Lessons Learned from NIH Study About Long-term Outcomes of Patients with ARPKD/CHF

Meral Gunay-Aygun, MD

"Living with Childhood Polycystic Kidney Disease"

Children's Hospital of Wisconsin

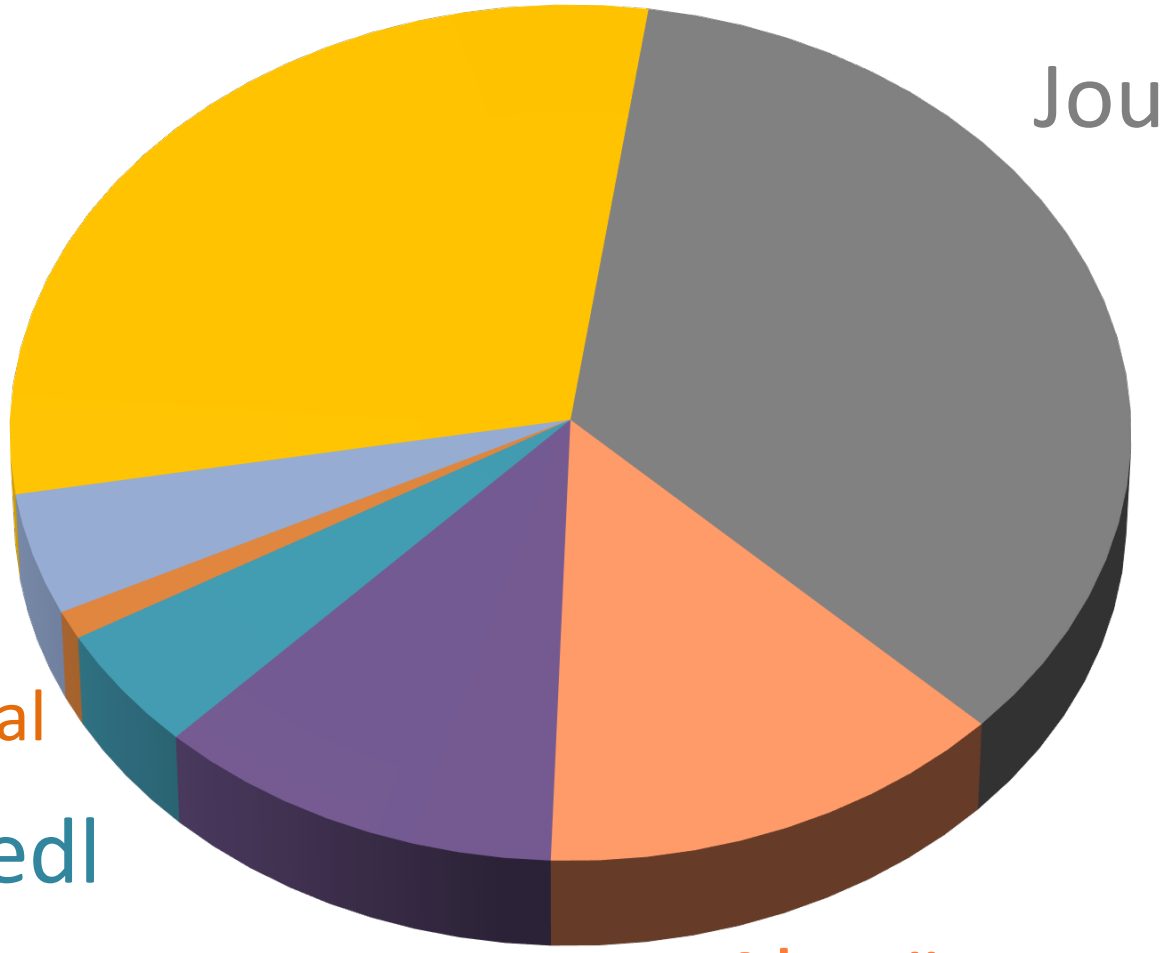
September 16, 2017

NATIONAL HUMAN GENOME RESEARCH INSTITUTE Division of Intramural Research

NIH Study

(www.clinicaltrials.gov, NCT00068224)

Since 2003
290 patients



NIH Study

(www.clinicaltrials.gov, NCT00068224)

- Aims
  - Define clinical and molecular characteristics
  - Identify correlations between gene mutations and clinical features
  - Identify outcome parameters for treatment trials

- Ages 6 months to 80 years

- 4-5 day evaluations at the NIH Clinical Center
  - Blood and urine tests for kidney, liver, and growth
  - MRI and Ultrasonography (USG) imaging
  - Cognitive evaluations
  - Sequencing of genes

Confirmation of Diagnosis

- 90 probable ARPKD patients evaluated
  - 78 patients (68 families) met clinical criteria
  - 73 patients (63 families) had *PKHD1* mutations
- Mutation detection rate 79 %
  - Kidney-predominant patients 82 %
  - Liver-predominant patients 63 %

Mol Genet and Metab, 2010

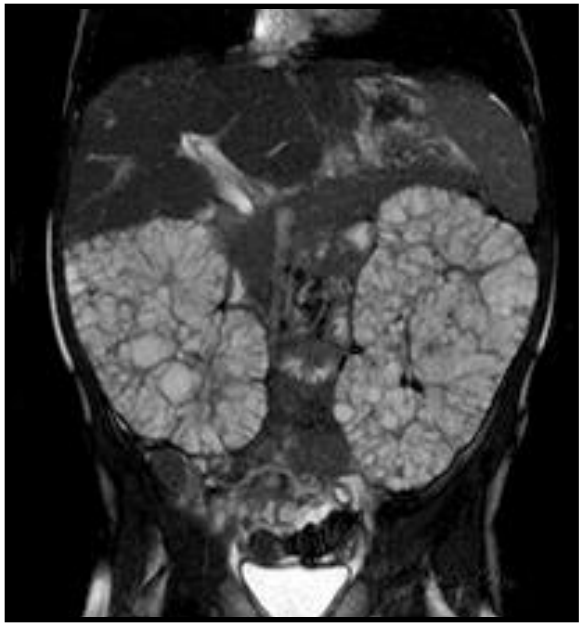
PKHD1 Mutations

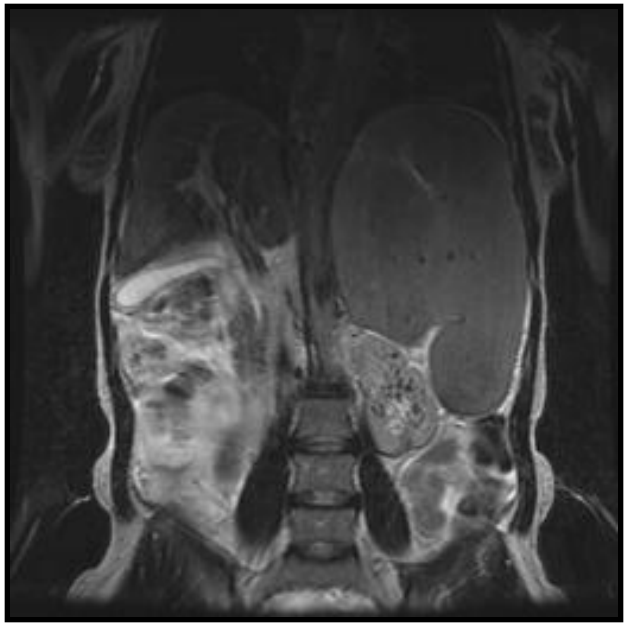
- 63 families (73 patients)
  - 43 families 2 mutations
  - 20 families 1 mutation
- Mutation types
  - Truncating (38 %)
  - Missense (62%)
- No patients with 2 truncating mutations

73 Molecularly Confirmed ARPKD Patients

- 29 males, 44 females
- Ages 1 to 56 y (14 ± 13 y)
    - 46 children
    - 17 adults
- 11 kidney transplantation before NIH visit
- 62 with native kidneys

Age at Diagnosis





	Perinatal (%) (Birth -1st month)	Non-perinatal (%) (After 1st month)
n	48	52
Age at NIH evaluation	9 ± 7 y	17 ± 15 y

48 Perinatally Diagnosed ARPKD

- Oligohydramnios in 90 %
- Respiratory distress at birth in 70 %
  - 70 % mechanical ventilation
  - 37 % pneumothorax

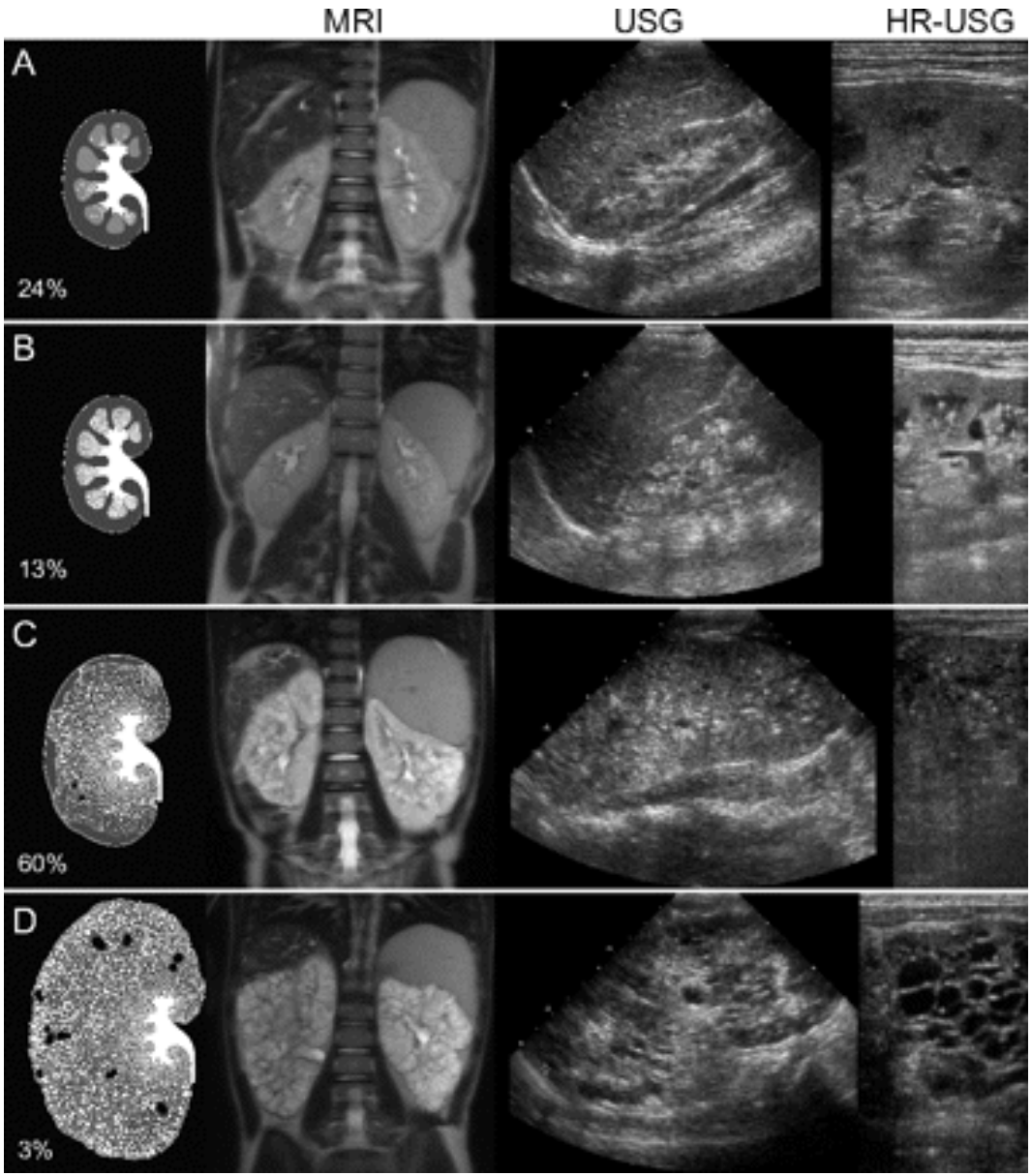
Spectrum of Kidney Involvement in ARPKD

Medullary only

37 %

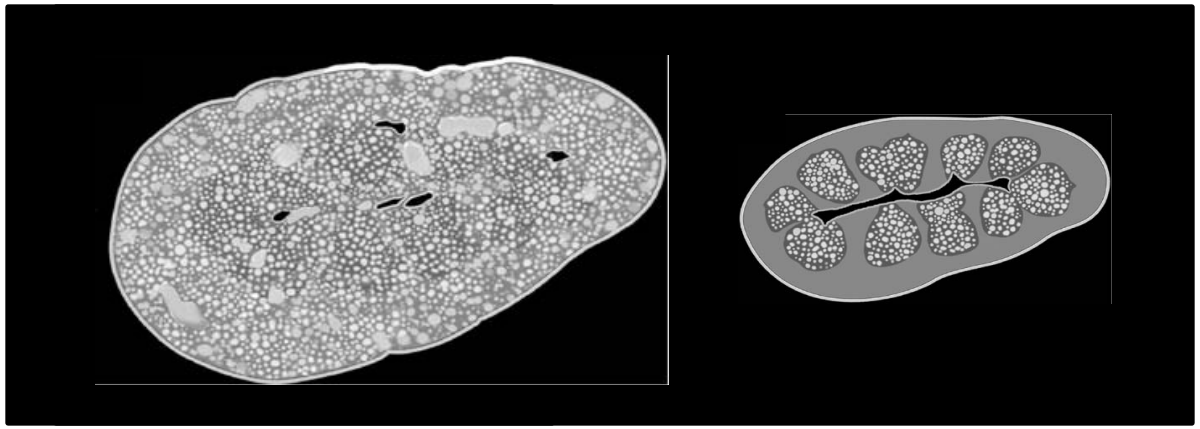
Corticomedullary

63 %

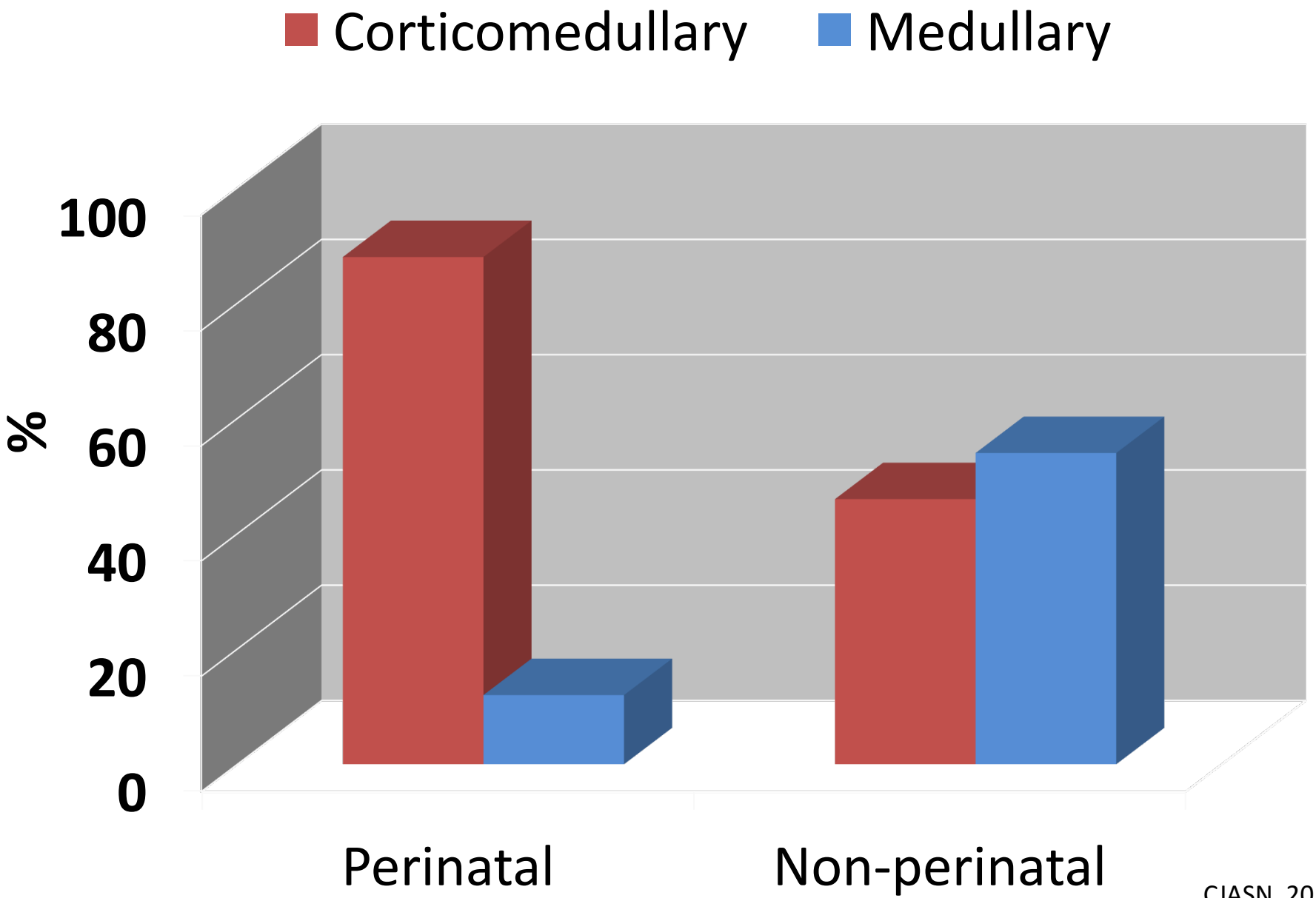


CJASN, 2010

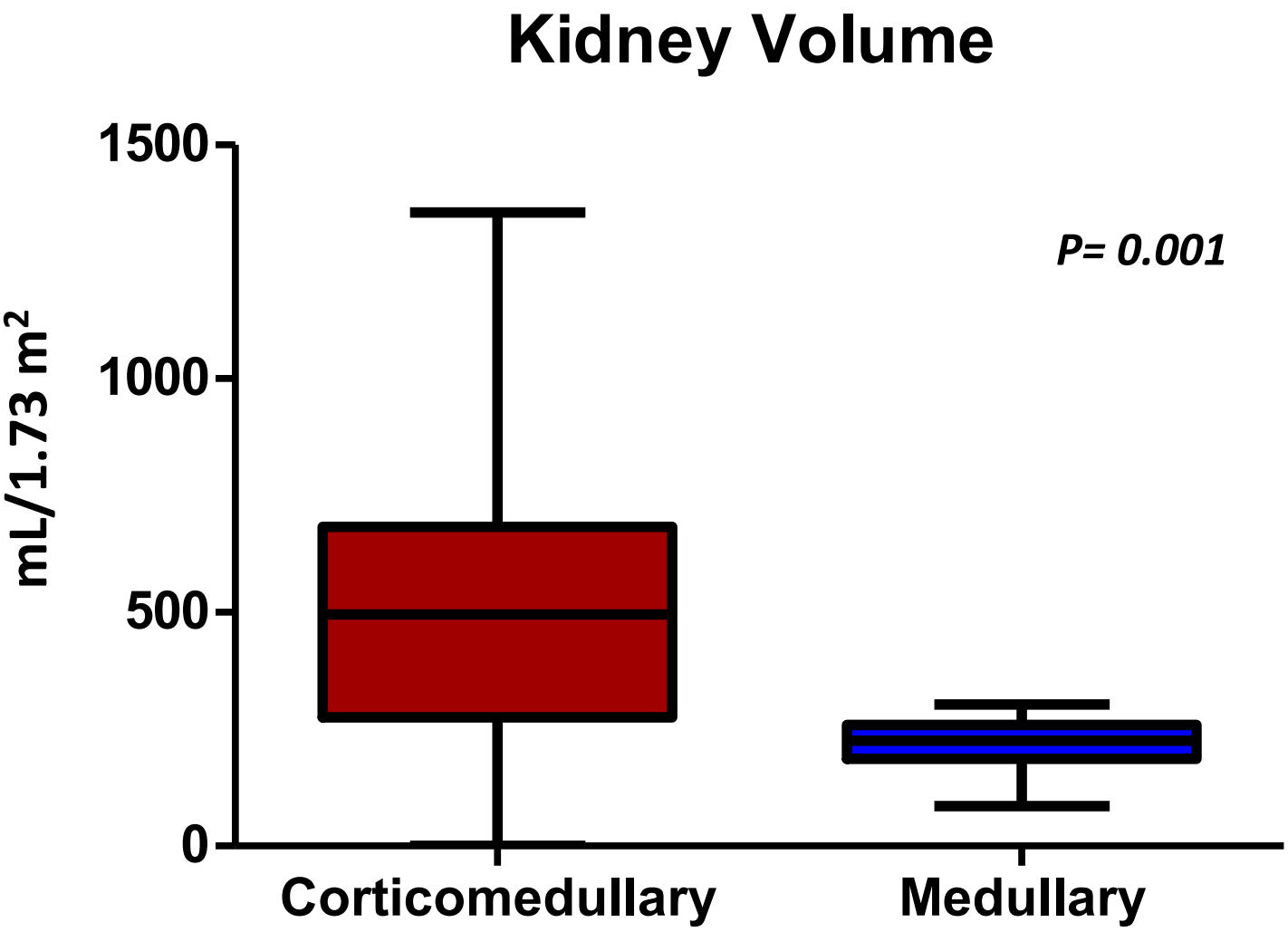
ARPKD: Ultrasound Classification



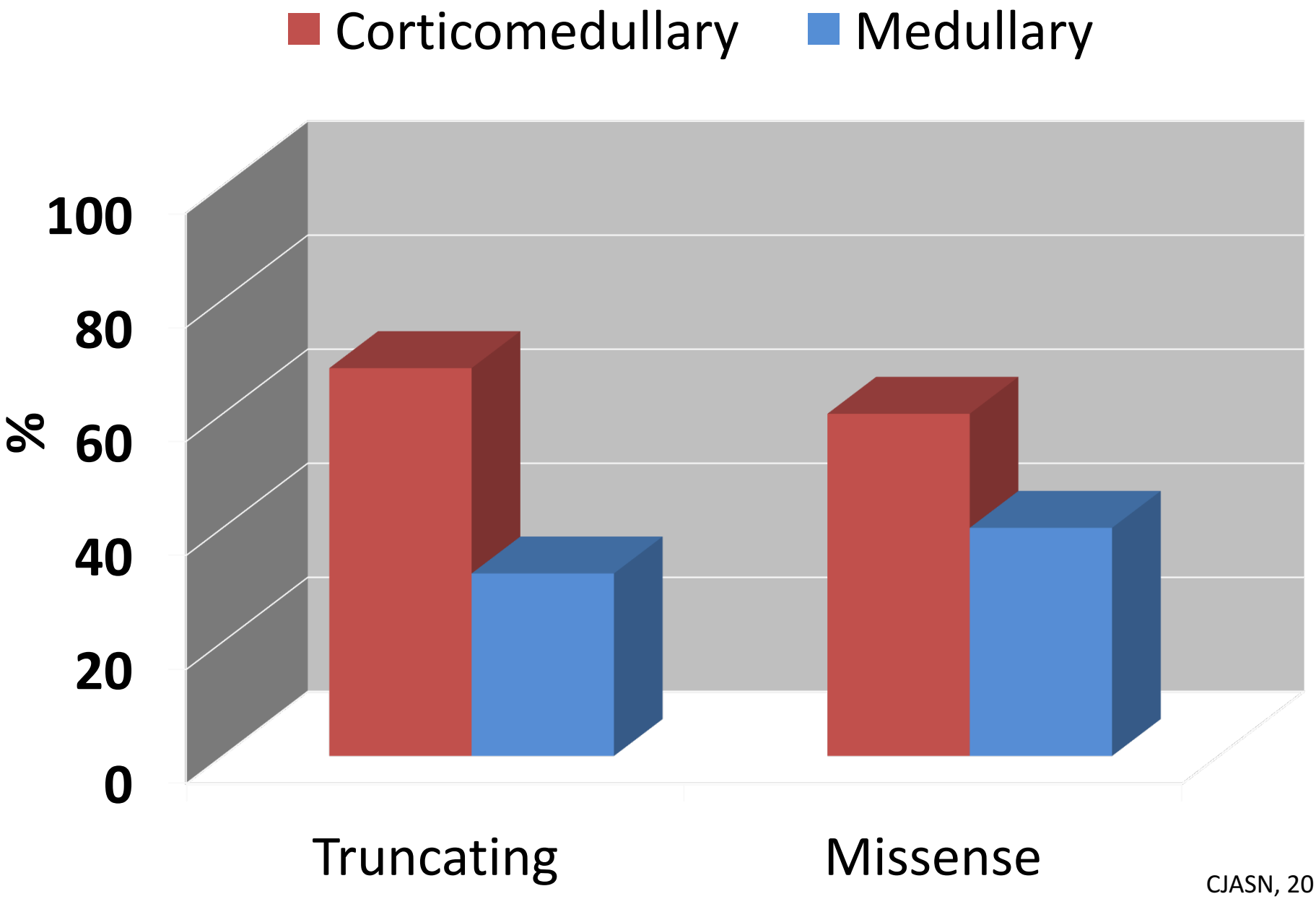
Ultrasound classification	Corticomedullary (%)	Medullary (%)
	63	37
Age at NIH evaluation	11 ± 12 y	14 ± 13 y


Corticomedullary
Medullary
100
80
60
40
20
0
%
Perinatal
Non-perinatal

CJASN, 2010

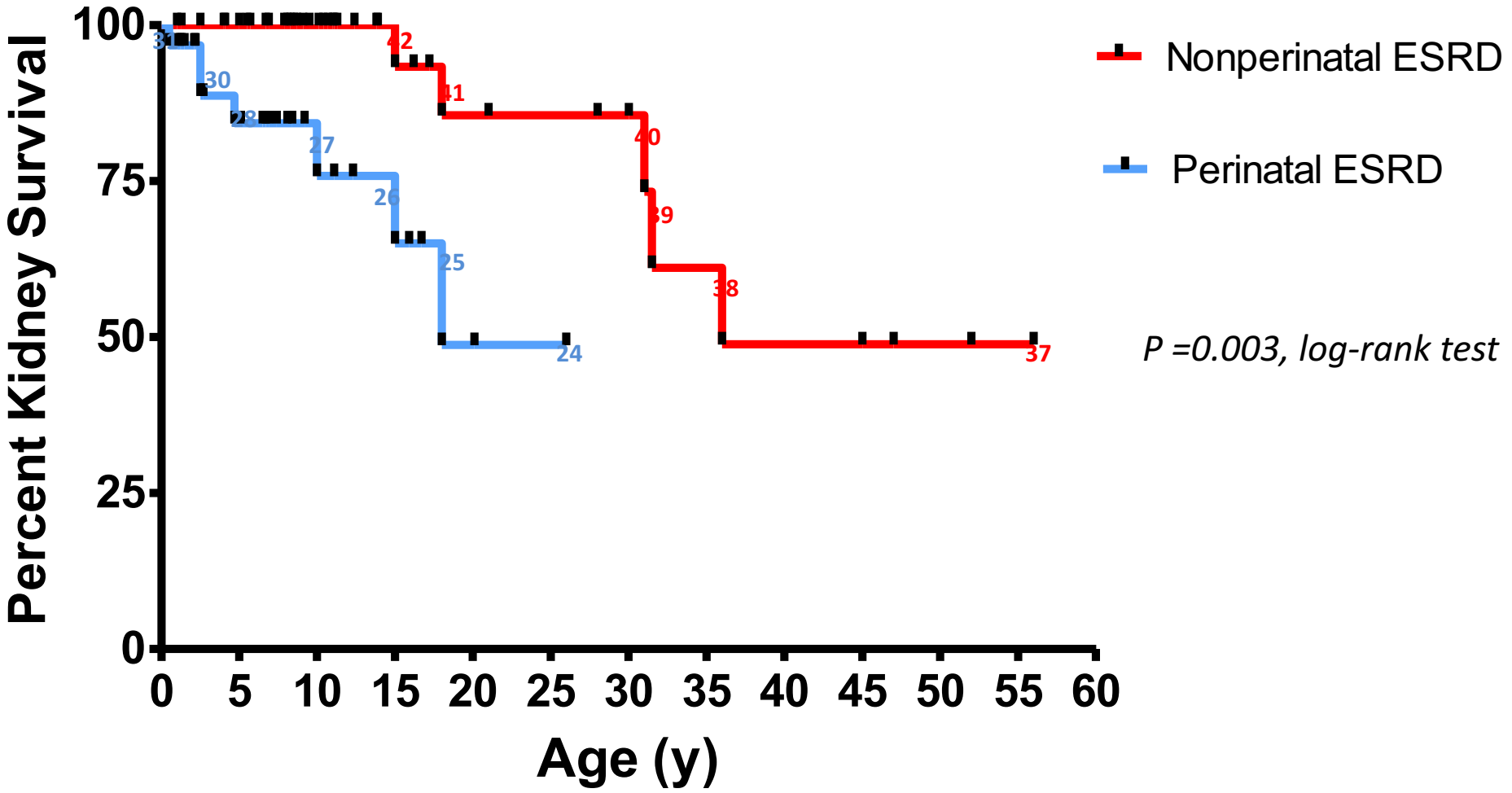

Kidney Volume
1500
1000
500
0
mL/1.73 m²
P= 0.001
Corticomedullary
Medullary
Age 11.3 ± 11.9 y
Age 14.2 ± 13.2 y

CJASN, 2010

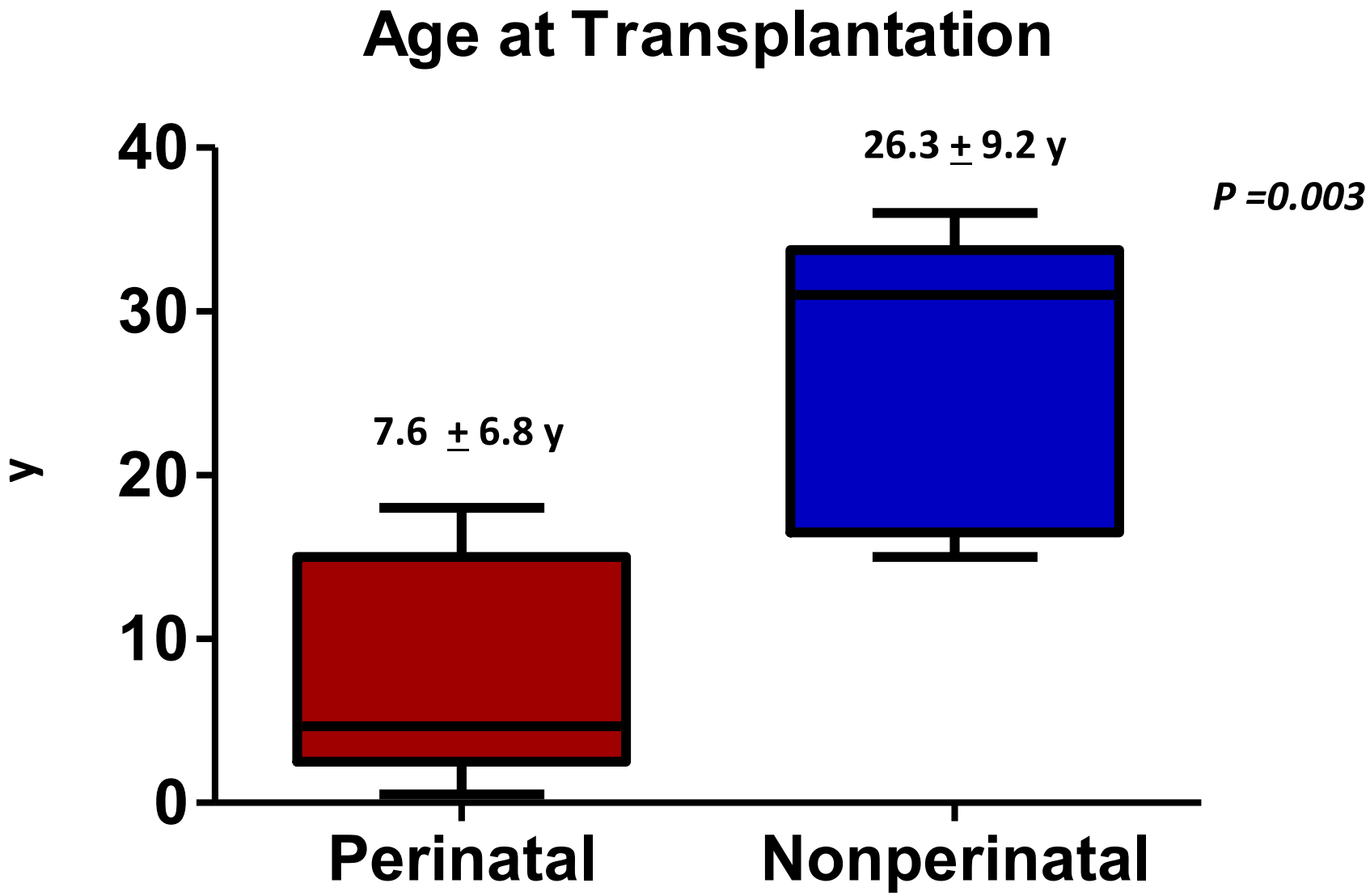

Corticomedullary
Medullary
100
80
60
40
20
0
%
Truncating
Missense

CJASN, 2010

Kidney Survival in ARPKD

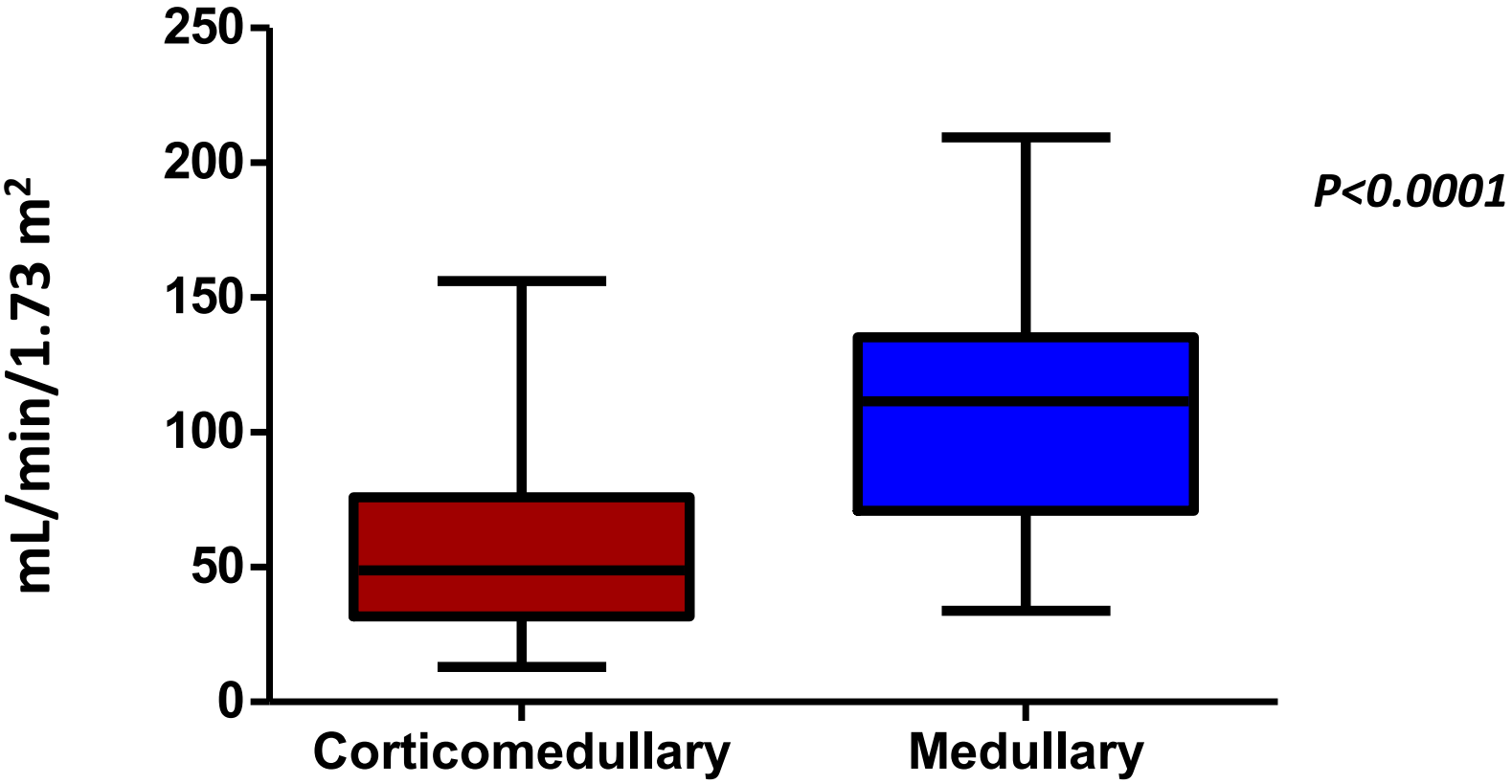


CJASN, 2010


Age at Transplantation
40
30
20
10
0
y
26.3 ± 9.2 y
P =0.003
7.6 ± 6.8 y
Perinatal
Nonperinatal

CJASN, 2010

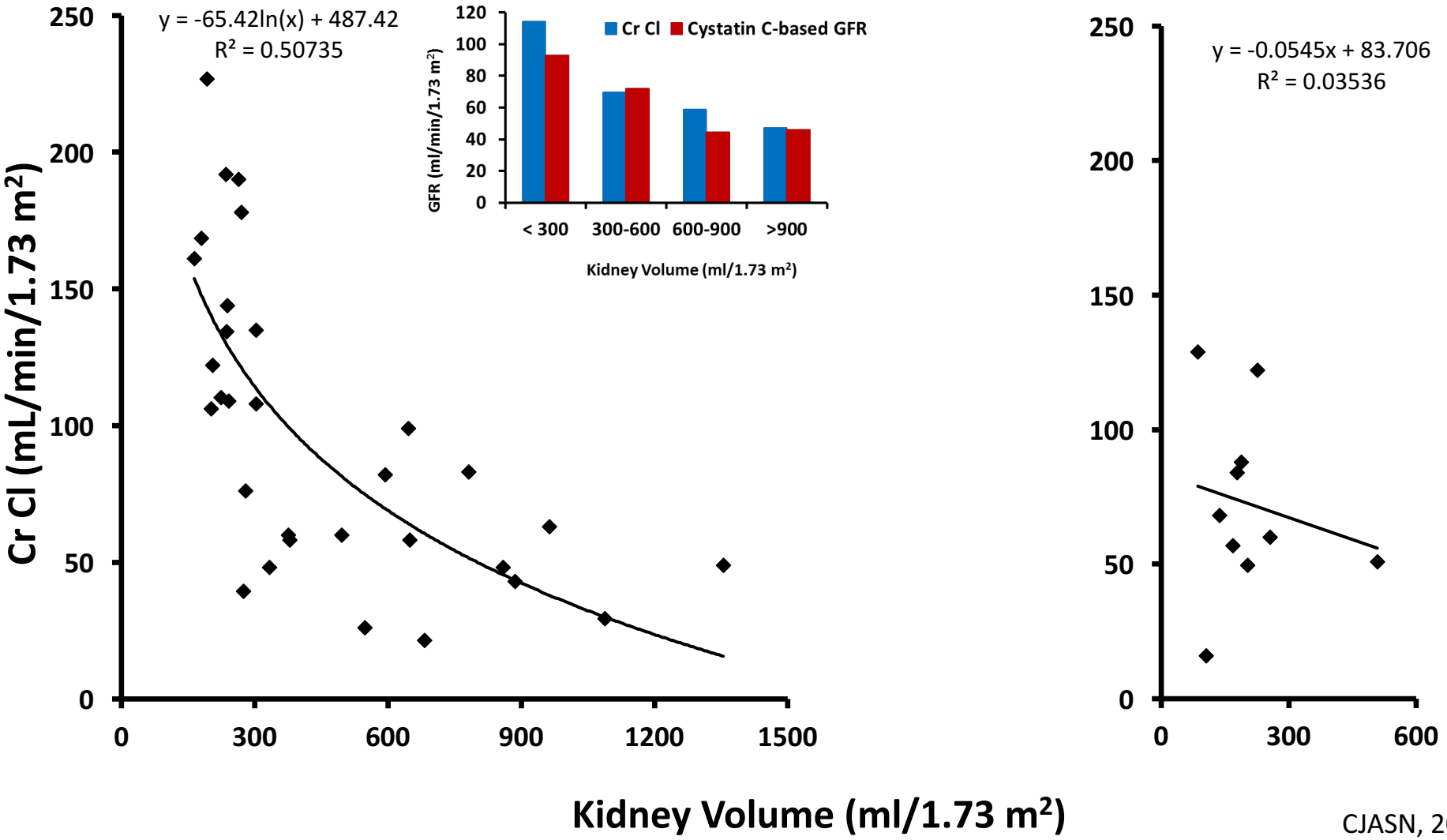
GFR



Age 11.3 ± 11.9 y

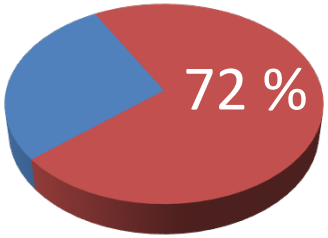
Age 14.2 ± 13.2 y

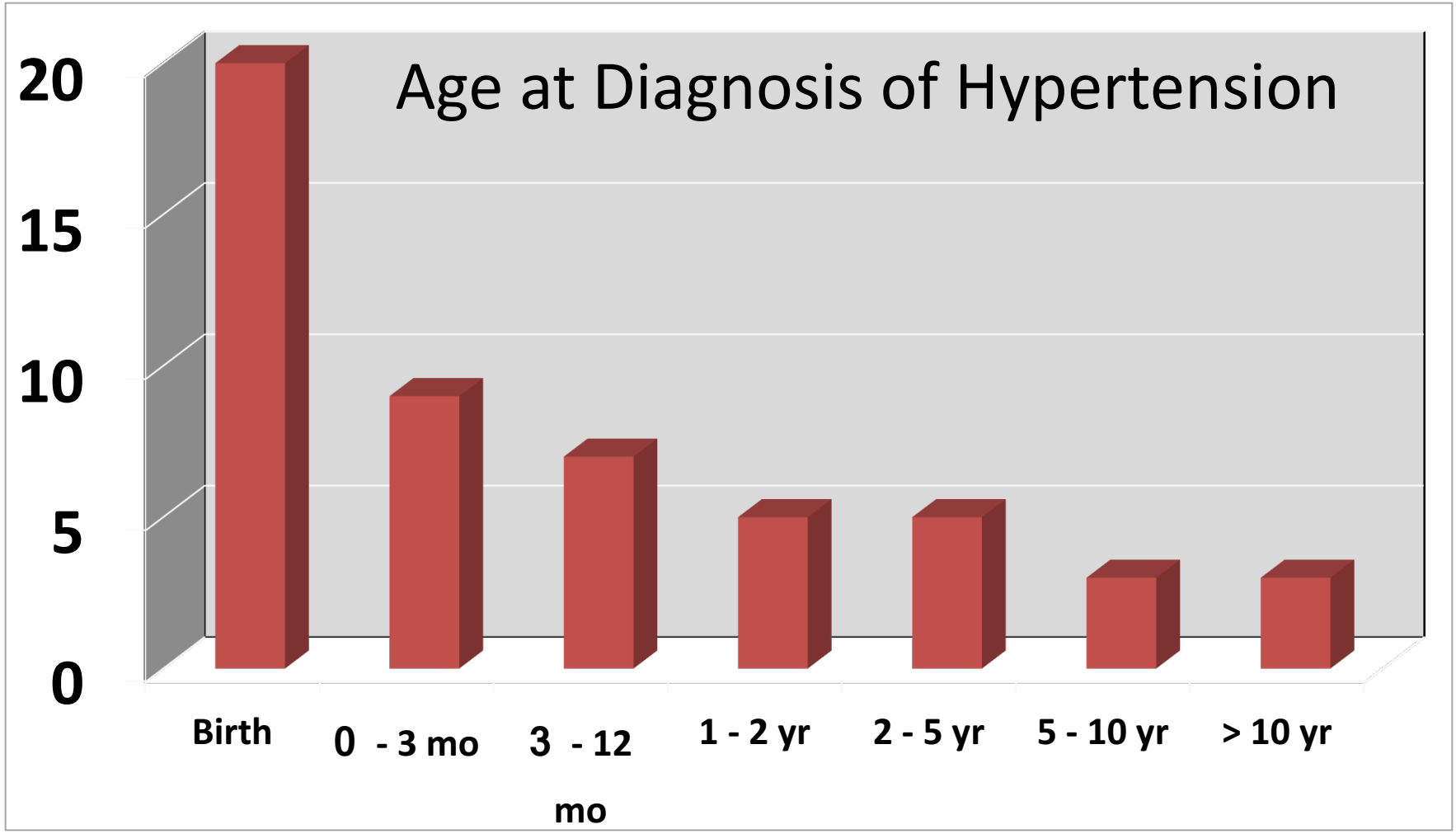
CJASN, 2010


Pediatric
Adult
y = -65.42ln(x) + 487.42
R² = 0.50735
y = -0.0545x + 83.706
R² = 0.03536
Cr Cl
Cystatin C-based GFR
GFR (ml/min/1.73 m²)
< 300
300-600
600-900
>900
Kidney Volume (ml/1.73 m²)
Cr Cl (mL/min/1.73 m²)
Kidney Volume (ml/1.73 m²)

CJASN, 2010

Hypertension





Liver Disease: Portal Hypertension

- Increased liver echogenicity in 92%
- Enlarged spleen in 65%
  - 60 % of children <5 y had enlarged spleen
  - Esophageal varices in 22 of 31 who had endoscopy
    - 5 had variceal bleeding at ages 5, 6, 32, 46, 50 y
  - Portosystemic shunt in 3 %
  - Liver transplantation in 1 %

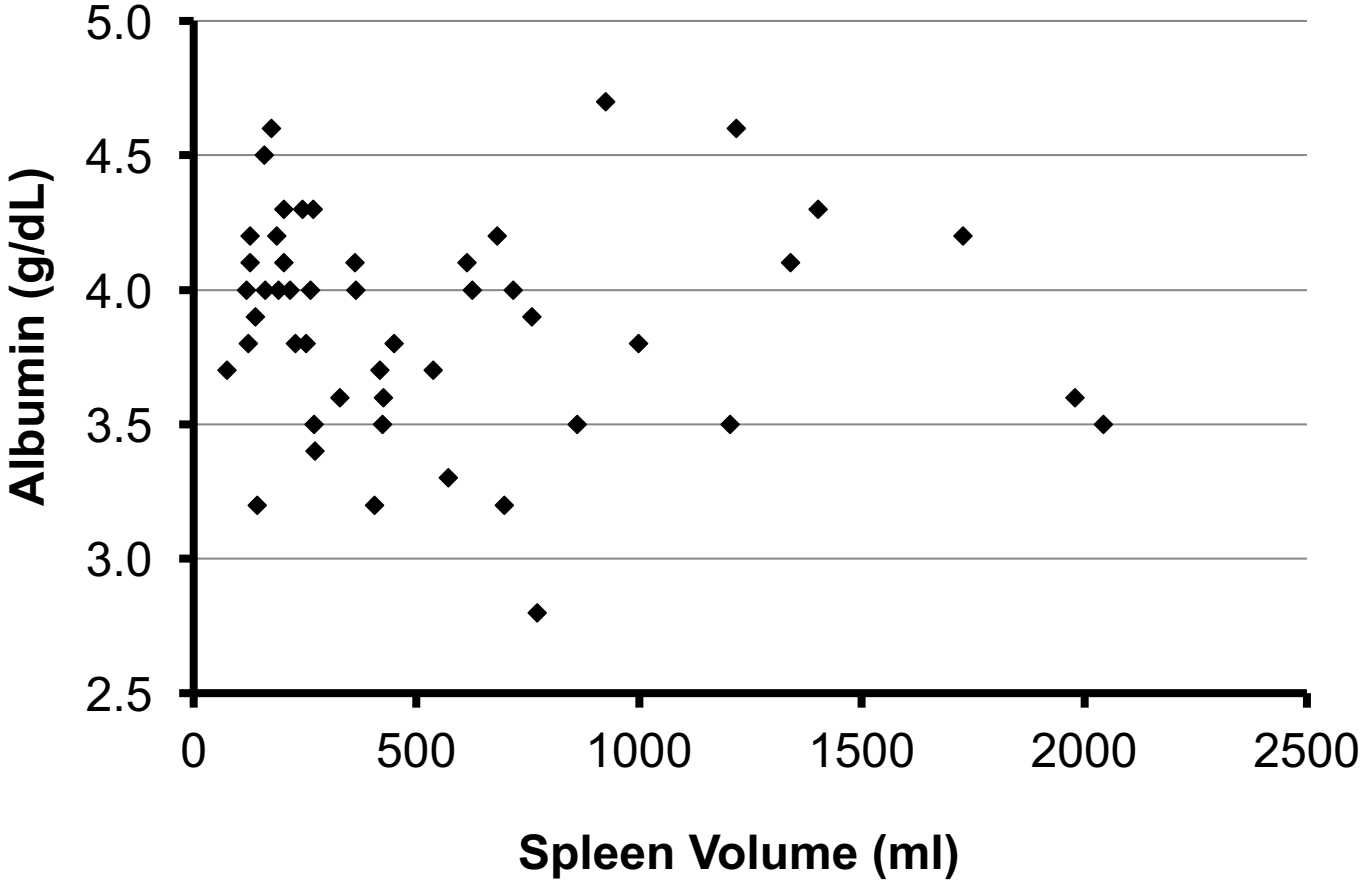
Gastroenterology, 2013

Liver Disease: Bile Duct Abnormalities

- Bile duct abnormality in 70 %
  - Caroli syndrome in 40 %
  - Dilated common bile duct in 56 %
  - Enlarged gall bladder in 56 %
- Cholangitis in 6 %
  - 1 dilated common bile duct only
  - 3 completely normal imaging of bile system

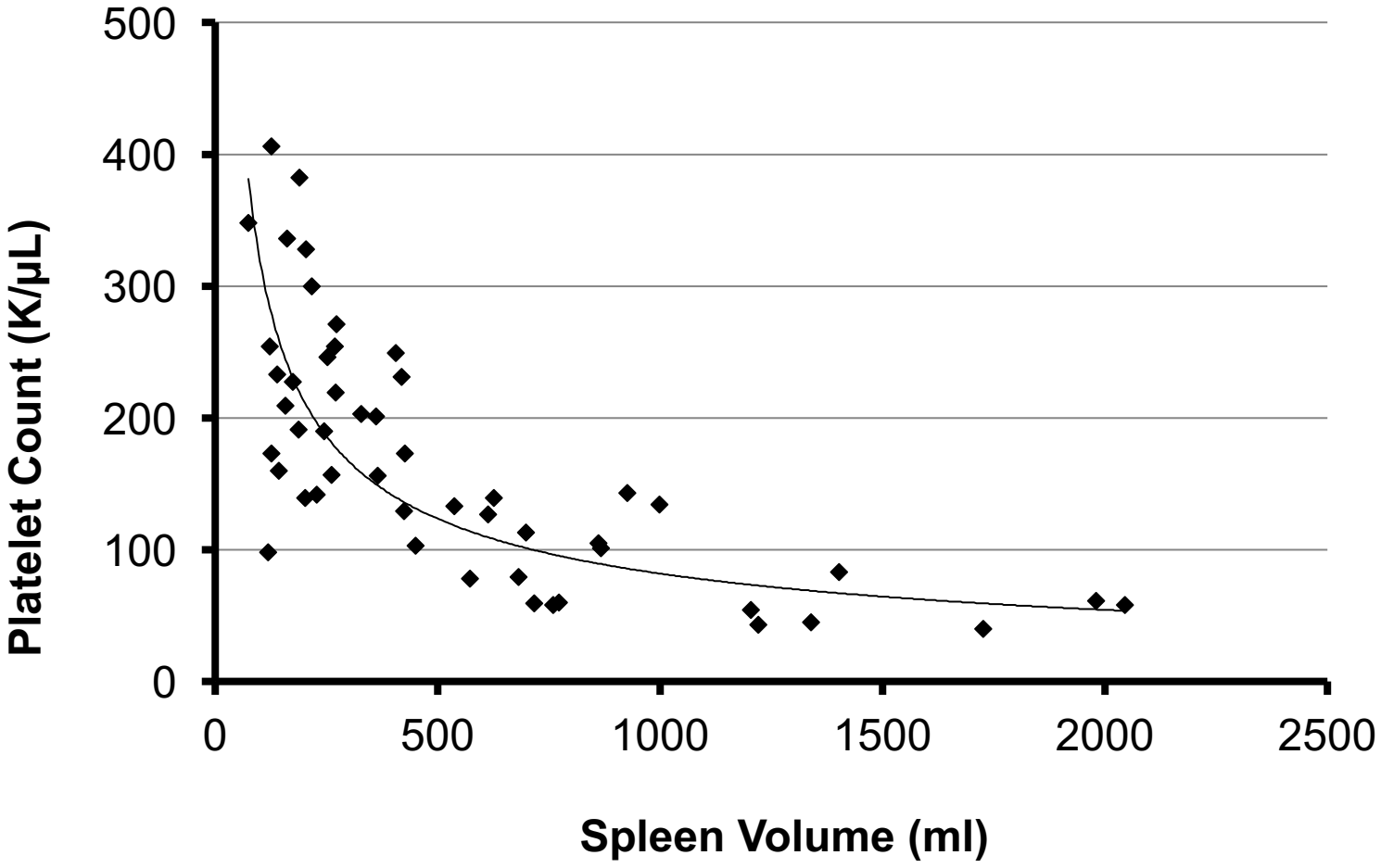
Gastroenterology, 2013

ARPKD: Liver Function Preserved



Gastroenterology, 2013

Platelet Count and Portal Hypertension



Gastroenterology, 2013

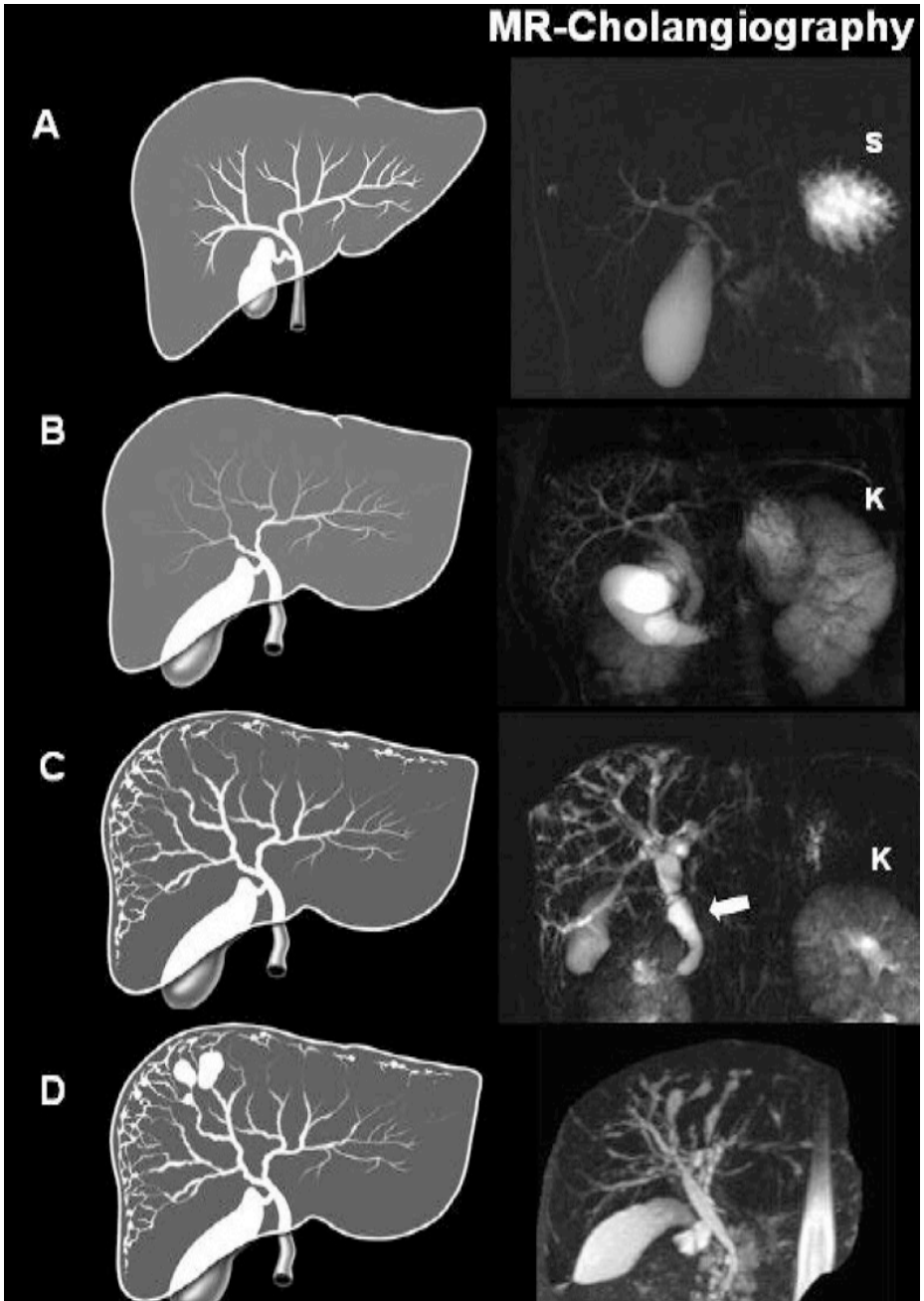
Biliary System Involvement in ARPKD/CHF

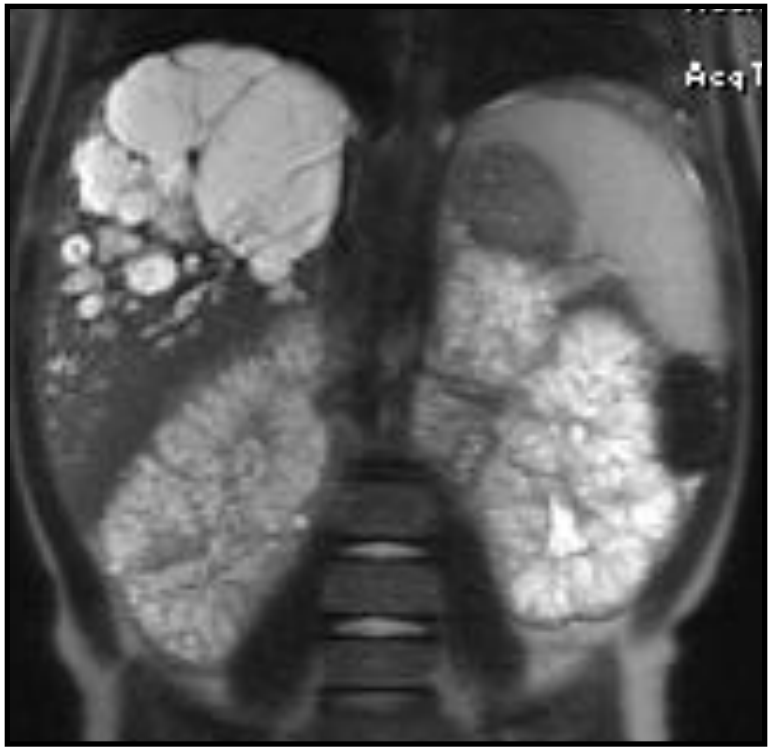
20%

35 %

30 %

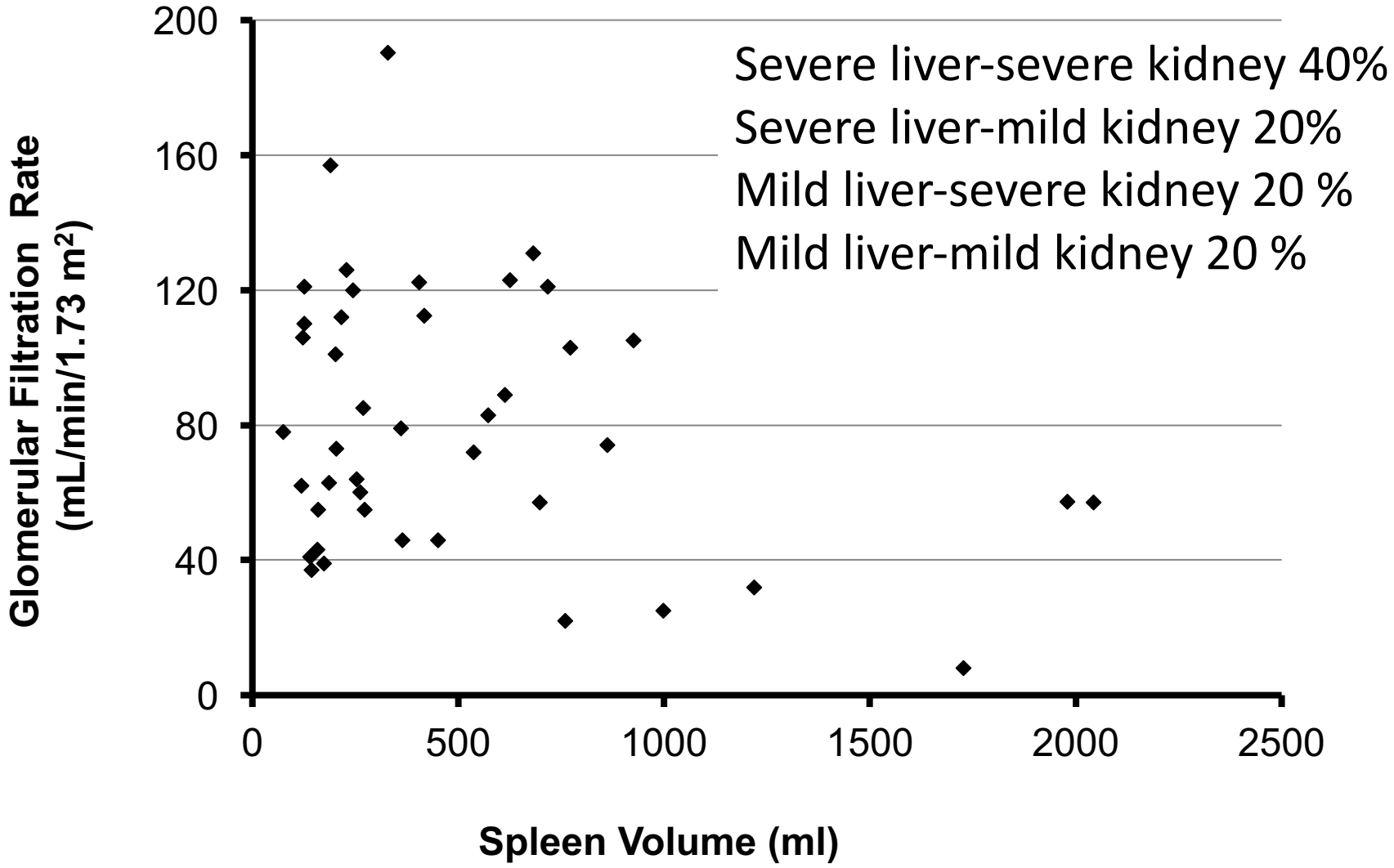
15 %





Gastroenterology, 2013

Kidney and Liver disease in ARPKD



Gastroenterology, 2013

Acknowledgements

Individuals with ARPKD and their families

Medical College of Wisconsin
Ellis Avner
Bill Sweeney

ARPKD/CHF ALLIANCE
improving the lives of those affected

NIDDK
Theo Heller

NHGRI
William A. Gahl
Joy Bryant
Jennifer Graf

NIMH
Joe Snow

NIH CC
Peter Choyke
Baris Turkbey
Kalish Daryanani

NIH Clinical Center
Pediatric Inpatient and Day Hospital

NIH Children's Inn