{120}. In general, incidence of esophageal varices and/or variceal bleeding was highly variable; six studies reported incidences of esophageal varices with a range from 6 – 23\%\textsuperscript{121,122} 123. In addition to the Guay-Woodford study, Roy et al. and Capisonda et al also documented varices. In the study by Roy et al., varices and/or bleeding from esophageal varices were reported in 23\% of patients (8/35)\textsuperscript{124}. In the study by Capisonda et al. varices and/or variceal bleeding were reported in 37\% (10/21) of patients\textsuperscript{125}. Treatment decisions for variceal bleeding were not well documented

\begin{thebibliography}{99}
\bibitem{117} Other types of portosystemic shunts exist, but discussion of these shunts are beyond the scope of this paper.
\bibitem{118} Bari and Garcia-Tsao, “Treatment of Portal Hypertension...”
\bibitem{119} Gugig and Rosenthal, “Management of Portal Hypertension in Children...”
\bibitem{120} Guay-Woodford and Desmond, “Autosomal Recessive Polycystic Kidney Disease: the Clinical Experience in North America.”
\bibitem{121} Ibid.
\bibitem{122} Roy, Dillon, Trompeter, and Barratt, “Autosomal Recessive Polycystic Kidney Disease: Long-Term Outcome of Neonatal Survivors.”
\bibitem{124} Roy, Dillon, Trompeter, and Barratt, “Autosomal Recessive Polycystic Kidney Disease: Long-Term Outcome of Neonatal Survivors.”
\bibitem{125} Capisonda et al, “Autosomal Recessive Polycystic Kidney Disease: Outcomes From a Single-Center Experience.”
\end{thebibliography}
but included endoscopic banding and/or sclerotherapy to control bleeding. In some cases portosystemic shunts were placed to divert portal flow. These procedures were done on a case-by-case basis and no specific information was reported on the patients receiving each type of treatment modality.

In the study by Guay-Woodford et al., seven patients received liver transplants: three from the older cohort and four from the younger cohort. Indications for the liver transplantation were not specified, but all patients receiving a liver transplant had histories of variceal bleeding and/or cholangitis. The median age of transplantation in the younger cohort was 8.2 years (range: 25th% - 5.4 yrs, 75th% - 10.0 yrs). Long-term outcomes and survival rates were not reported in these patients.

III. Organ Transplantation in ARPKD/CHF

As mentioned before, kidney transplantation has been an effective means of curing morbidity and mortality related to end-stage renal disease due to ARPKD. Likewise liver transplantation also remains a possible cure for end-stage liver disease seen in ARPKD/CHF, although the indications of when to transplant a liver are not clear. To place this question in context, I will briefly review the past and current state of kidney and liver transplantation in pediatrics, with a specific focus on North American pediatric patients.

Pediatric organ transplantation poses unique challenges compared to adult transplantation. For one, dosing and pharmacokinetics of immunosuppressive medications in pediatric patients remains complicated as these drugs may affect growth and development. Also given that pediatric patients’ immune systems are still developing, they are at high risk for pre and post-operative infectious diseases. Besides treating end-organ failure, organ transplantation in pediatric patients also has the added goal of facilitating growth and development as near as normal as possible. The frequency of pediatric organ transplantsations range from 4-15% of that in adults for all organs, except for small intestine transplantation which is even less frequent than in adults. The two most frequently transplanted organs in pediatric patients are kidneys and livers.

Much of the data and literature existing on kidney transplantation comes from large databases and national registries such as the North American Pediatric Renal Trials.

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126 Guay-Woodford and Desmond, “Autosomal Recessive Polycystic Kidney Disease: the Clinical Experience in North America.”
127 ibid.
129 ibid.
130 ibid.
131 ibid.
132 ibid.
and Collaborative Research, or NAPRTCS database. The first kidney transplant performed in a pediatric patient was in 1987. In a study by Sweet et al. looking at transplantation of solid organs among pediatric patients in the US, it was shown that between 1987 and 1990, 1-year graft survival rates for living donor and deceased donor kidney grafts were 89% and 75%. These statistics improved to 96% and 93% between 1999-2004. Similarly, the probability of an acute graft rejection within 1 year was initially 54% for living donor grafts, and 69% for deceased donor grafts from 1987 – 1990; these rates improved to 16% and 21%, respectively, between 1999-2004. Long-term survival of kidney grafts at 7 years improved from 72% (for living donor grafts) and 55% (for deceased donor grafts) from 1987 – 1990, to 76% and 65%, respectively, between 1999-2004.

Liver transplantation was first attempted in the 1960’s, but carried high rates of recipient mortality, thus it was considered by most as an “experimental procedure”. At first, liver transplant grafts were taken from deceased donors (known as deceased donor liver transplantation or, “DDLT”) following cardiac death and the livers were transplanted as whole organs. Initially, pediatric patients had long wait times because they had to wait for a size-matched liver graft from a deceased donor. As techniques and understanding of transplantation medicine improved, doctors were able to reduce the size of adult liver grafts for pediatric patients. However, this was not ideal because the remaining liver not used for the graft was discarded, merely shifting the donor shortage from pediatric patients to adult patients. Advances in medicine eventually led to the advent of splitting a liver from a living donor (known as living donor liver transplantation or, “LDLT”) in pediatric patients. In this procedure, the donor would donate a part of their liver (typically the left lateral lobe) while retaining part of their liver. LDLT in pediatric patients was first performed in 1989 using a partial liver graft from a mother to her son. However, the liver only functioned for one year. Since then, living donor transplantation techniques have greatly improved with much better outcomes for both donor and recipient.

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133 ibid.
134 ibid.
135 ibid.
136 ibid.
137 ibid.
138 ibid.
139 Bartlett and Rela, “Progress in Surgical Techniques in Pediatric Liver Transplantation..”
140 ibid.
141 ibid.
142 ibid.
143 ibid.
144 ibid.
146 Bartlett and Rela, “Progress in Surgical Techniques in Pediatric Liver Transplantation..”
147 ibid.
Both LDLT and DDLT liver grafts are used today, but the former are used more frequently because they involve less ischemic time for the graft, less wait time for the recipient, and the surgery can be performed when the donor is healthy and under optimal conditions. Secondly, another advantage of LDLT in pediatric patients is that it frees up split liver deceased donor grafts for two adult patients, thus minimizing the need for splitting a liver for adult-to-adult living donor transplantations.

Current data and trends in liver transplantation in pediatrics come from large databases such as the Scientific Registry on Transplant Recipients’ “Studies on Pediatric Liver Transplant” or “SPLIT” database. Current data show that patient survival rates are now about 83-90% at five years, and grafts have a survival rate of about 84-89% at five years as well. The main reasons for liver transplantation in children are biliary atresia, cholestatic liver disease, malignancies, and fulminant hepatic failure. Biliary atresia accounts for 41% of pediatric liver transplant cases, of which about 25% of patients are less than 1 year old. In ARPKD/CHF patients who are post-renal transplant, Caroli’s Disease is the most common indication for liver transplantation most likely due to the natural history of the disease leading to progressive biliary disease and portal hypertension. Likewise, immunosuppressive medications in post-renal transplant APRKD/CHF patients may increase the risks of biliary infections and cholangitis.

Few studies have looked at the outcomes of liver transplantation and/or combined liver and kidney transplantation in ARPKD/CHF patients. One study by Chapal et al. looked at outcomes of 14 ARPKD patients who were either recipients of a kidney or combined liver and kidney transplants. Two of the 14 patients received orthotopic liver transplants 7-20 years post-renal transplant, and one patient had a simultaneous liver and kidney transplantation surgery. In this study, there were three deaths: one was in the patient with the combined simultaneous liver-kidney transplantation, and two other patients who were renal transplant patients. All three deaths were attributed to complications of Caroli’s Disease (all three died from sepsis due to cholangitis). This study suggests that Caroli’s Disease in the

148 ibid.
149 ibid.
151 Karnsakul et al., “Living Donor Liver Transplantation in Children: a Single North American Center Experience Over Two Decades..”
152 O’Leary, Lepe, and Davis, “Indications for Liver Transplantation..”
153 ibid.
155 ibid.
156 ibid.
157 ibid.
158 ibid.
setting of ARPKD/CHF carries a high risk of mortality and morbidity, but the authors did not state if this is a contraindication for liver transplantation. Instead, I think this study suggests that it is a complicating factor that may affect transplant outcomes; the author states that: "In the presence of severe Caroli’s Disease, a combined liver and kidney transplantation should be discussed."159

A study by Sakamoto et al. reported four patients with ARPKD/CHF and Caroli’s Disease who underwent either combined simultaneous liver and kidney transplantation (one patient); sequential liver, then kidney transplantation (two patients); or sequential kidney, then liver transplantation (one patient). Because of complications of cholangitis and sepsis 160, these authors also suggested that combined liver and kidney transplantation should be considered in patients with severe and progressive liver disease in the setting of ARPKD/CHF161

While existing literature and multiple studies agree that liver transplantation is indicated in patients with complications from Caroli’s Disease such as severe and/or recurrent cholangitis, there is no consensus on the best time to transplant. Also it is still unclear if it is best to combine liver transplantation with kidney transplantation or if sequential transplantation is better. The literature seems to suggest that isolated renal transplantation may increase the risk of cholangitis and recurrent cholangitis, especially in patients with Caroli’s Disease 162. The existing literature also suggests that immunosuppressive medications may exacerbate renal dysfunction in ARPKD/CHF because some of these drugs may be nephrotoxic 163. Thus, more research is needed to compare the outcomes of combined liver and kidney transplantation versus sequential organ transplantation, as well as studies looking at the effects of age or stage of disease and time to transplantation.

Portal hypertension by itself is not an indication for liver transplantation. Portosystemic shunting is considered the first-line treatment for portal hypertension in children 164. However, liver transplantation may be indicated if complications from portal hypertension such as recurrent variceal bleeding and/or ascites are not well controlled with endoscopic treatment, portosystemic shunts, and/or medical management 165. Since ARPKD/CHF presents with a wide spectrum of disease severity, it remains unclear if and when a patient with ARPKD/CHF should undergo liver transplantation for the treatment of portal hypertension.

159 ibid.
163 Kelly, “Current Issues in Pediatric Transplantation..”
164 Chava, Singh, Pal, Dhawan, and Heaton, “Indications for Combined Liver and Kidney Transplantation in Children..”
165 ibid.
Studies looking for predictors of progression to portal hypertension and/or worsening progression of the associated biliary disease may help inform the discussion of liver transplantation with patients with progressive liver disease in ARPKD/CHF.

**IV. Limitations of the Studies Reviewed**

Clinical studies on ARPKD vary greatly in terms of demographics, population size, disease severity, and methods for diagnosing portal hypertension and CHF. The study by Roy et al. only included patients that survived the first year of life; these findings are not applicable to the larger population that dies within the neonatal period or the first year of life. The study by Guay-Woodford et al. only looked at patients who were referred from a nephrology unit of a hospital, thus they may also have a selection biased towards a specific population of patients with ARPKD that have a different disease profile than the general ARPKD population. This same study is likewise under-representative of patients with more severe disease who died in the neonatal period because it did not include patients from birthing centers.

In the discussion section of a study by Bergmann et al. researchers summarize some of the limitations in the body of clinical studies on ARPKD, citing that many of the studies lack a consensus method for diagnosing portal hypertension in their patients. Thus, even with existing estimates of the prevalence of portal hypertension, we may not fully know how many patients are actually affected, to what degree, and at what age.

Furthermore, the study by Bergmann et al. as well as another study by Meral-Aygun et al., cite the difficulties in matching disease manifestations to detected genetic mutations due to two factors: genetic mutation analysis of ARPKD gene sequences has limited specificity and sensitivity and in general can only detect a confirmed mutation in 70% of cases; and PKHD1 is a large gene with multiple exons and open reading frames, thus allowing for a large variability in the types of mutations. To date, not all pathogenic mutations in PKHD1 have been demonstrated and sequenced. Thus, genetic mutation analysis may only be clinically valuable in qualitatively predicting disease severity based on the homozygous presentation of

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166 Roy, Dillon, Trompeter, and Barratt, “Autosomal Recessive Polycystic Kidney Disease: Long-Term Outcome of Neonatal Survivors..”


168 ibid.

169 Bergmann, Senderek, Windelen, Küpper, Middendorf, Schneider, Dornia, Rudnik-Schöneborn, Konrad, Schmitt, Seeman, Neuhaus, Vester, Kirfel, Büttner, Zerrres, APN (Arbeitsgemeinschaft für Pädiatrische Nephrologie), “Clinical Consequences of PKHD1 Mutations in 164 Patients with Autosomal-Recessive Polycystic Kidney Disease (ARPKD)..”

170 ibid.; Gunay-Aygun et al., “Correlation of Kidney Function, Volume and Imaging Findings, and PKHD1 Mutations in 73 Patients with Autosomal Recessive Polycystic Kidney Disease;” Gunay-Aygun et al., “PKHD1 Sequence Variations in 78 Children and Adults with Autosomal Recessive Polycystic Kidney Disease and Congenital Hepatic Fibrosis..”
truncating mutations. Lastly, no studies have linked genetic mutation analysis, clinical disease manifestations, and treatment outcomes to look at how to best manage liver disease in ARPKD.

While portal hypertension rarely causes significant mortality in ARPKD, it is not very well understood in terms of pathogenesis and progression, thus further research is needed to look specifically at the clinical picture of patients who develop portal hypertension versus those who do not in age/gender matched case-control studies. However, given the rarity of this disease and the high rates of neonatal morbidity, most studies are limited to retrospective analysis of pooled database information from national registries rather than robust prospective case-matched studies. Still, there is room for further research that may help further illuminate if there are identifiable risk factors or predictors for progression to complications of liver disease in ARPKD.

V. Conclusions:
This review shows that liver disease in ARPKD usually presents later in life, whereas kidney disease is often the cause of initial clinical presentations. Liver manifestations of ARPKD were frequently documented only when there was clinical evidence of existing portal hypertension, but no studies evaluated liver involvement before the onset of portal hypertension. Also, no studies provided serial imaging data of the portal vein to demonstrate longitudinal progression of the associated congenital hepatic fibrosis/peri-portal fibrosis. While the existing literature demonstrates extra-hepatic complications such as hypersplenism, esophageal varices, cholangitis, sepsis, and even cholangiocarcinoma with liver disease in ARPKD, little is known about disease progression and clinical predictors of such complications.

What is known about ARPKD to date has mostly focused on kidney pathology and kidney disease as it has been the greatest source of mortality among young children who survive the neonatal period. As such, no standard protocol exists for the screening or treatment of liver disease in ARPKD. Furthermore, while portal hypertension may occur in only a subset of patients with ARPKD, the predictors of portal hypertension are not well understood and more studies are needed. This remains difficult as all patients with ARPKD invariably have some development of peri-portal fibrosis from the congenital hepatic fibrosis associated with ARPKD.

While mortality from portal hypertension in ARPKD has not been common in older literature, morbidity associated with portal hypertension in ARPKD presents a major challenge to medical management of patients. Patients with ARPKD that

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progress to portal hypertension are not only at greatest risk of developing varices and variceal bleeding, but also for developing recurrent bouts of cholangitis. Cholangitis may progress to cholangiocarcinoma in a select few patients; therefore more studies are also needed to assess which patients are at greatest risk for developing cancer in the setting of recurrent cholangitis 172.

Currently, the only cure for ARPKD and CHF is both kidney and liver transplantation. However, these are major medical procedures and it is unclear when they are indicated. Most patients do not initially present with liver disease from birth and, therefore, it is difficult to know when the liver should be transplanted. Also, transplantation surgery is complex and carries significant risks. Patients will require lifelong immunosuppression and it is not well understood what the long-term consequences are for transplanting both liver and kidneys in infants.

Aggressive monitoring and management of progression to portal hypertension may result in better outcomes for patients with ARPKD. Portal hypertension can also exacerbate the renal manifestations of ARPKD 173. CHF and portal hypertension can increase the risks of developing renal insufficiency to a greater degree than in patients without CHF 174.

In summary, ARPKD is a rare congenital disease that affects primarily the kidney and the liver. Infant mortality is highest in the first month of life. For those who do survive the neonatal period, kidney transplantation is the only definitive cure, but many patients are placed on either continuous peritoneal dialysis or hemodialysis temporarily.

Liver disease in ARPKD remains understudied. It is thought to present later in life and about a third of patients progress towards serious complications of portal hypertension. The main liver manifestation of ARPKD is biliary obstruction/dysfunction due to cystic biliary ducts. Cholestasis from improper bile duct formation and function can lead to cholangitis and sepsis. Recurrent cholangitis also seems to increase the risk of cholangiocarcinoma. Complications from portal hypertension include variceal formation and variceal bleeding, as well as splenomegaly and sequestration. Hypersplenism may affect hemostasis as thrombocytopenia may compromise normal clotting. Morbidity from portal hypertension is common and there currently is no consensus on how to manage and treat portal hypertension in ARPKD. Studying which patients progress to portal hypertension and its onset may better inform clinical management and treatment of liver disease in ARPKD.

172 Shorbagi and Bayraktar, “Experience of a Single Center with Congenital Hepatic Fibrosis: a Review of the Literature.”
173 Arikan, Ozgenc, Akman, Kilic, Tokat, Yagci, and Aydogdu, “Impact of Liver Transplantation on Renal Function of Patients with Congenital Hepatic Fibrosis Associated with Autosomal Recessive Polycystic Kidney Disease.”
174 ibid.
In response to the lack of studies looking specifically at predictors for the development of portal hypertension in ARPKD/CHF, I will conduct a retrospective chart review of 30 pediatric patients at the University of California, San Francisco. This study will look at patients who are post-renal transplantation so as to focus only on liver disease in these patients. My main research question is: “What are the predictors for progression of portal hypertension among post-renal transplantation ARPKD patients?” Secondary questions will include first: “What is the time to development of portal hypertension among these patients?” and secondly: “What factors are associated with worse clinical outcomes in patients with ARPKD who develop portal hypertension?” The planned research project will include chart review and descriptive statistical analysis of the findings and trends given that the patient population size is too small to make generalizable conclusions.

I hope that in conducting this research, better understanding of the pathology and progression of CHF, and the risk factors for developing portal hypertension in ARPKD/CHF may be better elucidated, and that this may lead to improved outcomes for patients with predominant liver manifestation of ARPKD/CHF.
PART 2: ORIGINAL RESEARCH

I. Background:
Autosomal Recessive Polycystic Kidney Disease (ARPKD) is a rare genetic disorder that causes the formation of cysts within the collecting tubules of the kidney and the larger intrahepatic bile ducts in the liver. It is estimated to have a prevalence of 1:20,000-40,000 live births. Early signs are predominantly related to renal dysfunction, such as fluid overload and systemic hypertension. ARPKD has a significant neonatal mortality rate of 30-50% within the first month of life. Those that survive usually require renal transplant as the cystic disease is progressive and eventually leads to kidney failure.

Liver manifestations of ARPKD are due to an associated disease called congenital hepatic fibrosis (CHF) and can become the dominant clinical feature in older children, adolescents, and adults (either have milder renal disease or have undergone renal transplant). Cystic disease does not recur in the transplanted kidney. Abnormal intracellular signaling in developing cholangiocytes leads to enlarged and immature biliary vessels that compromise bile production and flow through the liver. This condition is known as “biliary dysgenesis.” CHF causes biliary and peri-portal fibrosis and scarring leading to chronic cholangitis, portal hypertension and associated morbidities. The pathogenesis of this scarring is not understood.

While most studies focus on the renal manifestations of ARPKD because they present earlier and more dramatically, scant research has focused on the liver manifestations of the disease. Little is known about when liver manifestations first appear or the risk factors for the most common complications of liver disease in ARPKD/CHF. There is no consensus on how to best treat and manage CHF and its complications in these patients. This research presents a case series of seven post-replant patients with ARPKD/CHF to compare those listed for liver transplantation versus those who were not listed for liver transplant at the end of the study period. These findings are then compared to the existing literature on

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1 Guay-Woodford and Desmond, "Autosomal Recessive Polycystic Kidney Disease: the Clinical Experience in North America..
2 ibid.
3 ibid.
4 ibid.
5 ibid.
7 ibid.
8 Shneider and Magid, "Liver Disease in Autosomal Recessive Polycystic Kidney Disease..
9 Guay-Woodford and Desmond, "Autosomal Recessive Polycystic Kidney Disease: the Clinical Experience in North America.."
portal hypertension and liver transplantation in ARPKD/CHF to highlight new findings and areas of future research.

II. Methods:
After receiving IRB approval from the University of California, San Francisco Medical Center (UCSF), an electronic medical archival system was used to generate a list of all patients who received kidney transplantation at UCSF from September 1996 to June 2012. A “Notice of Intent to Rely” was filed with UC Berkeley CPHS to rely on UCSF’s review board for IRB approval.

Paper charts were reviewed to confirm a diagnosis of ARPKD to eliminate patients with other polycystic kidney and/or liver diseases such as autosomal dominant polycystic kidney disease (ADPKD). Patients who were older than 25 years at the beginning of the study period were excluded from the case series. A total of 60 patients were reviewed, and 10 patients were selected for this study. One patient received a combined liver and kidney transplant at the beginning of the study and was excluded because there was no data between kidney transplant and liver transplant. Two patients were later dropped due to a lack of follow up data, leaving seven patients available for data analysis.

The remaining seven patients were evaluated for liver disease manifestations of portal hypertension including hepatosplenomegaly, thrombocytopenia, esophageal, rectal or gastric varices, and variceal bleeding. Portal hypertension (PHTN) in this study was defined as one or more of the following:

- Portal venous pressures $\geq 10$ mmHg as measured by intravenous catheter
- Portal vein dilation $\geq 10$ mm in diameter as measured by Doppler or ultrasonography
- The presence of splenomegaly or hepatosplenomegaly on ultrasound or other imaging modalities
- Presence of varices (esophageal, gastric, or rectal) as confirmed by esophagastroduodenoscopy (EGD) or colonoscopy.

All seven patients were followed up in an outpatient pediatric renal and/or gastrointestinal clinic. Data from clinic appointments were collected at 3, 6, 12, and 18 months post-renal transplant, as well as 2, 3, 4, 5, 10, and 12 years post-renal transplant if available. Charts were reviewed for basic vital signs and anthropometrics, clinical data from physical examination, basic blood chemistries, and any imaging data during that time-point.

Blood lab information collected included:
1. Complete Blood Count
2. Metabolic Panel
   a. $\text{Na}^+$, $\text{K}^+$, serum albumin, serum creatinine, blood-urea nitrogen,
3. Liver Labs
a. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, and gamma-glutamyl transpeptidase (GGT) if available

4. Blood Coagulation Tests
   a. International normalized ratio (INR)

Medications were reviewed as well and any changes in immunosuppressive medications were noted. Charts were reviewed at each time point for existing signs of portal hypertension (see above) and new signs were recorded along with the age of the patient at the time signs of portal hypertension developed.

Any acute hospitalization for a suspected or confirmed infection was also recorded. Charts from emergency department and acute hospitalizations were reviewed for clinical history, vital signs, blood and urine cultures, urinalysis, blood chemistries and blood count, and liver function tests if available. Any use of antibiotics or new added medications was also recorded as well as duration of treatment with these medications. Diagnoses at the time of discharge were noted as well. Data was analyzed using descriptive statistics and compared to existing literature. The primary end point of this study was listing for liver transplantation. For those who did not receive a liver transplant, data was collected up until up until each patient's most recent visit or September 1, 2012 (the end of the data collection period).

III. Results:

III.a Demographics

Table 2 below shows the demographics of the seven included patients.

Table 2: Baseline Demographics of 7 patients

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age at Diagnosis (with ARPKD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Patients – n = 5</td>
<td>Mean Age: 25.20 days of life \ Range: Prenatally – 90 days</td>
</tr>
<tr>
<td>Female Patients – n = 2</td>
<td>Mean Age: 5.33 days of life \ Range: prenatally – 12 days</td>
</tr>
<tr>
<td>All Patients – n = 7</td>
<td>Mean Age: 17.75 days of life \ Range: prenatally – 90 days</td>
</tr>
</tbody>
</table>

The median follow up time was 120 months post kidney transplantation (mean: 120 months, range: 6 months – 144 months). The median age at last follow up visit was 14 years (mean: 14 years, range: 8-19 years). Two patients were brothers– the elder was diagnosed at 36 days of life and the younger was diagnosed prenatally. All seven patients were ethnically non-Hispanic, White.

III.b Age and Presentation at Diagnosis

Five total patients were diagnosed either prenatally or within the first month of life: three patients were diagnosed prenatally, and two patients were diagnosed within the first 30 days of life. For the three prenatally diagnosed patients,
ultrasonographic evidence around 20 weeks gestation of bilaterally enlarged cystic kidneys was used to make the diagnosis of ARPKD. For the five patients diagnosed either prenatally or within the first 30 days of life, hypertension was the most common presenting symptom (n=3). One patient presented at birth with respiratory distress and required mechanical ventilation. This patient became oliguric and was diagnosed with ARPKD by ultrasonography.

III.c Kidney Transplantation
One patient received his first kidney transplant at 1 year of age, two patients at 2 years, one patient at 4 years, one patient at 10 years, one patient at 13 years, and one patient at 14 years. The patients who were later listed for liver transplant are described below in the section titled: “Liver Transplant Patients”.

III.d Immunosuppression and Infections:
All seven patients were on immunosuppressive medications after kidney transplantation. Medication data for these seven patients is listed in Table 3 below.

Table 3: Individual Immunosuppressive Medication Regimens

<table>
<thead>
<tr>
<th>Patient ID#</th>
<th>Immunosuppressive Medications at last follow-up</th>
<th>Medications Added/Discontinued During Study Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>tacrolimus, mycophenolate, prednisone</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>tacrolimus, azathioprine, prednisone</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>tacrolimus, azathioprine**, prednisone</td>
<td>**Switched from azathioprine to mycophenolate at 1-year post kidney transplant. Also received pulse sirolimus for acute renal rejection.</td>
</tr>
<tr>
<td>4</td>
<td>mycophenolate, cyclosporine, prednisone</td>
<td>Received pulse sirolimus for acute renal graft rejection.</td>
</tr>
<tr>
<td>5</td>
<td>tacrolimus, mycophenolate</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>mycophenolate, cyclosporine, prednisone</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>tacrolimus, prednisone</td>
<td></td>
</tr>
</tbody>
</table>

Infections were common among these patients. These included: urinary tract infections (n= 3 patients), upper/lower respiratory infections (n=2 patients), skin infections (n=3 patients), infections of indwelling hemocatheters (n=2 patients), surgical wound infections (n= 2 patients), gastroenteritis (n = 1 patient), middle ear infections (otitis media, n= 1 patient), and oral candidiasis (n = 1 patient). There were no confirmed episodes of cholangitis. A total of nine episodes of confirmed sepsis were documented in four patients. All infections, episodes of sepsis, and episodes of FWS’s are listed below in Table 4.

Bacteremia was also common in these patients (n= 4 patients). Often patients presented to the emergency department with recurrent fevers and signs of sepsis (such as high white blood cell counts, hypotension, and/or elevated heart rates) but had negative blood and urine cultures both upon admission and upon discharge. In these episodes where no source of infection was identified, patients were admitted
and treated with antibiotics to rule out sepsis. In these episodes where no pathogen or source of infection was identified, they were given the diagnosis of “fever without a source” or “FWS” – fever without source - suggest viral as a possible cause in kids (common cold, flu, gastroenteritis – Healthy 1-2 year olds get 12 viral infections per year) – issue is that they are immunosuppressed so fever has to be presumptively treated as a bacterial infection. In this case series, three patients were hospitalized for recurrent episodes of “fever without a source” (FWS). Patient 1 had three separate episodes of FWS and was hospitalized for a total of 16 days. Patient 2 had a total of 4 episodes of FWS and was hospitalized a total of 13 days. Patient 3 had 2 episodes FUO for a total of seven days. Table 3 below summarizes all episodes of infections, sepsis, and “fever without a source”.

Table 4: Summary of Infections in all seven ARPKD/CHF patients

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Infections (excluding sepsis)</th>
<th>Episodes of Sepsis</th>
<th>Sepsis Pathogen(s) (from positive blood cultures)</th>
<th>Episodes of FWS</th>
<th>Total # of days hospitalized for infections &amp; FWS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pneumonia – 2 UTI – 1 URI – 1 Hemodialysis catheter infection - 1</td>
<td>2</td>
<td>GBS – 1 Enterobacter - 1</td>
<td>2</td>
<td>29</td>
</tr>
<tr>
<td>2</td>
<td>Otitis media – 1 Surgical wound infection – 1 Hemodialysis catheter infection - 2</td>
<td>2</td>
<td>H. influenzae – 1 Escherichia coli - 1</td>
<td>3</td>
<td>31</td>
</tr>
<tr>
<td>3</td>
<td>Gastroenteritis – 1</td>
<td>1</td>
<td>GAS - 1</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>UTI – 1 Oral candidiasis - 1</td>
<td>4</td>
<td>MSSA – 3 Klebsiella spp. – 1 Enterobacter spp. - 1</td>
<td>1</td>
<td>33</td>
</tr>
<tr>
<td>5</td>
<td>None</td>
<td>0</td>
<td>N/A</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Surgical wound infection - 1</td>
<td>0</td>
<td>N/A</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>None</td>
<td>0</td>
<td>N/A</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: UTI – urinary tract infection GAS = Group A Streptococcal infection; GBS = Group B Streptococcal infection; MSSA = Methicillin sensitive Staphylococcus aureus; H. influenza = Haemophilus influenza; spp. = species; FWS = “Fever without a source”;

III.e Liver Disease in Post-Kidney Transplant ARPKD Patients:

Table 5 below lists the liver disease manifestations for the seven included patients. Signs of portal hypertension were present in all seven patients by the end of the study period, however not all patients progressed to clinically severe liver disease. All seven patients had abdominal ultrasound data available. All seven patients developed hepatomegaly, splenomegaly, or hepatosplenomegaly by the end of the
study. One patient developed signs of splenomegaly at 2 months of age. The other six patients with organomegaly developed signs later in life ranging from 2.7 years to 13 years of age.

All seven patients had long-term data on platelet counts. Six of seven patients had trends of decreasing platelet counts post-kidney transplantation; only one patient had stable and/or rising platelet counts over time. Three out of seven patients had platelet counts significantly below the lower limit of normal by ten years post-kidney transplant. Decreasing platelet counts correlated with increasing spleen size and progression of hepatosplenomegaly. All patients with a low baseline platelet count of \( \leq 200 \times 10^9 \) cells/L at the first follow up period after kidney transplantation were eventually listed for liver transplant.

All seven patients had esophago-gastroduodenoscopy (EGD) data available; four of the seven patients developed varices. Varices were typically diagnosed in late childhood– one patient at 6 years, one at 7 years, one at 8 years, and one at 10 years of age. Of the four patients who developed varices, only one patient had variceal bleeding (see Table 5 below). This patient received platelet and blood transfusions every three months.
### Table 5: Signs of Liver Disease and Platelet Counts at 1, 4 and 10 years Post-KTX

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Age at 1st KTX</th>
<th>Age 1st Developed Hepatosplenomegaly</th>
<th>Age 1st Developed Varices (years)</th>
<th># of Episodes of GI Bleeding</th>
<th>Platelet Counts (in years after 1st KTX)</th>
<th>Age at LTX listing (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>6 yrs</td>
<td>6</td>
<td>0</td>
<td>94</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>2 mo</td>
<td>10</td>
<td>0</td>
<td>161§</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>2.7 yrs</td>
<td>7</td>
<td>0</td>
<td>109</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>3.07</td>
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<td>0</td>
<td>418§</td>
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</tr>
<tr>
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<td>14</td>
<td>NA</td>
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<td>0</td>
<td>242</td>
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</tr>
<tr>
<td>6</td>
<td>10</td>
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<td>395</td>
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</tr>
<tr>
<td>7**</td>
<td>13</td>
<td>At Birth</td>
<td>6</td>
<td>1</td>
<td>167**</td>
<td>Not Listed</td>
</tr>
</tbody>
</table>

Abbreviations:
KTX = Kidney Transplant; LTX = Liver Transplant; Plts. = platelets, listed in $10^6$/mL

Notes:
1. *At 5 years after kidney transplantation.
2. **Patient 7 had a splenectomy at age 13 due to progressive hypersplenism, thrombocytopenia, and varices that were refractory to shunting. This patient also received platelet transfusions every two months for three years prior to her kidney transplantation. Thus this platelet count at year 1 post-KTX is not representative of a true baseline value.
3. § At 9 months after kidney transplantation
4. -- Denotes lost or incomplete data
Figure 4: This graph shows platelet counts of the 7 ARPKD/CHF patients from 0-140 months post kidney transplantation. The dotted lines represent the upper and lower normal limits of platelet counts. LTX = liver transplant; KTX = kidney transplant.
IV. Liver Transplant Patients:

**Patient 1**

*Signs of Portal Hypertension:*
Patient 1 developed splenomegaly at 5 years of age, with worsening thrombocytopenia and leukopenia thought secondary to his splenomegaly. His platelet count fell from $122 \times 10^9$ cells/L at 3 months post kidney transplant, to $42 \times 10^9$ cells/L 4 years later. He developed esophageal varices at age 7 that were diagnosed by EGD. He did not have any episodes of acute bleeding, ascites or encephalopathy. He received a liver transplant at age 8½ (43 months after 1st kidney transplant – see Figure 4 above).

*Hospitalizations due to infections:*
In between his kidney and liver transplantation, Patient 1 was hospitalized 5 times for suspected serious infections: pneumonia (2), sepsis (1), and “Fever of Unknown Source” (3). There were no episodes of suspected or confirmed cholangitis or spontaneous bacterial peritonitis.

**Patient 2**

*Birth and Neonatal Period:*
Patient 2 was delivered at 34 weeks due to oligohydramnios and diagnosed with ARPKD at birth. His postnatal period was complicated by respiratory distress requiring 1 week of mechanical ventilation, refractory hypertension, and episode of culture-negative sepsis, a PDA, and bilateral inguinal hernias, and anemia requiring epoetin alfa. At 1 month he suffered a stroke that resulted in hypotonia, seizures, and residual developmental delay.

*Renal transplant:*
He underwent living-related kidney transplant at 1.8 years of age. The postoperative course was complicated by sepsis and pulmonary edema. Due to poor feeding, a gastrostomy tube was surgically inserted. At age 3, he had one episode of acute kidney rejection, treated with a prednisone taper and a switch from tacrolimus to sirolimus. However, his serum creatinine levels remained chronically elevated (1.8 – 2.1 mg/dL). At age 11, he was diagnosed with chronic nephropathy due to BK viremia treated with IV cidofovir and leuflunomide. At last follow up visit, Patient 2 was 12 years old and his serum creatinine levels remained chronically >2 mg/dL.

*Signs of Portal Hypertension:*
By 2 months of age, he developed hepatosplenomegaly. On ultrasound at age 10, he was noted to have dilation of the right and left intrahepatic biliary ducts consistent with Caroli’s disease. His platelet count at age 2 was $156 \times 10^9$ cells/L which dropped to $33 \times 10^9$ cells/L by age 12. At age 3, he developed chronic rectal bleeding
and epistaxis. Workup led to a diagnosis of von Willebrand’s disease and hypercoagulability. Work up for esophageal varices was negative at the time.

Liver transplantation:
By age 9, he had hepatosplenomegaly, chronic pancytopenia, and grade 2-4 esophageal varices. He had no episodes of acute variceal bleeding and did not receive prophylactic treatment for the varices. He was listed for liver transplant at age 10 and received a combined deceased donor liver-kidney transplant at age 12 (120 months after 1st kidney transplant – see Figure 1 above). No post-liver transplantation data was collected.

Patient 3

Birth and infancy:
At the end of this study, Patient 4 was 14 years old. She was first diagnosed with ARPKD prenatally via ultrasonography. She developed dilated cardiomyopathy at 4 months of life, treated with digoxin. She was also noted to have failure to thrive and poor growth at 1 year of age and a gastrostomy tube was inserted for enteral feeds.

Renal Transplant:
She first received kidney transplantation at age 2.5 years, and later developed two episodes of rejection. She developed chronic nephropathy at age 7 and acute on chronic renal failure at age 14.

Signs of Portal Hypertension:
She first developed hepatomegaly at age 2 and later hepatosplenomegaly at age 4.5. She developed chronic thrombocytopenia with elevated clotting time as measured by the international normalized ratio (INR) of clotting time, and intermittent leukopenia and anemia. She was treated with epogen and vitamin K. She developed grade 3 esophageal varices by age 7, which worsened and gave rise to grade 4 esophageal and gastric varices by age 14. She did not have any episodes of acute bleeding and was started on a proton pump inhibitor for gastric bleeding prophylaxis. She did not require banding or other treatment for her varices. She was listed for a combined liver and kidney transplant at age 14 (143 months after 1st kidney transplant – see Figure 1 above). At the end of this study, she was active on the waiting list and restarted on hemodialysis for her end stage renal disease.

V. Discussion:
This study aimed to evaluate clinical and laboratory findings predictive of progression to liver transplant among post-kidney transplant ARPKD patients. Few studies have evaluated the long-term progression of liver disease in ARPKD. All of our patients had evidence of portal hypertension. In the existing literature, estimates of the prevalence of portal hypertension range from 11% to 60% of
patients, with a median of 35% \(^1\). However, many of these studies looked at infants and pre-kidney transplanted patients. The ages at which patients developed portal hypertension in the reviewed literature ranged from 0.9 to 4.7 years. In contrast, our study found that all patients developed portal hypertension. Also, our study differs from the existing literature in that most patients were older than those reviewed in the literature at the end of the study period. Thus, portal hypertension may be an inevitable part of the natural history of ARPKD, but one that usually presents later than infancy. Though all patients in this study developed portal hypertension, as indicated by splenomegaly and thrombocytopenia, only four of the patients required a liver transplant during the study period. This suggests that some patients have more rapidly progressive liver disease whereas other patients remained relatively stable.

Often hepatosplenomegaly was the initial clinical sign of liver disease in both the reviewed literature and in this study. In the reviewed literature, the median incidence of hepatosplenomegaly was estimated to be 35.7% with a range of 2.4 – 83% \(^2\). As stated in the previous review of literature, this wide range in incidence rates of hepatosplenomegaly could be attributed to the highly diverse patient populations of the studies reviewed. This study estimated the incidence rates of hepatosplenomegaly to be 75%. However, as previously stated, these patients typically were older than those reviewed in the existing literature. The median age at which our patients develop hepatosplenomegaly was 2.9 years. There was insufficient data on the ages at which patients developed hepatosplenomegaly in the existing literature thus we cannot compare our results to the existing literature.

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Our data suggests that, contrary to the reviewed literature, liver disease and portal hypertension may be more common than suggested in the literature. This finding may have been previously obscured by the tendency for studies to select younger patient populations to study. However, given our small sample size, it is impossible to infer the exact prevalence of either portal hypertension in the ARPKD/CHF patient population at large. Furthermore, considering that only four patients in this study eventually required a liver transplantation, it is not known if patients with ARPKD/CHF and hepatosplenomegaly will progress to needing a liver transplant or if their portal hypertension can remain stable.

In this study, declining platelet count was a good proxy for progression and severity of hepatosplenomegaly and a good predictor for progression to liver transplantation. Splenomegaly is likely an indicator of progressive liver fibrosis. A recent study by Gunay-Aygun et al, also found that spleen size was inversely correlated with platelet counts 3. This same study also found that kidney disease severity and liver disease severity were independent 4. This is in contrast to the previously held hypothesis that patients with more severe kidney disease manifestations had milder liver disease 5. In our study we also found similar results that platelet count was inversely predictive of worsening hepatosplenomegaly and eventual progression to liver transplantation. In our study, patients with a 1-year post-kidney transplant baseline platelet count of ≤ 200 x 10^6 cells/mL later received liver transplants. Thus our data suggests that platelet counts may be useful as a noninvasive means of tracking the progression of clinically significant liver disease, as well as predictive of which patients may progress to liver transplant in ARPKD. Patients with low baseline platelet counts, and/or rapidly declining platelet counts should be evaluated earlier for liver transplant. Liver biopsy may not be necessary to evaluate the level of fibrosis of longitudinal platelet counts and/or ultrasonographic monitoring of spleen size reveals rapidly progressing splenomegaly.

Also, there did not seem to be an association with worse baseline kidney function, age at first kidney transplantation, or length of stay on hemodialysis with eventual progression to liver transplantation, thus our data is consistent with the findings of Gunay-Aygun et al. that the liver and kidney manifestations of ARPKD/CHF are indeed independent despite sharing the same pathogenesis. This study lacked sufficient liver biopsy samples to assess the progression of fibrosis in our patients, however it was shown that platelet counts did serve as a useful non-invasive of tracking the progression of portal hypertension in this population. Future clinical

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4 ibid.

5 Blyth and Ockenden, “Polycystic Disease of Kidney and Liver Presenting in Childhood;” Kaplan et al., “Variable Expression of Autosomal Recessive Polycystic Kidney Disease and Congenital Hepatic Fibrosis Within a Family.”
research should combine platelet counts with data from liver biopsies or other means of assessing fibrosis scores in these patients over time to determine a cut off point for liver transplantation.

In this study, thrombocytopenia later developed in patients who had a low baseline platelet count of 200 x 10^6 cells/mL or less post-KTX. Patients with a baseline platelet count higher than 200 x 10^6 cells/mL post-KTX did not progress to thrombocytopenia. Thus, while splenomegaly may be an invariable part of liver disease in ARPKD/CHF, thrombocytopenia is suggestive of a more rapidly progressing liver disease.

However, coagulopathy was not seen in association with decreasing platelet counts. Instead, patients with coagulopathy in our series had an unrelated chronic medical condition such as von Willebrand's disease. In this study, coagulopathy was not evaluated as a primary focus. Mild elevations of the INR at 1.3 to 1.4 may be suggestive of mild liver synthetic dysfunction or vitamin K deficiency due to poor nutritional status. It is possible that poor feeding due to illness, or organomegaly, or chronic diarrhea from infections, as well as frequent hospitalizations all may contribute to vitamin deficiencies and thus mild coagulopathy as well. Liver synthesis of clotting factors have not been well studied in this populations but most sources agree that liver function is well preserved in congenital hepatic function and is only later affected if patients progress to cirrhosis 6.

While varices were not uncommon in this population (n=5), only 1 patient with known varices had variceal bleeding. It is possible that once variceal bleeding develops, liver transplantation is indicated. It is not well known if TIPS shunting in this patient population is sufficient to control further episodes of bleeding. However, TIPS is not generally considered a long-term solution of portal hypertension.

In the reviewed literature, varices were present in 6-23% of patients in five studies 7. Our study seemed to have found a higher incidence of varices than expected, but this could be due to the fact that our patient population all had portal hypertension. Also, in our study, the median age at which patients developed varices was 6.5 years of age. The reviewed literature did not provide data on the age at which patients

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6 Schneider and Magid, "Liver Disease in Autosomal Recessive Polycystic Kidney Disease.;" Ueno et al., "Liver and Kidney Transplantation for Polycystic Liver and Kidney-Renal Function and Outcome.;"
developed varices, but most studies sampled a much younger patient population (infancy to pre-kidney transplantation).

Currently, there is no consensus on how to best manage portal hypertension and its complications in this patient population. Existing recommendations come from expert opinions from the Baveno V Consensus Workshop on the Methodology of Diagnosis and Therapy in Portal Hypertension. However, further studies are needed looking at how to manage portal hypertension and varices specifically in ARPKD/CHF patients.

Infections were a frequent complication and cause for hospitalization seen in post-kidney transplant ARPKD patients. Sepsis was also a common finding in this study (n = 3 patients: 9 episodes total). However, sources of blood borne pathogens were plentiful: many of these patients were hospitalized frequently during infancy, some required multiple surgeries, some were placed on long-term hemodialysis with either indwelling peritoneal or central line catheters, and all patients were on immunosuppressive medications.

Three patients suffered from repeat episodes of “Fever Without a Source” or, “FWS”, and bacteremia often with gram-negative pathogens. It is possible that these were episodes of undiagnosed cholangitis. Typical clinical presentation of cholangitis includes fever, jaundice, and right upper quadrant pain, but is also non-specific. Atypical presentations are not uncommon. It is also important to consider cholangitis in the absence of typical clinical presentations. In a study by Kashtan et al., 8 children with ARPKD were found to have bacterial cholangitis despite atypical clinical presentations. Confirming a diagnosis of cholangitis can be somewhat difficult, and typically requires endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasonography (EUS), and/or magnetic retrograde cholangiopancreatography (MRCP) imaging studies showing bile obstruction or impaired flow. Laboratory studies may show evidence of bilirubinuria and/or hyperbilirubinemia, elevated serum alkaline phosphatase levels, however these findings are non-specific. Unfortunately, given the retrospective nature of this study, there is no way to confirm or disprove these suspected cases. Existing literature found that recurrent cholangitis was an infrequent complication of ARPKD/CHF estimated to be seen in 3.6%, 14%, and 30% of patients in three different studies.

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9 Kashtan et al., “Recurrent Bacteremia with Enteric Pathogens in Recessive Polycystic Kidney Disease.”
However, cholangitis was also noted to be associated with significant risk for morbidity and mortality due to sepsis in these patients \(^{11}\).

In this population, cholangitis should be suspected in patients with fevers, jaundice, and gram-negative bacteremia or sepsis. Further research should include a careful plan for diagnosis and treatment of cholangitis in ARPKD/CHF patients because cholangitis carries a high risk of morbidity and mortality from sepsis.

Third, many unrelated comorbidities and hereditary disease not associated with ARPKD/CHF were seen in this patient cohort. Non-infectious comorbid complications seen in this population included: retinoblastoma (n = 1 patient) and rectal prolapse (n = 1 patient). One patient had a hereditary coagulopathy not directly related to chronic liver disease due to ARPKD/CHF, called: Von Willebrand's disease. This could be due to increased inborn genetic disorders and mutations seen in ARPKD patients. No studies exist looking at common comorbid non-renal/non-hepatic diseases and/or disorders seen in ARPKD. It would be interesting to see if ARPKD patients have higher rates of inherited or acquired oncogenic mutations as cholangiocarcinoma is a rare but serious complication of CHF and Caroli's disease \(^{12}\). Further studies are needed to assess if ARPKD is associated with increased risk of inheriting other genetic abnormalities that could predispose towards higher risk of cancers.

VI. Study Limitations
The small sample size and retrospective nature of this study prevents the ability to infer statistically significant results from the data. However, our findings have been echoed in other publications Also, our data set remains one of the first studies to look at the isolated liver disease manifestations in ARPKD/CHF since all our patients were studied after having received a kidney transplant. Thus the contribution of this study to research is in focusing on liver disease manifestations in an older ARPKD population. Also, this study is one of the first to look at predictors for progression to liver transplantation.

Still, our study was lacking in sufficient liver imaging, lab, and biopsy data. Also, it is unknown if the measure used in this study accurately capture the severity of disease progression in our patient population as there was no correlation with laboratory values with gross pathology. It is unknown if the progression of the hepatosplenomegaly is due to the worsening fibrosis alone, or if there is also some other pathology that leads to worsening thrombocytopenia and hepatosplenomegaly.

\(^{11}\) Khan, Schwarzenberg, Sharp, Matas, and Chavers, "Morbidity From Congenital Hepatic Fibrosis After Renal Transplantation for Autosomal Recessive Polycystic Kidney Disease,;" Shorbagi and Bayraktar, "Experience of a Single Center with Congenital Hepatic Fibrosis: a Review of the Literature."

Another limitation of this study is that no data was collect post-liver transplantation to assess outcomes and if there are any permanent disease manifestations even after kidney and liver transplantation. Also, no studies have assessed if the age of liver transplantation affects outcomes and long-term prognosis. Still, this study provides valuable data on a rare disease with relatively grim outcomes.

Another limitation of this study is that there was insufficient data regarding the nature of infections in this population. As stated above, cholangitis remains an under-diagnosed disease in this population, and may have been a cause of unexplained fevers/infections without an identifiable source. Future research should carefully test for the possibility of biliary infections as they contribute to a significant risk of morbidity and mortality from sepsis in this patient population.

VII. Conclusions:
While many studies have looked at the management of renal disease in ARPKD, few studies have evaluated the progression of liver disease and the period between kidney transplantation and liver transplantation in these patients. This study aimed to assess the clinical predictors of progression to liver transplantation among post-kidney transplant ARPKD patients. Platelet counts were inversely related to spleen size, and spleen size was a good indicator of the progression of liver fibrosis and portal hypertension. Monitoring platelet counts may be a simple, non-invasive means of tracking liver disease in ARPKD patients. Patients with low baseline platelet counts of \( \leq 200 \times 10^6 \) cells/mL, and/or with rapidly declining platelet counts should be evaluated for liver transplantation. Lastly, since no standard guidelines exist for when to begin endoscopic surveillance for esophageal varices in pediatric patients with ARPKD/CHF, we recommend considering EGD surveillance in patients who develop thrombocytopenia. Future clinical research of ARPKD/CHF patients should focus correlating laboratory and imaging studies with the onset of milestones such as development of varices, variceal bleeding, and/or liver transplantation so that clinical management can be tailored to anticipate and treat complications of portal hypertension early.
PART 3: REFERENCES


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