The gut-liver axis and microbiome in the coagulation disorder of cirrhosis:

From dysbiosis to endothelial dysfunction and immunothrombosis

Agustín Albillos

Hospital Universitario Ramón y Cajal, IRYCIS,

Universidad de Alcalá, CIBERehd, Madrid

DIGESTIVO RAMON Y CAJAL MADRID

Universidad de Alcalá

ciberehd

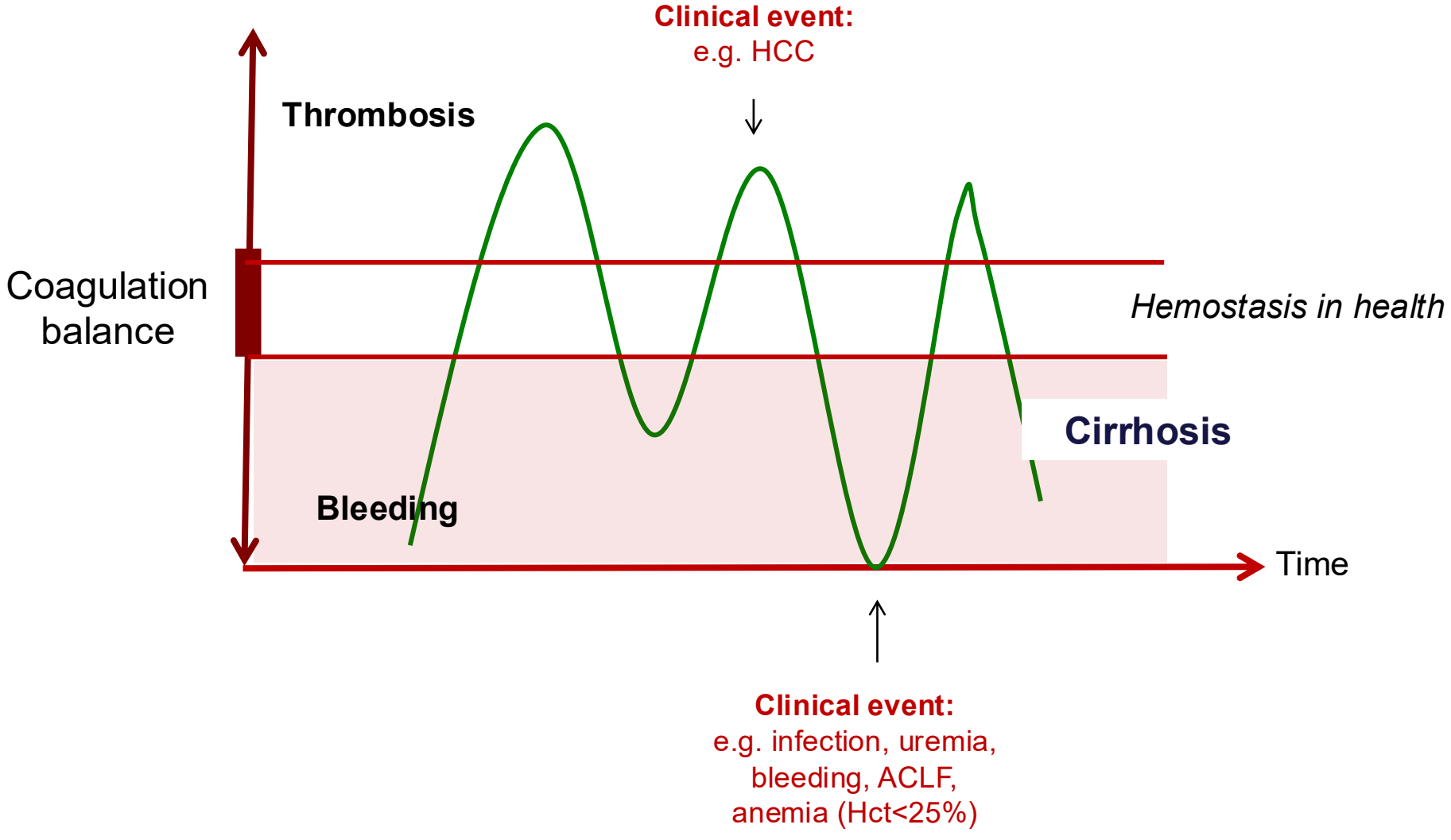
INSTITUTO RAMÓN Y CAJAL DE INVESTIGACIÓN SANITARIA IRYCIS

Agenda

- Mechanisms linking the gut and coagulation
- Endothelial activation as the most consistent signal
- Beyond PVT
- NETs and immunothrombosis as an additional layer

Rebalanced but unstable hemostasis in cirrhosis

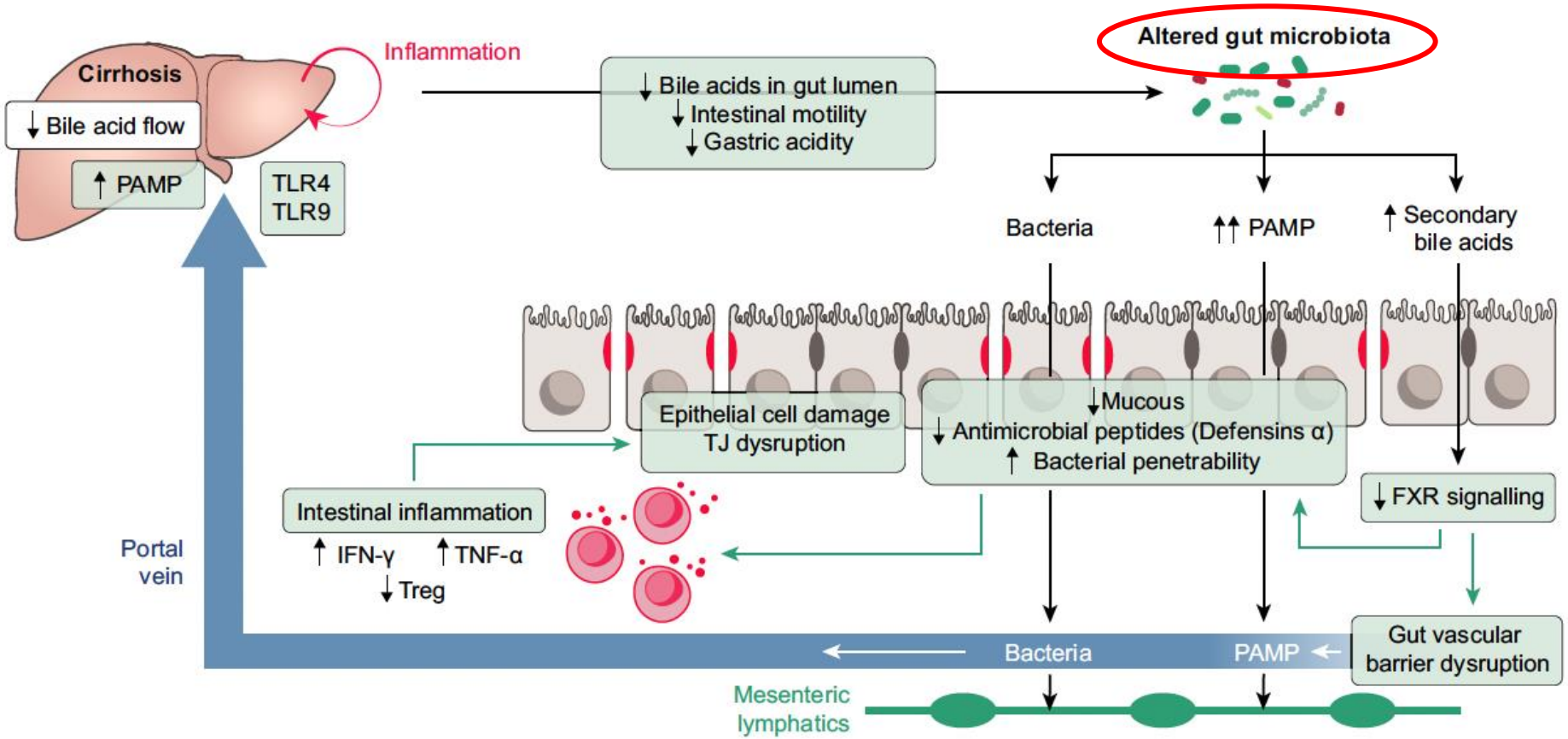
Inflammatory signals can shift the balance toward thrombosis or bleeding



A Albillos own elaboration

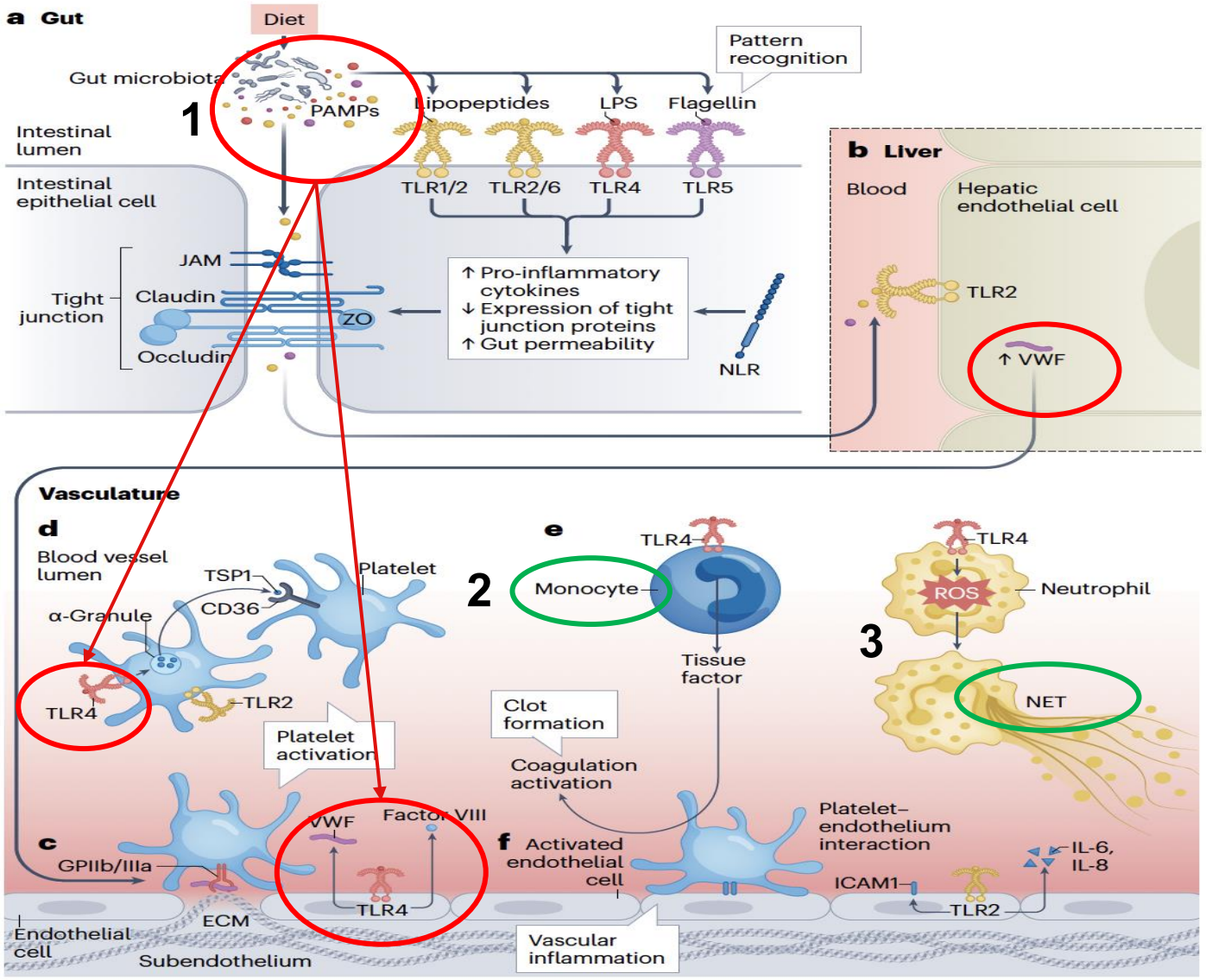
The gut-liver axis in cirrhosis: the upstream event

Dysbiosis, barrier dysfunction and bacterial translocation expose the liver to gut-derived microbial signals



A Albillos et al. JHEP 2020

Mechanisms linking the gut-liver axis and coagulation in cirrhosis



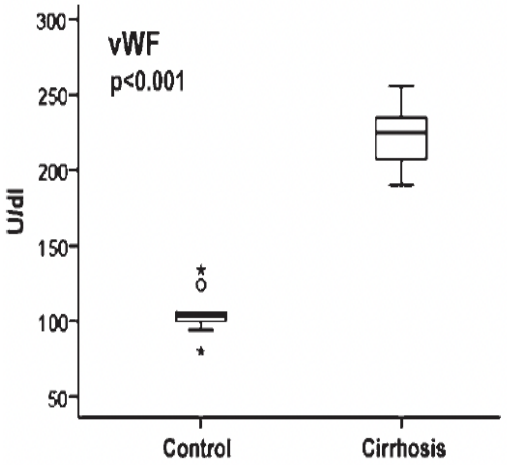
1. PAMPs-driven endothelial activation
2. Chronic inflammatory and metabolic signalling
3. NET formation, immunothrombosis

Modified from Khuu MP et al, Nat Rev Cardiol 2025

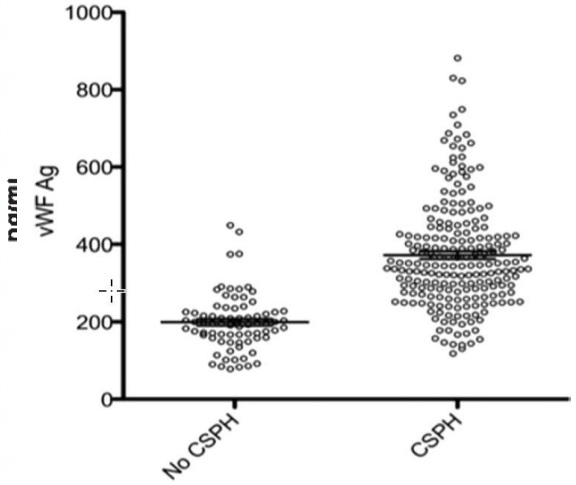
Endothelial activacion in cirrhosis: vWF and factor VIII

Markers of endothelial activation, inflammation and vascular stress

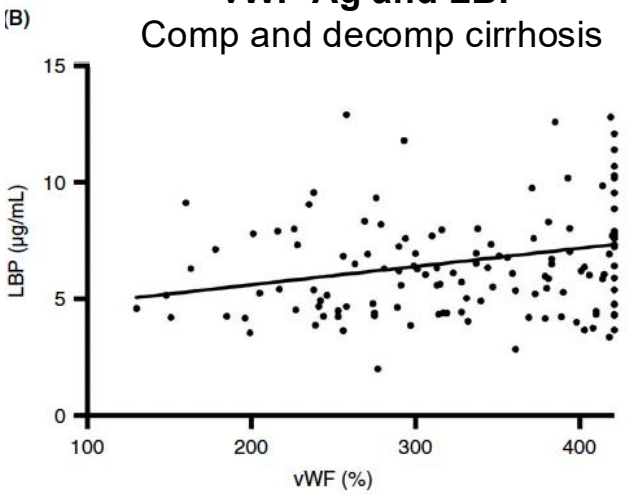
vWF in serum
Comp and decomp cirrhosis



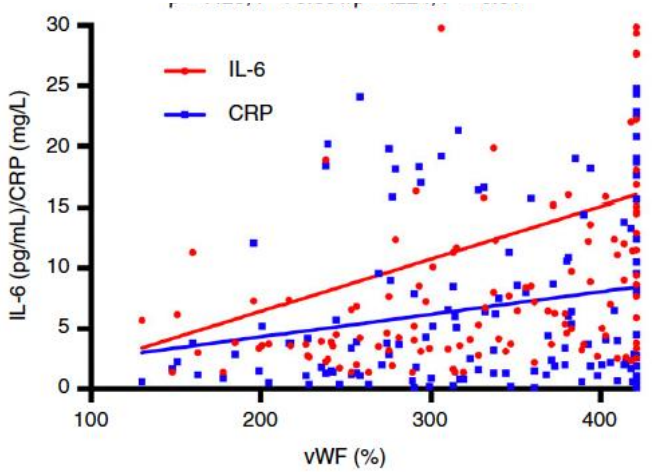
vWF-Ag in serum
Comp cirrhosis



vWF-Ag and LBP
Comp and decomp cirrhosis



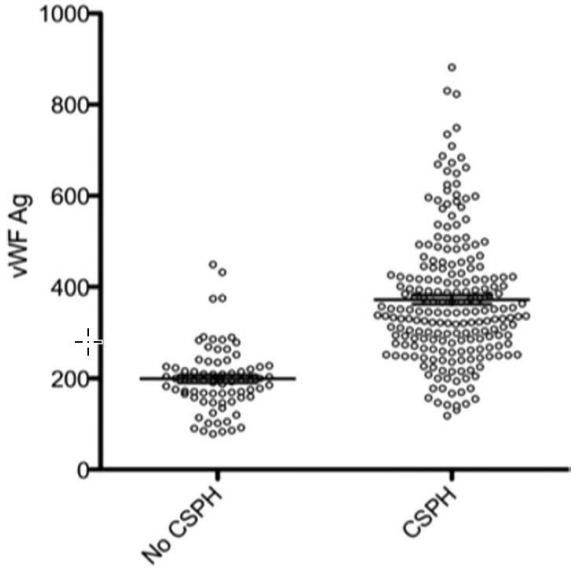
vWF-Ag and IL6/CRP
Comp and decomp cirrhosis



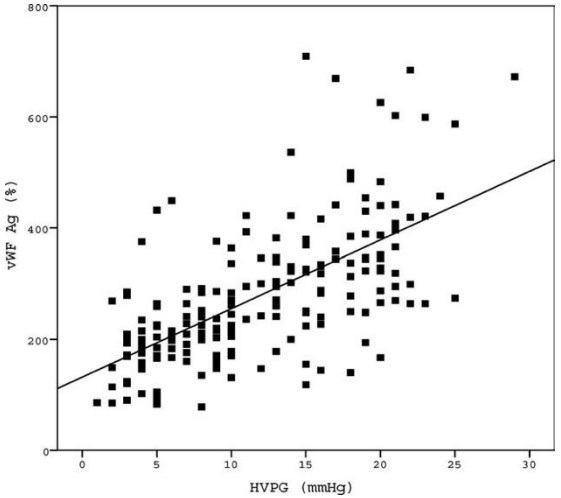
V Lamura et al, Gut 2011.
M Ferlisch et al. Hepatology 2012
M Mandorfer et al, APT 2017
R Carnevale et al, JHEP 2017

vWF and portal hypertension in cirrhosis

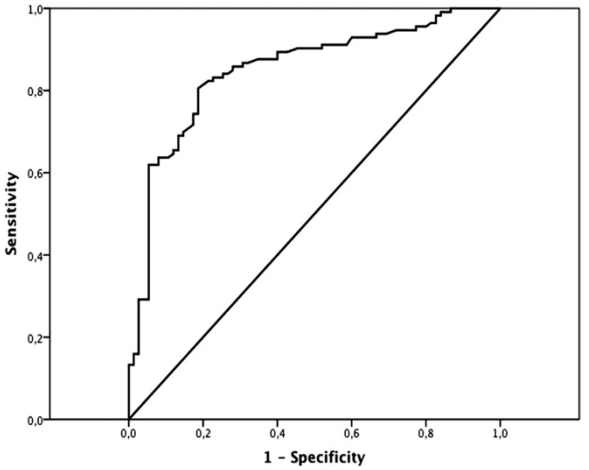
Correlates with HVPG and helps identify CSPH



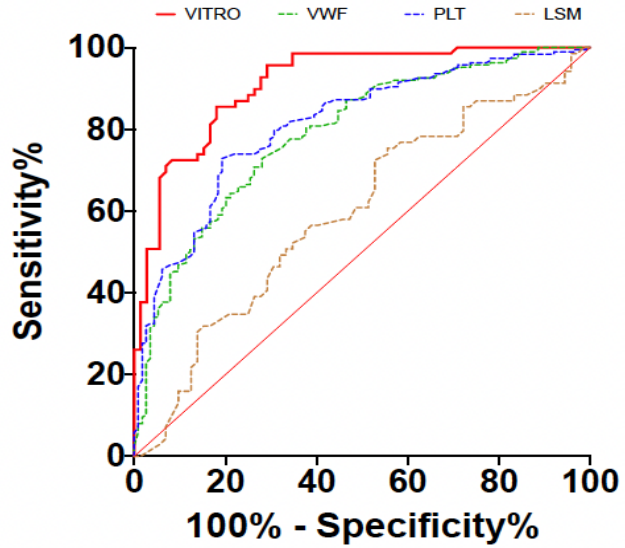
vWF-Ag and HVPG
Comp cirrhosis



AUC of vWF-Ag to predict CSPH
Comp cirrhosis



AUC of vWF-Ag and VITRO to predict HVPG
Comp cirrhosis



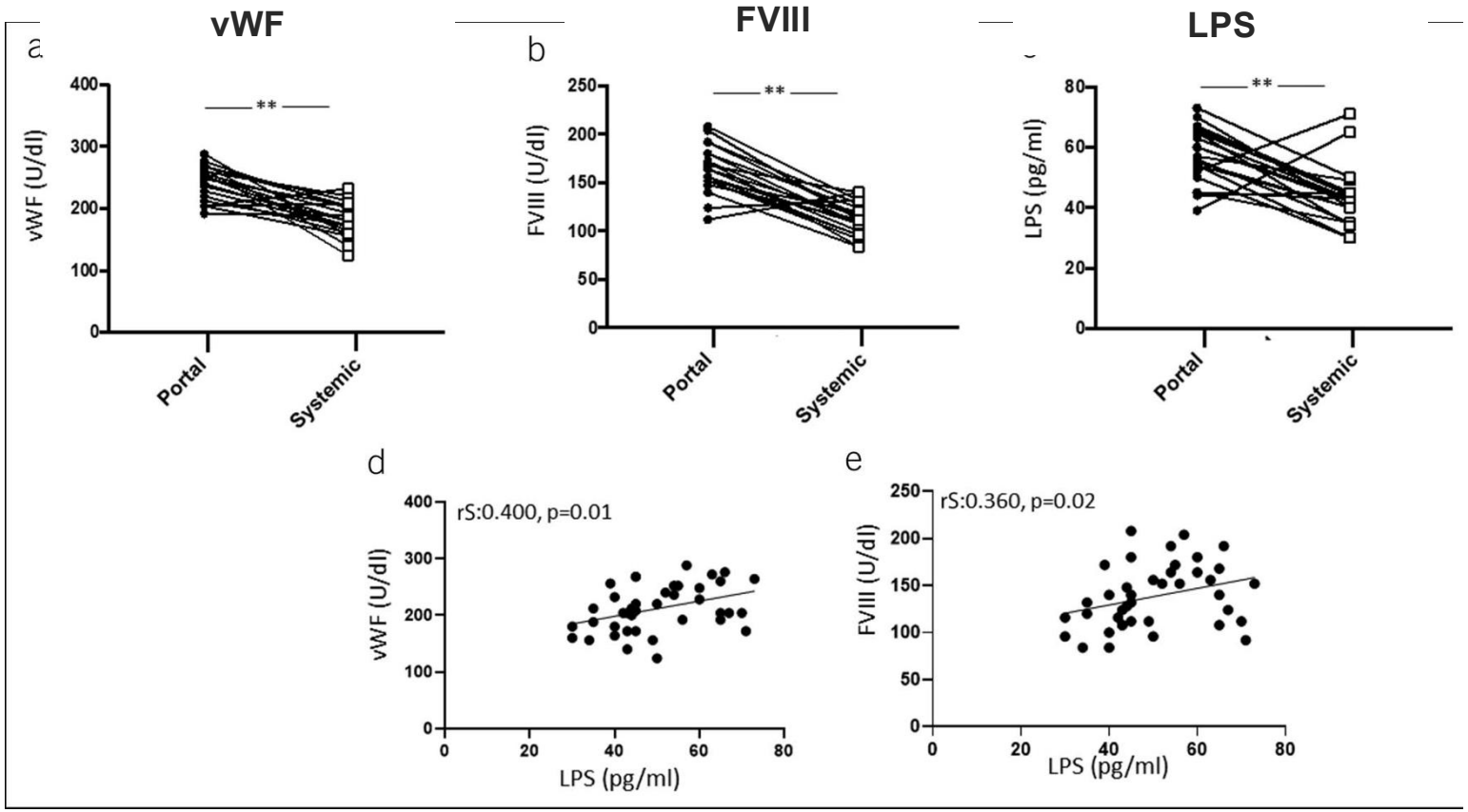
VITRO = vWF/Platelet count

M Ferlisch et al, Hepatology 2012
M. Jachs et al, CGH 2023

Portal-to-peripheral gradient: evidence of a gut-derived vascular signal

Portal blood is enriched in LPS and and associated with greater endothelial activation than peripheral blood

20 patients with cirrhosis who underwent TIPS



M Praktiknjo et al, Clin Trans Gastro 2020

PVT: first level of evidence

Greater portal-to-peripheral gradients and distinct portal microbial signatures in PVT

28 patients with cirrhosis who underwent TIPS
12 with PVT, 16 w/o PVT
Severity of PVT not described

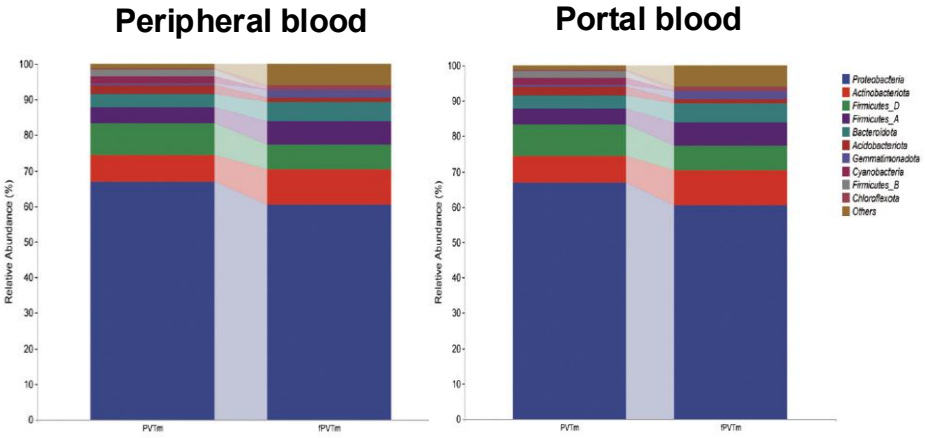
LPS and Inflammatory markers in portal and peripheral blood

Varibles	Portal vein blood	Peripheral vein blood	*P*
Cirrhotic patients			
LPS (pg/ml)	23.37 (4.40–37.26)	18.79 (4.40–37.26)	<0.001
IL-6 (pg/ml)	29.85 (12.80–44.01)	24.95 (4.40–37.27)	<0.001
IL-8 (pg/ml)	79.64 (46.18–104.88)	67.84 (4.40–37.28)	<0.001
TNFα (pg/ml)	38.24 (16.79–57.81)	34.46 (4.40–37.29)	0.007
sNox2-dp (pg/ml)	9.53 (4.66–13.60)	7.89 (4.39–9.90)	<0.001
PVT patients			
LPS (pg/ml)	29.76 (17.01–37.26)	19.92 (11.33–30.15)	0.002
IL-6 (pg/ml)	38.53 (24.82–48.06)	31.56 (22.11–36.13)	0.003
IL-8 (pg/ml)	93.28 (62.4–118.28)	77.05 (52.41–94.59)	0.005
TNFα (pg/ml)	48.60 (34.59–61.56)	40.55 (23.52–38.03)	0.002
sNox2-dp (pg/ml)	12.45 (9.48–14.01)	7.38 (4.52–9.31)	0.005

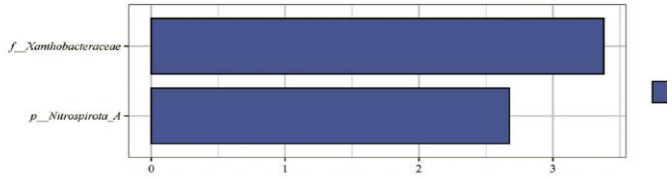
Greater portal-to-peripheral gradient in PVT vs. No-PVT:

- LPS
- Inflammatory markers
- ↑ Proteobacteria and ↓ Firmicutes

Microflora



Distinctive of enrichment of portal blood in PVT



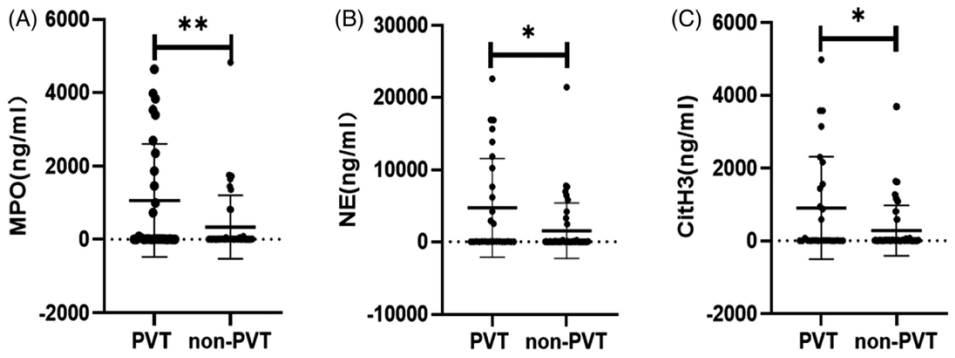
Y Sun et al, Front Med 2026

PVT: second level of evidence – NETs, hypercoagulability, endotoxin

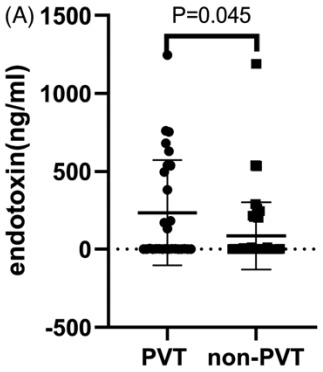
Supports biological plausibility, but remains associative

72 patients with cirrhosis who underwent TIPS
28 with PVT, 44 w/o PVT
75% involving the main trunk

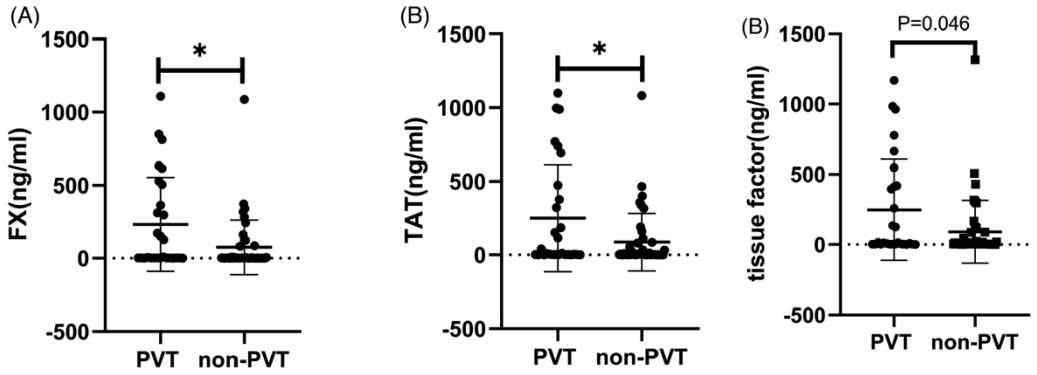
Serum NETs markers



Serum Endotoxin



Peripheral hypercoagulation state



Correlation between endotoxin and NETs and TAT

	TF		Endotoxin	
	Rs	*p* Value	Rs	*p* Value
MPO	0.8045	<0.0001	0.8910	<0.0001
NE	0.8297	<0.0001	0.9584	<0.0001
CitH3	0.8834	<0.0001	0.9425	<0.0001
TAT	0.9704	<0.0001	0.7581	<0.0001
FX	0.8867	<0.0001	0.7203	<0.0001
D-dimer	0.0899	0.6495	0.0967	0.6247

Y Xing et al, J Clin Lab Anal 2022

PVT: third level of evidence – probably more related to cirrhosis severity

PVT is likely a downstream phenotype of advanced portal hypertensive disea

369 cirrhotic patients, f-up 48 ± 27 months
PVT in 29 patients

Independent risk factors for portal vein thrombosis

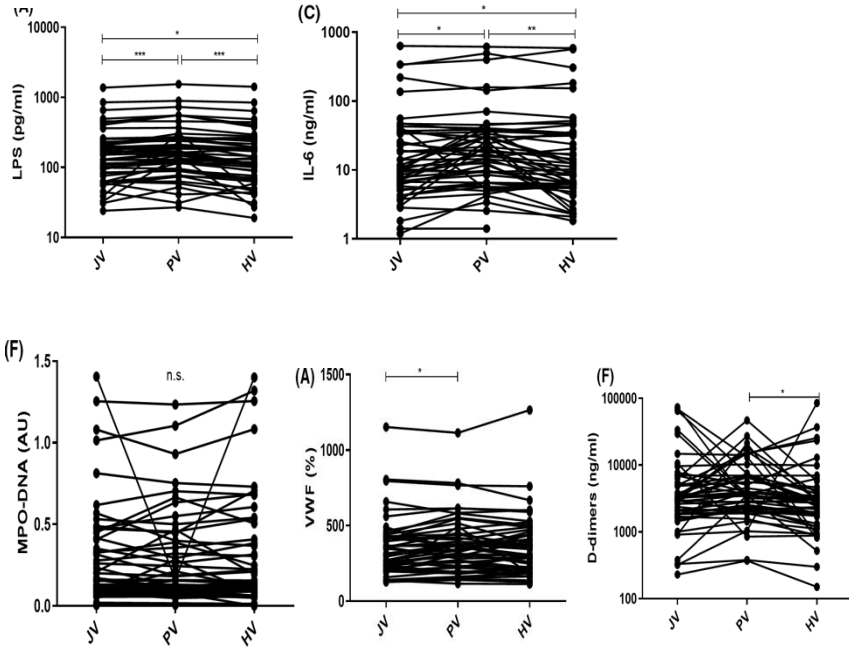
Platelet count	0.98 (0.97-0.99)	**0.002**
PBFV <15 cm/sec	2.28 (0.99-5.26)	**0.05**
Variceal bleeding	2.52 (1.06-5.99)	**0.036**

No differences of inflammatory, coagulation and NETs markers

F Turon et al. JHEP 2021

Portal-to-peripheral gradient of inflammation and vWF

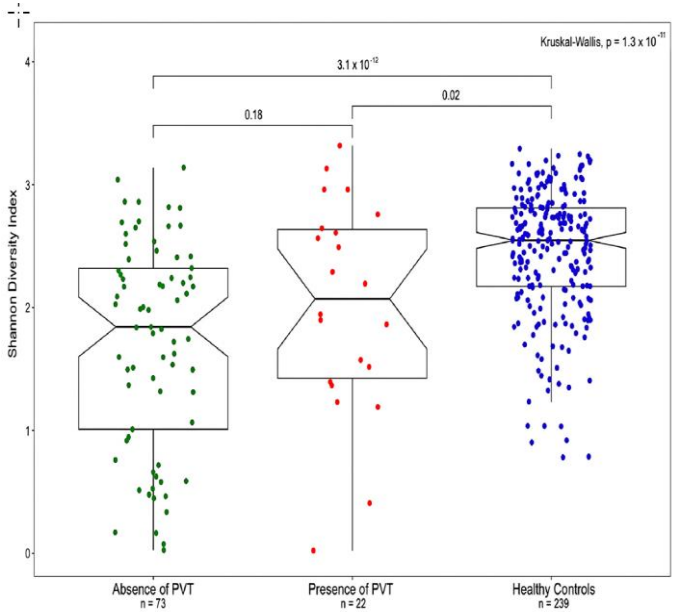
51 patients with cirrhosis who underwent TIPS
5 with occlusive PVT



No differences in PVT patients

EG Driever et al. J Thromb Hemost 2022

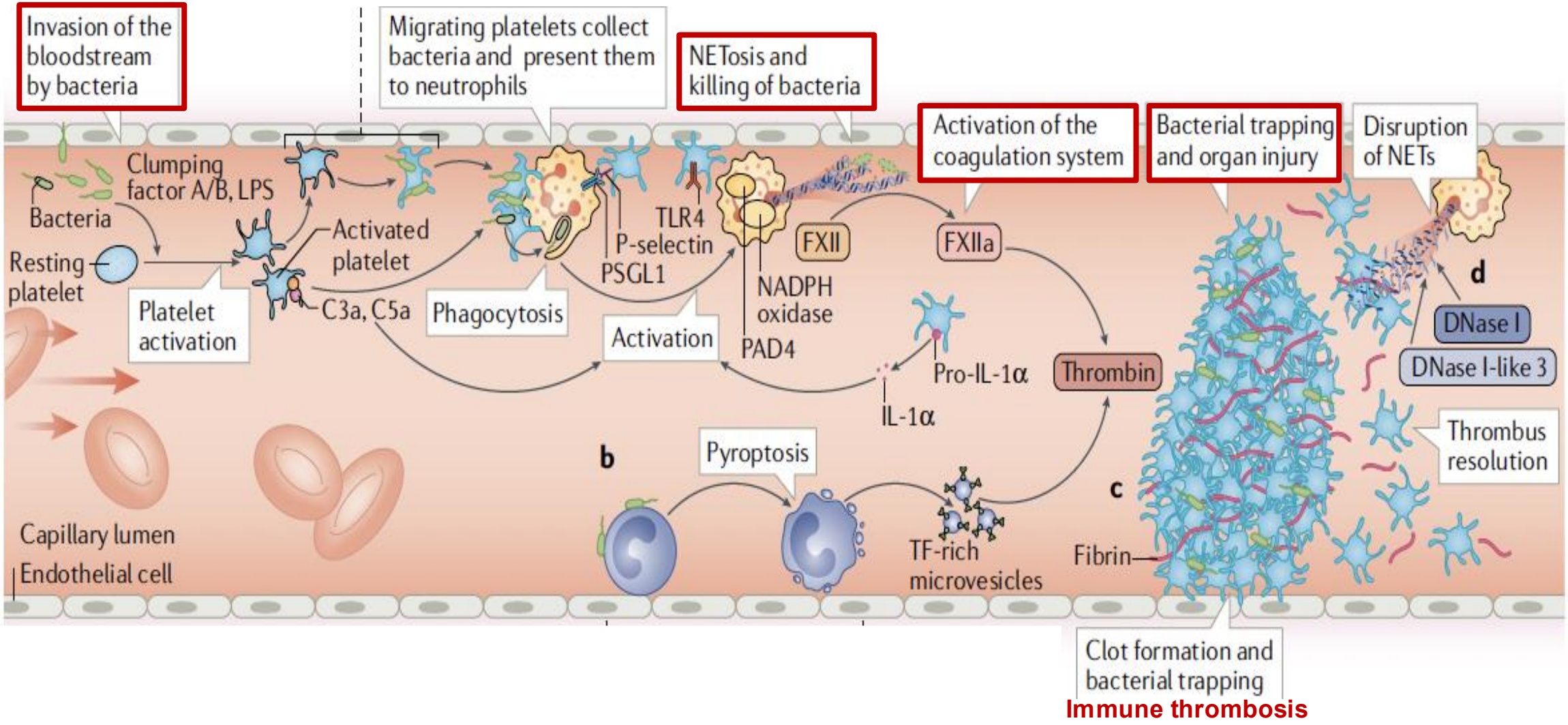
Shannon diversity in patients with cirrhosis w and w/o PVT



RR Aleksandrova et al. J Thromb Hemost 2025

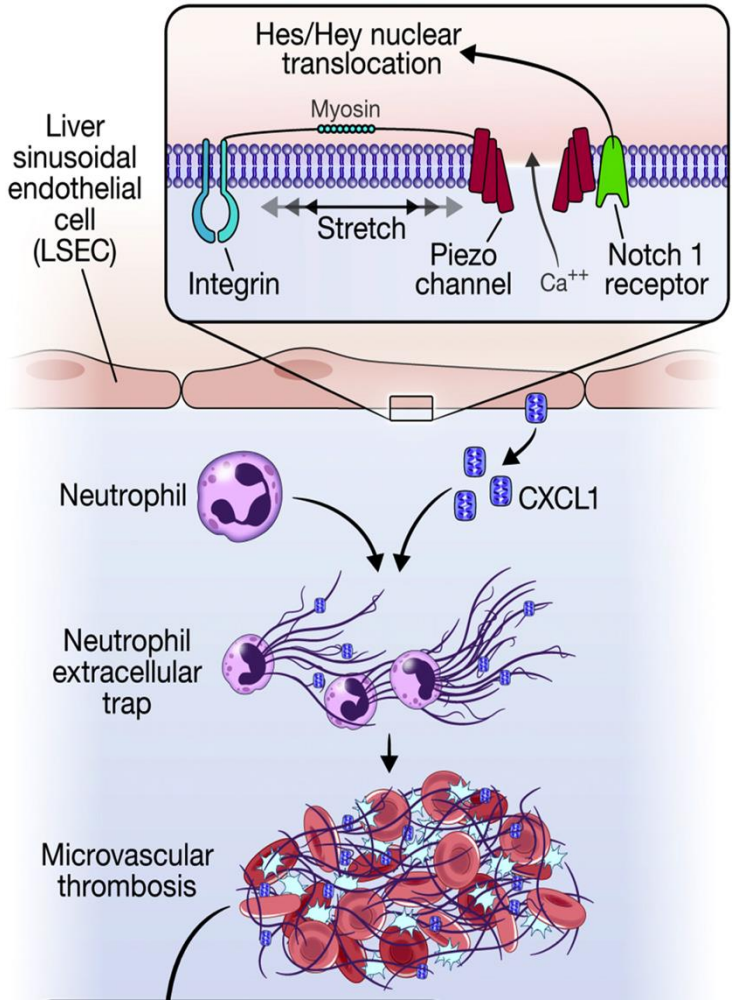
NETs and immunothrombosis: an additional mechanism

A mechanistic bridge between innate immunity and thrombosis



Modified from Stark et al

NET formation as a driver of sinusoidal microvascular thrombosis and fibrosis in congestive hepatopathy



Congestive hepatopathy model
by partial ligation of the suprahepatic IVC

• Mechanical stretch → CXCL1 secretion by LSECs → recruitment of neutrophils → NET formation → sinusoidal microvascular thrombosis and fibrosis

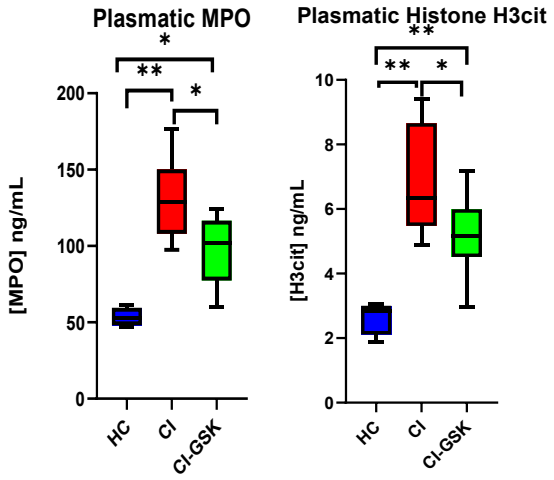
• **Prevention of NET formation** by Pad4 knockout or sivelestat:
  - **Congestive hepatopathy:**
    ↓ sinusoidal MPO, ↓ sinusoidal fibrin, ↓ fibrosis
  - **BDL model:**
    ↓ sinusoidal MPO, ↓ sinusoidal fibrin, = fibrosis

MB Hilscher et al. Gastroenterology 2019

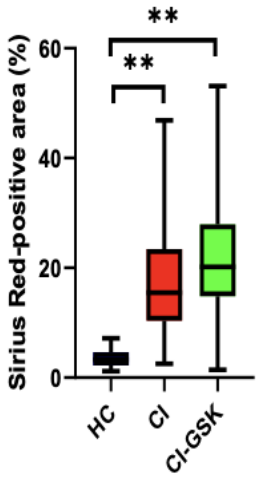
NETs in a preclinical model of cirrhosis

Rats with CCl_4 cirrhosis and ascites treated with **GSK484** (Pad4 inhibitor) ip for 2 weeks

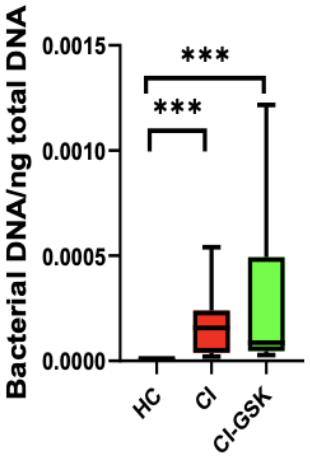
↓ Markers of NETs in plasma



= Liver fibrosis



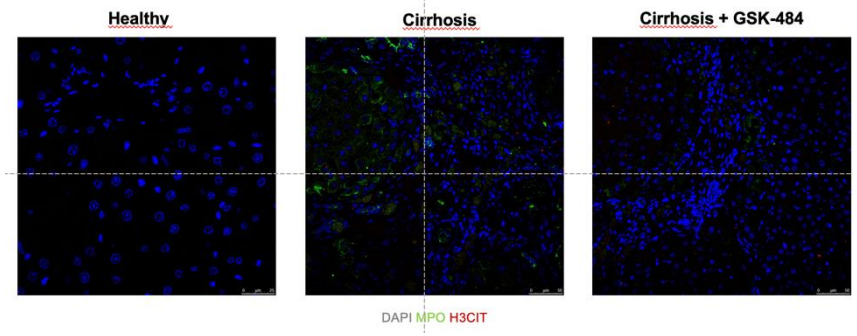
= Bacterial translocation to the liver



= Gut barrier integrity

- Epithelial: ZO-1 positivity
- Vascular: PV1 positivity

↓ NETs in the liver

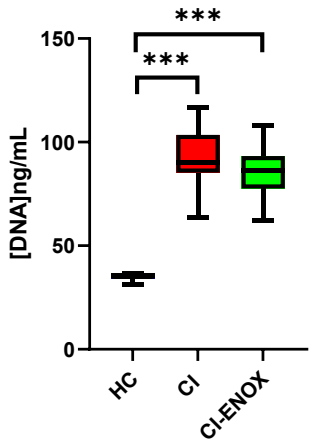


Unpublished data

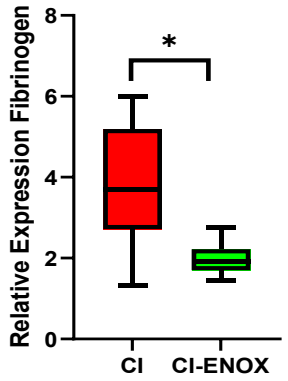
Enoxaparin reduces NETs in a preclinical model of cirrhosis, but broader vascular effects

Rats with CCl_4 cirrhosis and ascites treated with **enoxaparin** sc for 2 weeks

↓ Plasma dsDNA

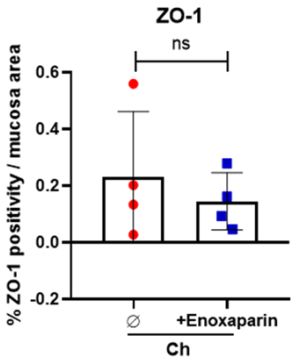


↓ Hepatic fibrinogen

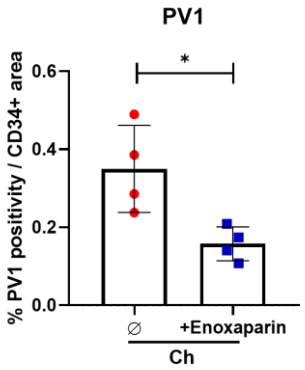


Gut barrier integrity

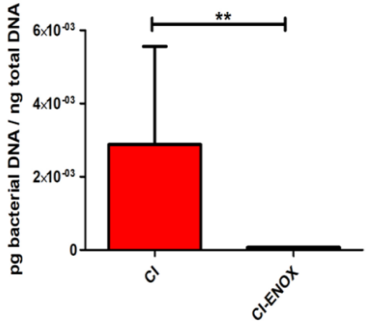
= Epithelial



Vascular



↓ Bacterial translocation to the liver



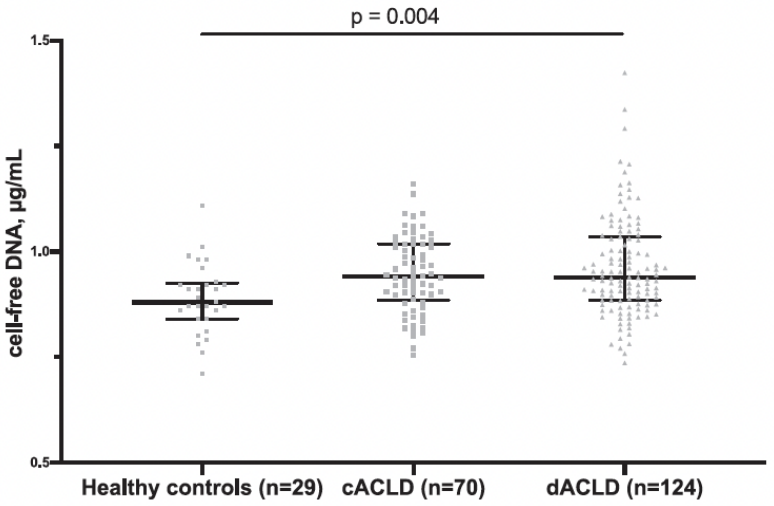
= Hepatic fibrosis

Unpublished data

NETs in cACLD vs. stable dACLD:
what human data actually show

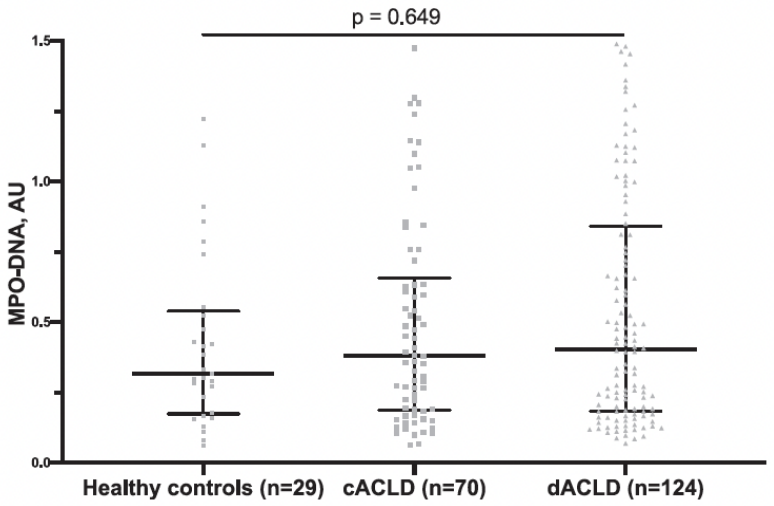
70 patients with compensated cirrhosis
124 patients with stable decompensated cirrhosis

Cell-free DNA in plasma



Not linked to bacterial DNA

MPO-DNA in plasma



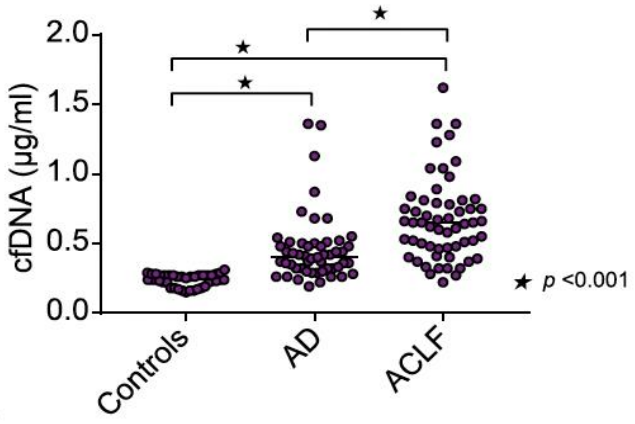
Not linked to clinical end-points

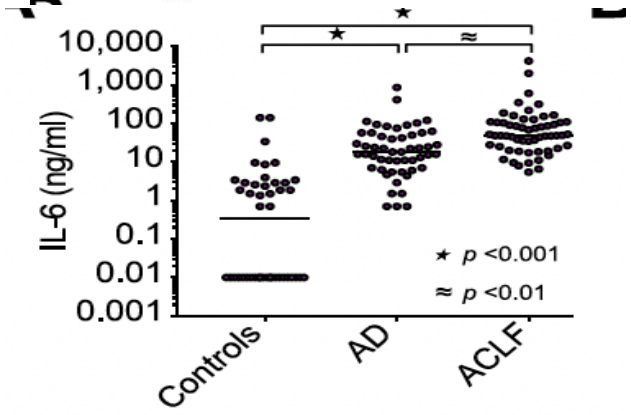
L Balcar et al. Liv Int 2025

NETs in acute decompensation and ACLF:
what human data actually show

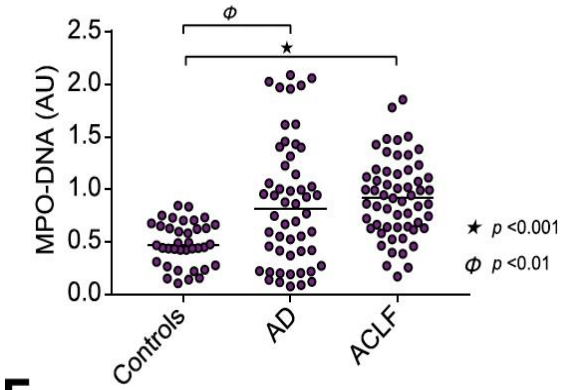
52 patients with acute decompensation (AD) of cirrhosis
57 patients with ACLF on admission
40 healthy controls.

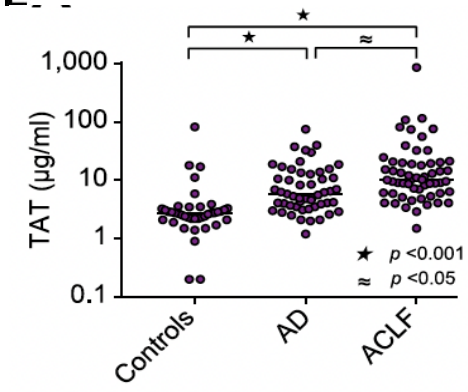
Related to 30-day survival





Unrelated to 30-day survival





Not associated with cfDNA or IL-6

A Blasi et al. JHEPR 2019

Final messages

- Endothelial dysfunction/activation is the strongest signal linking the gut–liver axis and coagulation in cirrhosis
- Portal inflammatory enrichment is real, but not specific to PVT
- NETs are biologically compelling, but context-dependent
- In stable dACLD, human evidence for a major NET-driven effect is limited