

NIH Study-Update

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NIDDK/NIH



Disclosures

- I love hepatology
- I love my job
- I love coffee!
- I have no financial disclosures but do wish I had some

History

MALADIE FIBRO-KYSTIQUE DU FOIE AVEC HYPERTENSION PORTALE CHEZ L'ENFANT. DEUX OBSERVATIONS

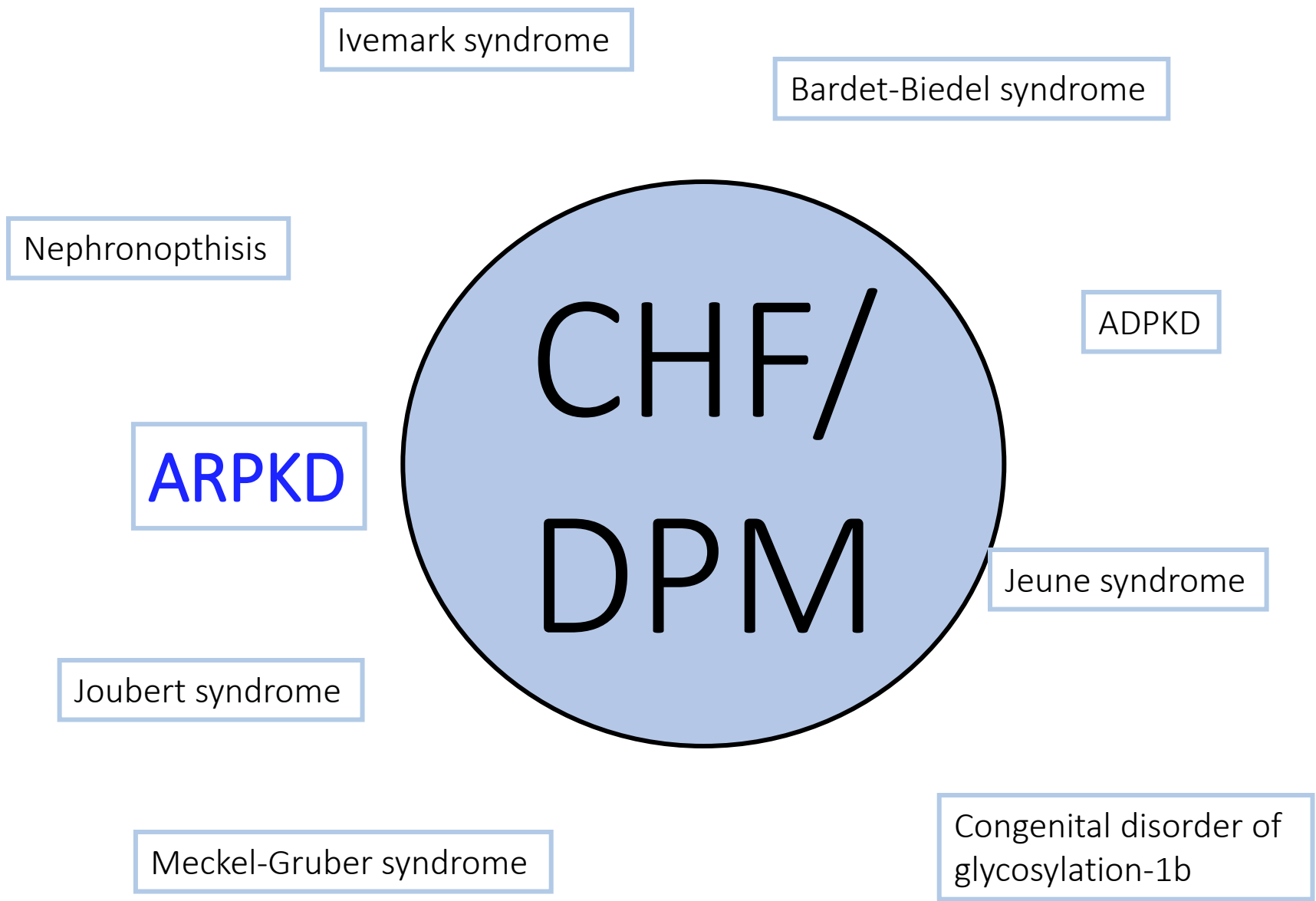
par Raymonde GRUMBACH, Josette BOURILLON
et Jean-Paul AUVERT

ARCH. D'ANAT. PATH.
10 MAI 1954

Stephen A. Geller, MD

Problems

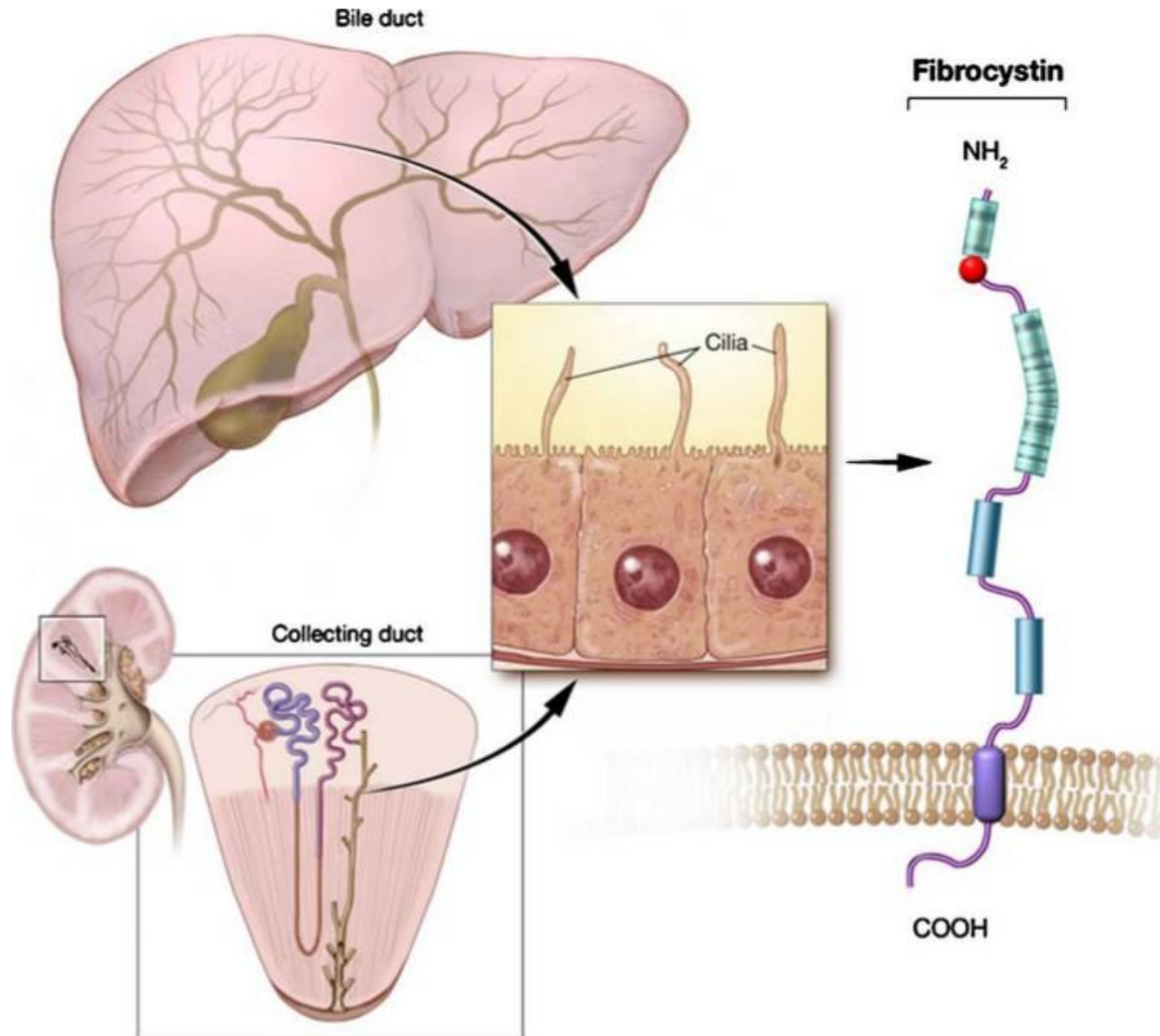
- Nephrocentric view of the world
- Multiple terms
- Variable clinical presentation of single gene defects
- Different gene defects give rise to similar presentations
- Selection bias in clinical studies



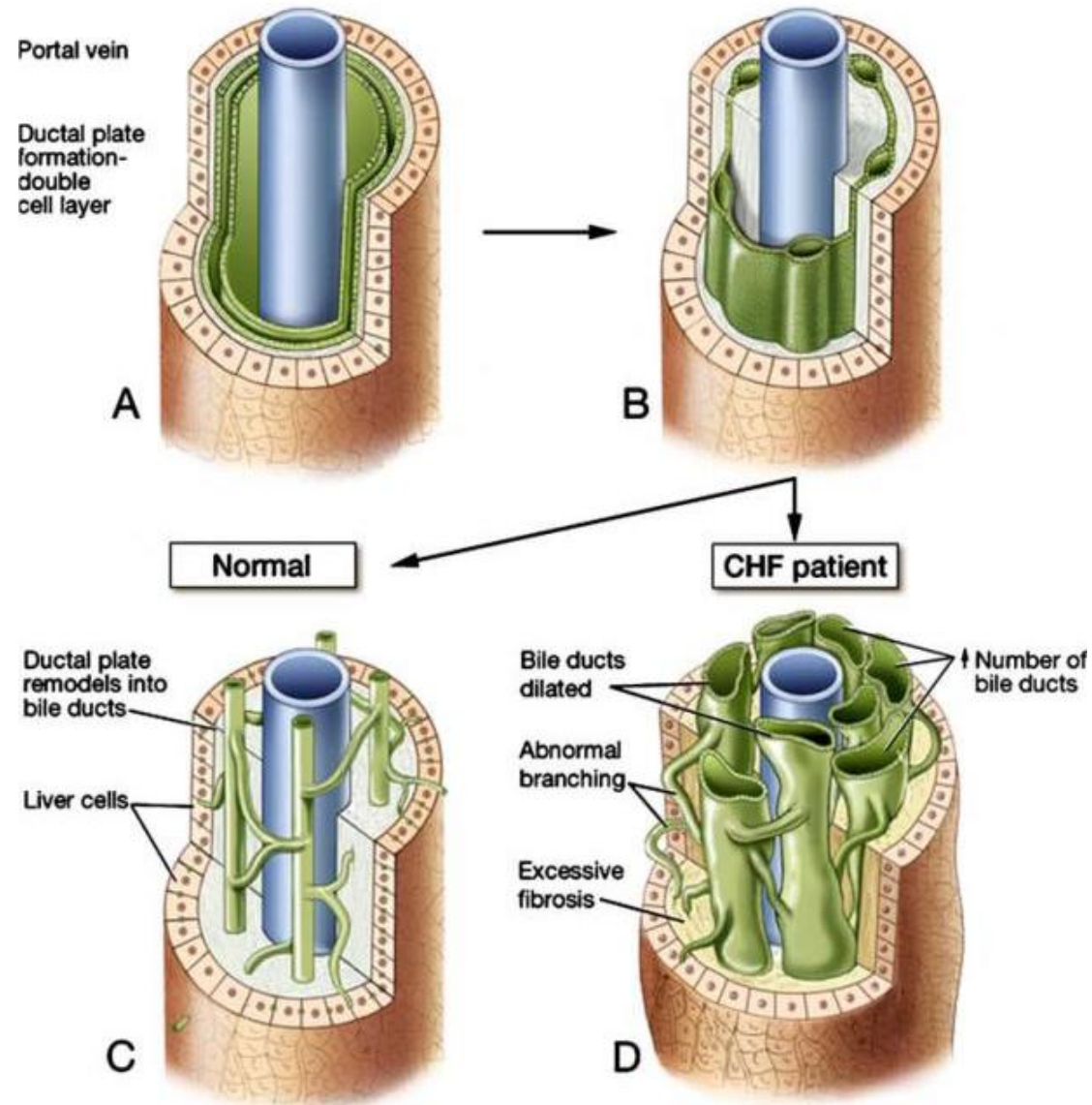
Implication

- Common pathway
 - Embryology
 - Cell biology
 - Basal body/Cilia

Ciliopathy



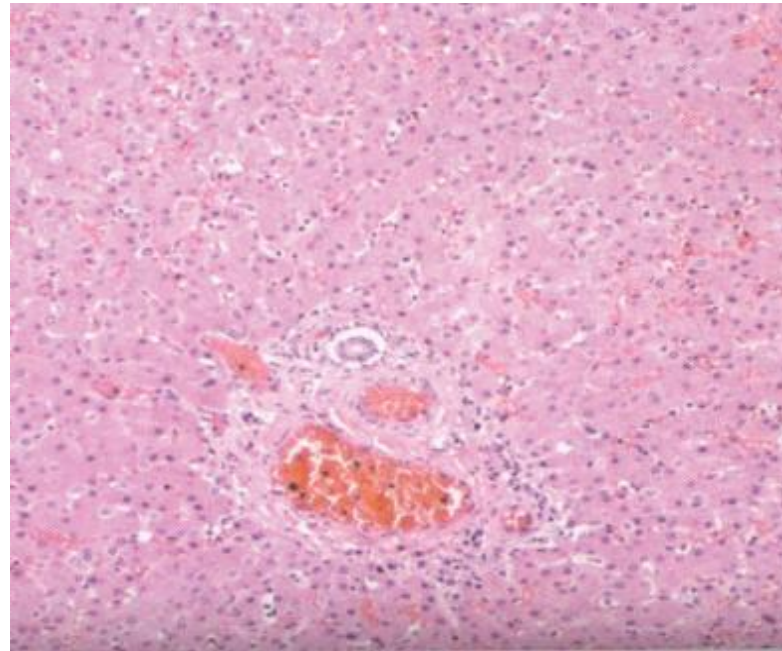
Ciliopathy



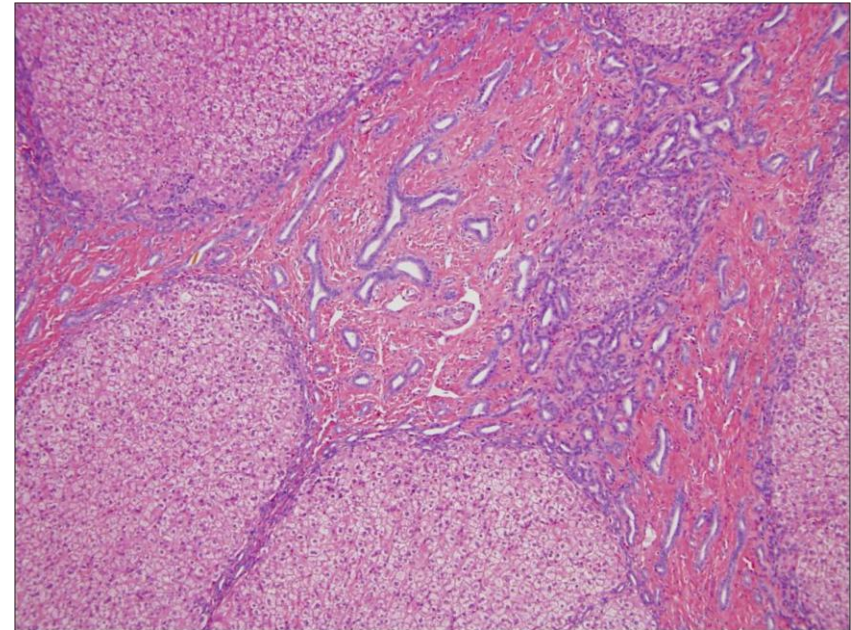
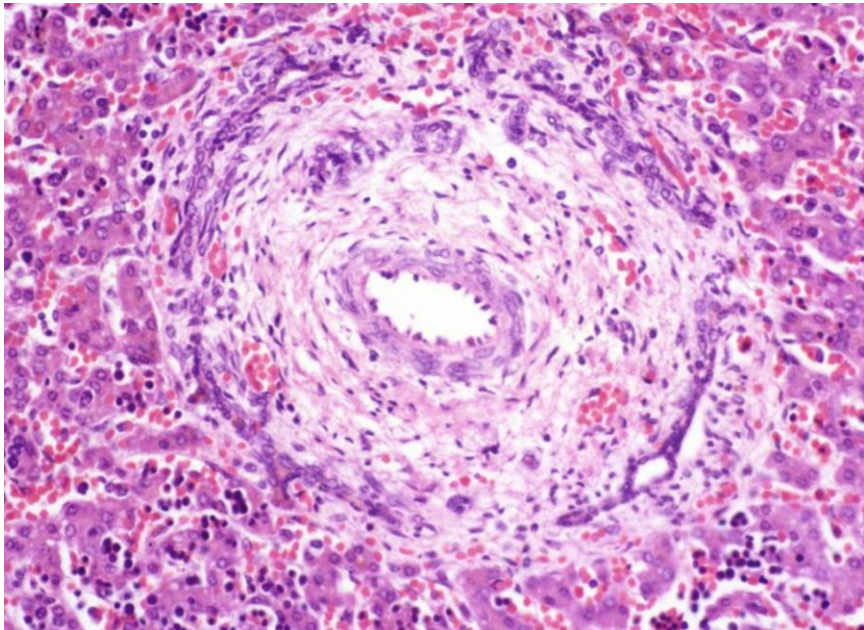
What is Congenital Hepatic Fibrosis?

- A bad term
- A ductal plate malformation
- A spectrum of liver disorders, part of fibrocystic diseases of the liver and kidney
- Ciliopathy

On Histology



Normal



Congenital Hepatic Fibrosis - Key Clinical Aspects

- Varices
- Cholangitis
- Cholangiocarcinoma
- Biliary stones
- Low white cell and platelet counts
- Splenomegaly

Why study Congenital Hepatic Fibrosis?

- Individual
- Similar diseases
- Understand portal hypertension without synthetic dysfunction
- Application to all liver diseases

Now to CHF-ARPKD-CD

Breakthrough

- Identification of genes associated with disease
 - *PKHD1* with CHF/ARPKD (Zerres 1994)
- Allows for study of single disorder

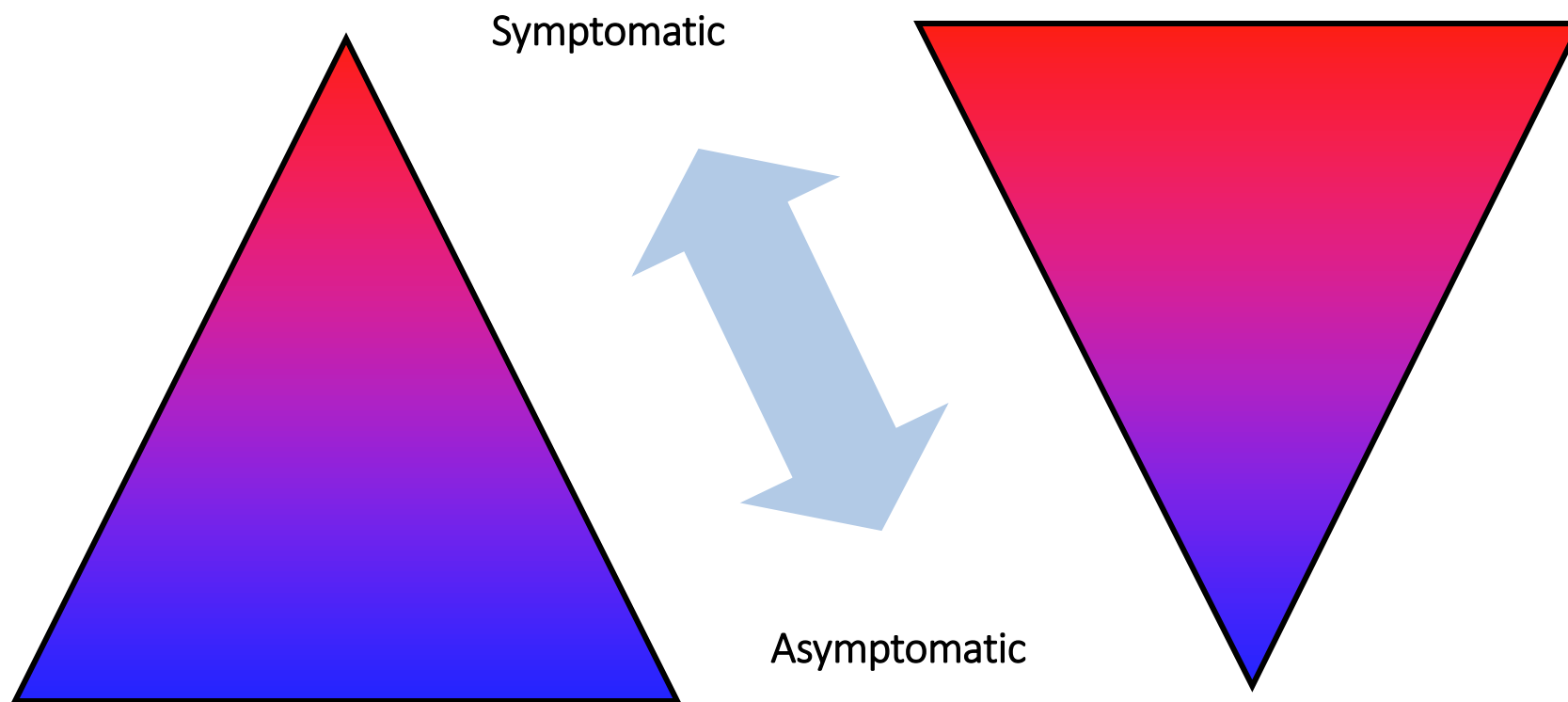
What is known about *PKDH1*?

- Chromosome 6p
- 470 kilobases
- 86 exons
- Product
 - Fibrocystin/Polyductin
- Integral membrane protein
 - Glycosylated extracellular portion
 - Single transmembrane-spanning domain
 - Short intracytoplasmic tail

What is known about the ARPKD-CHF-CD spectrum?

- **Variability** in mutations in *PKHD1*
- **Variability** in organ involvement
 - Liver (later)
 - Kidney (earlier)
- **Variability** in progression
- **Variability** in severity
 - Neonatal death
 - Asymptomatic adult
- **Variability** in families

Unknown



Bergmann et al, Human Mutation, 2004

- 271 unrelated families
- 135 mutations
 - No clustering
 - Most were unique

Adeva et al, Medicine, 2006

- DNA analysis in 38/65 patients, 31 families
- No clear trend between mutation score and severity of disease
- Isolated CHF/CD also had mutations in *PKHD1*

Related but really Unrelated...

- **1 yo male** - biliary/renal disease
- **Sister at 51 yo** normal

Adeva et al, 2006

5 sibling sets:

- 3 sets concordant (perinatal)
- 2 sets discordant

Capisonda et al, 2003

- **9 mo male** – organomegaly
- **2 siblings**-few renal cysts

Adeva et al, 2006

- **Female:** Perinatal demise
- **21 yo sister** well

Bergmann et al, 2004

3 sibling sets:

- 2 sets discordant (1 sib death < 1 year, 1 sib > 20)
- 1 set concordant (mild)

Fonck et al, 2001

The NIH study



Ciliopathies

- 03-HG-0264
- PI: [Dr. Meral Gunay-Aygun](#)
- Supported by the ARPKD/CHF Alliance
- Strict criteria for CHF/ARPKD

Problems

- No neonatal deaths included
- No histological evaluation
- No invasive measure of portal hypertension
- Selection bias

Strengths

- Molecular Confirmation
- Detailed Phenotyping
- Prospective Evaluation

Demographics

Table 1. Summary of Patient Demographics and Main Clinical and Molecular Findings

	All patients	Younger than 5 y	5–18 y	Older than 18 y
No. of patients	73	25	31	17
Age at NIH visit (y)	12.7 ± 13.1	2.7 ± 1.4	9.6 ± 2.8	33.3 ± 11.3
Sex				
Female	44 (60)	14 (56)	18 (58)	12 (71)
Liver echogenicity				
Normal	6 (8)	1 (4)	0 (0)	5 (29)
Mildly increased	15 (21)	4 (16)	8 (26)	3 (17)
Moderately increased	37 (51)	15 (60)	17 (57)	5 (29)
Severely increased	14 (20)	5 (20)	5 (17)	4 (25)
Liver volume (mL)	1368 ± 690	624 ± 103	1203 ± 419	2110 ± 609
Spleen volume (mL)	548 ± 491	162 ± 47	514 ± 340	887 ± 686
Splenomegaly ^a	47 (65)	15 (60)	20 (65)	12 (71)
Varices ^b	22 (71)	5 (63)	10 (83)	7 (64)
Platelet count (1,000/ μ L)	189 ± 95	211 ± 76	187 ± 111	159 ± 86
Caroli syndrome	51 (71)	18 (72)	21 (70)	12 (71)
Elongated gallbladder	14 (20)	4 (16)	6 (21)	4 (25)
Cholangitis	4 (6)	0 (0)	1 (3)	3 (18)
Portosplenic shunt	2 (3)	0 (0)	1 (3)	1 (6)
Liver transplantation	1 (1)	0 (0)	1 (3)	0 (0)
Kidney transplantation	11 (15)	2 (8)	3 (10)	6 (35)
Kidney function/GFR (mL/min/1.73 m ²) ^c	77 ± 37	66 ± 28	85 ± 35	79 ± 51

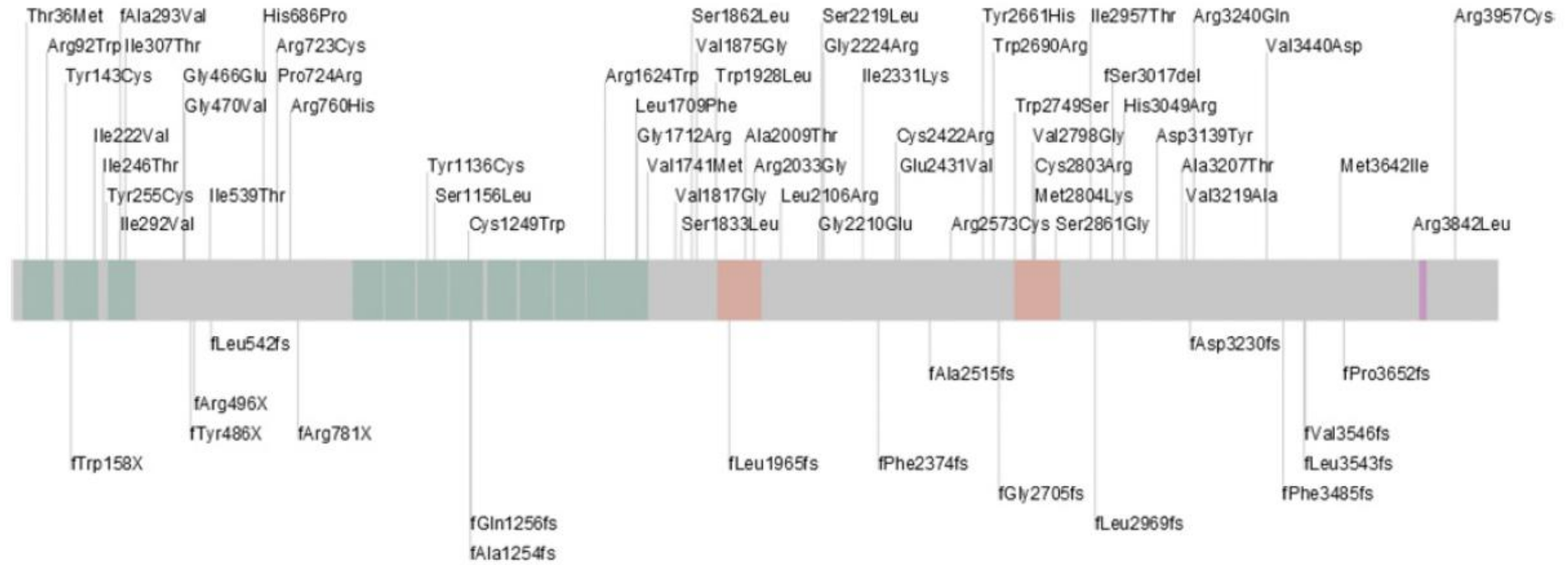
NOTE. Values are reported as number (percentage) or mean ± SD.

^aExcluding the patient with hereditary spherocytosis.

^bThirty-one patients underwent upper gastrointestinal endoscopy.

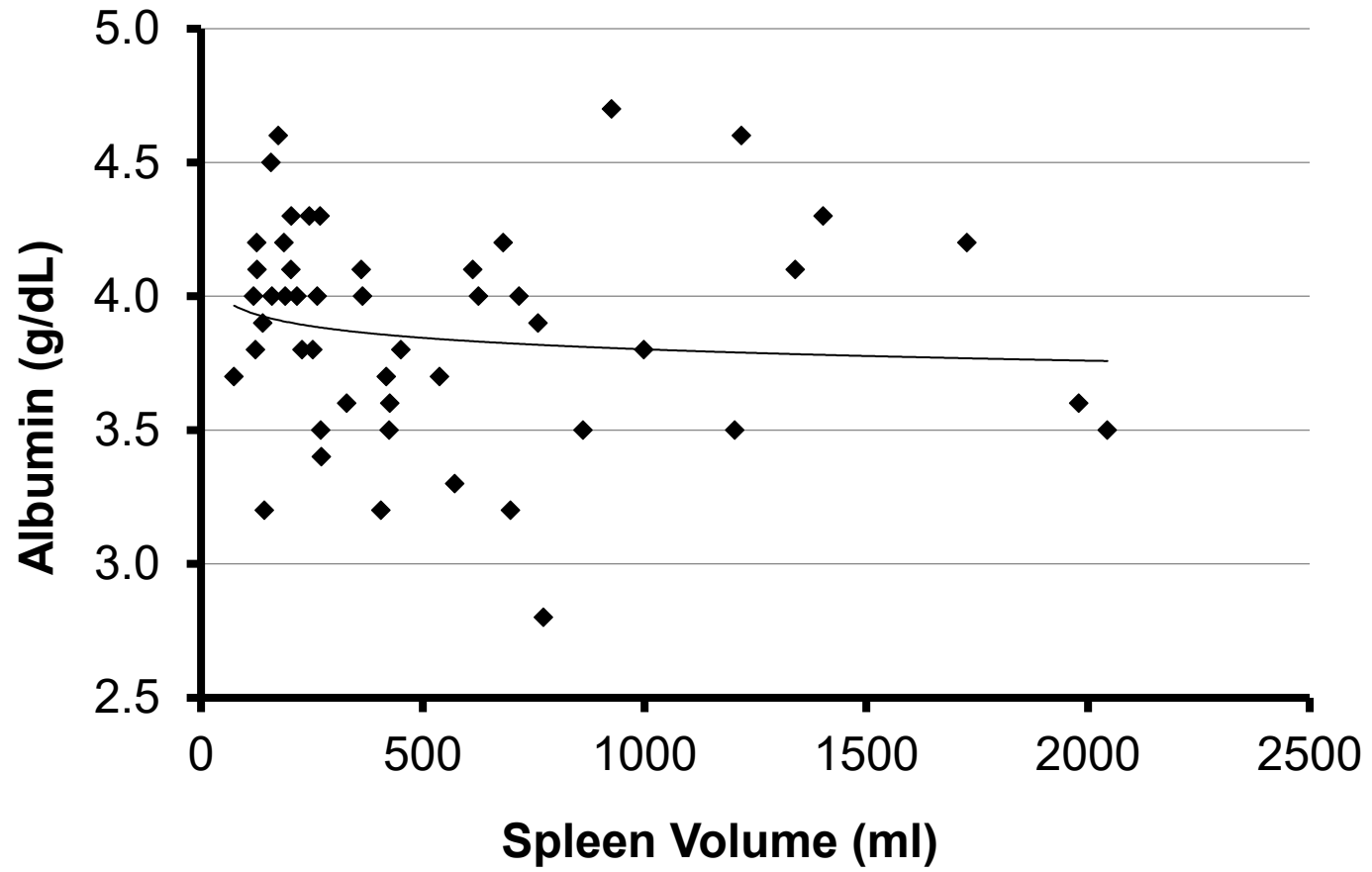
^cOnly patients with native kidneys were included.

Mutations

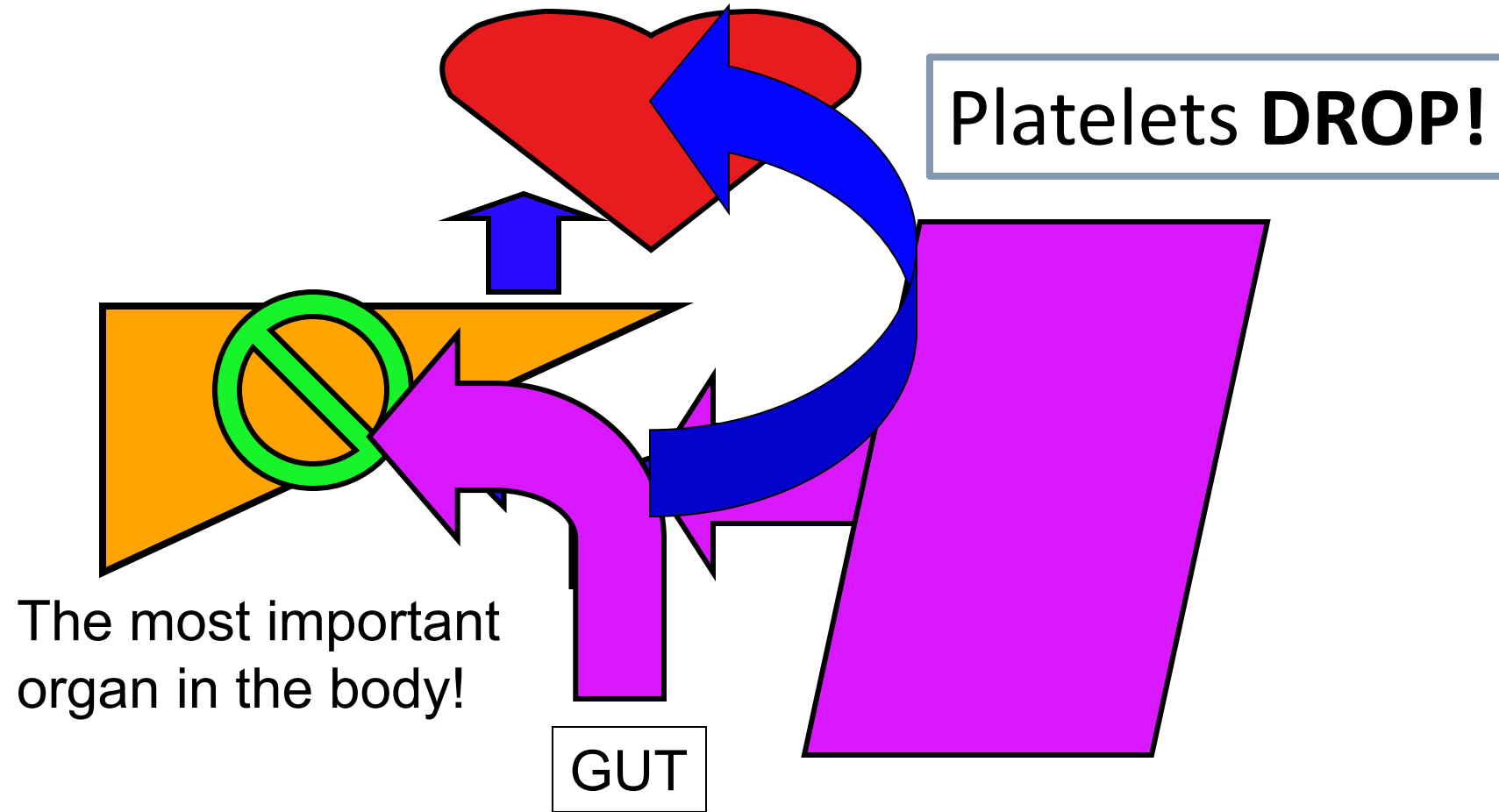


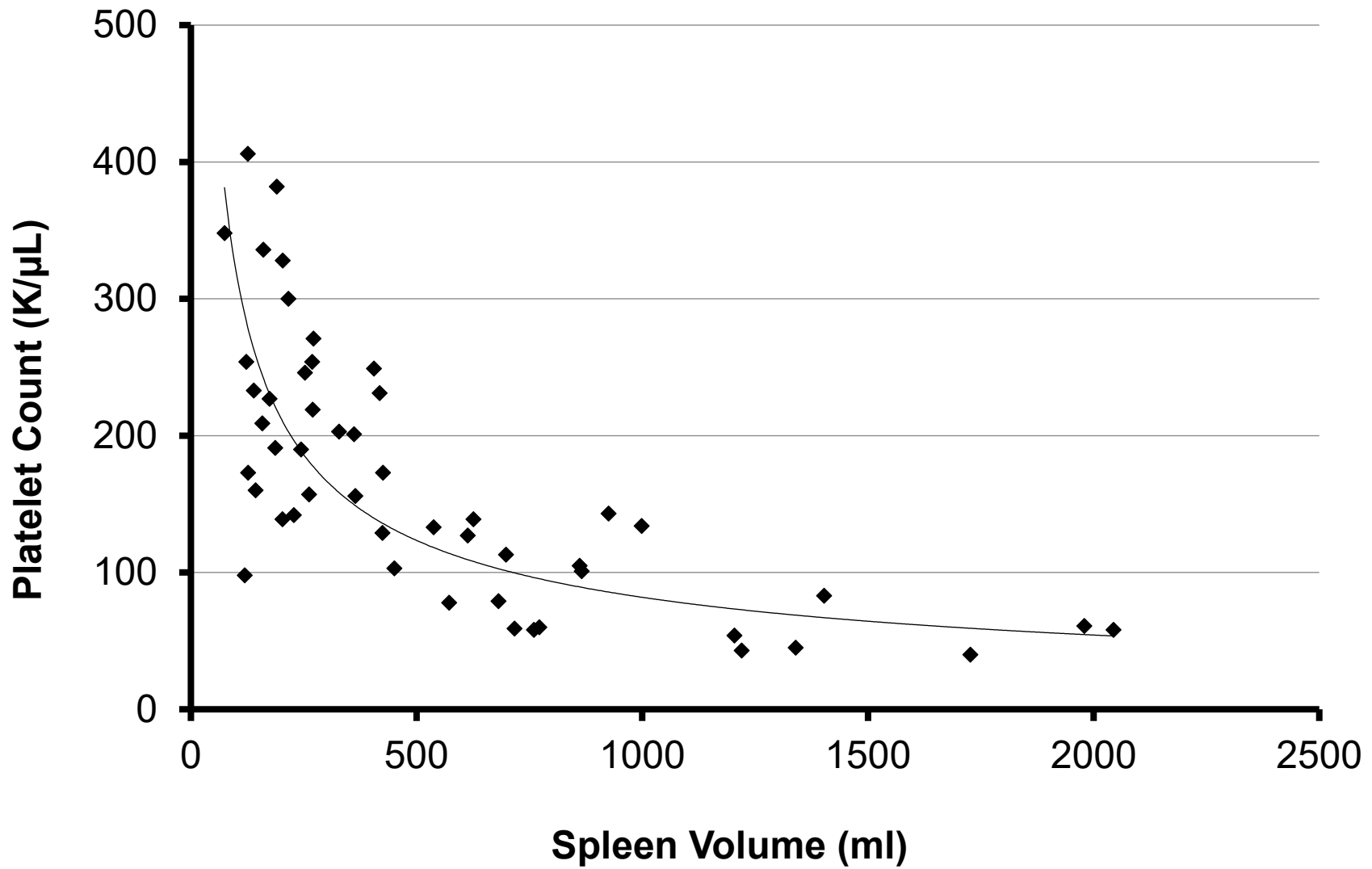
Biology Break

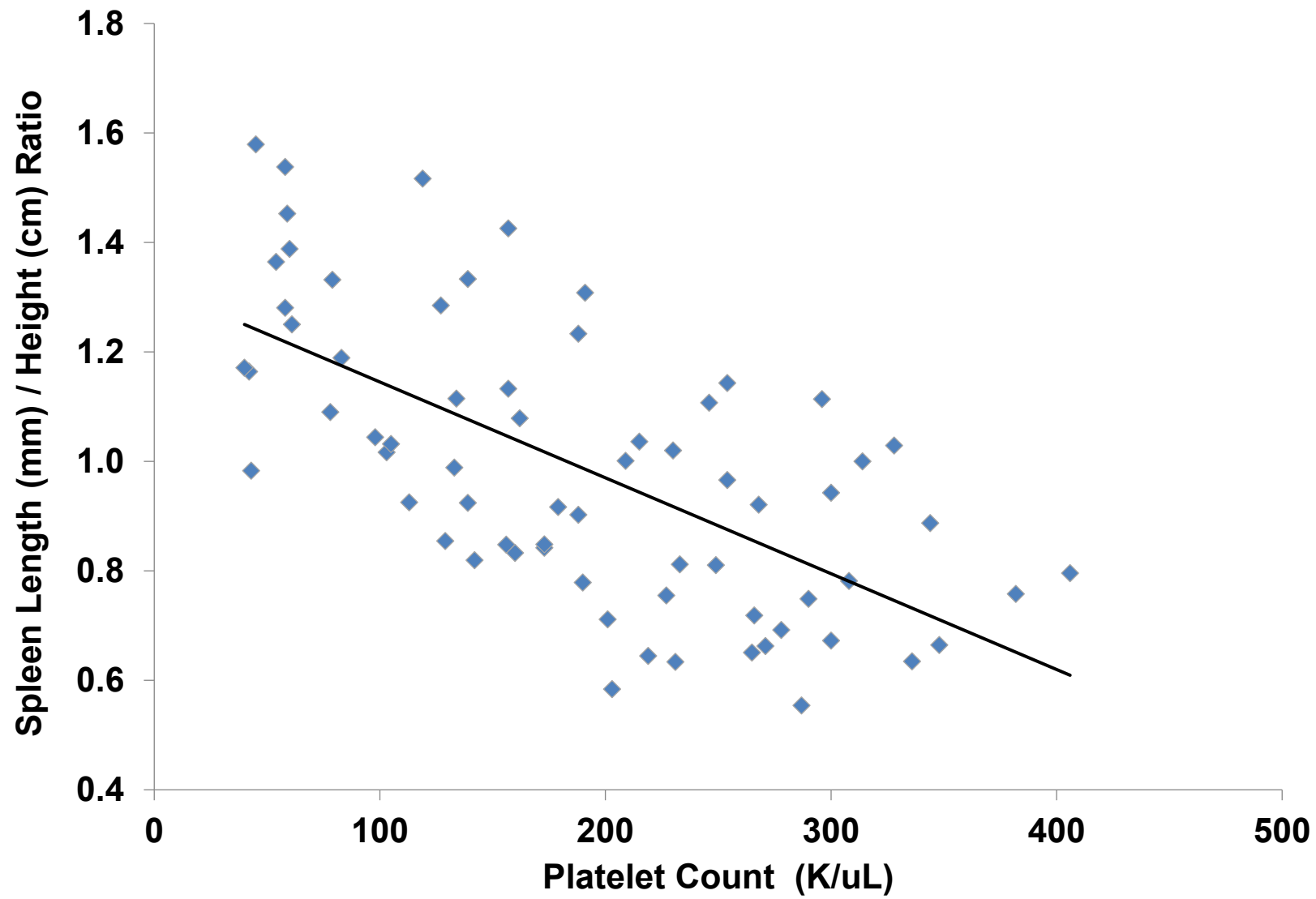
Synthetic Function
(Chores)



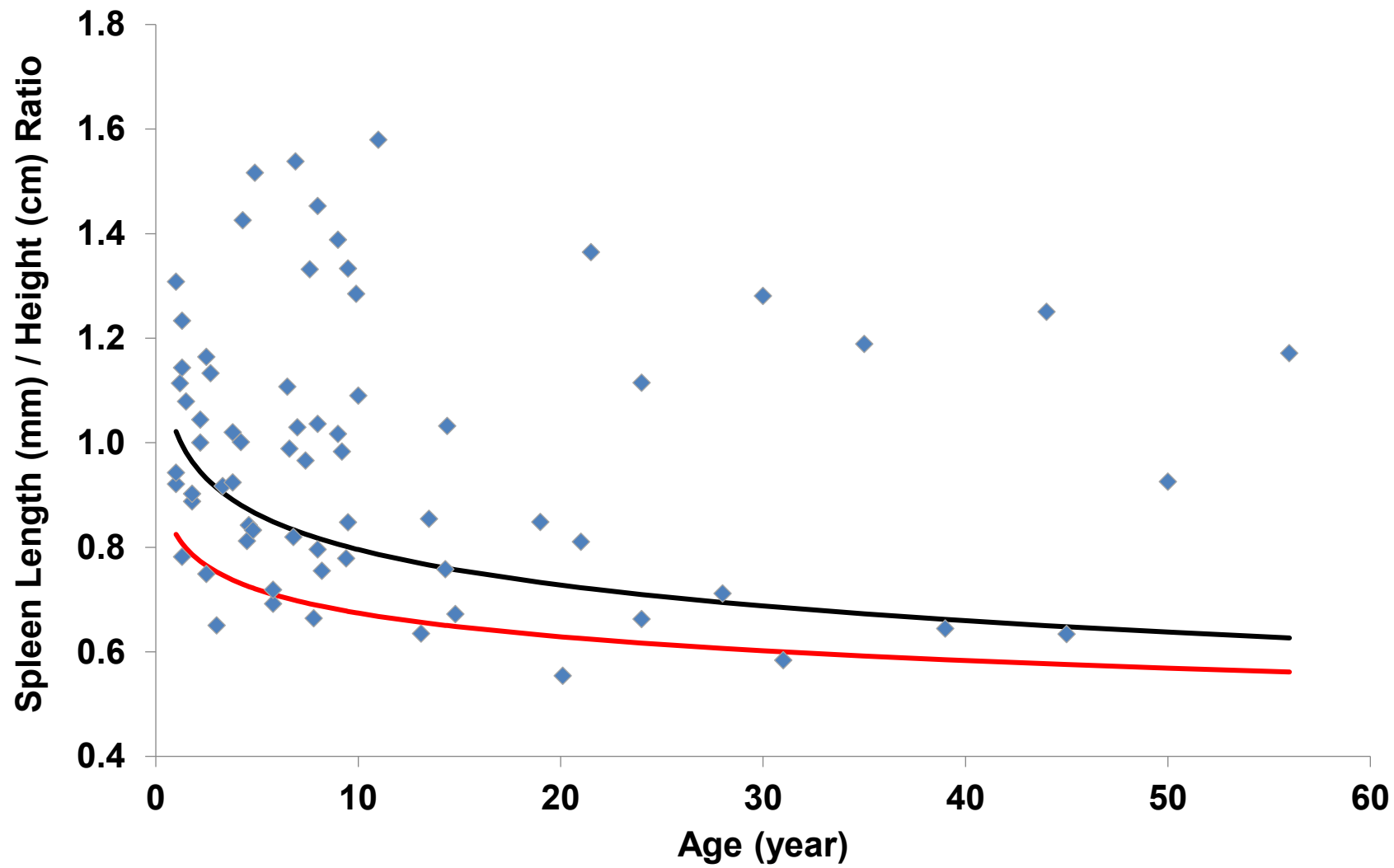
Biology Break



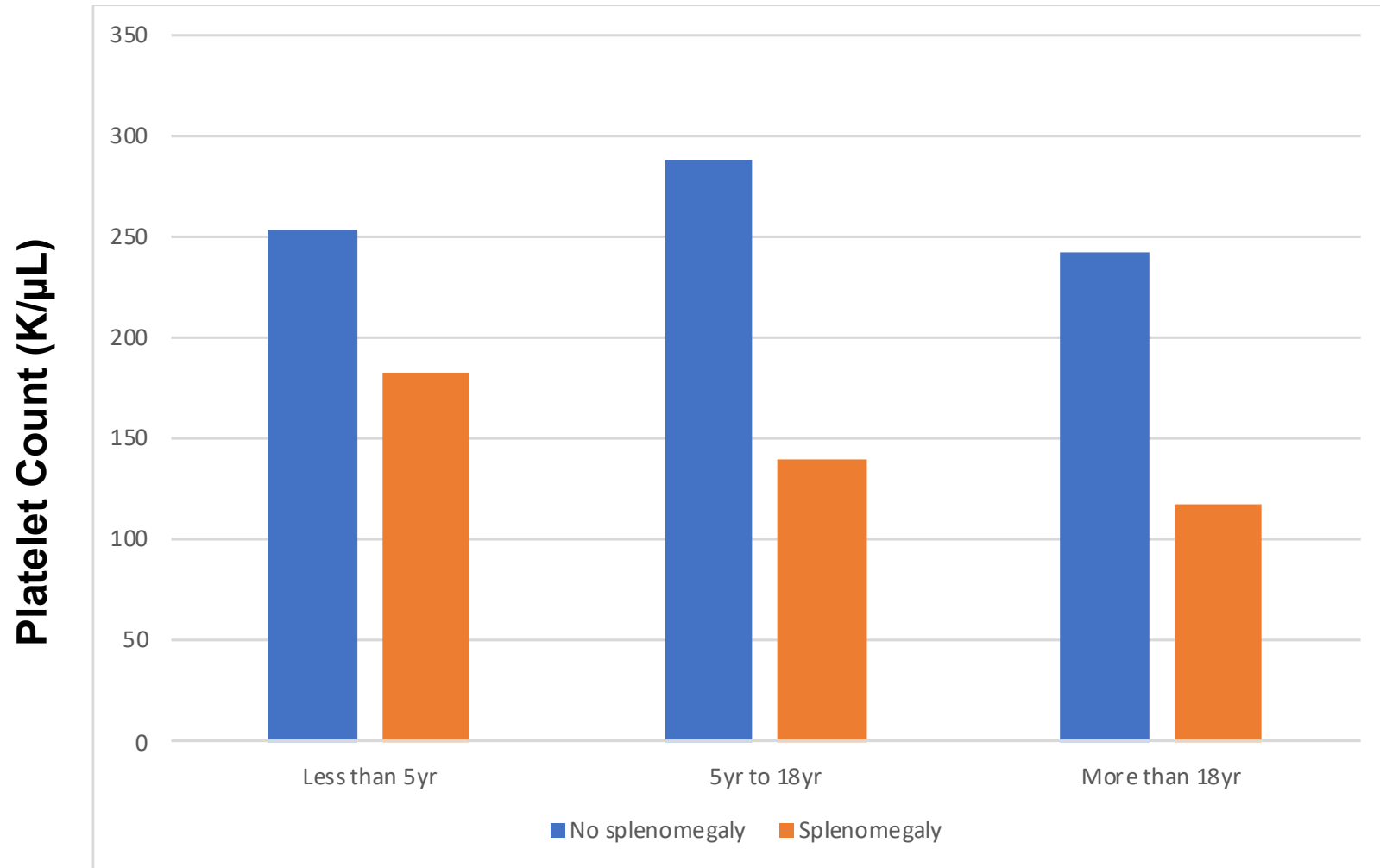




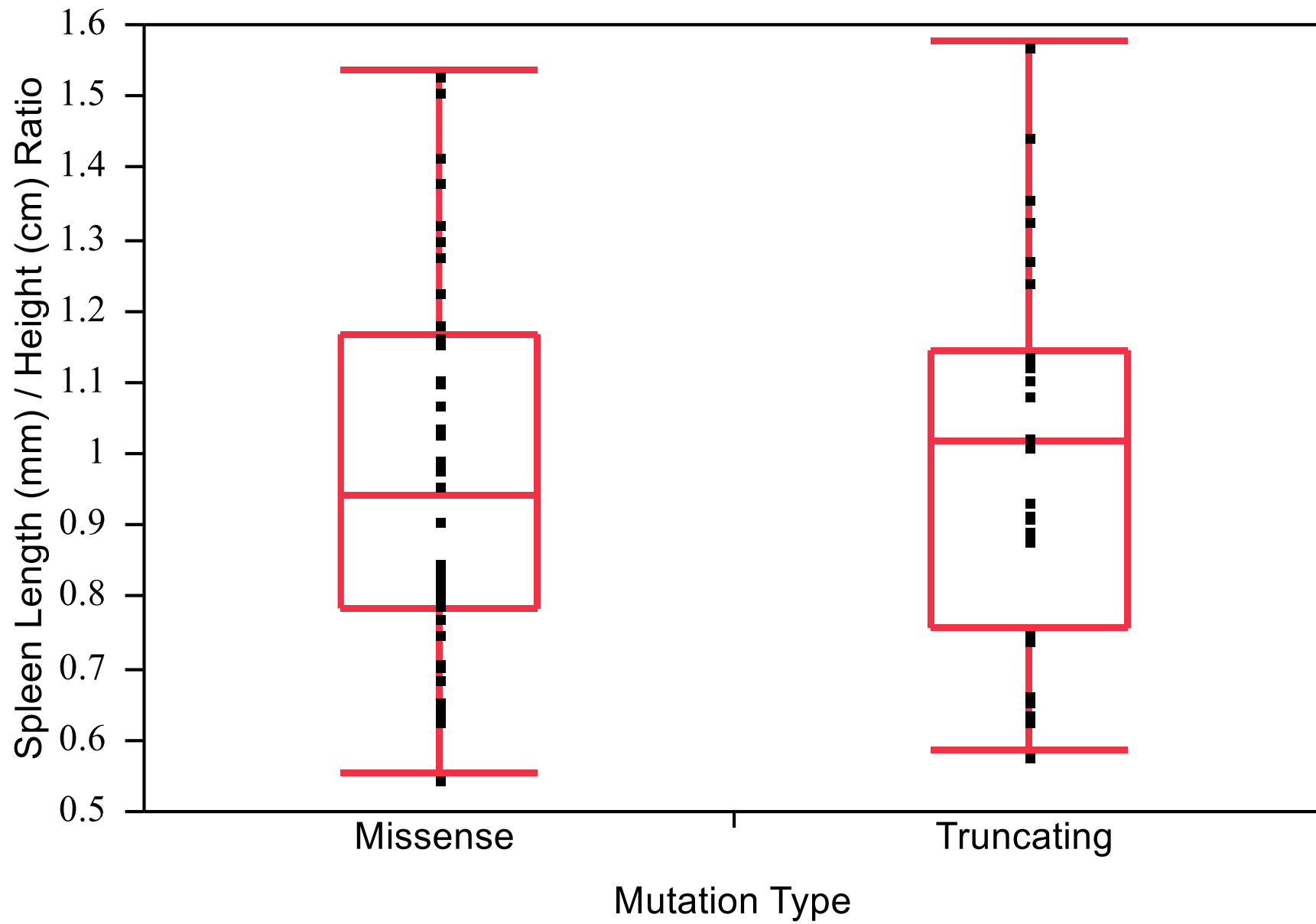
Progression?

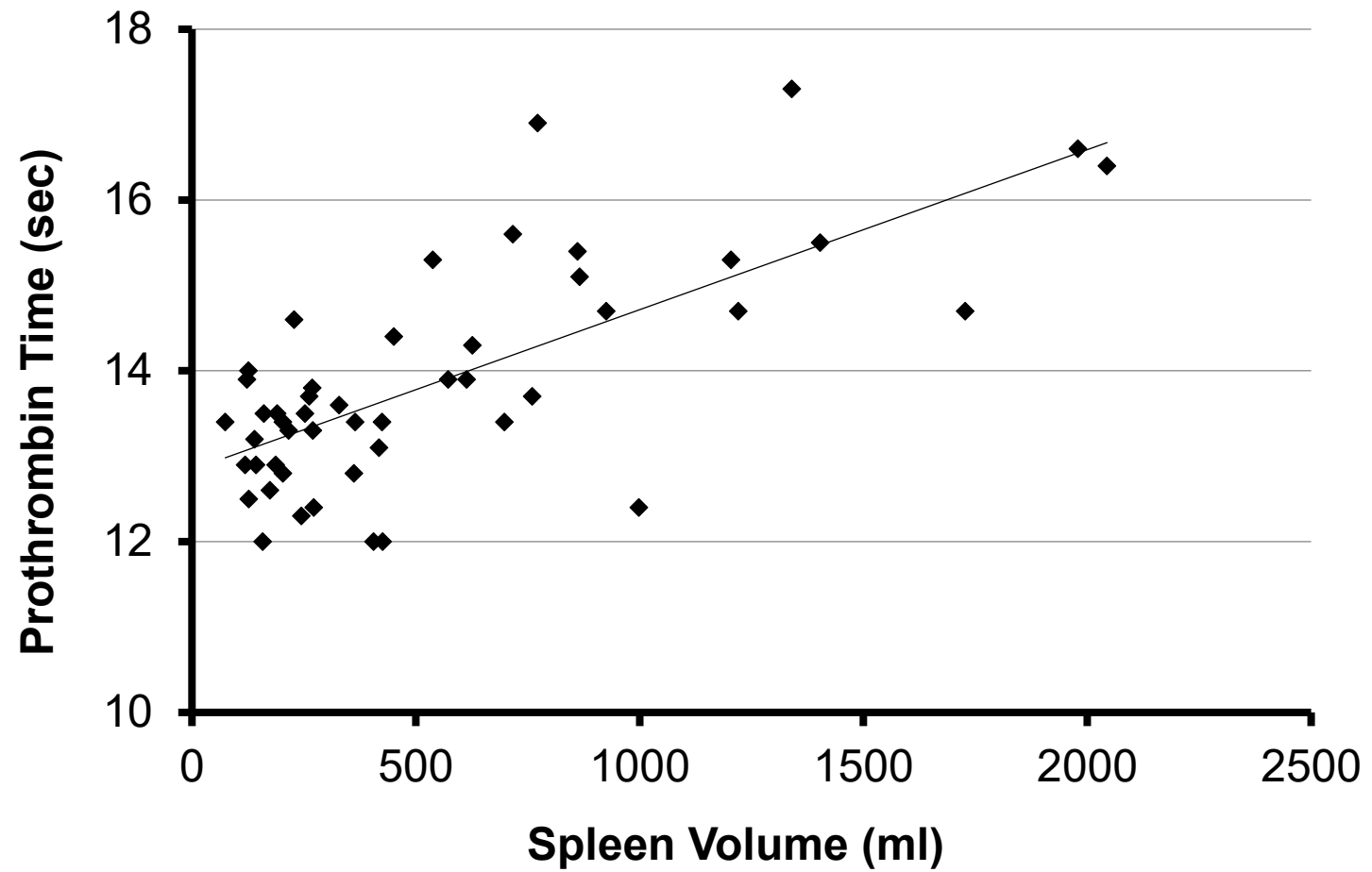


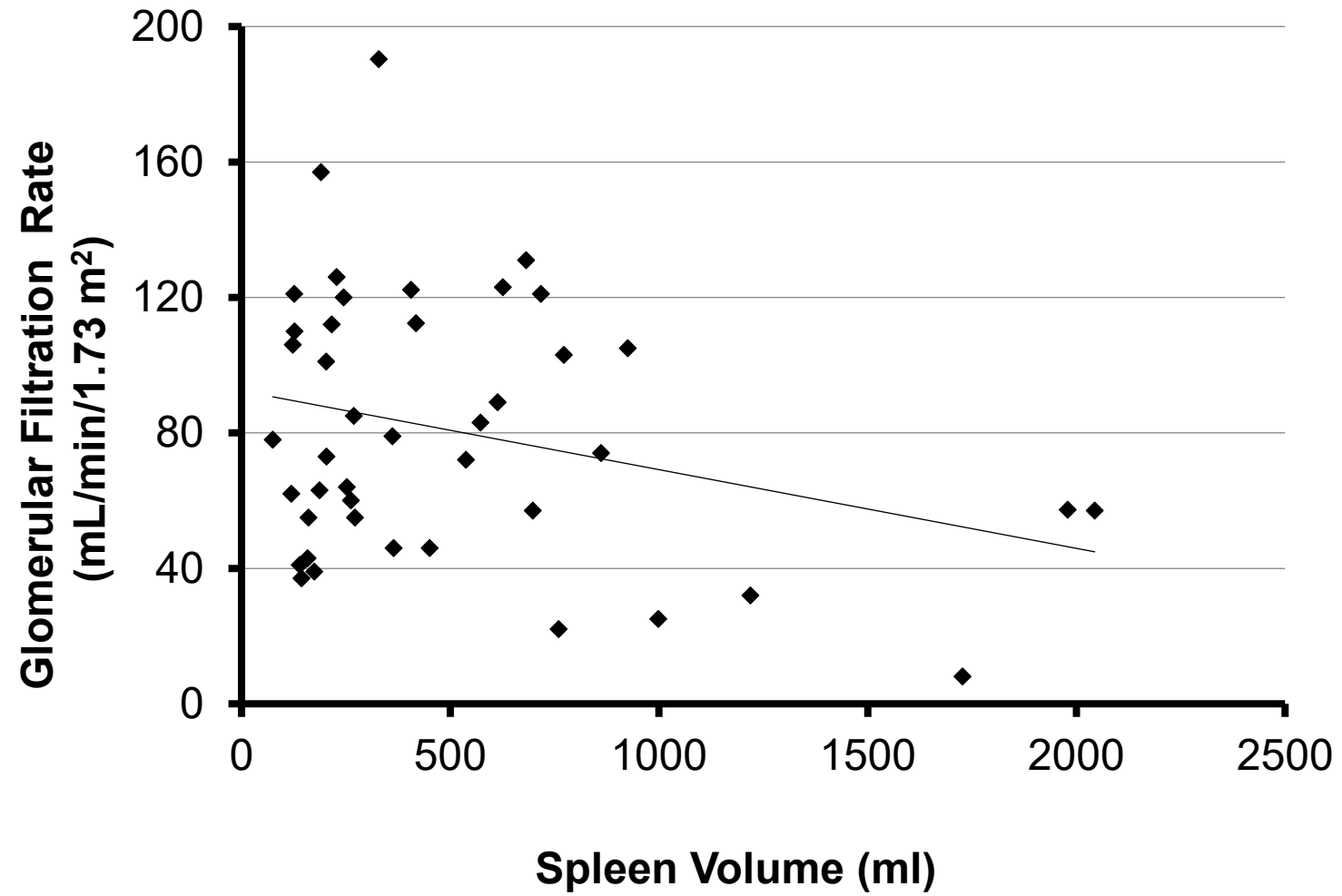
Spleen and Platelets with Time



Details







Images

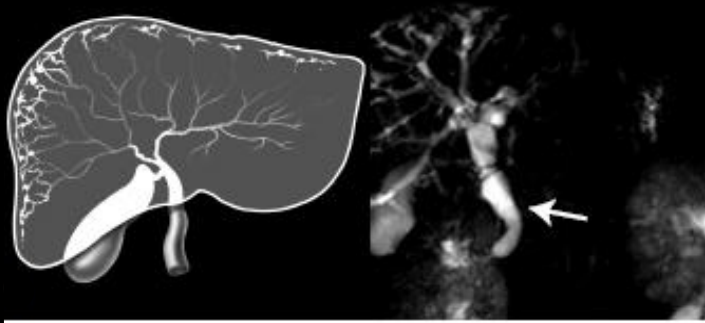
A



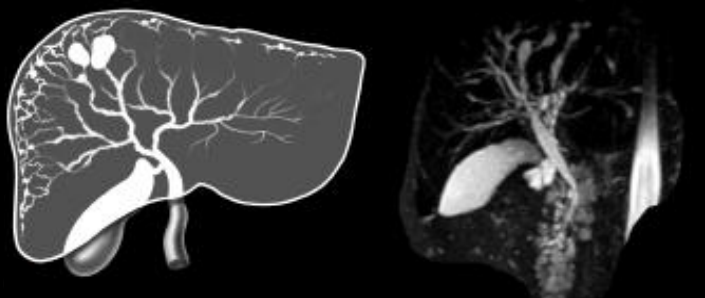
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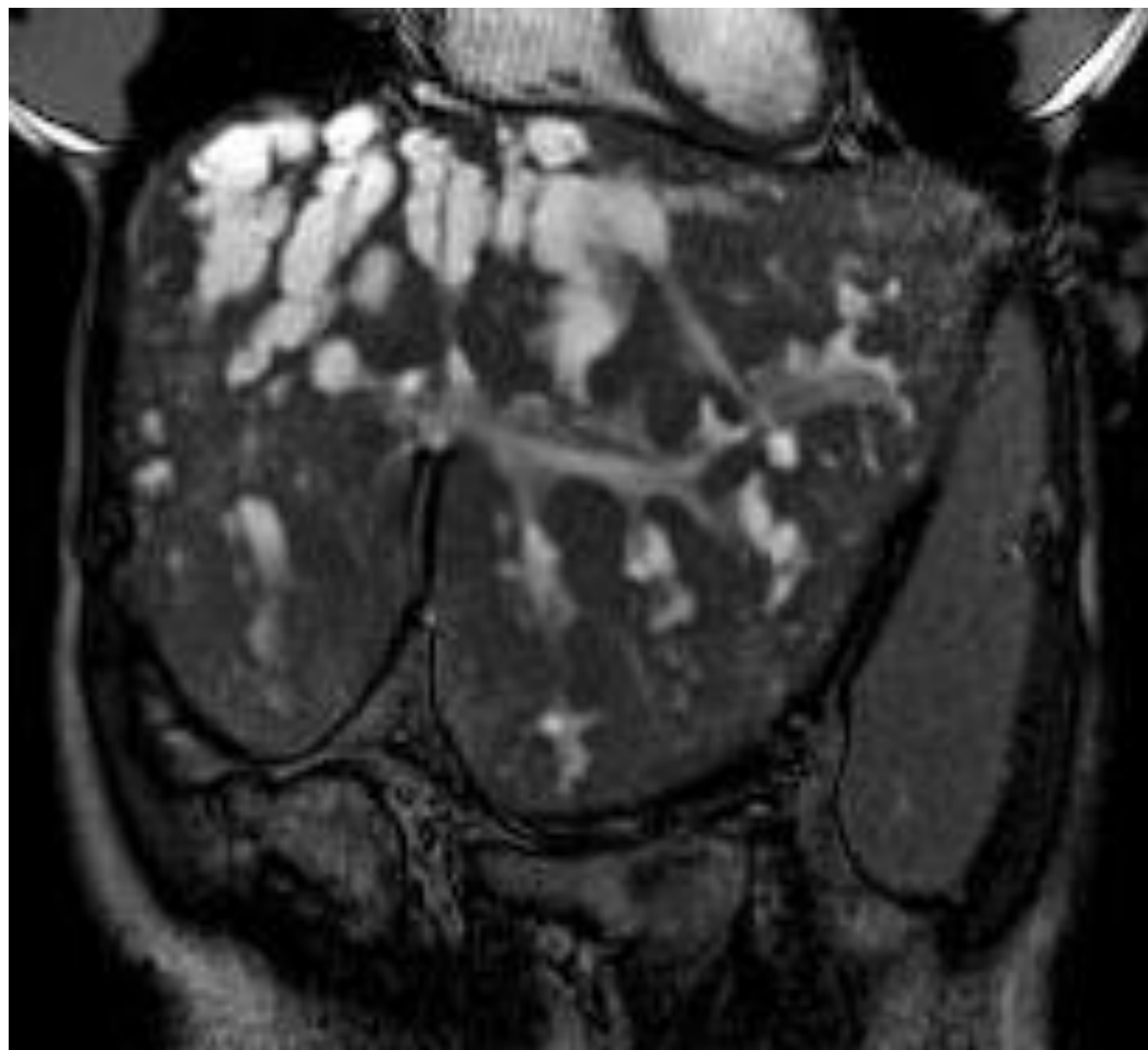
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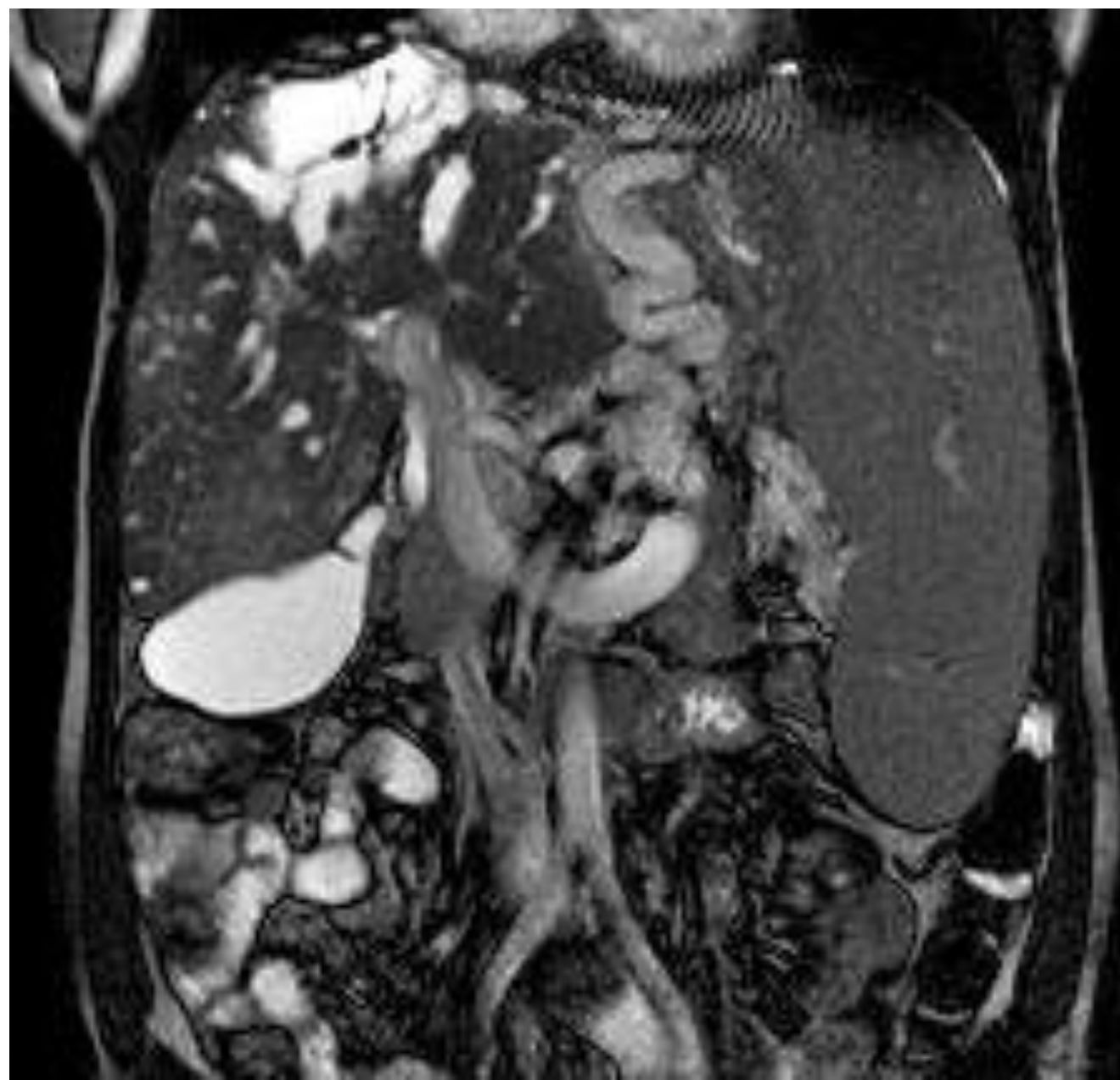


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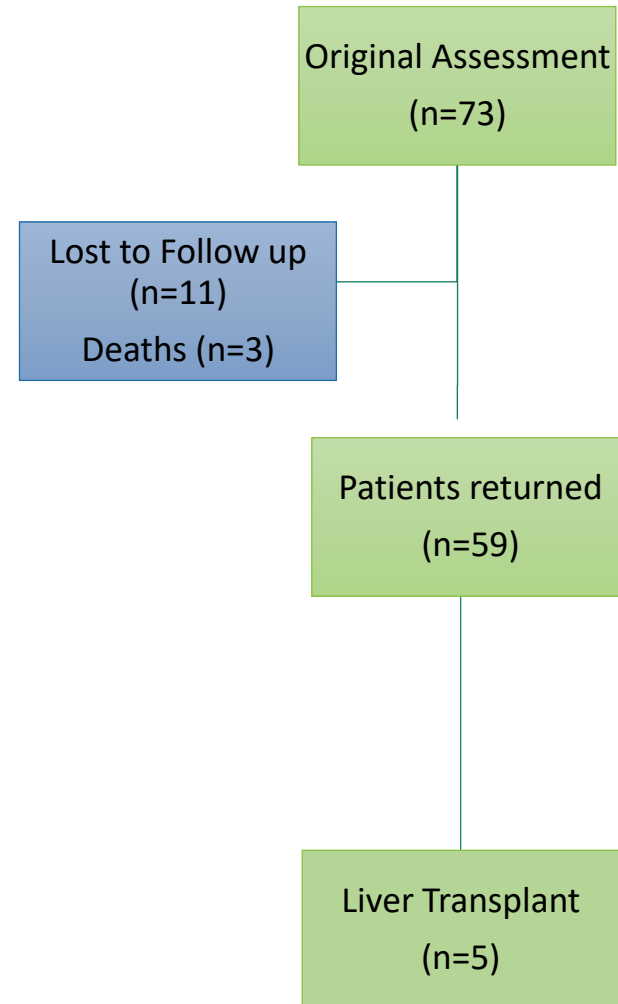




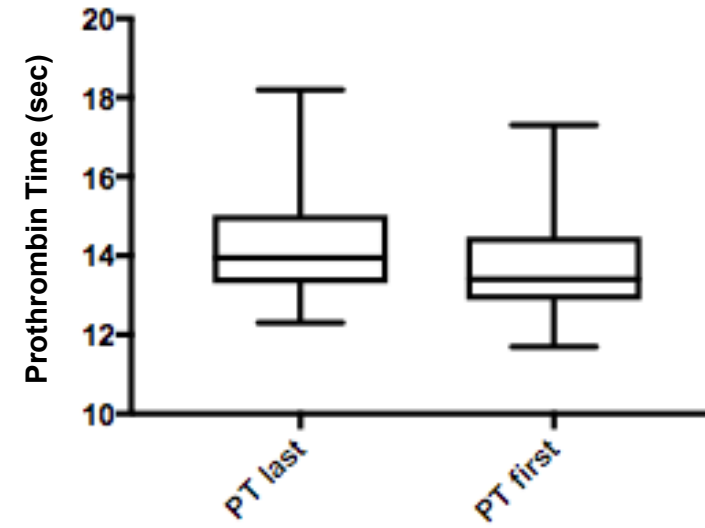
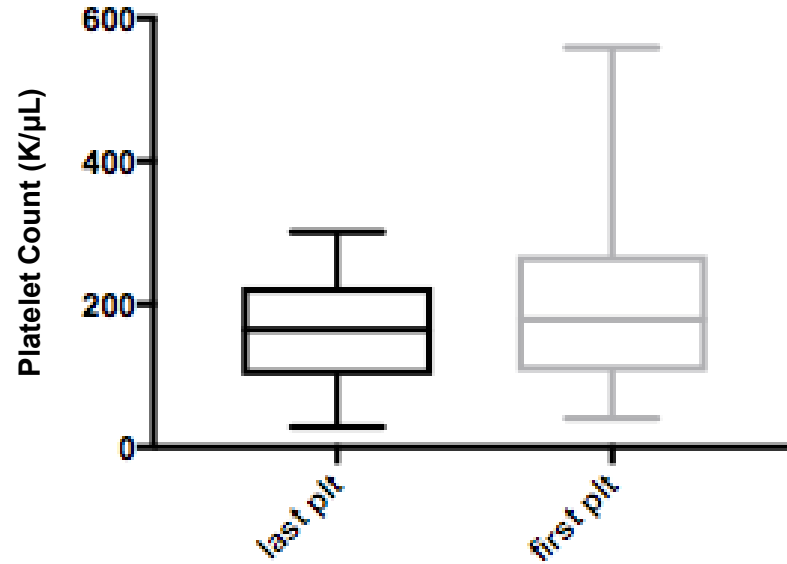




6.5 years of Follow up



Follow up – Preliminary Data



What can be done

- Everyone is different
- Most things can be dealt with
 - I do know that bad things happen to good people
- The ostrich that puts its head into the sand will still be eaten by the lion
 - Better to preempt than catch up

My job!

- Screening
 - Labs
 - Imaging
- Monitoring
 - Labs, imaging
 - Frequency depends on disease severity
- Management
 - Team approach
 - Long-term

Essentials

- Find a team you trust and like
- Center of excellence
- With knowledge
 - Or are willing to learn
- This is more than marriage, there is no divorce
- Establish relationships in case of crisis

Thanks

A silhouette of a person fishing on a pier at sunset. The person is standing on a wooden pier, holding a fishing rod that is bent, indicating a catch. The background shows a calm body of water reflecting the orange and red hues of the setting sun. In the distance, there are utility poles and a few boats on the water.

Patients

Dr. Meral Gunay - Aygun

Dr. William Gahl

Dr. Parvathi Mohan

Dr. David Kleiner

ARPKD/CHF Alliance

CHOP

Colleen Zak