Prospective Evaluation of Kidney and Liver disease in Autosomal Recessive Polycystic Kidney Disease-Congenital Hepatic Fibrosis

Results from NIH Study

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ARPKD/CHF Alliance Virtual Conference

Oct 3, 2020

NATIONAL HUMAN GENOME RESEARCH INSTITUTE Division of Intramural Research

Acknowledgements

ARPKD-CHF Patients and Families

Colleen Zak

ARPKD/CHF ALLIANCE
improving the lives of those affected

NHGRI
William A. Gahl
Joy Bryant, RN

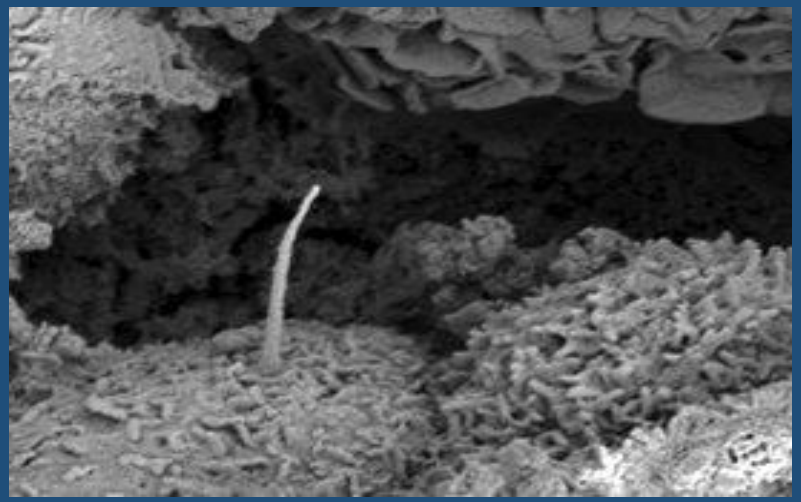
NIDDK
Theo Heller

NIH Imaging
Peter Choyke
Baris Turkbey

“Clinical and Molecular Investigations into Ciliopathies”

www.clinicaltrials.gov, NCT00068224

2003 - Present



Image, https://www.utsouthwestern.edu/labs/emcf/services/

NIH study goals

- Define the characteristics of kidney and liver disease
- Understand the causes of the variation in severity
- Contribute to clinical management guidelines
- Identify outcome parameters for treatment trials

Window of opportunity for treatment

slowly progressing disease

Kidneys

Liver

Targeted disease-changing therapies

Polycystic kidney	• Tesevatinib (c-Src inhibitor) Phase 1 trial (pediatric ARPKD)
Congenital hepatic fibrosis	• Pasireotide (somatostatin analog) Animal model

Lack of quantitative measures of response to treatment

Kidney	? Kidney size ? Kidney imaging findings ? Decline rate of eGFR
Liver	? Platelet count ? Spleen size ? Liver elastography

NIH study patients, 2003 - 2019

- 90 patients referred with a clinical diagnosis of ARPKD evaluated at the NIH Clinical center
- 78 fulfilled the clinical diagnostic criteria for ARPKD
- 73 had at least one pathogenic variant in *PKHD1*
- 60 patients had multiple (2 – 7) NIH visits
- All contacted in 2019 to update information on disease progression

  variceal bleeding
  shunt placement
  transplantation
  infections

NIH study: follow up duration and ages

- The 60 patients with 2–7 visits (3.5 ± 1.5 visits), 34 females, 26 males
- Ages at the initial NIH visit ranged from 0.8 to 50 y (10.6 ± 10.3 y)
- Ages at the most recent NIH visit ranged from 3.4 to 54.9 y (17.5 ± 10.7)
- Duration of prospective follow up (NIH visits) ranged from 1 to 14 y (7 ± 4.2 y)
- Age at most recent contact for 73 patients ranged from 6.7 to 67 y (22.2 ± 12.9 y)

NIH study evaluations

- Blood and urine tests

- Ultrasound
- Magnetic resonance

- Echocardiograms
- Neurocognitive testing

- DNA sequencing

NIH Clinical Center
Bethesda, MD

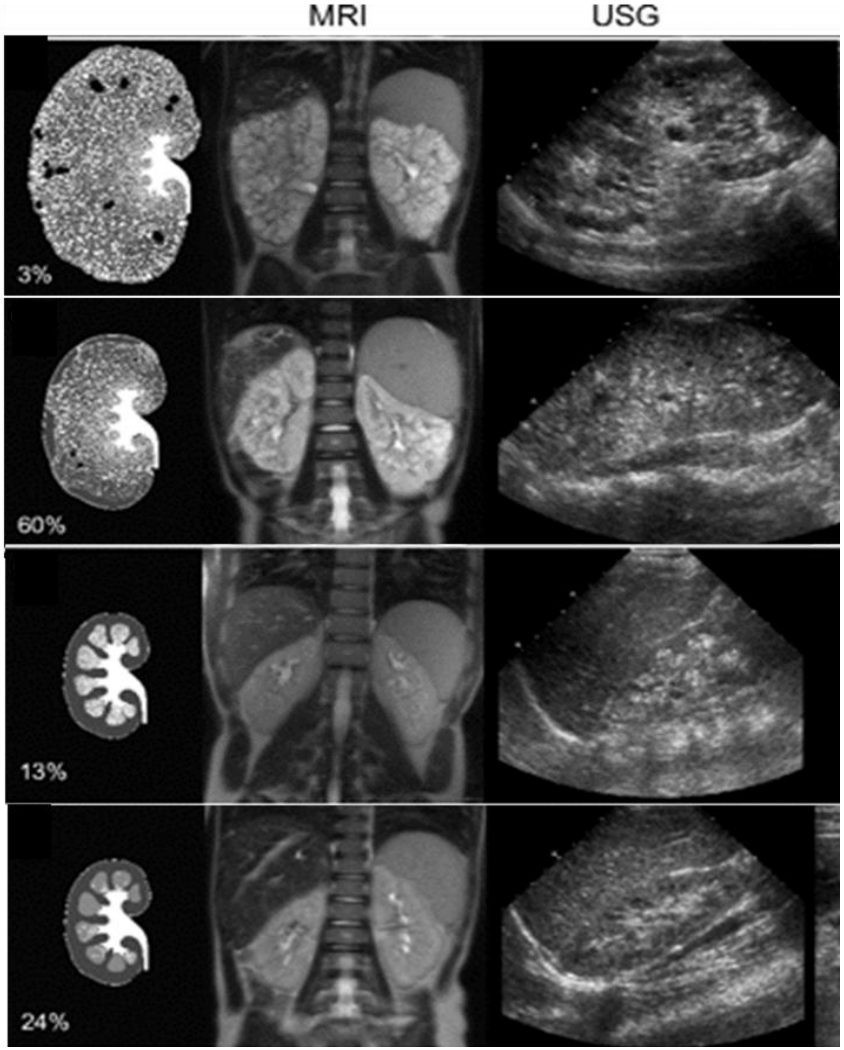
Types of mutations in *PKHD1*

- Non-truncating (mild) 62 %
- Truncating (severe) 38 %

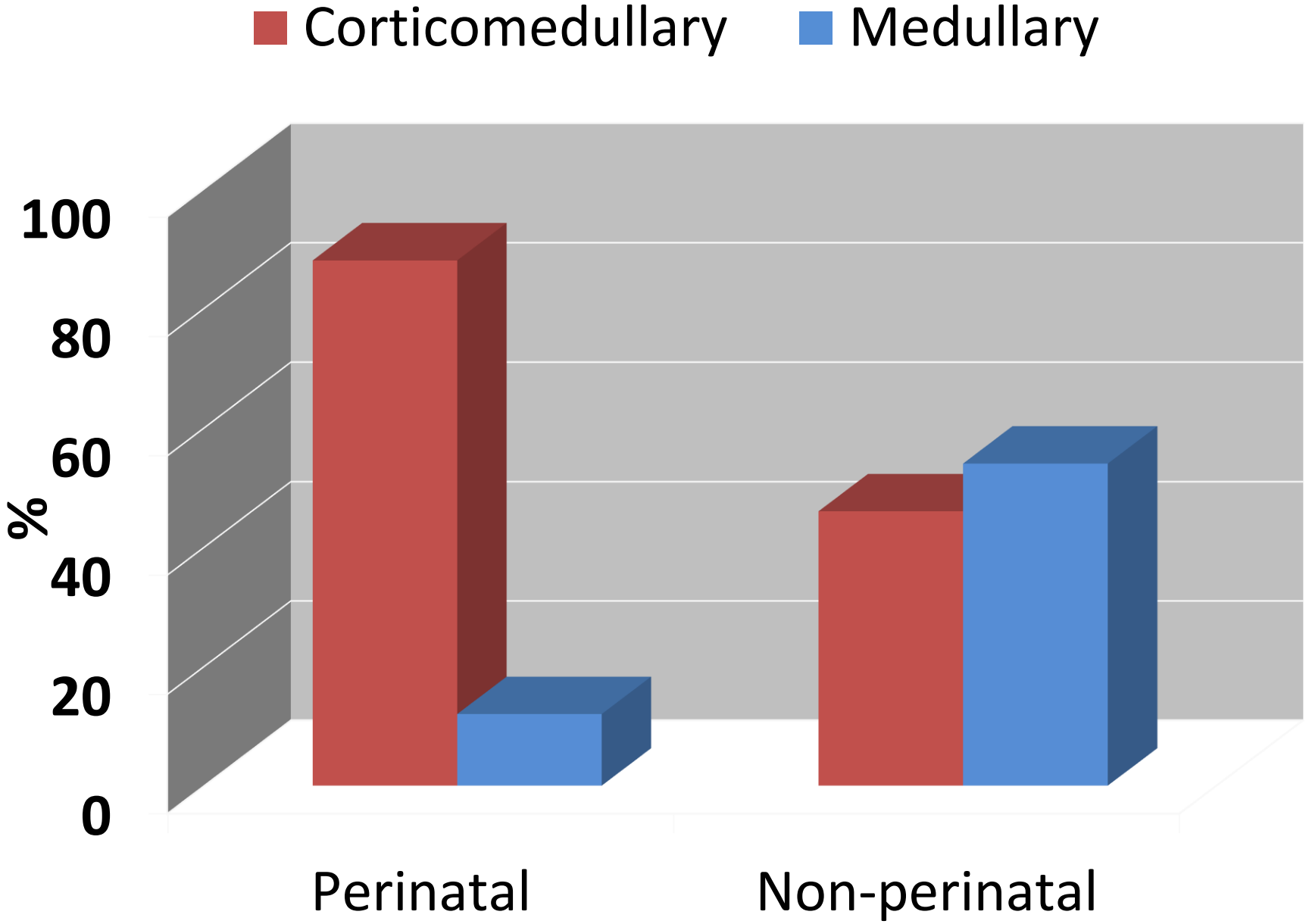
Spectrum of Kidney Disease in 73 patients

Corticomedullary
63 %

Medullary
37 %



Clin J Am Soc Nephrol. 2010



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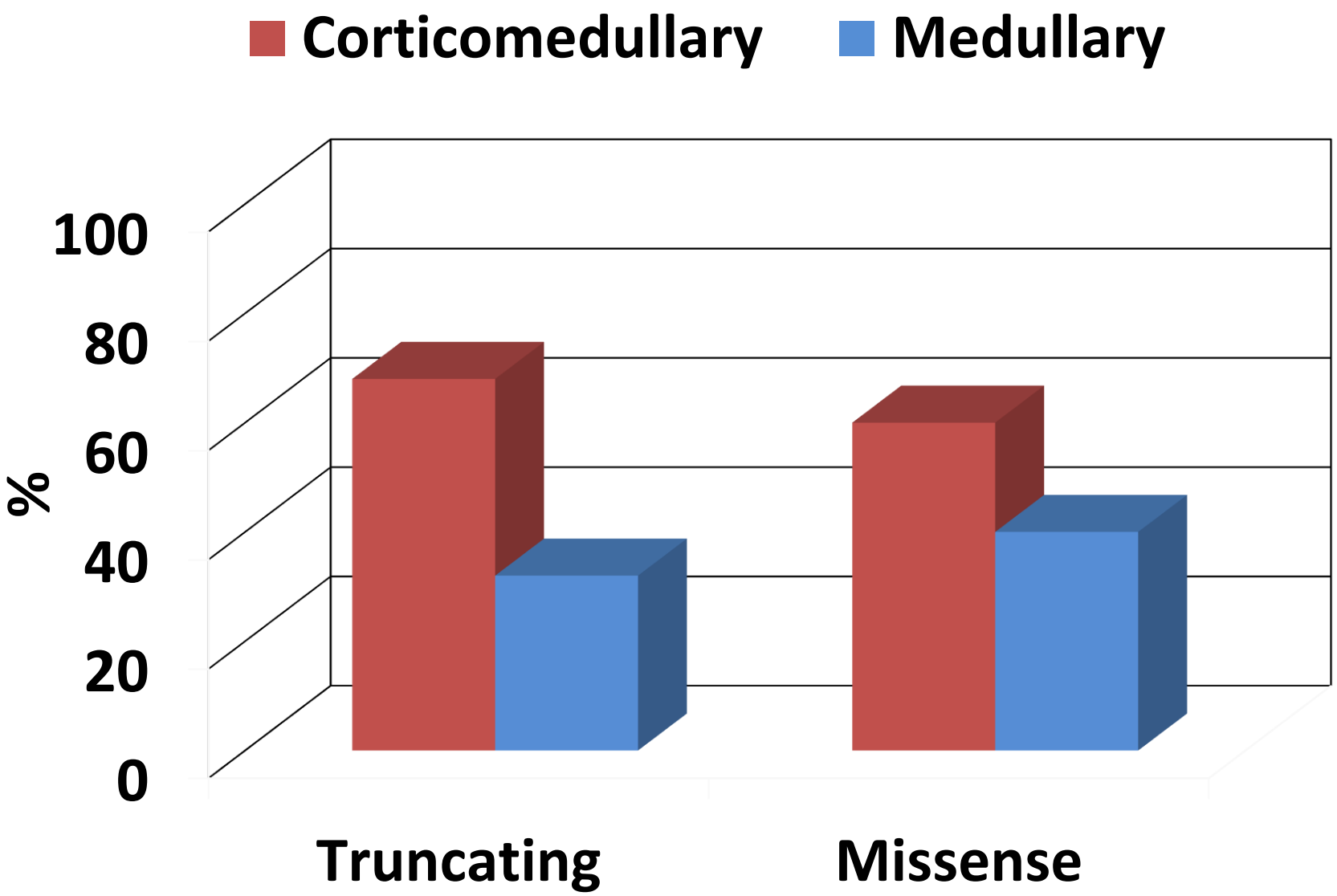
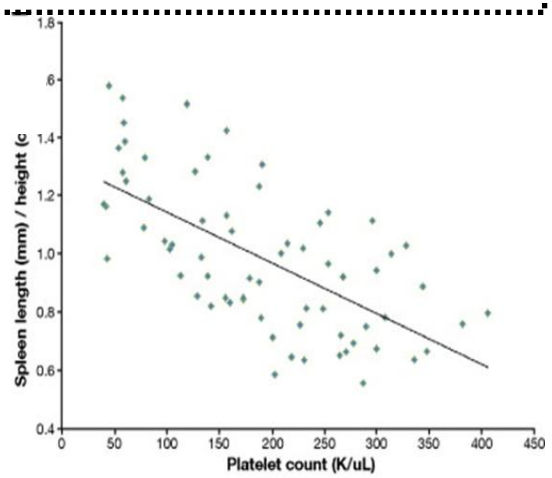


Clin J Am Soc Nephrol. 2010

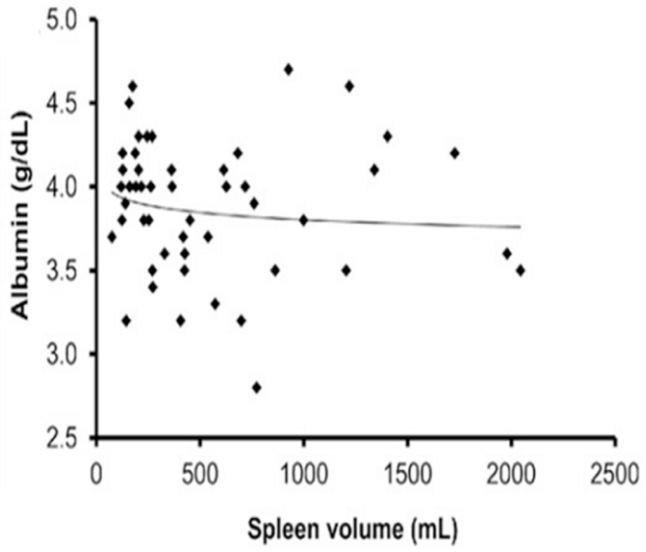
All ARPKD patients have some degree of congenital hepatic fibrosis

Portal Hypertension 71 %

- Esophageal varices
- Enlarged spleen
- Low platelet count



Liver function is preserved

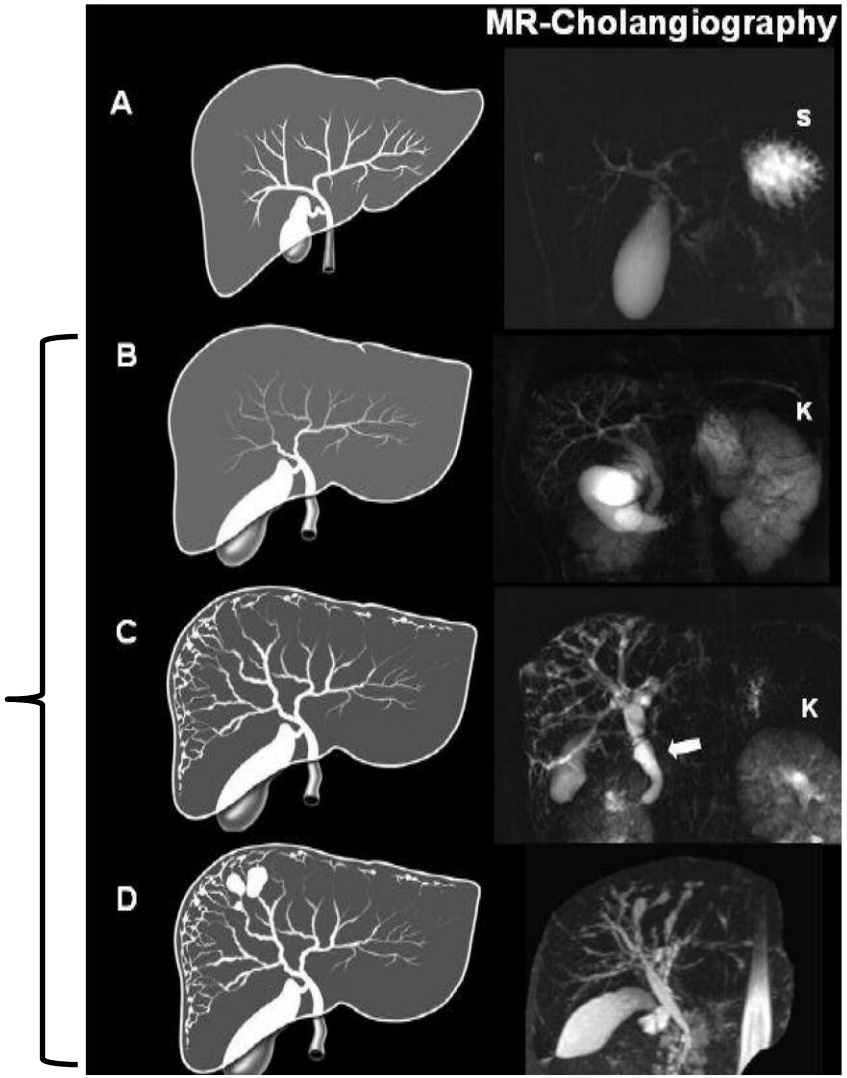


Gastroenterology, 2013

70 % of ARPKD patients have bile duct abnormalities

Dilated
common bile duct

Enlarged gall
bladder

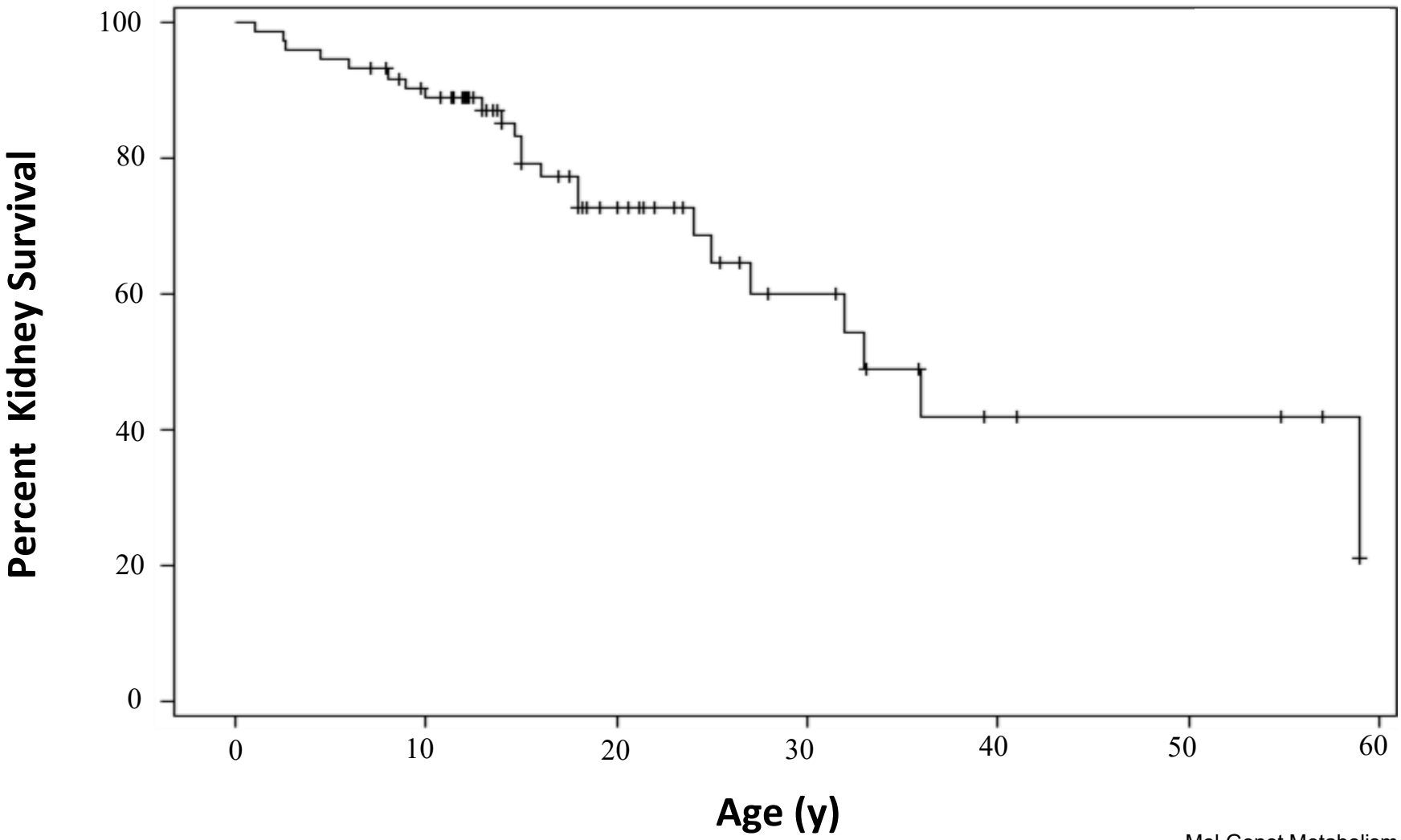


Gastroenterology, 2013

NIH Study: 73 patients

Overall progression of kidney and liver disease

60 % of ARPKD patients required kidney transplantation by age 35 y



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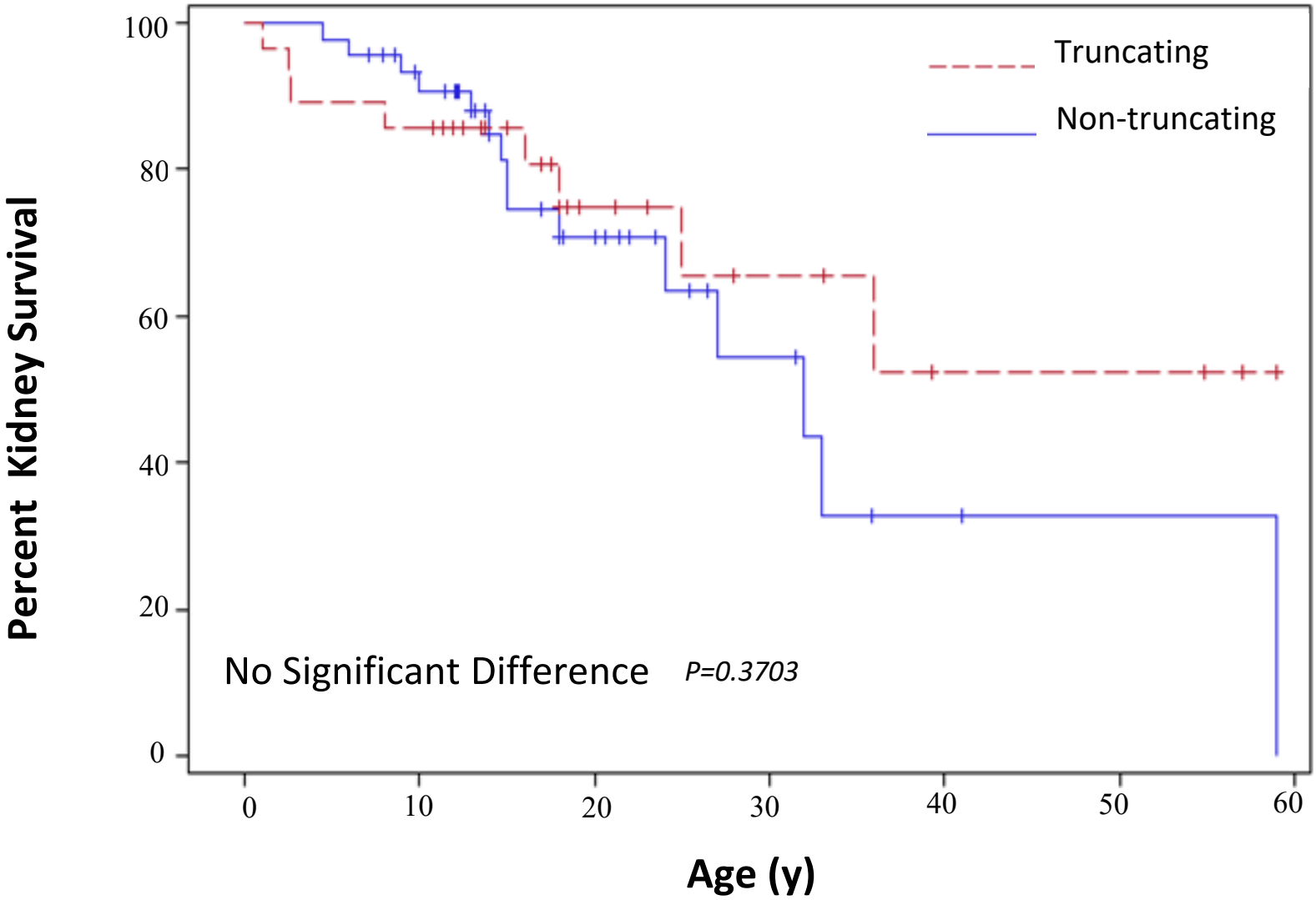
Kidney Survival across *PKHD1* variants



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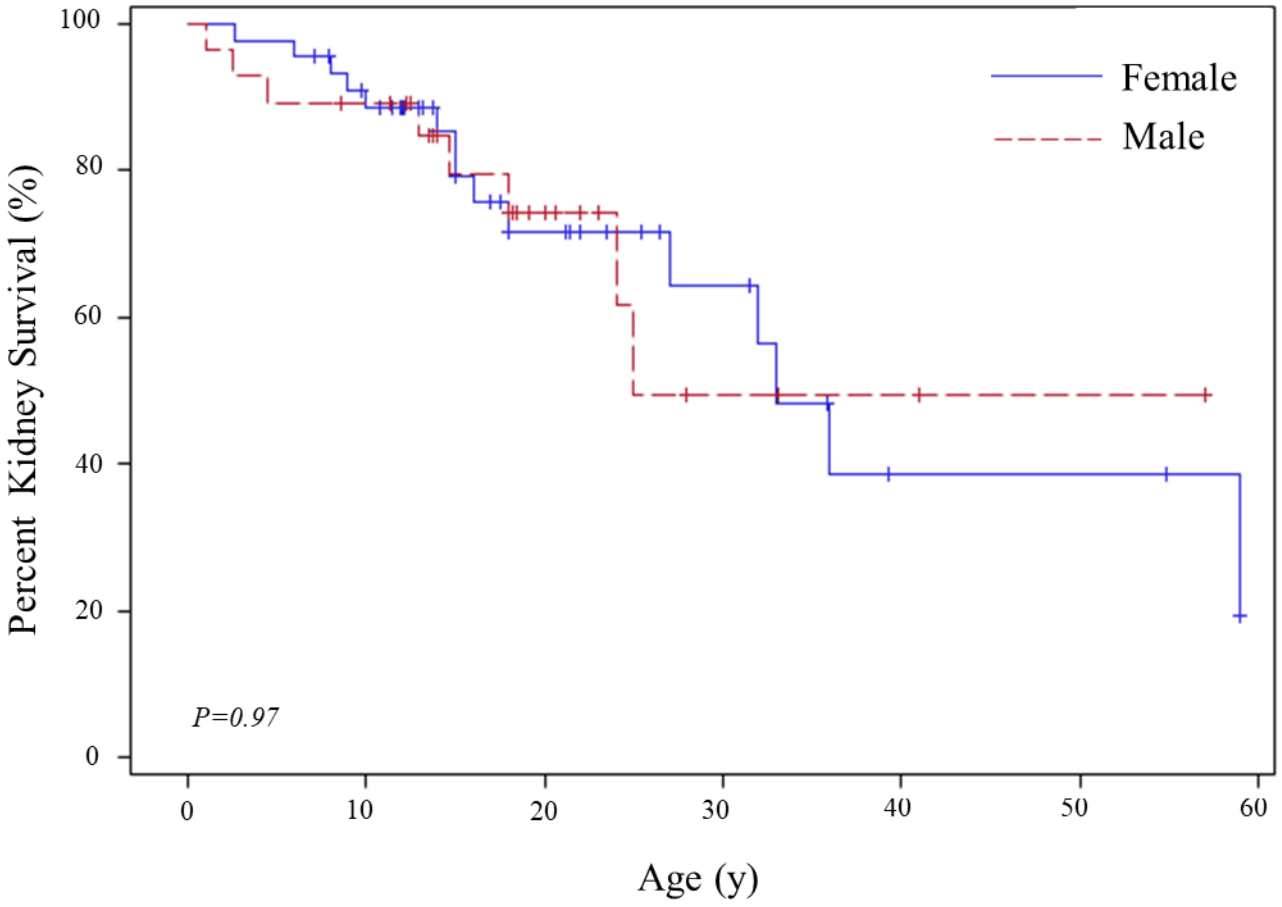
Kidney Survival in males and females



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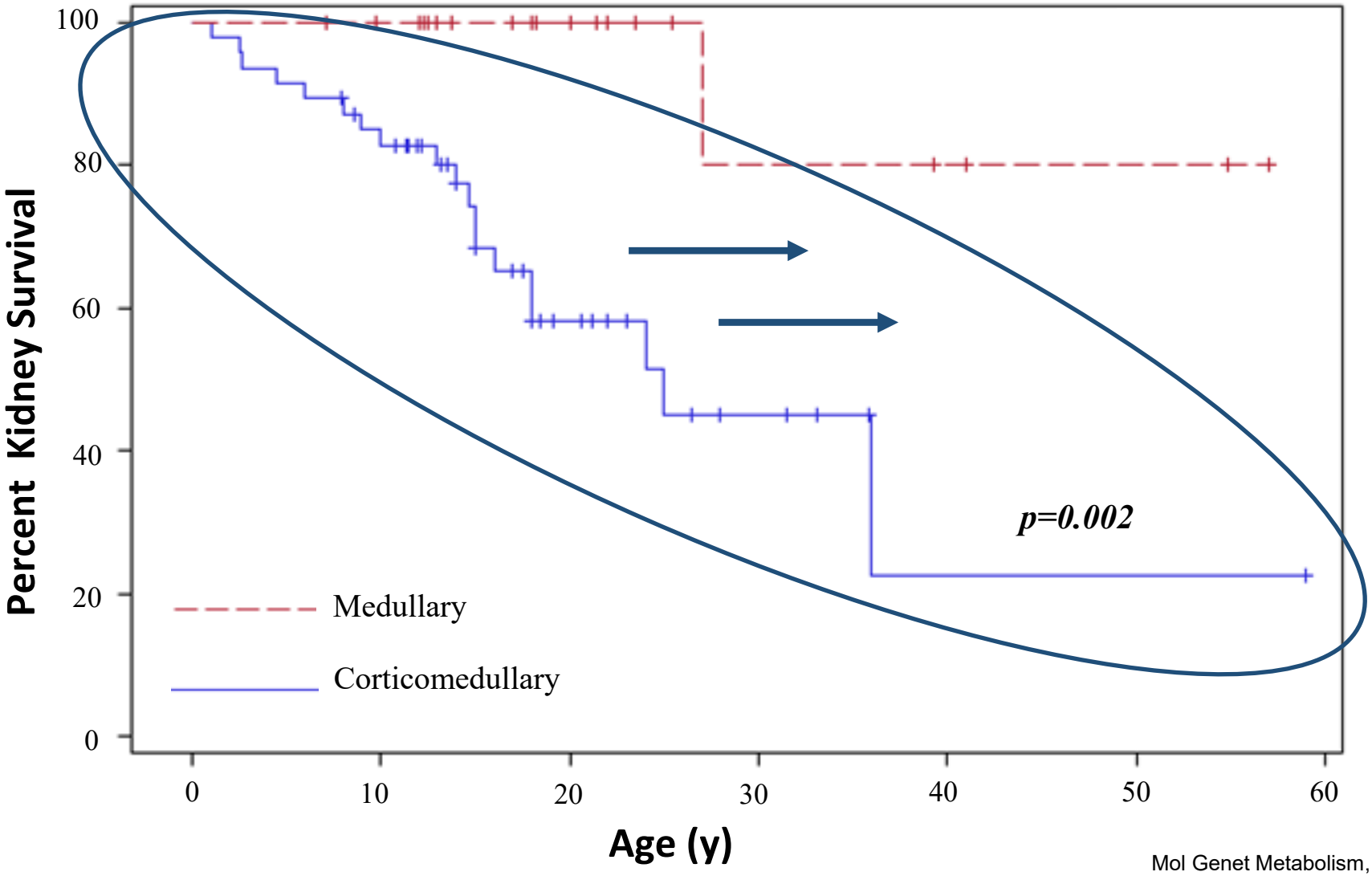
ARPKD patients with corticomedullary disease require earlier transplant



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Kidney transplantation

Corticomedullary	Medullary
19 of 47 at ages 1.1 to 36 (13.2 ± 8.8 y)	1 of 23 at age 27 y

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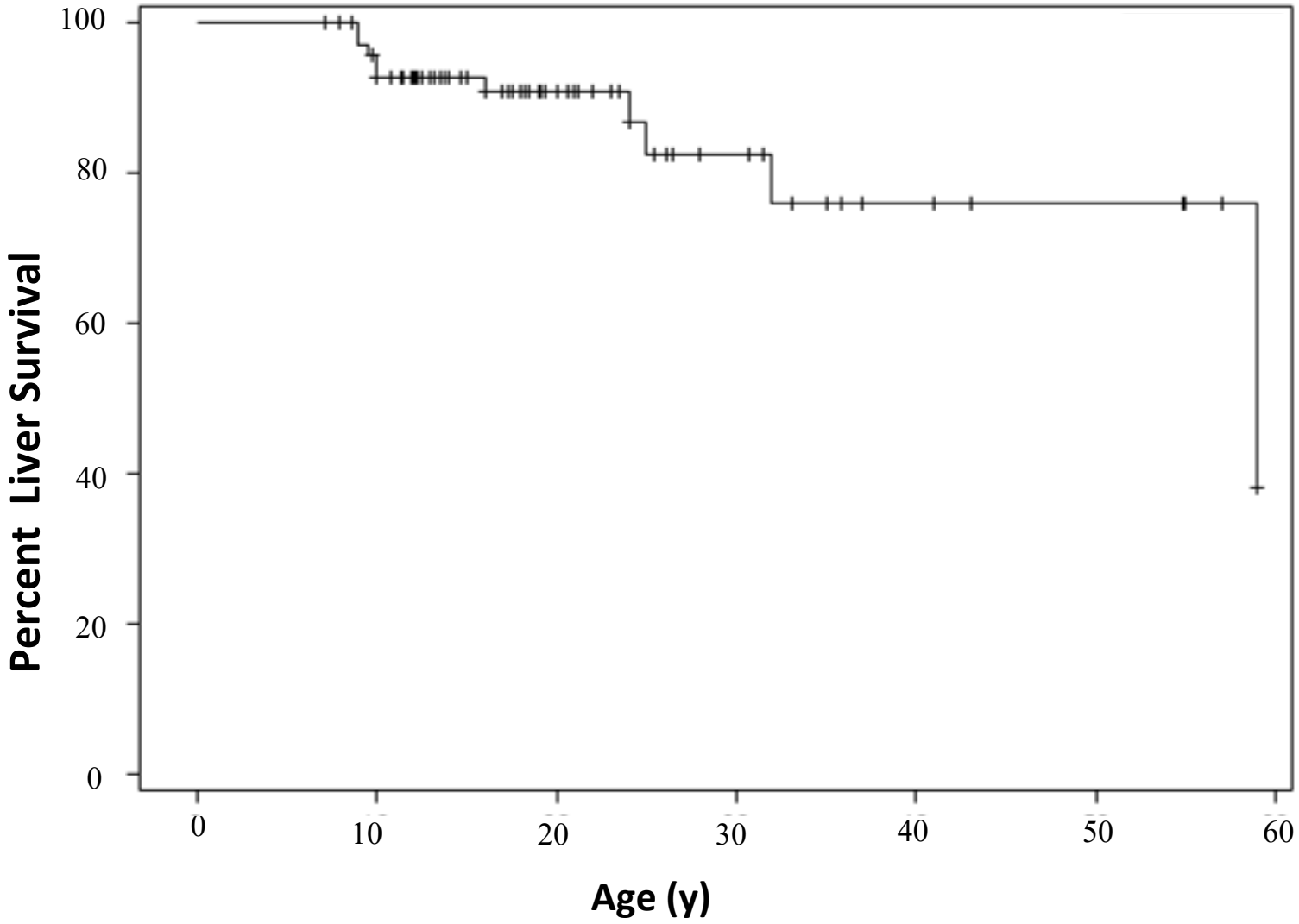
25% of ARPKD patients require liver transplantation by age 35



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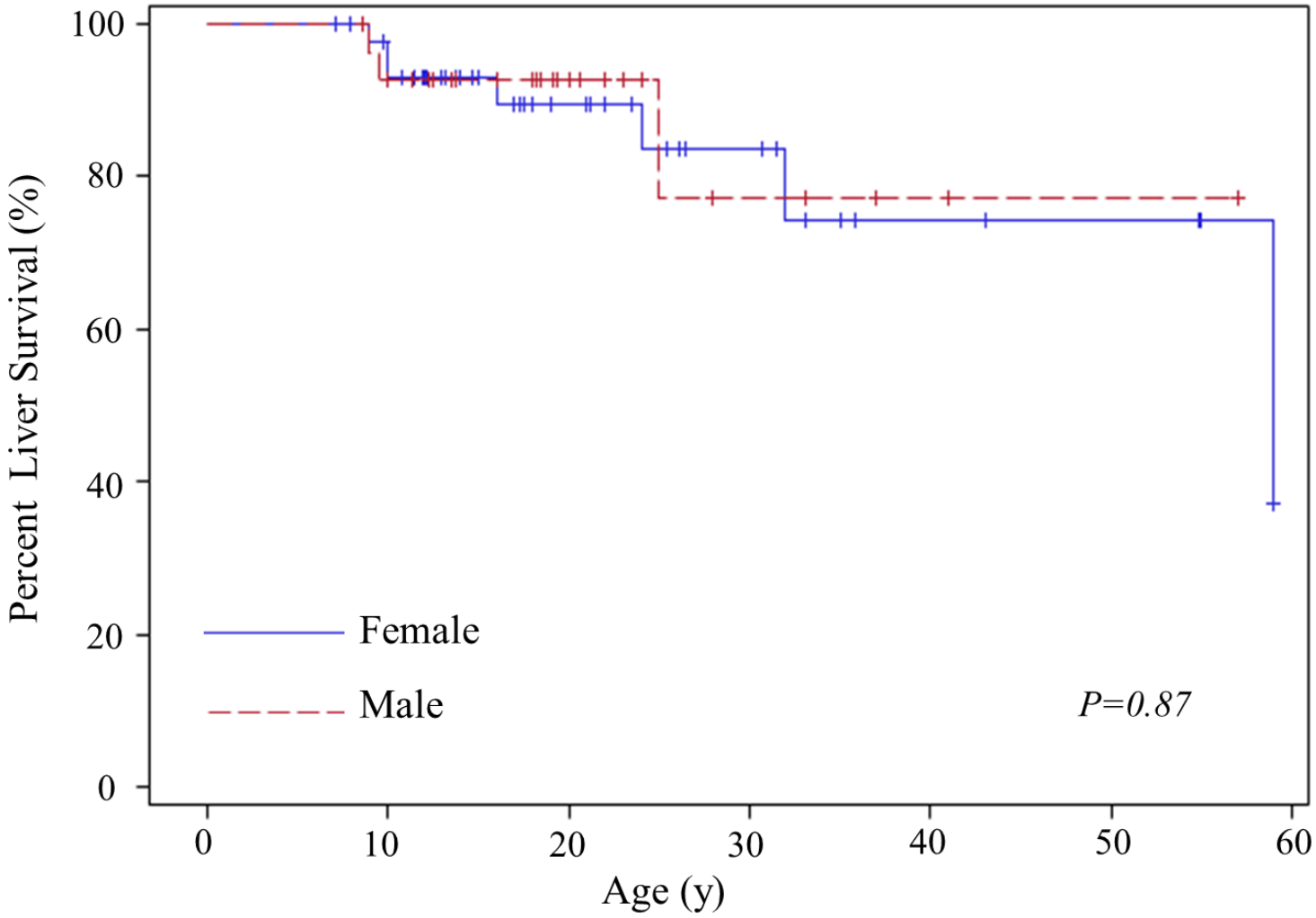
Liver transplantation in males vs. females



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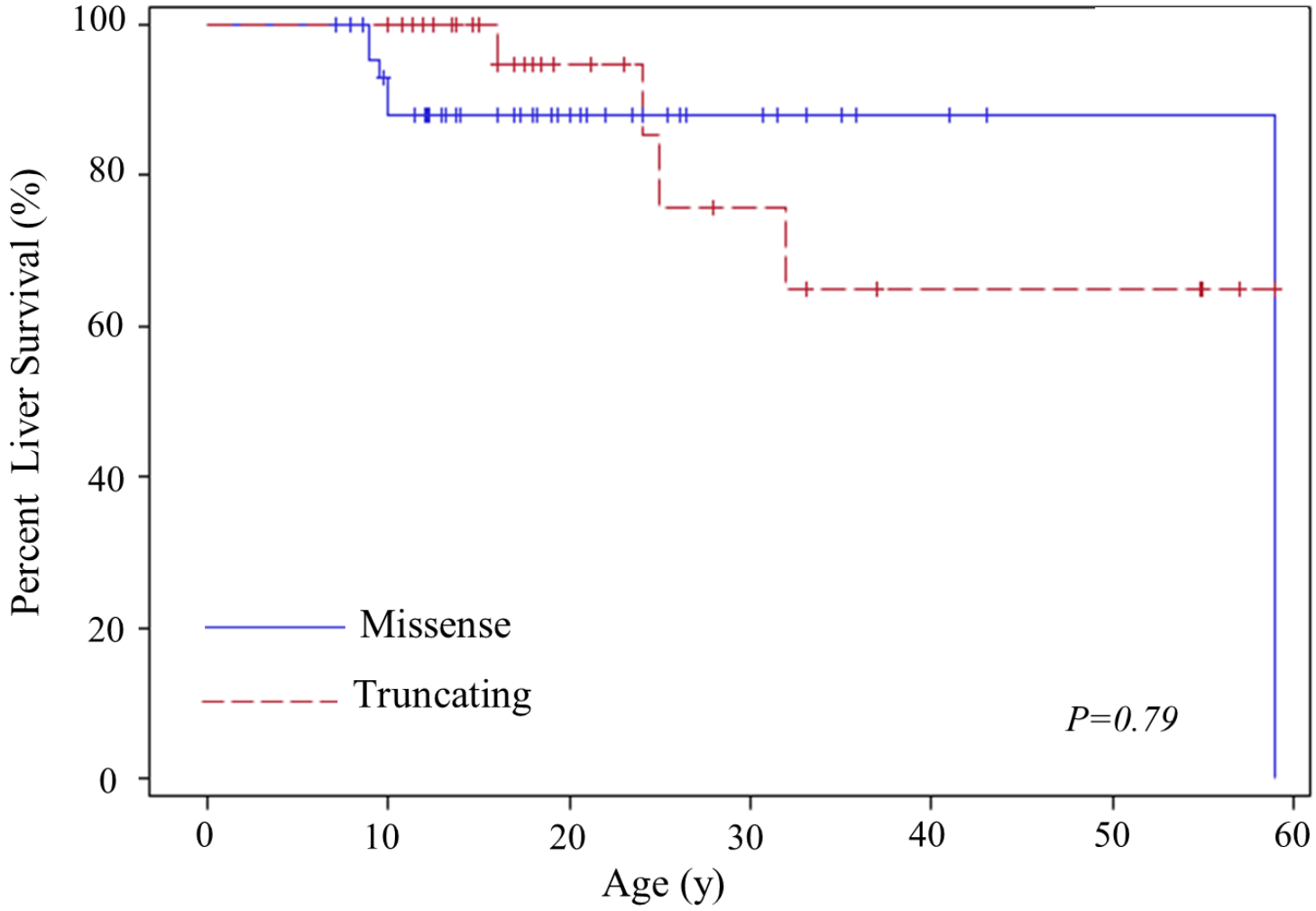
Liver transplantation across *PKHD1* variants



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Portal hypertension

	Number (%)
Portal Hypertension	51 of 72* (71)
Males with portal hypertension	25 of 51
Females with portal hypertension	26 of 51
Esophagogastroduodenoscopy performed	45 of 72 (63)
Esophageal Varices	31 of 45 (69)
Variceal Banding	17 of 31 (55)
Variceal Bleeding	6 of 31 (19)

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Esophageal varices

- Ages of 31 patients with varices: 2 to 47 y
  (16.8 ± 12 y)
- Ages of the 14 patients without varices: 4 to 52 y
  (17.6 ± 11.4 y)
- Ages of 6 patients with variceal bleeding: 2 to 51 y
  (18.7 ± 21 y)

4 combined liver-kidney transplantations

10 liver transplants

- 4 of 10 combined liver-kidney transplants
  end stage kidney disease and moderate-severe portal hypertension

  1 of 4 had initial kidney transplantation and received combined liver-kidney as the 2nd transplant.

- 3 of 10 received renal transplant 4, 8 and 14 years prior to the liver transplant

- Indications for liver transplantation 6 patients
  severe portal hypertension in 5
  recurrent cholangitis in 1

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Portosystemic shunt improved portal hypertension in the majority of patients

- 7 had surgical portosystemic shunt placement at ages 2 to 32 y (11.7 ± 9.6 y)

  1 patient required liver transplantation 2 years after shunt due to recurrent severe hepatic encephalopathy that occurred after shunt placement

Patient No	Age at shunt placement	Doing well at most recent contact at age
Patient 1	2	13
Patient 2	8	17
Patient 3	10	11
Patient 4	11	14
Patient 5	11	37
Patient 6	32	33

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Recurrent infections were common

- Urinary tract infections in 25 patients
- Cholangitis in 10 patients
  - 4 recurrent episodes
- Severe febrile illness (sepsis) of unknown etiology in 8 patients
  - 4 of 8 also had episodes of cholangitis and urinary infections
  - 1 of 8 also had cholangitis
  - 1 of 8 also had urinary infections
  - 2 of 8 only had febrile illness of unknown origin

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NIH Study: 60 patients with multiple visits

Longitudinal changes in
kidney imaging findings and kidney size

Longitudinal changes in kidney imaging

- Extent of disease on renal ultrasound remained largely unchanged
- No patient progressed from “medullary” to “corticomedullary”

  6 “corticomedullary” patients, the extent of cystic changes in the cortex increased

  1 “medullary” patient, advanced from partial to complete medullary involvement

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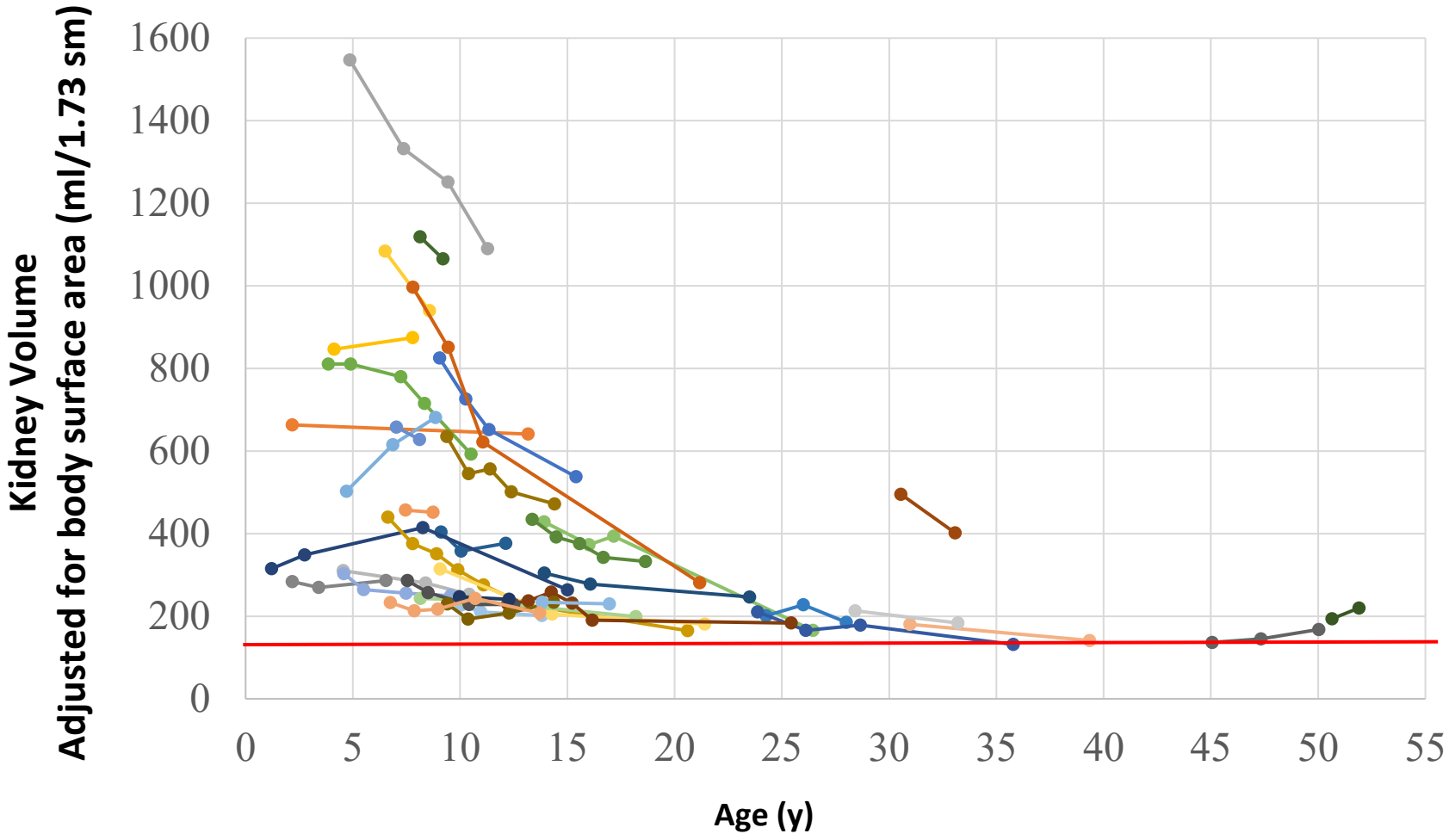
In ARPKD, kidney volume remains unchanged



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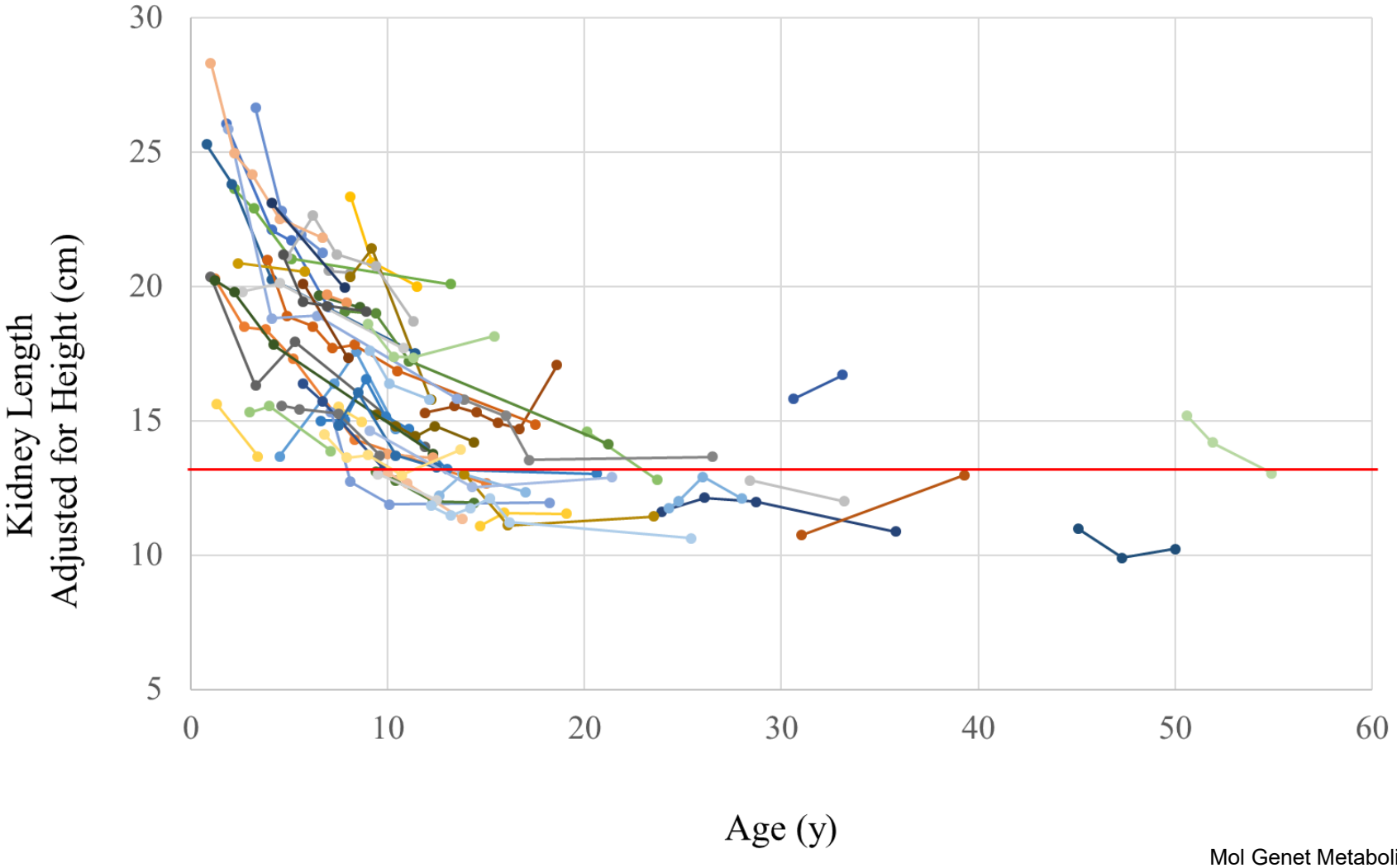
In ARPKD, kidney length remains unchanged



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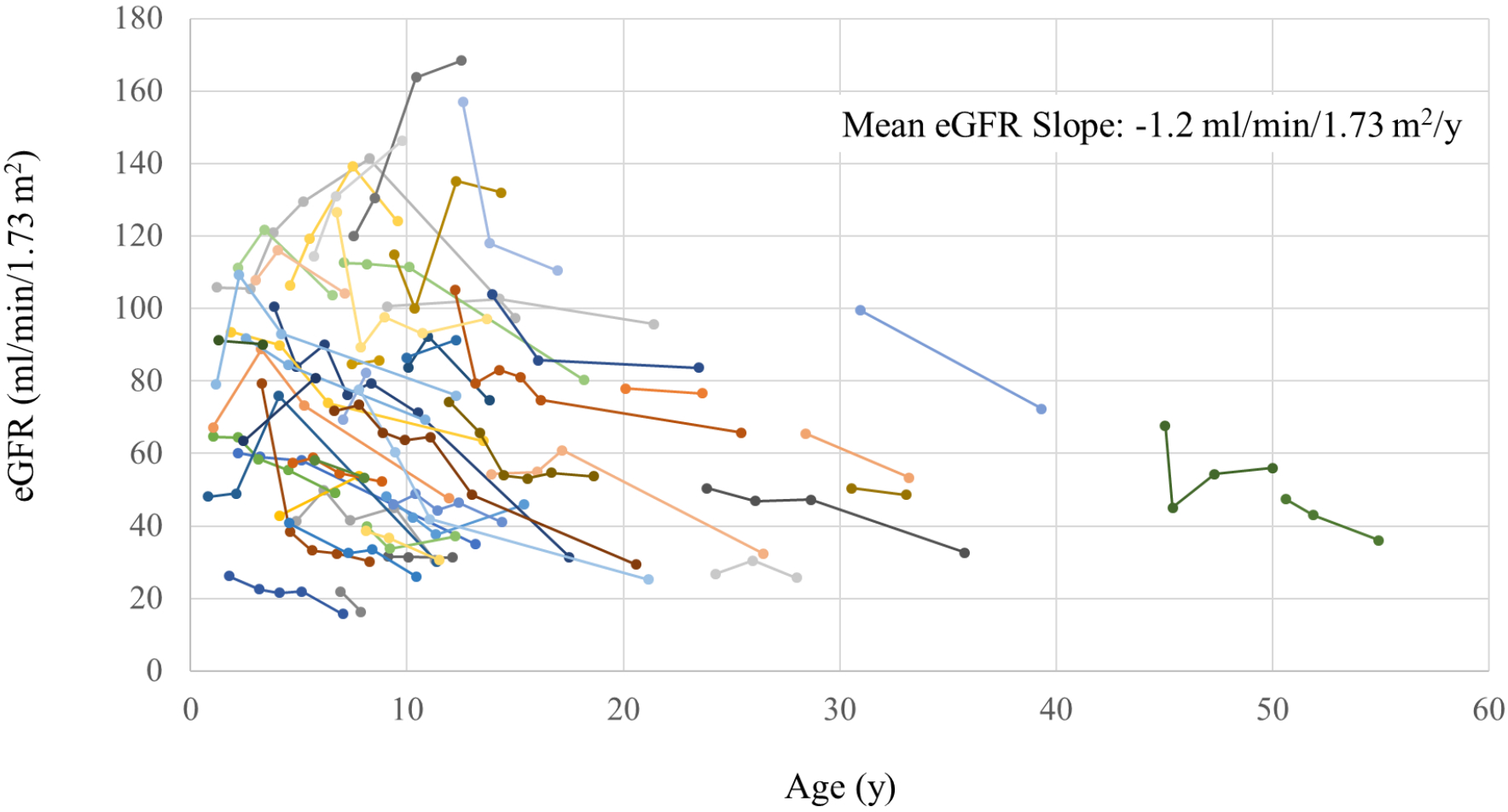
NIH Study: 60 patients with multiple visits

Longitudinal changes in kidney function

What is the rate of decline in kidney function?



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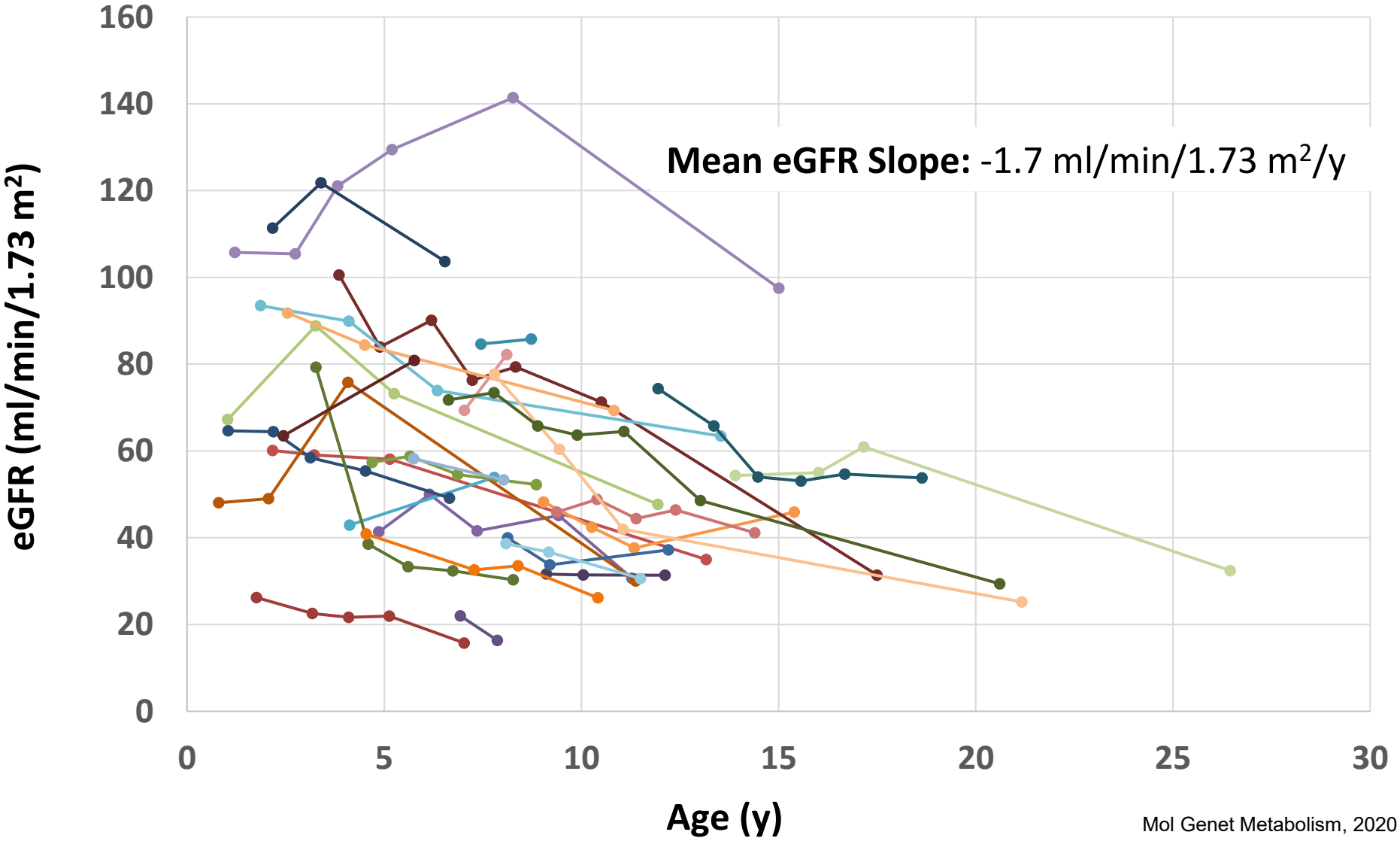
What is the rate of decline in kidney function in children with corticomedullary disease?



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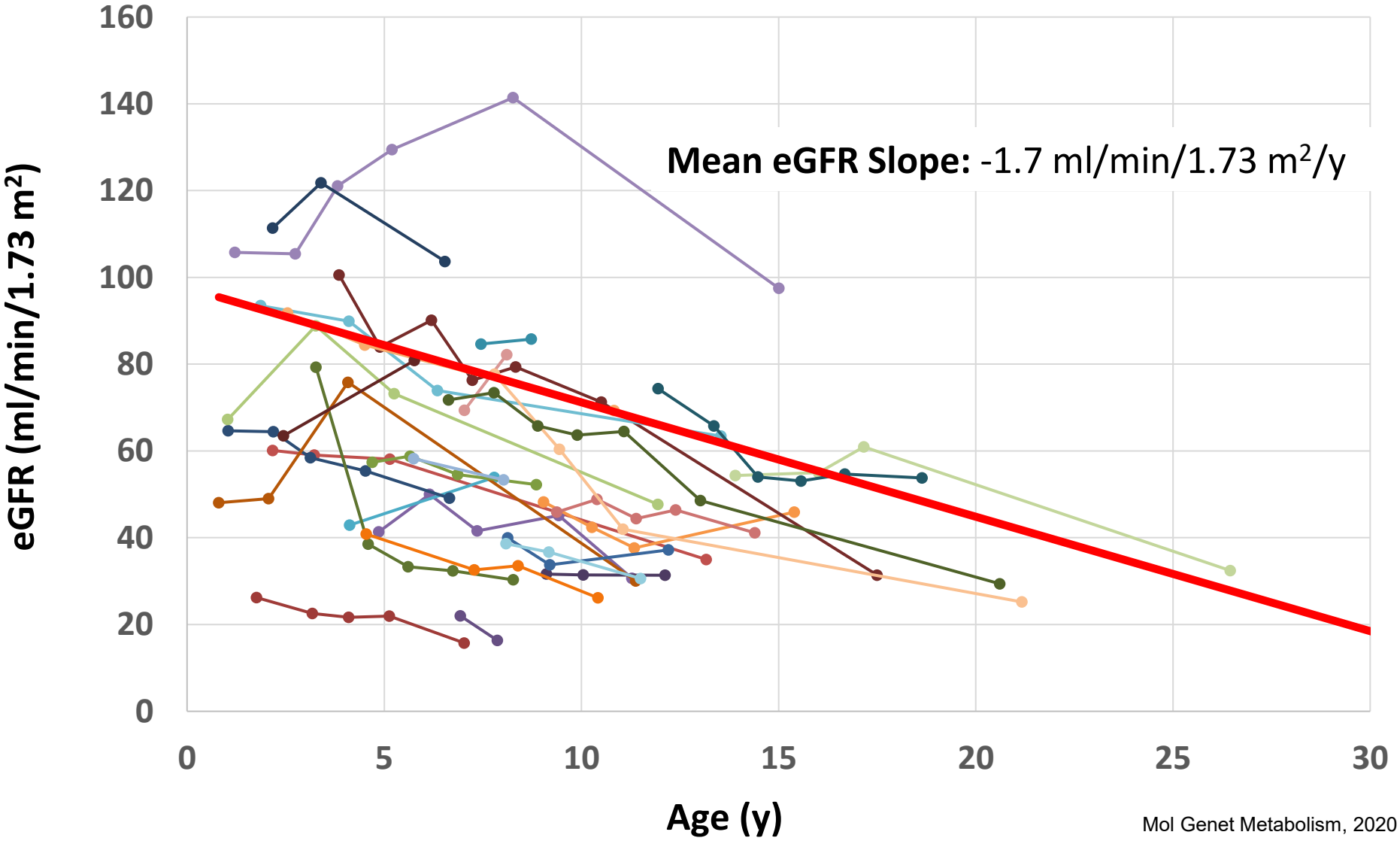

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Average decline rate of eGFR

- All patients

  1.2 (SD = 3.7, range = −9.0 to 11.8)

- Corticomedullary

  1.6 (SD = 3.0, range –6.3 to 11.8)

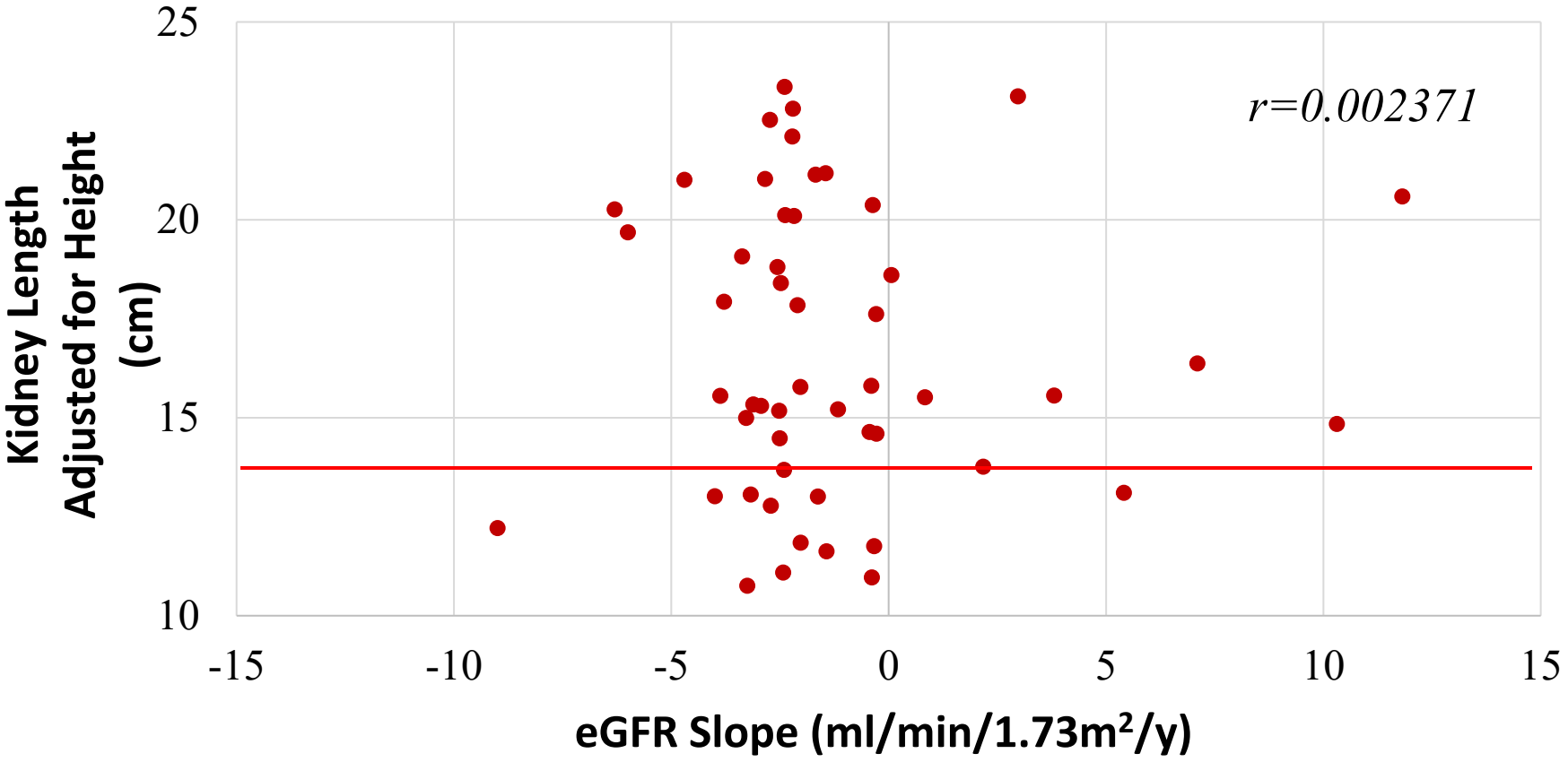
- Medullary

  0.6 (SD = 4.7, range: −9.0 to 10.3)

- Children with corticomedullary

  1.7 (SD = 3.3, range: −6.3 to 11.8)

Is there a correlation between kidney size and decline rate of kidney function ?



There is no correlation.

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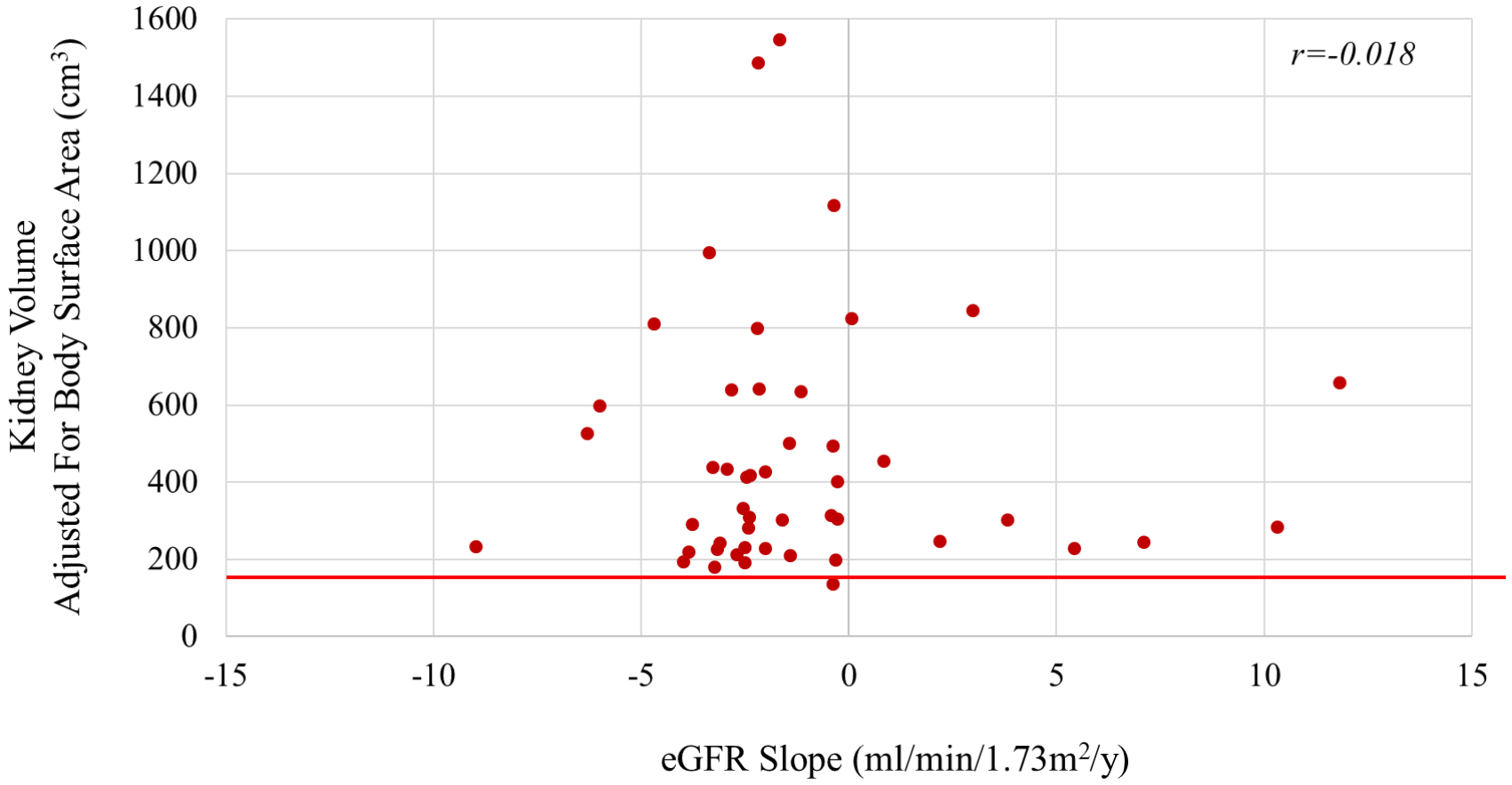

There is no correlation.

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NIH Study: 60 patients with multiple visits

Longitudinal changes in liver disease

Changes in liver imaging over time

First visit Liver Echogenicity Normal/Mildly Increased	21 of 72 (29)
First Visit Liver Echogenicity Moderately/Severely Increased	51 of 72 (71)
Liver echogenicity progressed during the study	14 of 72 (19)

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Changes in liver imaging over time

First visit Intrahepatic Cysts	29 of 72 (40)
First Visit Dilated Common Bile Duct	38 of 71 (54)
Biliary cystic disease progressed during the study	20 of 57 (35)

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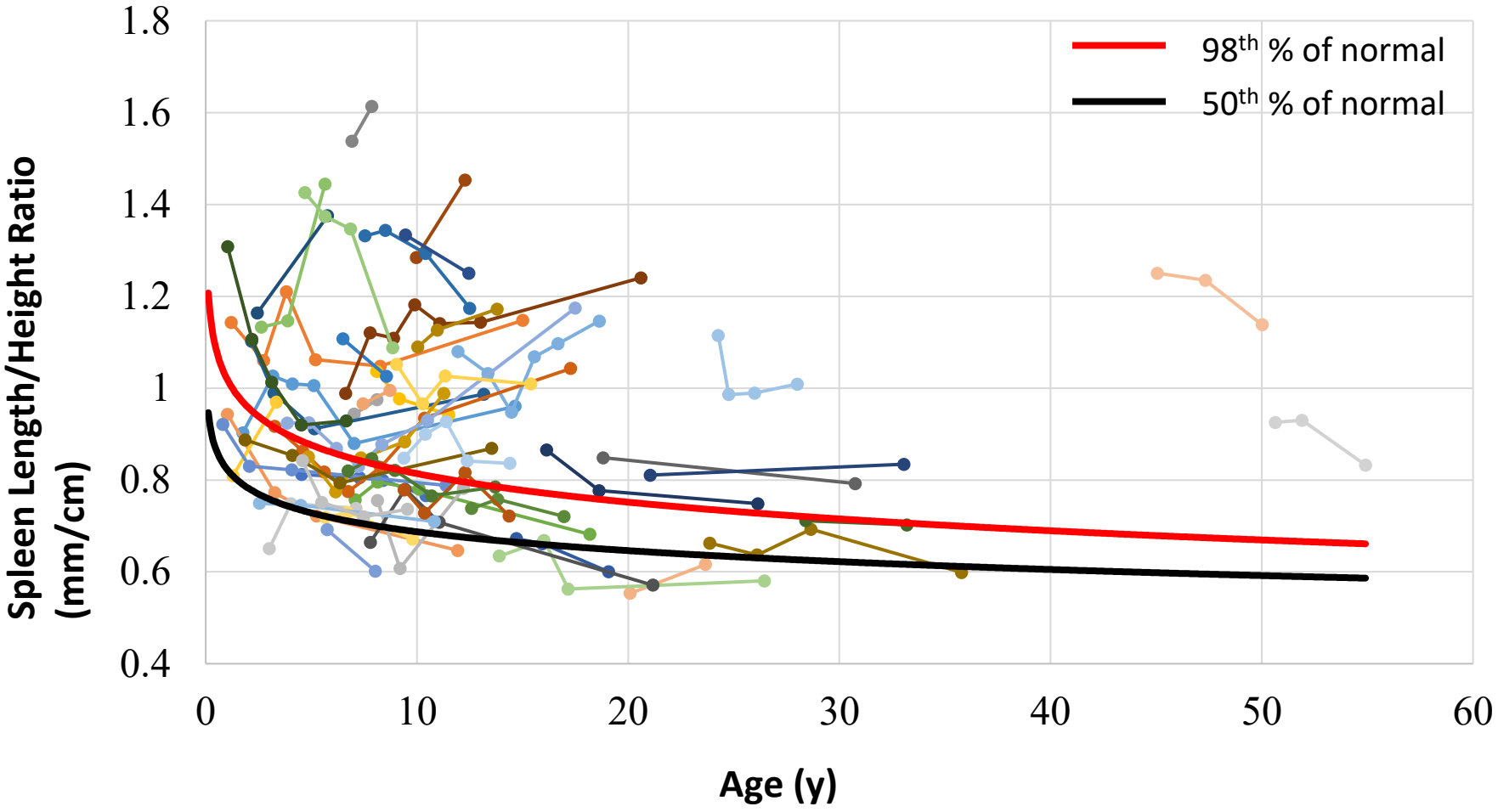
Progression of portal hypertension



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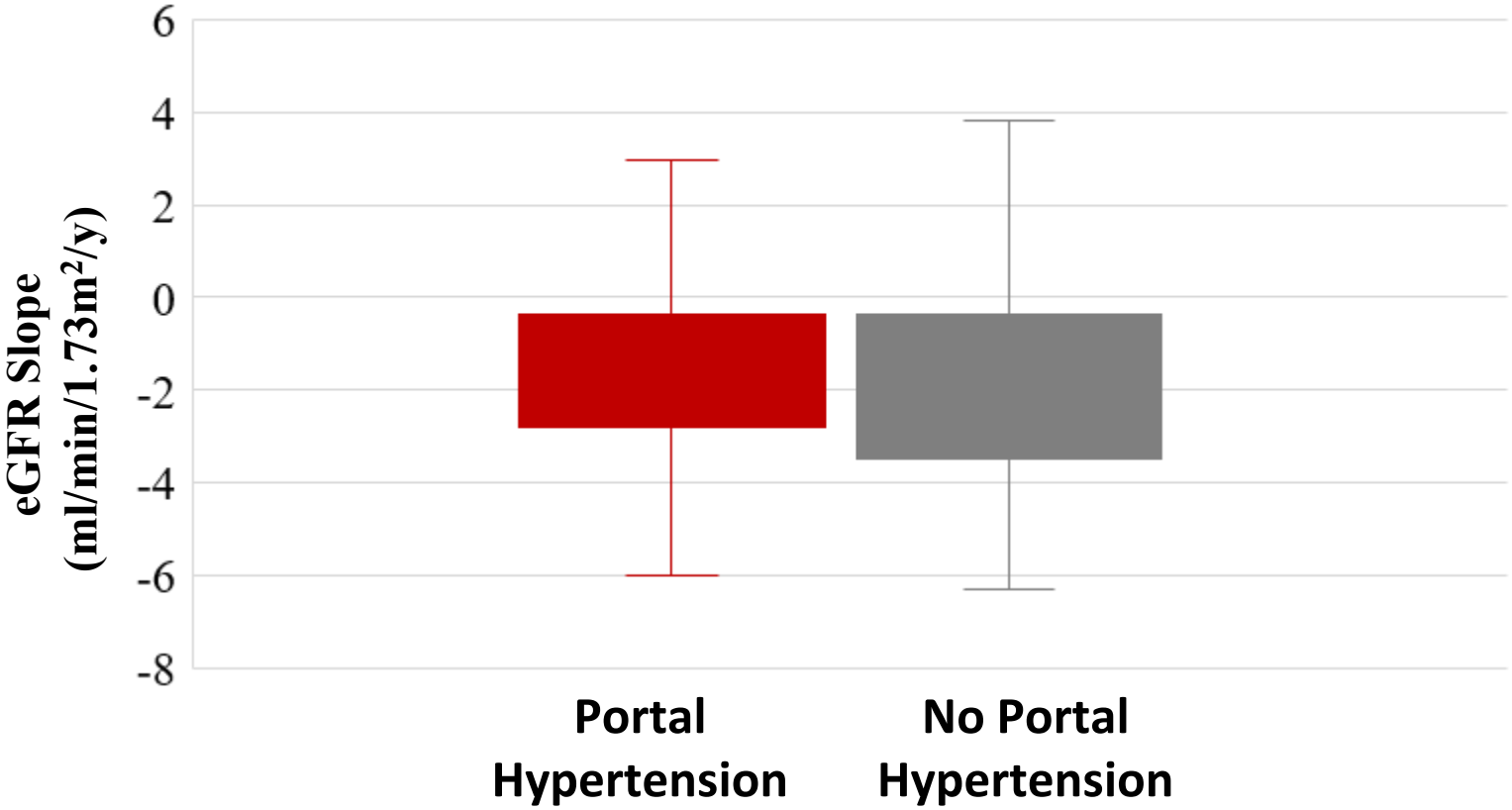
Is kidney disease worse in patients with portal hypertension?



Kidney disease and liver disease are independent from one another.

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Outcome measure for kidney disease

- Kidney size excluded

  Kidney size in ARPKD remains unchanged

  Kidney size does not correlate with the decline rate of kidney function

- eGFR decline rate may be used as outcome measure

  Given the very slow rate of decline and wide variability, large number of patients have to be followed for a long time

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Outcome measures for liver disease

- Portal hypertension
  - Spleen length/height ratio and platelet count
  - Liver elastography

- Liver fibrosis
  - Elastography

- Classification of patients into
  - “no splenomegaly”,
  - “stable splenomegaly”
  - “progressive splenomegaly”

  may be useful in research studies aiming to
  1) identify biological markers of liver disease progression
  2) design of treatment trials

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Outcome measures for kidney and liver disease

- Future research is needed for identification of a biological plasma and/or urine marker(s) to measure progression for kidney and liver disease in ARPKD

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Acknowledgements

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Overall disease progression in kidneys and liver

Table 1. History of kidney and liver transplantation and surgical portosystemic shunt placement in 73 ARPKD patients evaluated at the NIH Clinical Center[€].

	All cohort	Truncating *PKHD1* Variants[£]	Non-Truncating *PKHD1* Variants[£]	*P value*	Perinatal Presentation	Non-Perinatal Presentation	*P value*	Corticomedullary Disease	Medullary Disease	*P value*
Total patients*	73 (100)	28 of 73 (38)	45 of 73 (62)	-	31 of 73 (42)	42 of 73 (58)	-	47 of 70[¥] (67)	23 of 70 (33)	-
Age**	22.2 ± 12.9	25.3 ± 15.2	20.3 ± 10.9	-	18.0 ± 7.5	25.3 ± 15.0	-	20.2 ± 10.9	22.9 ± 12.9	-
Kidney transplantation	23 of 73 (32)	8 of 28 (29)	15 of 45 (33)	*0.72*	13 of 31 (42)	10 of 42 (24)	*0.18*	19 of 47 (40)	1 of 23 (4)	*0.01*
Age at kidney transplantation[¥]	17.5 ± 13.5	13.7 ± 12.5	19.6 ± 14.0	*0.37*	10.1 ± 7.1	27.2 ± 13.9	*0.0005*	13.2 ± 8.8	27.0 ± 0.0	*0.002*
Liver transplantation	10 of 73 (14)	4 of 28 (14)	6 of 45 (13)	-	6 of 31 (19)	4 of 42 (10)	-	6 of 47 (13)	3 of 23 (13)	-
Age at liver transplantation	20.3 ± 15.9	24.3 ± 6.6	17.8 ± 20.2	-	15.6 ± 7.4	27.5 ± 23.5	-	15.6 ± 7.4	17.0 ± 3.0	-
Surgical Portosystemic shunt	7 of 73 (10)	2 of 28 (7)	5 of 45 (11)	-	2 of 31 (7)	5 of 42 (12)	-	6 of 47 (13)	1 of 23 (4)	-
Age at surgical portosystemic shunt	11.7 ± 9.6	21.0 ± 15.6	8.0 ± 4.1	-	4.5 ± 3.5	14.6 ± 9.9	-	11.5 ± 10.5	13.0 ± 0.0	-

[€] This table presents data on all patients evaluated under this study (13 with single and 60 with multiple visits). *Results are reported as number (percentage), and mean ± standard deviation. **Age at the time of most recent data collection. Ages reported in years. [¥] Three patients who could not be classified into corticomedullary or medullary groups (because their ultrasound results from the time of diagnosis were not available) received kidney transplantation at ages 32, 33 and 59 years. [£] Based on the severity of the pathogenic variants in *PKHD1*, patients were classified into "truncating" (one protein truncating only or one truncating in combination with a missense variants) and "non-truncating" (one or two missense variants) groups.

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Kidney Disease

Table 2. Characteristics of kidney disease and *PKHD1* variants in 60 ARPKD patients prospectively evaluated at the NIH Clinical Center on multiple visits.

	***PKHD1* Variant Type**			**Presentation**			**Extent of Kidney Disease on USG**		
	Truncating[£]	**Non-truncating[£]**	***P Value***	**Perinatal**	**Non-perinatal**	***P Value***	**Corticomedullary**	**Medullary**	***P Value***
Number of patients*	22 of 60 (37)	38 of 60 (63)	-	27 of 60 (45)	33 of 60 (55)	-	40 of 60 (67)	20 of 60 (33)	-
Age (y)**	14.5 ± 13.8	9.1 ± 6.3	-	8.9 ± 6.9	12.8 ± 11.7	-	10.1 ± 9.0	13.1 ± 11.7	-
Patients with truncating *PKHD1* mutations	22 of 22 (100)	0 of 38 (0)	-	10 of 27 (37)	12 of 33 (36)	-	17 of 40 (43)	5 of 20 (25)	-
Patients with perinatal presentation	10 of 22 (46)	17 of 38 (45)	-	27 of 27 (100)	0 of 33 (0)	-	24 of 40 (60)	3 of 20 (15)	-
Patients with corticomedullary involvement	17 of 22 (77)	23 of 38 (61)	-	24 of 27 (89)	16 of 33 (49)	-	40 of 40 (100)	0 of 20 (0)	-
Kidney length corrected for height (cm)[¥]	16.3 ± 3.8	17.1 ± 3.8	*0.46*	18.0 ± 4.1	15.9 ± 3.4	*0.05*	18.4 ± 3.7	14.0 ± 1.7	*< 0.0001*
Kidney volume corrected for BSA (ml)[¥]	433 ± 258	498 ± 370	*0.47*	611 ± 417	394 ± 218	*0.04*	603 ± 348	240 ± 39	*< 0.0001*
eGFR slope (ml/min/1.73m^2/y)	-2.2 + 3.9	-0.6 + 3.4	*0.14*	-1.6 + 3.7	-1.0 + 3.7	*0.60*	-1.6 + 3.1	-0.6 + 4.7	*0.46*

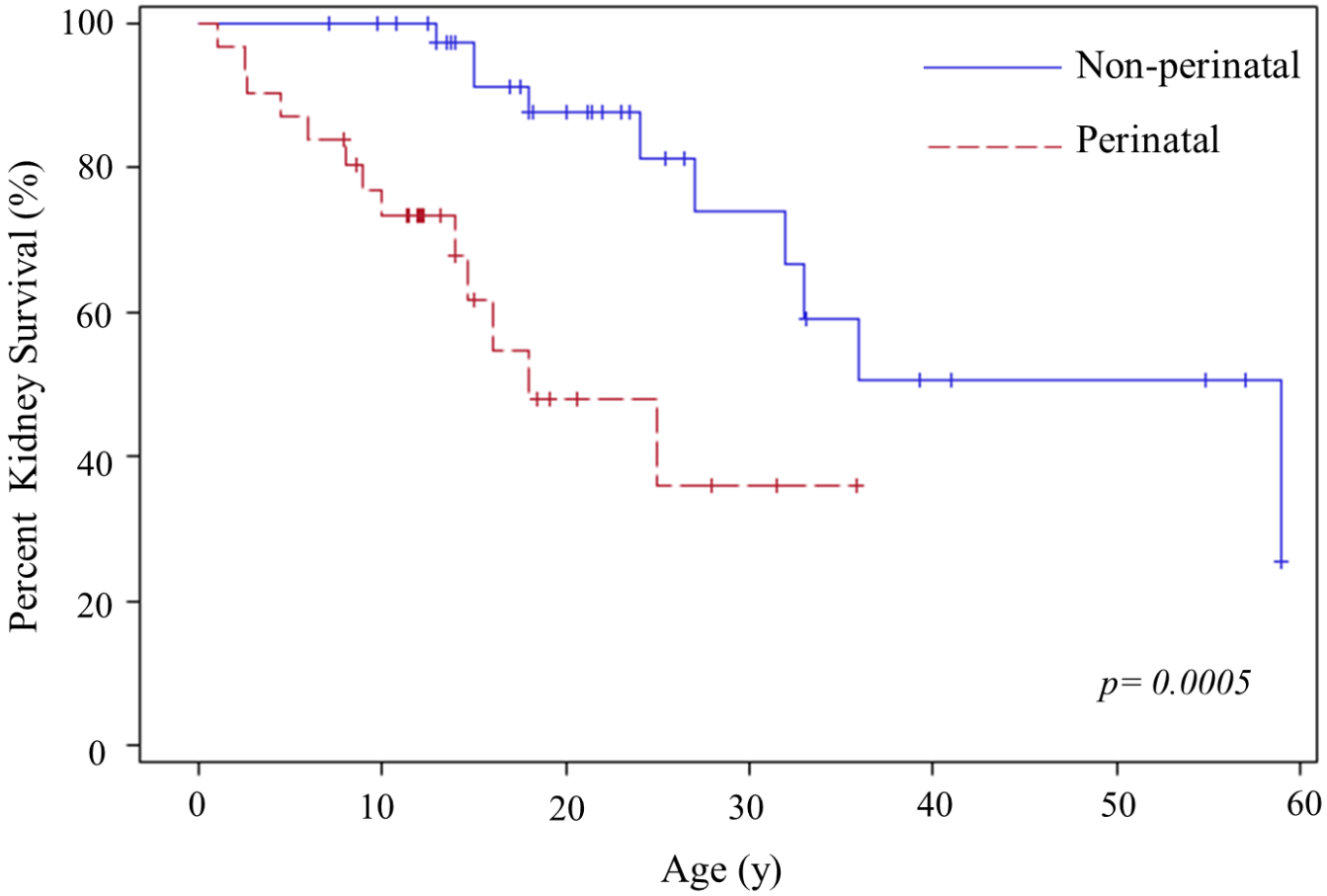
*Results are reported as number (percentage), and mean ± standard deviation, **Age at the time of first NIH evaluation, [¥]Data from first NIH visit, [£]Based on the severity of the pathogenic variants in *PKHD1*, patients were classified into "truncating" (one protein truncating only or one truncating in combination with a missense variants) and "non-truncating" (one or two missense variants) groups.

Table 4. Clinical characteristics of 54 prospectively followed ARPKD patients with respect to portal hypertension.

	No Portal Hypertension	Portal Hypertension	*p value*	Stable Portal Hypertension	Progressive Portal Hypertension	*P value*
Number of patients (%)	18 of 54 (40%)	36 of 54 (60)	-	14 of 36 (39)	22 of 36 (61)	-
Age*	9.0 ± 5.8	11.2 ±11.5	-	15.4 ± 15.5	8.6 ± 7.4	-
Number of Patients with Truncating[£] *PKHD1* Variants (%)	6 of 18 (33)	14 of 36 (39)	*0.690*	3 of 14 (21)	11 of 22 (50)	*0.087*
ALT	23 ± 8	29 ± 18	*0.193*	22 ± 4	34 ± 22	*0.081*
AST	33 ± 11	41 ± 18	*0.088*	32 ±11	48 ± 19	*0.013*
GGT	15 ± 6	26 ± 20	*0.030*	23 ± 17	29 ± 22	*0.467*
PT	12.97 ± 0.58	13.53 ± 1.22	*0.075*	13.58 ± 1.24	13.50 ± 1.06	*0.858*
Direct bilirubin	0.11 ± 0.03	0.16 ± 0.08	*0.048*	0.13 ± 0.07	0.18 ± 0.09	*0.197*
Albumin	4.14 ± 0.31	3.94 ± 0.40	*0.086*	4.01 ± 0.45	3.88 ± 0.36	*0.375*
Ammonia	26 ± 9	50 ± 27	*0.014*	35 ± 15	62 ± 30	*0.016*
Platelet count	271 ± 61	171 ± 84	*<0.0001*	179 ± 74	167 ± 91	*0.684*
APRI	0.30 ± 0.12	0.83 ± 0.84	*0.018*	0.53 ± 0.29	1.04 ± 1.05	*0.115*
Increased liver echogenicity**	9 of 18 (50)	28 of 36 (78)	*0.051*	11 of 14 (79)	17 of 22 (77)	*0.943*
Number of Patients with Liver cysts (%)	3 of 18 (17)	19 of 36 (53)	*0.038*	4 of 14 (29)	15 of 22 (68)	*0.065*
eGFR slope	- 0.91 + 4.05	- 0.43 + 4.4	*0.743*	-0.15 + 4.4	-0.63 + 4.6	*0.809*

Six of the 60 patients with multiple NIH visits were excluded from portal hypertension-related analysis because 2 had surgical portosystemic shunt placed, 3 received liver transplantation after the first NIH visit and 1had hereditary spherocytosis. *Age at first NIH evaluation. **Moderate to severe liver echogenicity on ultrasound, ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; PT, prothrombin time; APRI, AST to Platelet Ratio Index; eGFR, estimated glomerular filtration rate. Laboratory values are from the first NIH visits. [£] Based on the severity of the pathogenic variants in PKHD1, patients were classified into "truncating" (one protein truncating only or one truncating in combination with a missense variants) and "non-truncating" (one or two missense variants) groups.

Kidney Survival in Perinatal vs Non-perinatal



Mol Genet Metabolism, 2020

ARPKD patients: *PKHD1* variants

- 90 probable ARPKD patients
  - 78 patients from 68 families met clinical criteria
  - 73 with *PKHD1* mutations
- 77 *PKHD1* sequence variants
  - 19 truncating
  - 55 missense (46 pathogenic)
  - 41 novel
- Mutation detection rate 79 % (108/137)
  - 82 % in Kidney-predominant patients
  - 63 % in Liver - predominant patients
- No patients with 2 truncating mutations

Gunay-Aygun et al., 2010 Mol Genet and Metab

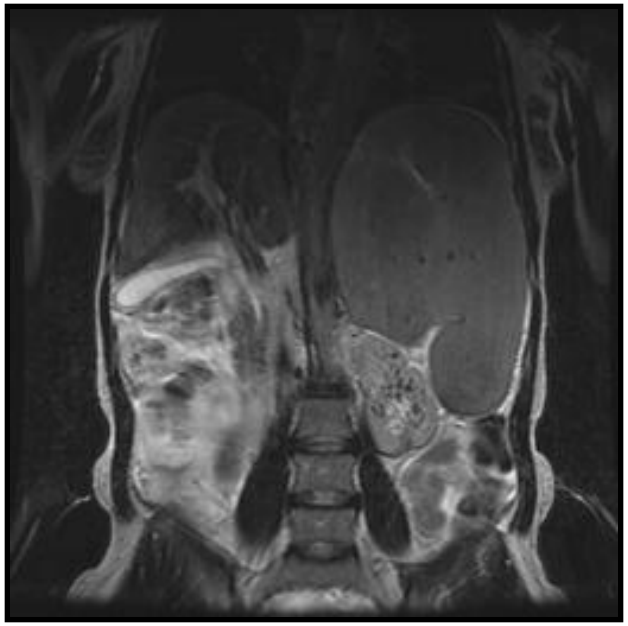
73 confirmed ARKPD patients with pathogenic variants in *PKHD1*

- 73 patients from 63 families

- 43 families, 2 mutations
- 20 families 1 mutation

- 29 males
- 44 females

NIH ARPKD Cohort: Age of Onset

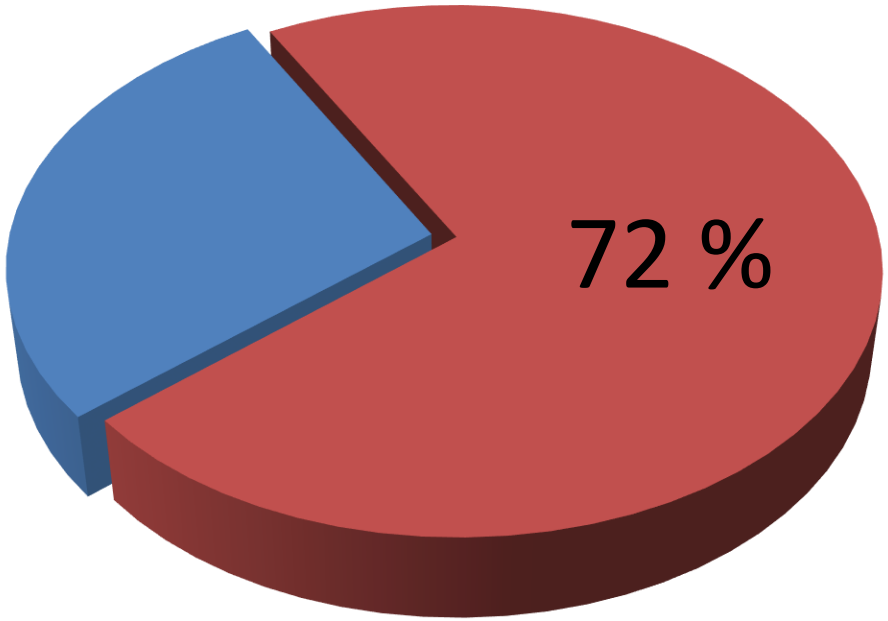


	Perinatal (%)	Non-perinatal (%)
Age of Onset	48	52
Age at NIH evaluation	9.2 ± 7.4 y	17.2 ± 15.1 y

ARPKD: Findings on Presentation

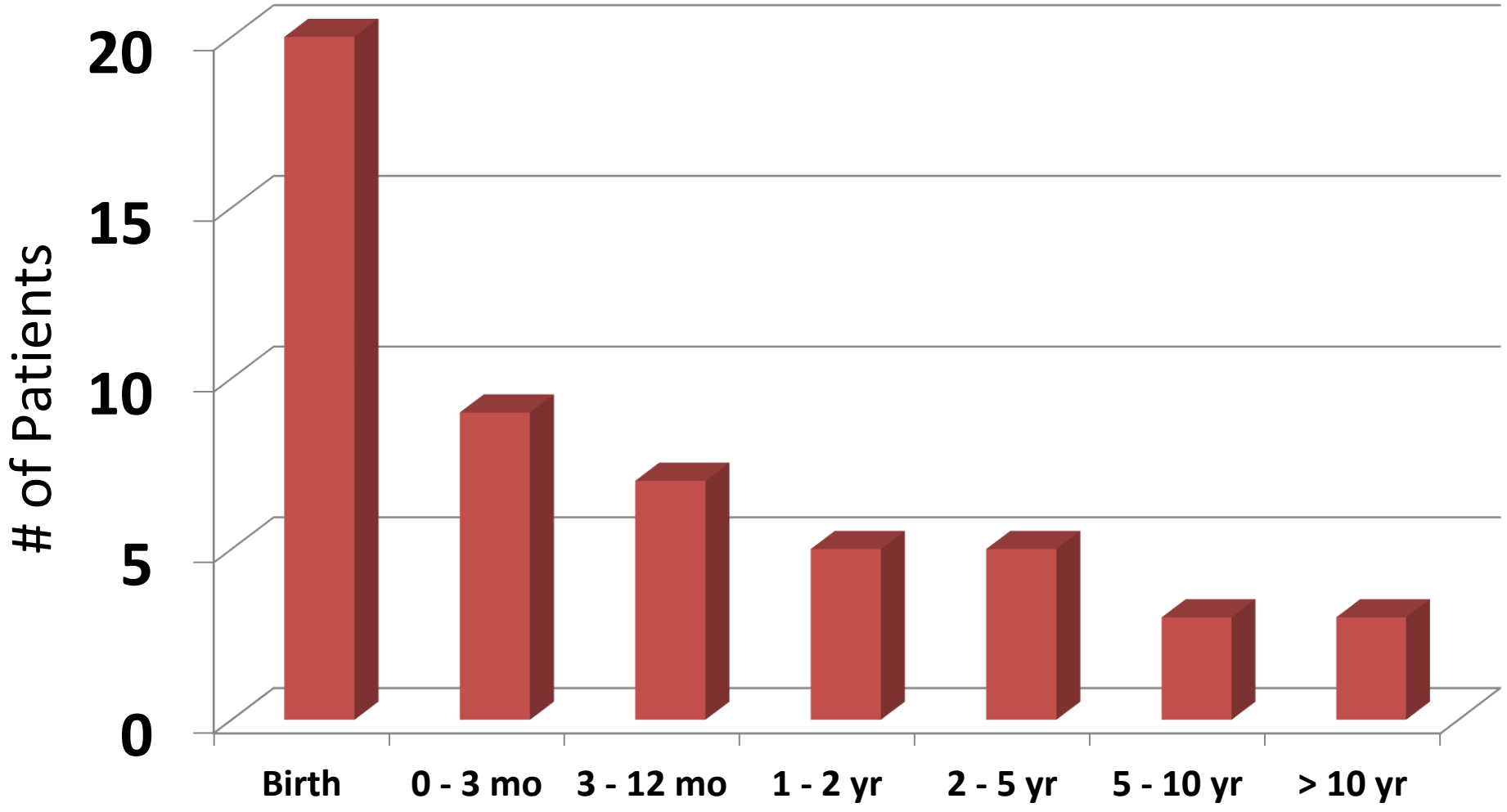
		%
Renal	Hypertension	32
	Cardiomyopathy	3
	Enlarged echogenic kidneys on USG	20
	Palpable kidneys	8
	Urinary infection	12
Hepatic	Splenomegaly	12
	Thrombocytopenia	6
	Cholangitis	6
	Liver cysts	3
	Esophageal variceal bleeding	1.4

ARPKD: Hypertension



Clin J Am Soc Nephrol. 2010

Age at Diagnosis of Hypertension

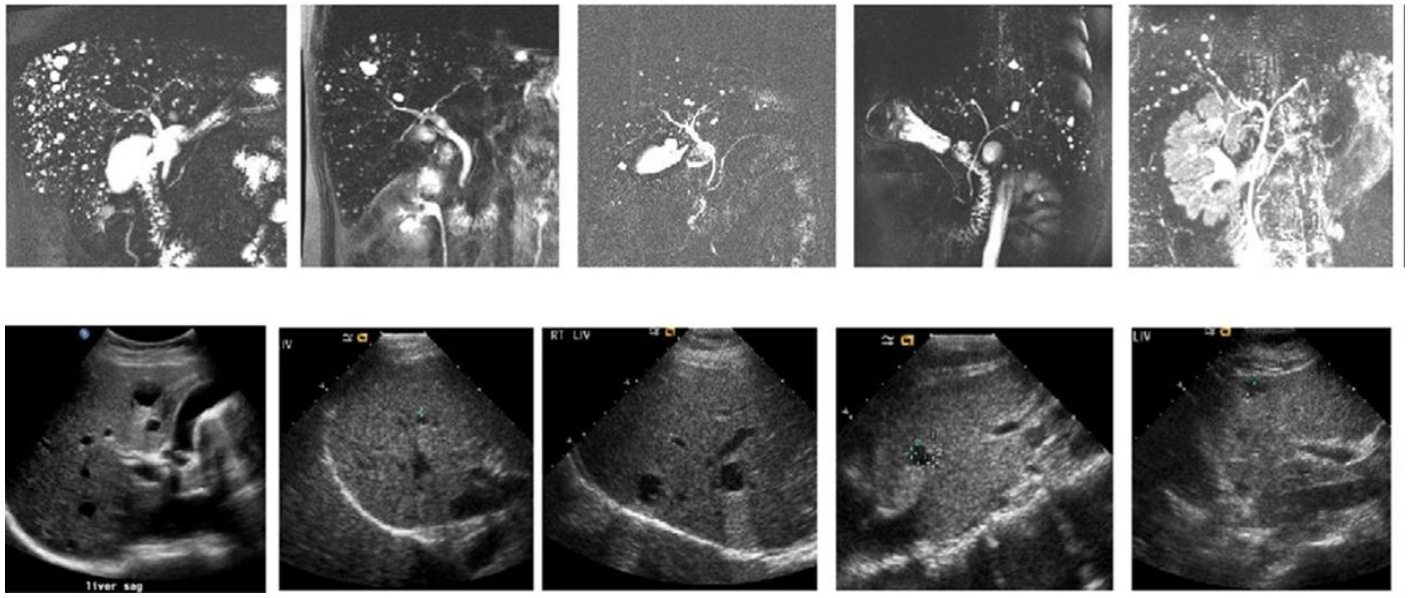


Other Renal Findings

- Hypercalciuria not typical
  - 92 % normal 24-hour calcium excretion
- Proteinuria not typical
  - 24-hour urine protein excretion normal in 61 %
  - Mild proteinuria in 39%
- Proximal tubular function intact
  - *No glucosuria*
  - *No aminoaciduria*

Liver findings in carriers for ARPKD

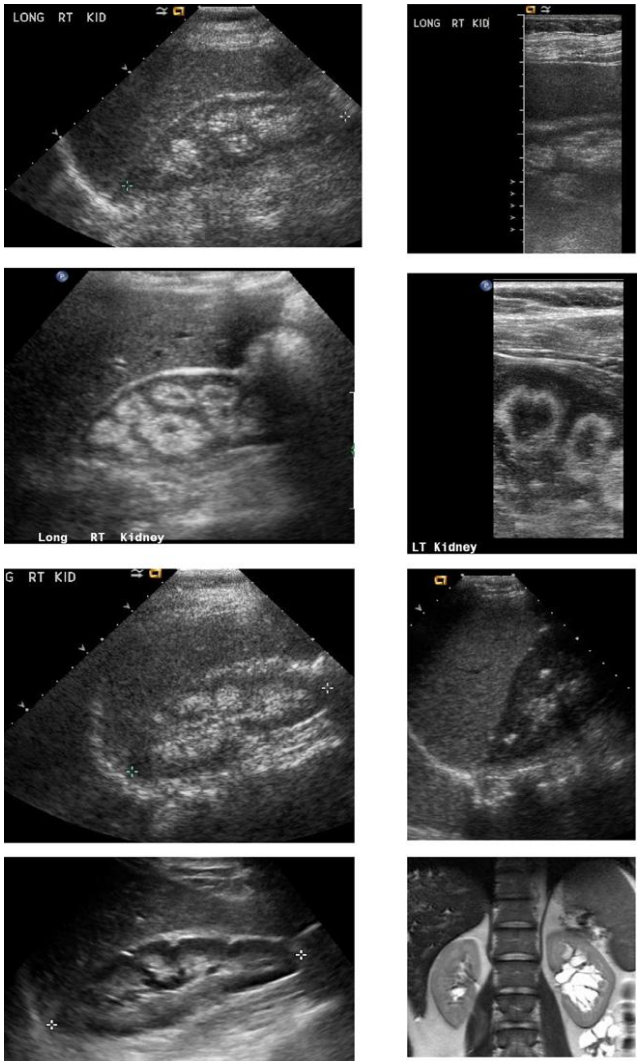
Multiple liver cysts
(9% of carriers)



Gunay-Aygun et al., Mol Genet Metab. 2011

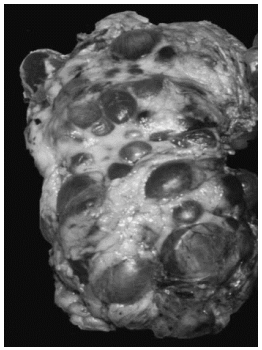
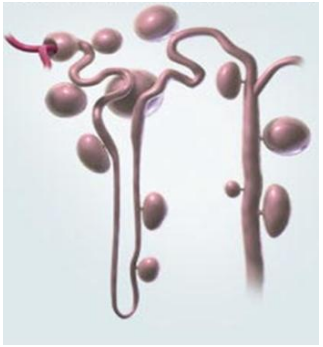
Kidney findings in carriers for ARPKD

"Medullary Nephrocalcinosis"
(5% of carriers)



Gunay-Aygun et al., Mol Genet Metab. 2011

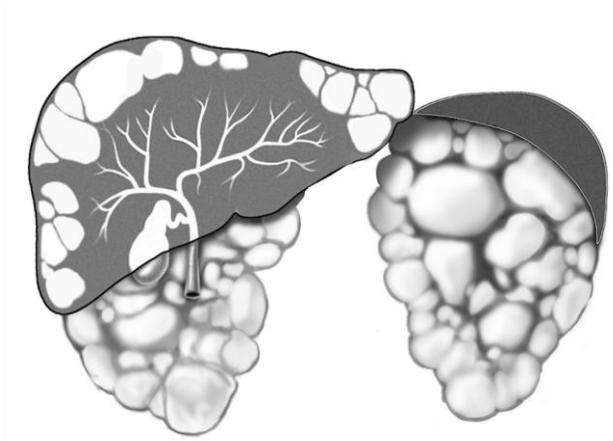
Polycystic kidney disease

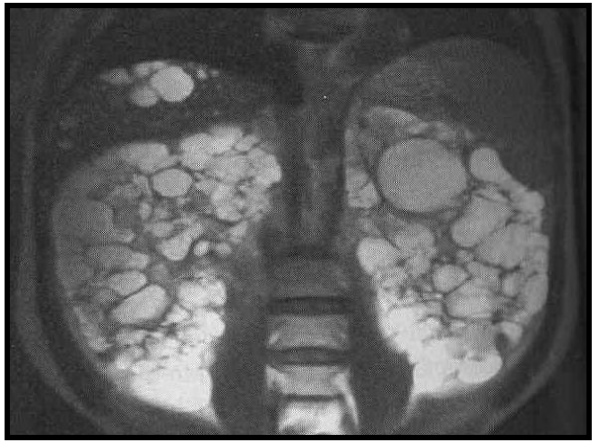
	Dominant PKD	Recessive PKD
Incidence	• 1 in 1,000 births	• 1 in 20,000 births
Gene	• ***PDK1, PDK2*** *(GANAB, DNAJB11)*  	• ***PKHD1*** *(DZIP1L)*  
Onset	• Adult onset (may present prenatally)	• Pediatric onset (may present in adulthood)
Cardio-vascular disease	• Arterial aneurysms • Dilation of the aorta • Mitral valve prolapse	• Not typical

Bisceglia et al, 2006 ;1:26-56. Wilson P., N Engl J Med. 2004;350:151-64.

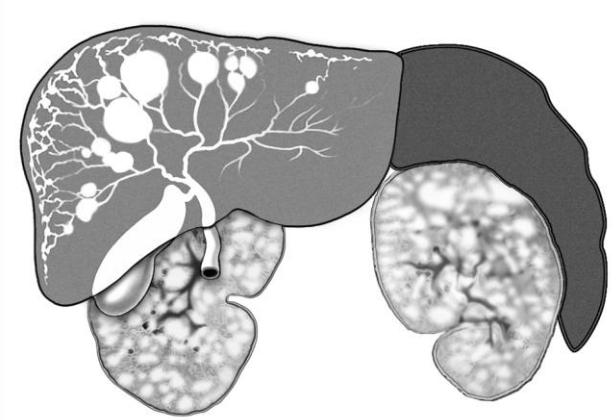
Liver involvement in polycystic kidney disease

Dominant PKD





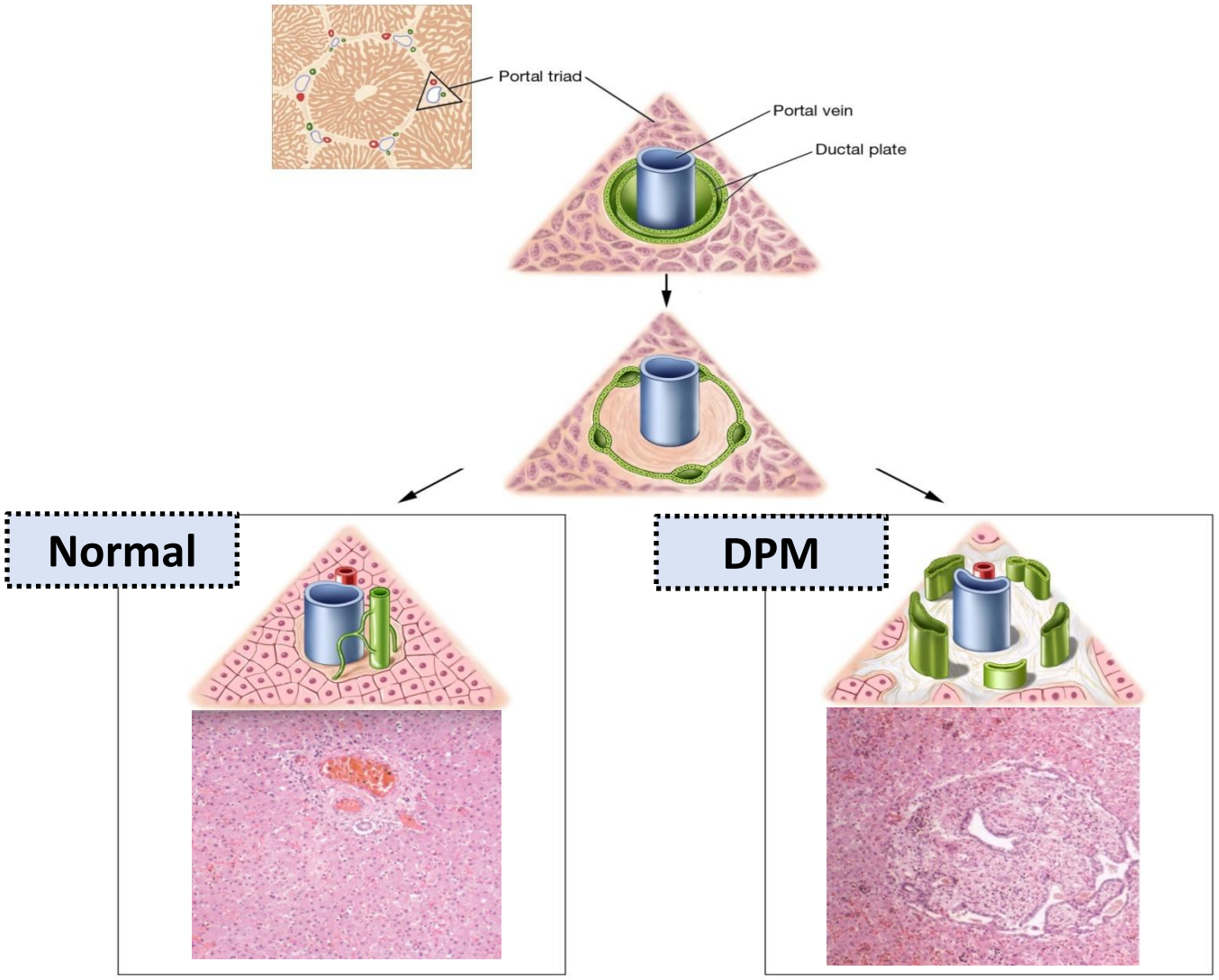
Recessive PKD



Gunay-Aygun, 2009 Am J Med Genet

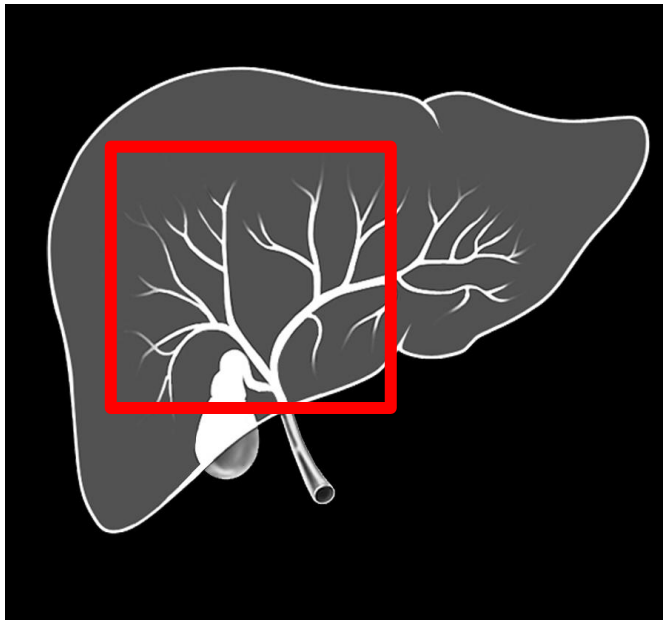
Congenital Hepatic Fibrosis

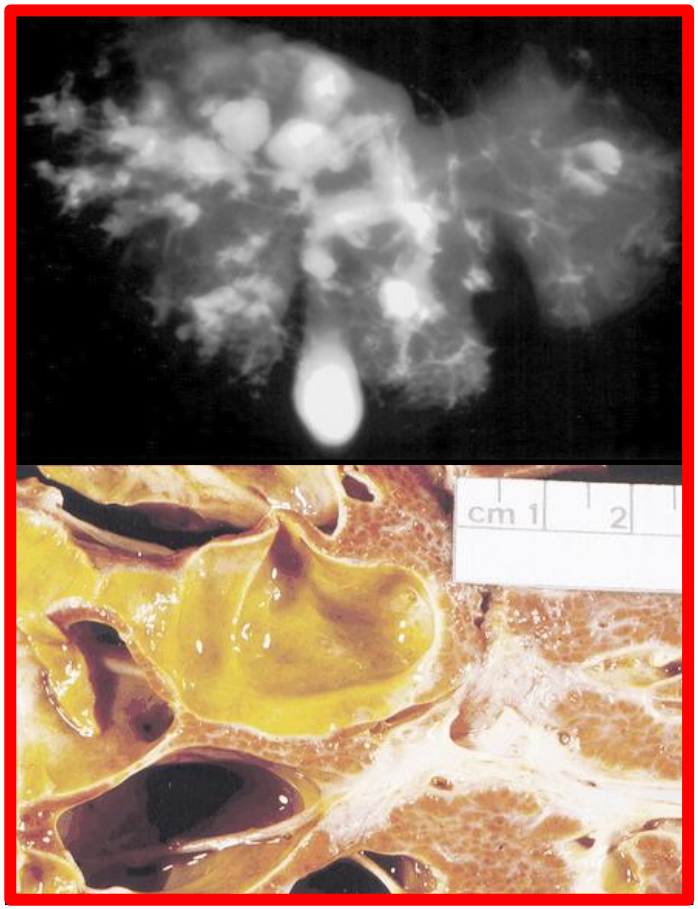
Ductal Plate Malformation (DPM)



Gunay-Aygun, 2009 Am J Med Genet

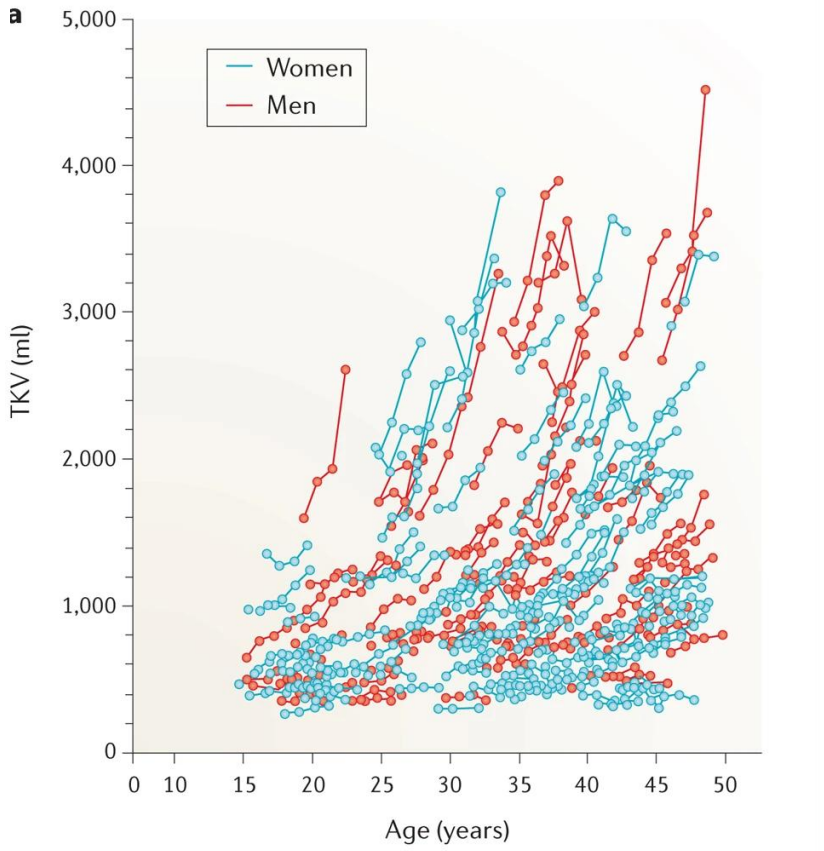
Caroli's Syndrome
DPM of the large bile ducts

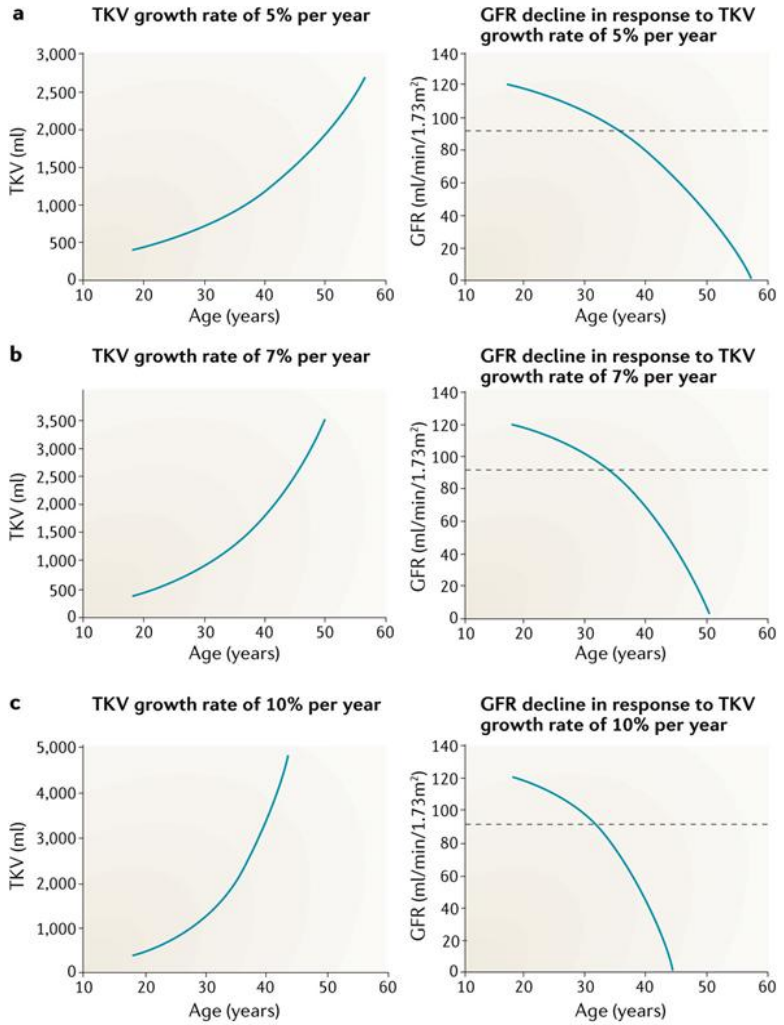




Lonergan GJ et al., Radiographics. 20:837-855, Desmet 1998

In ADPKD patients, kidney volume correlates negatively with function





Grantham, J. J. *et al*. *N. Engl. J. Med.* **354**, 2122–2130 (2006)

Grantham et al., Nature reviews Nephrology. 2016;12(11):667-77