Paris PVT Meeting

1st Congress on Portal Vein Thrombosis

Session 2: PVT in Patients With Cirrhosis

Epidemiology And Risk Factors

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29th november 2022

Clínica do Fígado

VALDIG
VASCULAR LIVER DISEASE GROUP

ISPUP
INSTITUTO DE SAÚDE PÚBLICA DA UNIVERSIDADE DO PORTO

LABORATORY FOR INTEGRATIVE AND TRANSLATIONAL RESEARCH IN POPULATION HEALTH

CHU Porto

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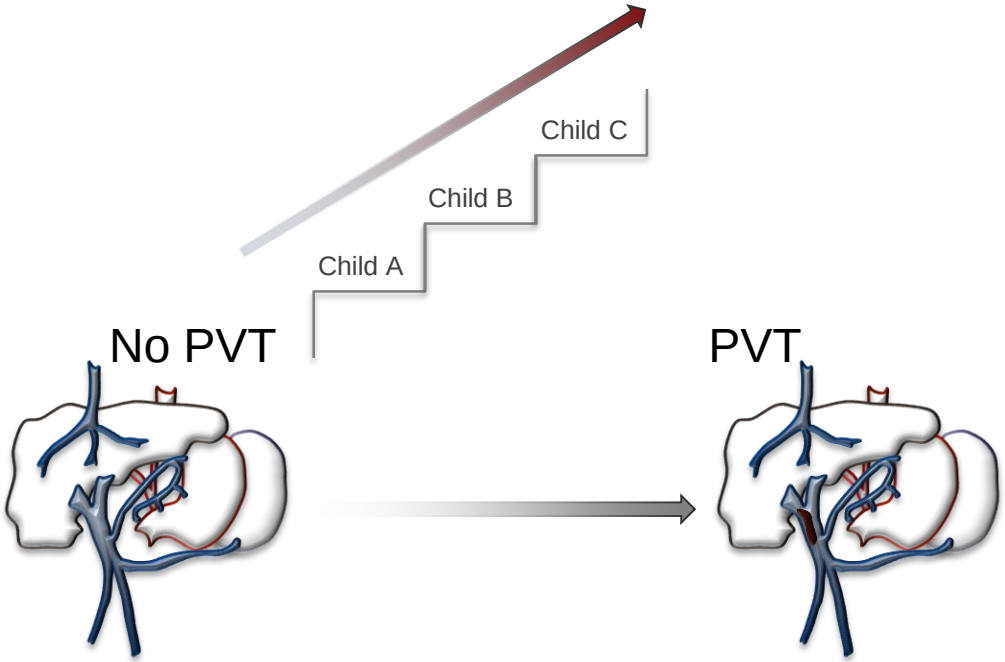
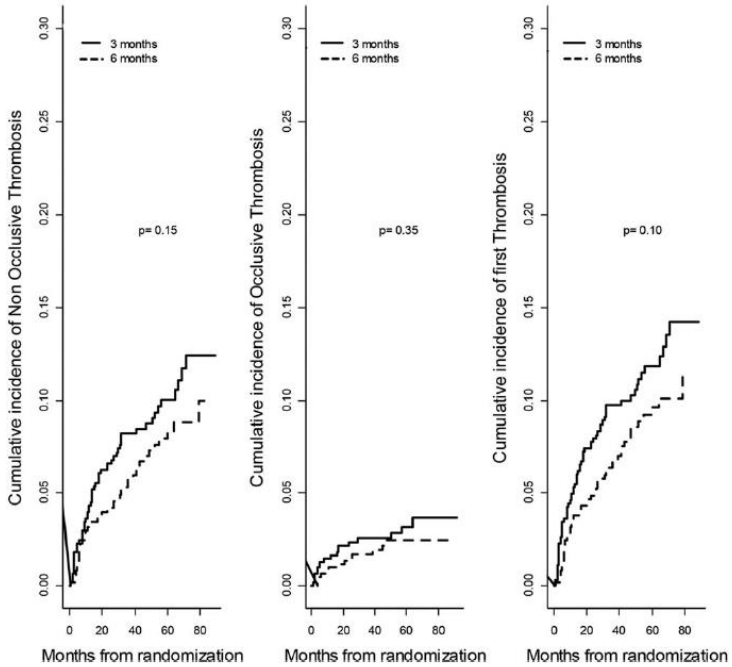
Epidemiology Risk factors Risk factors for further progression

Epidemiology

Risk factors

Risk factors for further progression

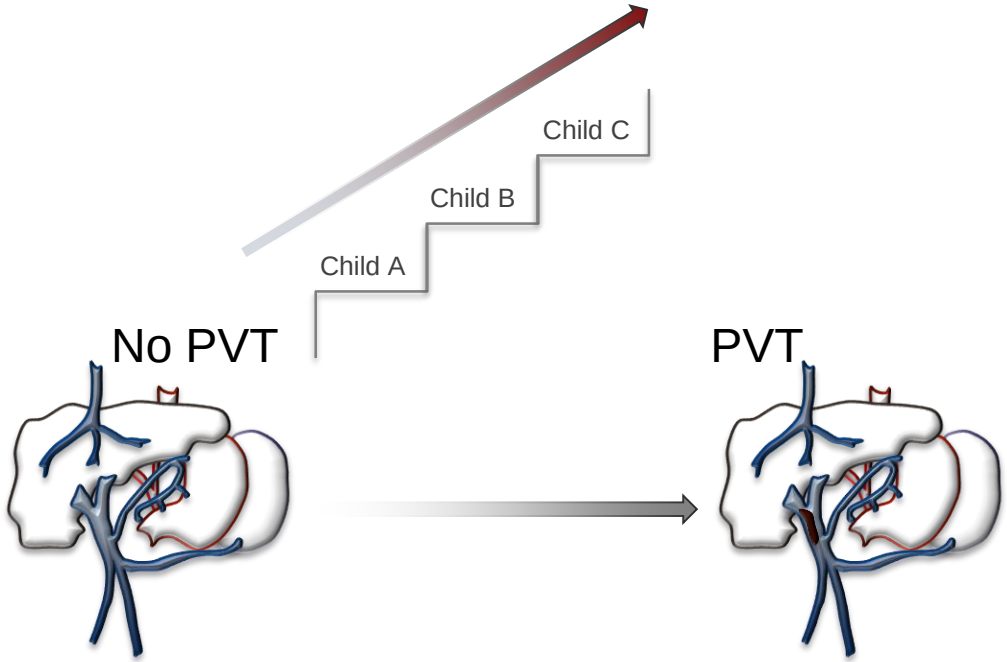


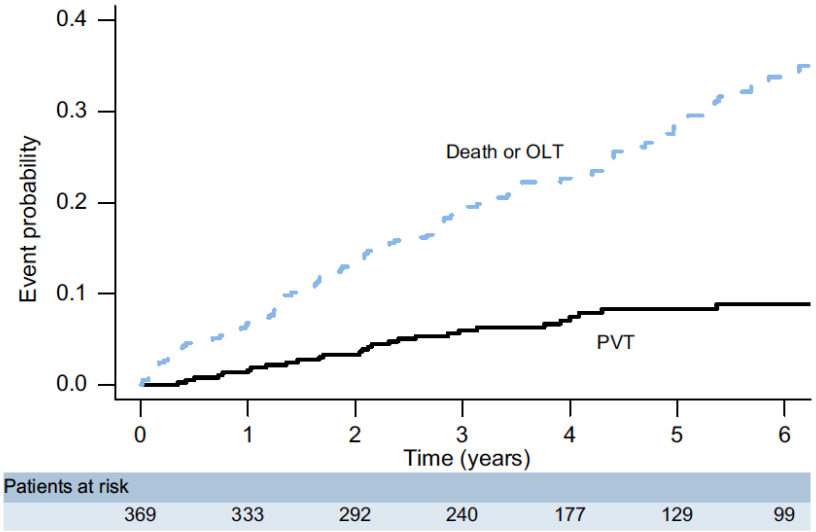


118 PVT in 1243 Child A and B patients

Incidence: 1Y=4.6%, 3Y=8.2%, 5Y=10.7%

Nery F. et al, Hepatology 2015

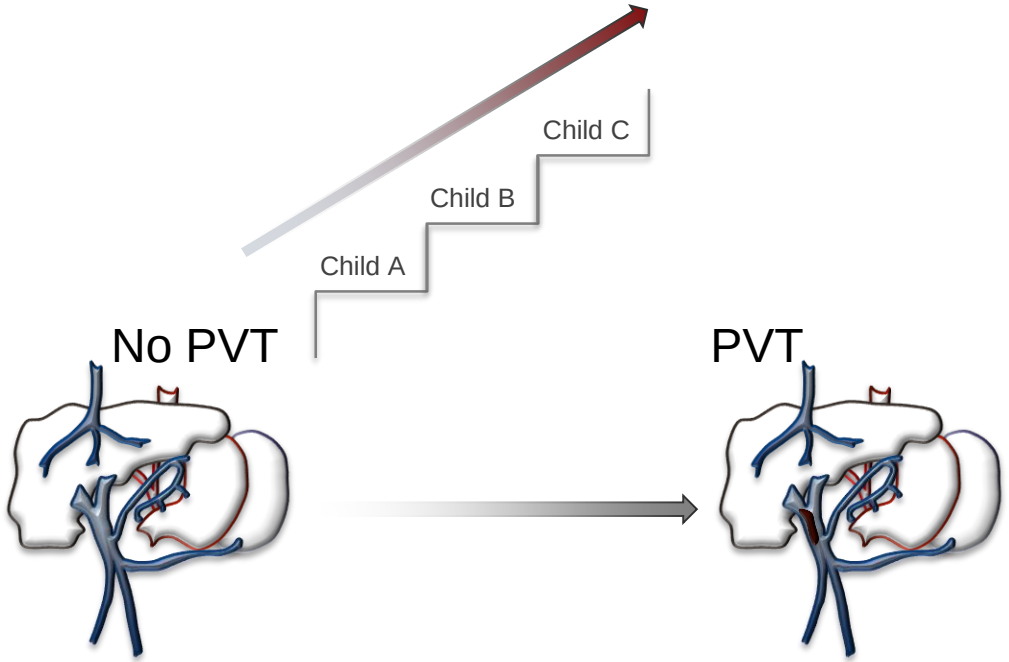


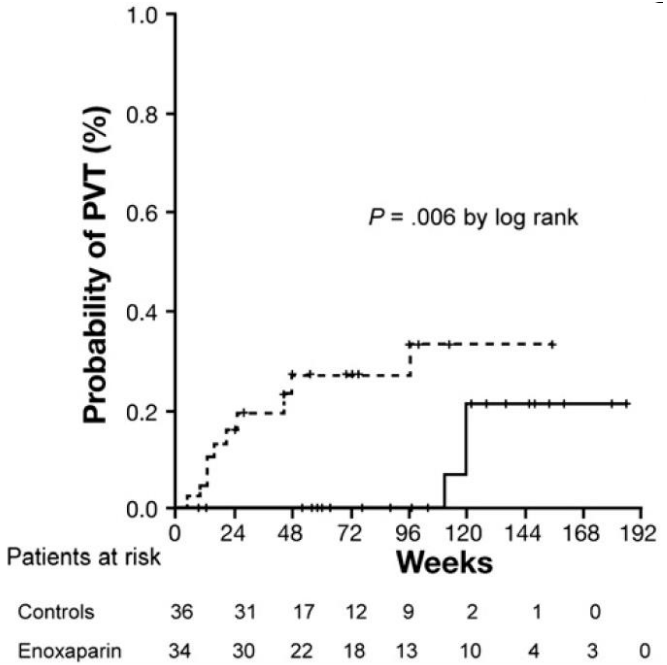


29 PVT in 369 mostly Child A and B patients

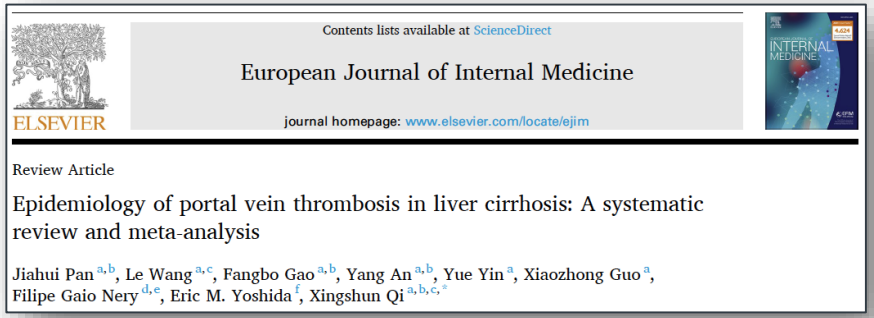
Incidence: 1Y=1.6%, 3Y=6%, 5Y=8.3%

Turon F. et al, J Hepatology 2021





Villa E. et al, Gastroenterology 2012



Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Review Article

Epidemiology of portal vein thrombosis in liver cirrhosis: A systematic review and meta-analysis

Jiahui Pan [a,b], Le Wang [a,c], Fangbo Gao [a,b], Yang An [a,b], Yue Yin [a], Xiaozhong Guo [a], Filipe Gaio Nery [d,e], Eric M. Yoshida [f], Xingshun Qi [a,b,c,*]

- 74 included papers (20 on prevalence, 71 on incidence, 3 on both)

- **Pooled incidence 10.4%** - Child-Pugh A 9.9%, Child-Pugh B/C 18.3%; *P*<0.1
  - Cumulative incidence 1Y=4.8%; 3Y=9.3%; P=0.08

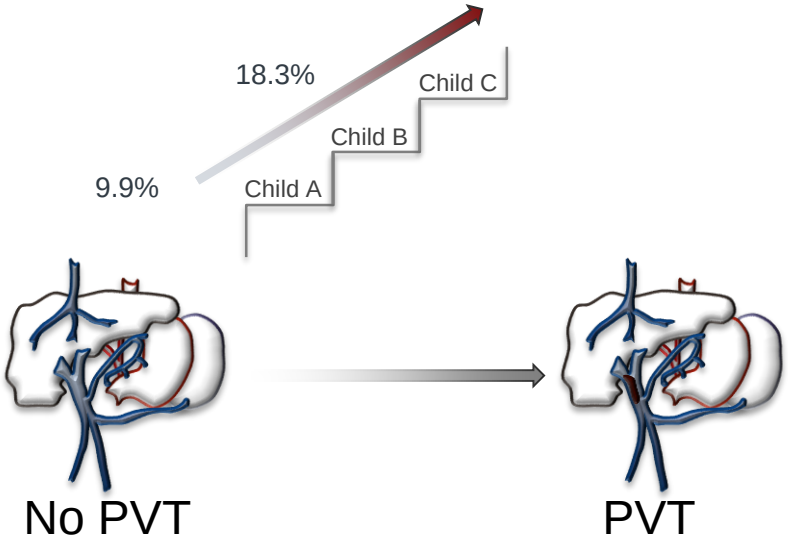
- **Pooled prevalence 13.9%** - Child-Pugh A 13.5%, Child-Pugh B/C 23.7%; *P*=0.02

Pan J. et al, Eur J Int Med 2022

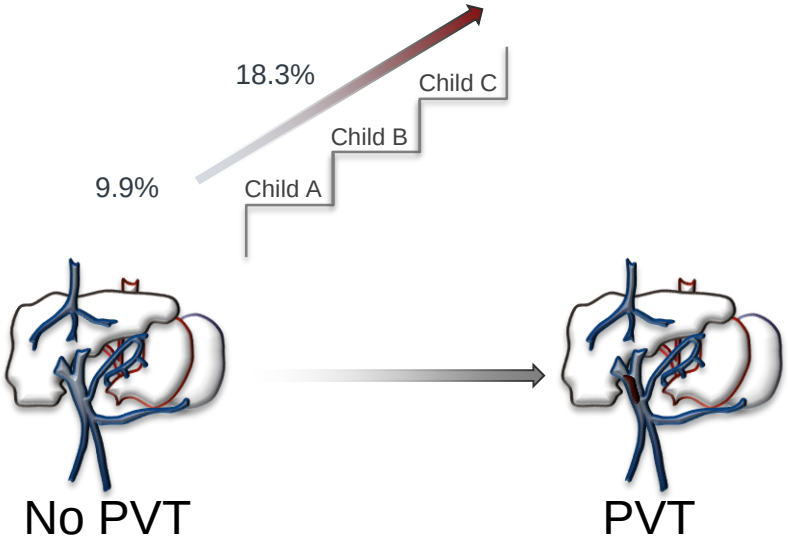
Epidemiology

Risk factors

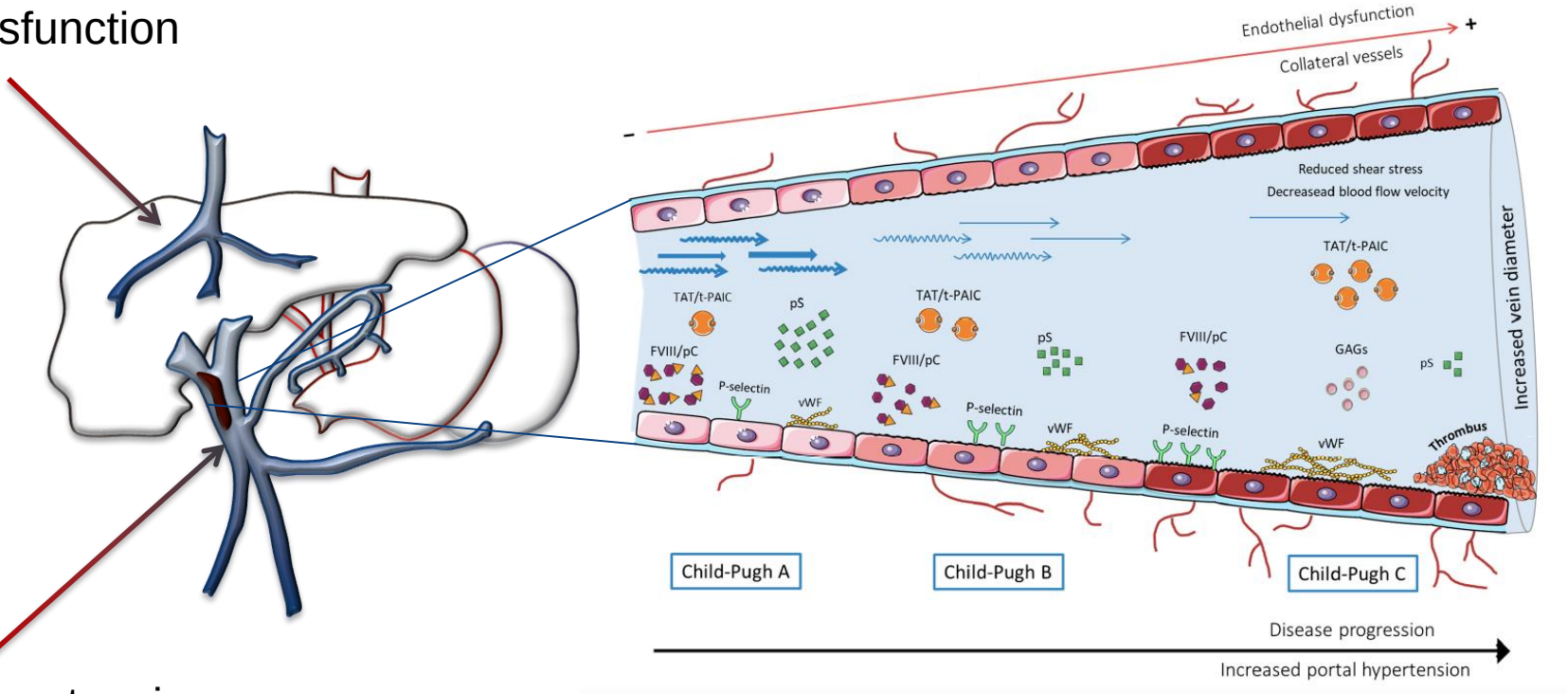
Risk factors for further progression



Epidemiology → Risk factors → Risk factors for further progression



Liver dysfunction



Portal hypertension

Anton A. et al, J Clin Med 2022

	Without PVT (N = 1,125)	With PVT (N = 118)	Total (N = 1,243)
Randomization			
3-monthly US arm	551 (49%)	67 (56.8%)	618 (49.7%)
6-monthly arm	574 (51%)	51 (43.2%)	625 (50.3%)
Male gender	778 (71.1%)	82 (70.1%)	860 (71%)
Age (<60 years)	765 (68.4%)	76 (65%)	598 (68%)
Etiology of cirrhosis			
HCV ± Alcohol	506 (45%)	45 (38.1%)	551 (44.3%)
Alcohol	432 (38.4%)	55 (46.6%)	487 (39.2%)
Current alcohol use	200 (17.8%)	16 (14.6%)	216 (17.4%)
Body-mass index (kg/m^2)	25.9 (23.1-29.4)	27 (23.6-29.4)	26 (23.1-29.4)
Ascites	30 (2.7%)	6 (5.1%)	36 (2.9%)
Splenomegaly	359 (31.9%)	39 (33%)	398 (32%)
Esophageal varices (grade ≥2)	183 (16.3%)	37 (31.5%)	220 (17.7%)
Platelet count (10^3/mm^3)	131 (92-175)	119 (89-164)	130 (91-174)
Serum sodium (mmol/L)	140 (138-142)	139 (137-141)	140 (138-142)
Serum creatinine (µmol/L)	77 (66-88)	76 (66-84)	77 (66-87)
Serum bilirubin (µmol/L)	15 (10.5-22)	19 (13-28)	15 (11-22)
AST (N <40 IU/L)	43 (29-72)	39 (29-55)	42 (29-70)
ALT (N <40 IU/L)	39 (24-74)	34 (22-52)	38 (23-70)
Prothrombin time (%)	80 (70-91)	76 (62-87)	80 (69-90)
Serum albumin (g/L)	40 (37-44)	40 (36-44)	41 (38-44)
Alkaline phosphatase (N <110 IU/L)	77 (57-108)	86 (64-124)	79 (58-109)

P=0.004

P=0.03

	HR	95% CI	*P*
Univariable models			
De novo ascites	1.81	1.14-2.89	0.01
Decreasing portal vein flow velocity	0.98	0.95-1.01	0.19
Non-specific beta blockers before PVT	1.67	1.02-2.73	0.04
Liver disease progression before PVT	1.92	1.19-3.08	0.007
Decompensation before PVT	2.11	1.23-3.63	0.007

	HR	95% CI	*P*
Multivariate Analysis			
Prothrombin time (%)	0.81	0.70-0.93	0.002
Esophageal varices (≥ grade2)	1.78	1.15-2.76	0.01

Time-dependent predictive factors from Univariate and Multivariate Cox models stratified on randomization arm

Nery F. et al, Hepatology 2015

Factor	No PVT ($n = 61$)	PVT ($n = 12$)	p Value
Age (yr)	59.2 (11.3)	55.2 (10.9)	0.265
Male	44 (72.1%)	10 (83.3%)	0.720
Ethiology			0.824
Viral	38 (62.3%)	6 (50.0%)	
Alcoholic	14 (23.0%)	4 (33.3%)	
Others	9 (14.7%)	2 (16.7%)	
MELD score >13	26 (42.6%)	10 (83.3%)	0.012
INR	1.35 (0.36)	1.34 (0.34)	0.434
Platelet cell count ($\times 10^3$/l)	103.3 (52.1)	58.3 (20.9)	**<0.001**
ATIII	54.7 (19.4)	41.2 (13.7)	**0.011**
Protein C (%)	45.9 (18.9)	27.8 (7.5)	**<0.001**
Protein S (%)	77.9 (20.0)	60.7 (22.8)	**0.028**
D-dimer (ng/ml)	1038 (1209)	1660 (2405)	0.399
APTT[a]	1.21 (0.33)	1.20 (0.20)	0.921
LAC positive	8 (13.1%)	2 (16.7%)	0.464
Anti-β2 glycoprotein 1 (U/ml) [<20]	34 (9)[b]	37 (5)[b]	0.645
Cryoglobulins positive	10 (16.4%)	2 (16.7%)	0.427
Homocysteine (μmol/l)	10.1 (4.4)	16.4 (16.0)	0.195
Portal flow rate <15 cm/s	12 (19.7%)	11 (91.7%)	**<0.001**
Oesophageal varices			0.682
0/F1	52 (85.2%)	9 (75.0%)	
F2	6 (9.8%)	2 (16.7%)	
F3	3 (4.9%)	1 (8.3)	

12 PVT in 73 patients with cirrhosis.

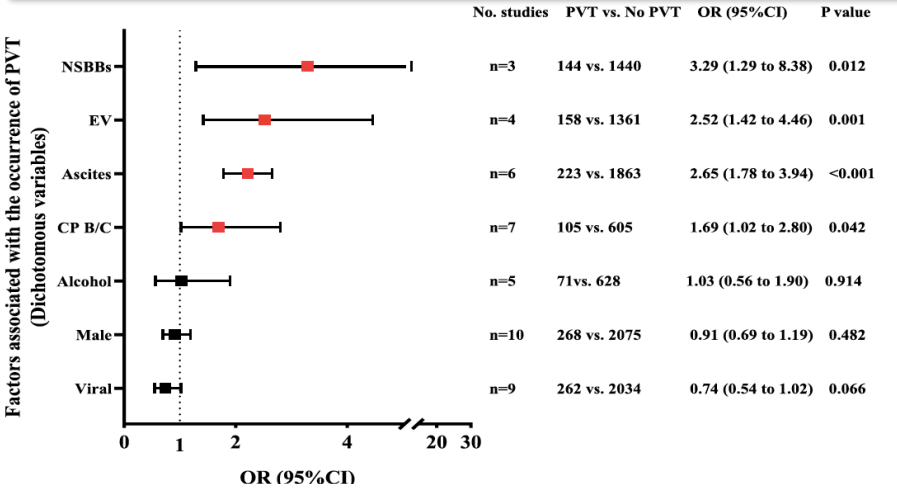
PBFV as the only independent associated risk factor (OR 44.9, 95% CI 5.3-382.7; p<0.001)

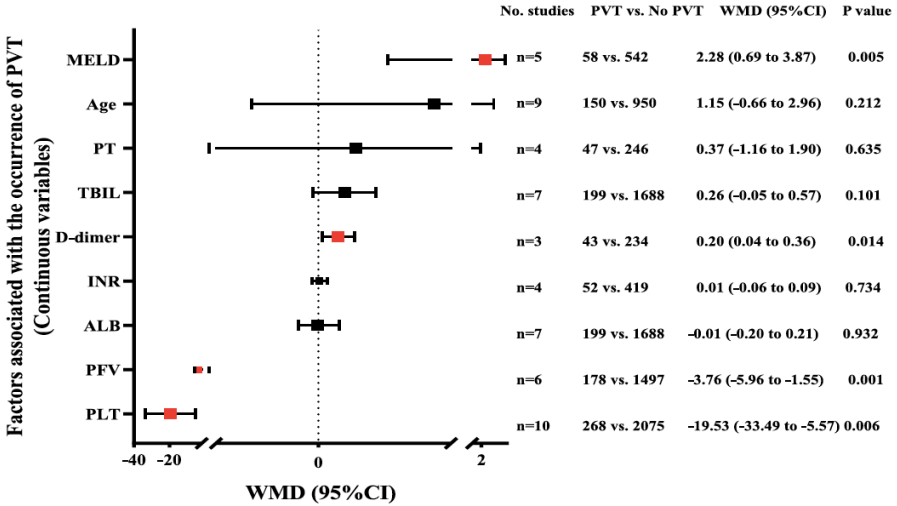
Zocco, MA et al, J Hepatology 2009

Univariate analysis			Multivariate analysis				
Variable	**sHR (95% CI)**	***p* value**		**Variables**	**sHR (95% CI)**	***p* value**	**Log-likelihood ratio test**
Body mass index, Kg/m^2	0.98 (0.89–1.09)	0.79	**Model 1**				
MAFLD	3.09 (0.98– 9.8)	**0.05**		Platelets	0.98 (0.97–0.99)	**0.002**	27
Platelets, 10^9/L	0.98 (0.97–0.99)	**<0.001**		PBFV <15 cm/sec	2.28 (0.99–5.26)	**0.05**	
INR	1.94 (1–3.07)	**0.049**		Variceal bleeding	2.52 (1.06–5.99)	**0.036**	
Albumin, g/L	0.93 (0.89–0.98)	**0.008**	**Model 2**				
Bilirubin, mg/dl	1.10 (0.97–1.24)	0.12		Spleen length	1.26 (1.11–1.42)	**<0.001**	25
Creatinine, mg/dl	0.25 (0.03–1.93)	0.18		PBFV <15 cm/sec	2.31 (1.02–5.26)	**0.046**	
MELD	1.05 (1–1.1)	**0.047**		Variceal bleeding	2.37 (0.99–5.67)	**0.05**	
Child-Pugh score	1.13 (0.99–1.28)	0.062	**Model 3**				
Child-Pugh class B/C	2.36 (1.14–4.88)	**0.021**		Child–Pugh score	1.00 (0.86–1.69)	0.94	22
Large varices	3.61 (1.64–7.94)	**0.001**		PBFV <15 cm/sec	2.92 (1.37–6.19)	**0.005**	
Previous decompensation	4.3 (1.77–10.5)	**0.001**		Platelets	0.98 (0.97–0.99)	**0.002**	
Variceal bleeding	3.37 (1.60–7.13)	**0.001**	**Model 4**				
Ascites	1.89 (0.91–3.96)	0.089		MELD	1.00 (0.93–1.06)	0.86	22
NSBBs	3.44 (1.57–7.53)	**0.002**		Variceal bleeding	2.91 (1.38–6.16)	**0.005**	
Primary prophylaxis	1.47 (0.68–3.16)	0.32		Platelets	0.98 (0.97–0.99)	**0.002**	
Secondary prophylaxis	3.54 (1.65–7.6))	**0.001**					
Spleen length, cm	1.28 (1.15–1.43)	**<0.001**					
Portal vein diameter, mm	1.10 (1.01–1.21)	**0.031**					
PBFV, cm/sec	0.91 (0.81–1.03)	0.15					
PBFV <15 cm/sec	2.70 (1.29–5.68)	**0.008**					
Porto-systemic collaterals	1.05 (0.57–1.91)	0.87					
HVPG, mmHg	1.10 (0.97–1.24)	0.13					
HVPG ≥20	8.08 (1.50–43.6)	**0.015**					

369 patients, 72% Child-Pugh A, 56% HCV related cirrhosis

Turon F. et al, J Hepatology 2021





Portal hypertension related risk factors:

- EV/ Previous bleeding
- Ascites
- Low platelet count
- Low portal vein blood flow

Liver dysfunction related risk factors:

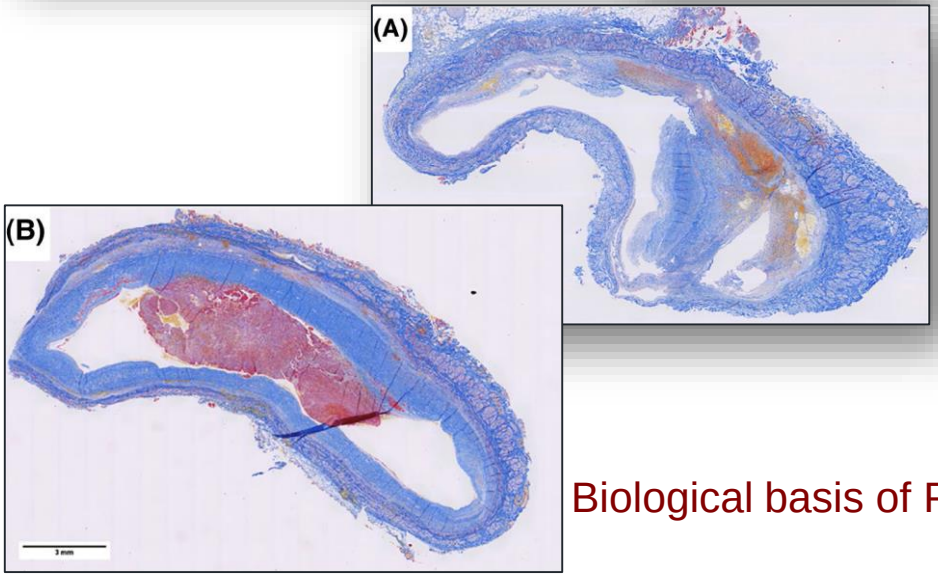
- Child-Pugh score
- MELD score

Pan J. et al, Eur J Int Med 2022

Nonmalignant portal vein thrombi in patients with cirrhosis consist of intimal fibrosis with or without a fibrin-rich thrombus

Ellen G. Driever[1] | Fien A. von Meijenfeldt[1] | Jelle Adelmeijer[1] | Robbert J. de Haas[2] | Marius C. van den Heuvel[3] | Chandrasekaran Nagasami[4] | John W. Weisel[4] | Constantino Fondevila[5] | Robert J. Porte[6] | Anabel Blasi[7] | Nigel Heaton[8] | Stephen Gregory[9] | Pauline Kane[9] | William Bernal[10,11] | Yoh Zen[12] | Ton Lisman[1,6]

Hepatology. 2022;75:898–911

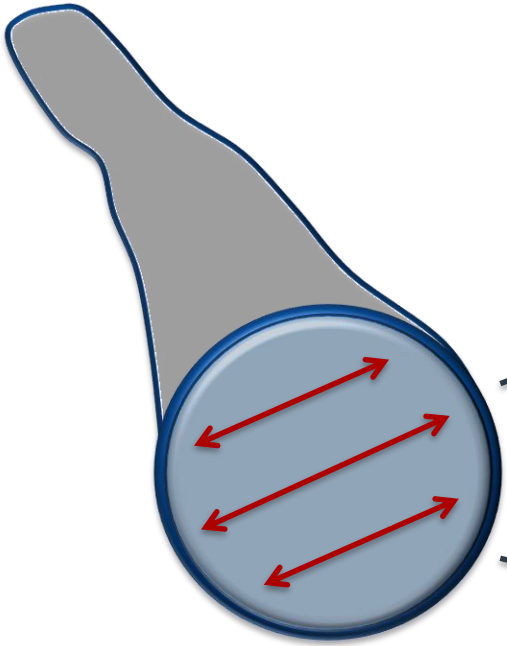


3 centres involved

- 16 PVT in LT (prospective) + 63 PVT (retrospective)

- Increased thickness and fibrosis of tunica intima in all samples
- 5/16 with thickened wall >50% of lumen
- 9/16 with associated fibrin thrombus

Biological basis of PVT probably different than other vessel beds

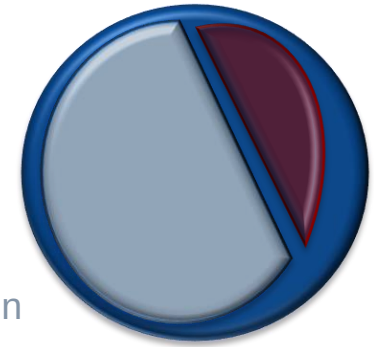


Portal vein

Shear stress

Portal hypertension

Inflammation



PVT

Fibrin rich thrombus

↓

Fibrotic structure

↓

Reendothelialization

Endothelial cell stress

Thrombin

PVT

Intimal hyperplasia

Driever EG. et al, Hepatology 2022

Particular considerations - NSBB

β1 – adrenergic blockade

β2 – adrenergic blockade

↓ Cardiac output

↓ Splanchnic blood flow

↓ Portal pressure

Nadolol + Propranolol

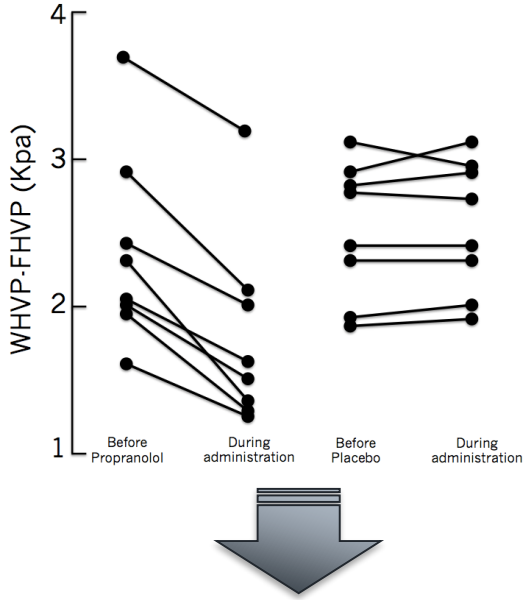
+

α1 – adrenergic blockade

↓ Hepatic vascular tone

↓ Portocollateral resistance

Carvedilol



Current indication in patients with compensated cirrhosis to avoid 1st decompensation. Primary and secondary prevention of variceal bleeding. De Franchis R et al BAVENO VII

Vaughan RB, Chin-Dusting JPF 2003; Tripathi D, Hayes PC 2010; Lebrec D, 1980

Particular considerations - NSBB

World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
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DOI: 10.3748/wjg.v20.i32.11463

World J Gastroenterol 2014 August 28; 20(32): 11463-11466
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LETTERS TO THE EDITOR

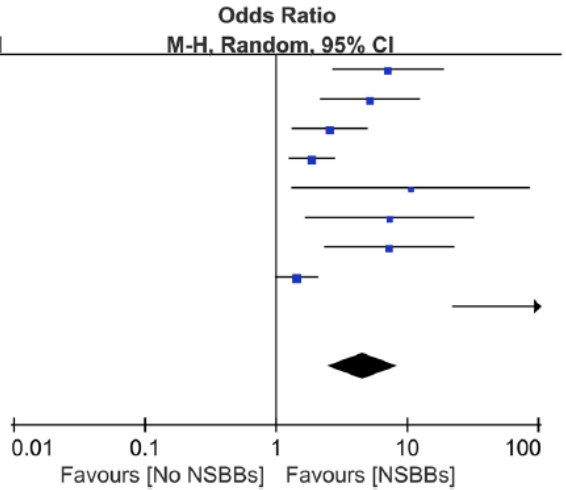
Nonselective β-blockers may induce development of portal vein thrombosis in cirrhosis

Xing-Shun Qi, Ming Bai, Dai-Ming Fan

From theory to scientific evidence

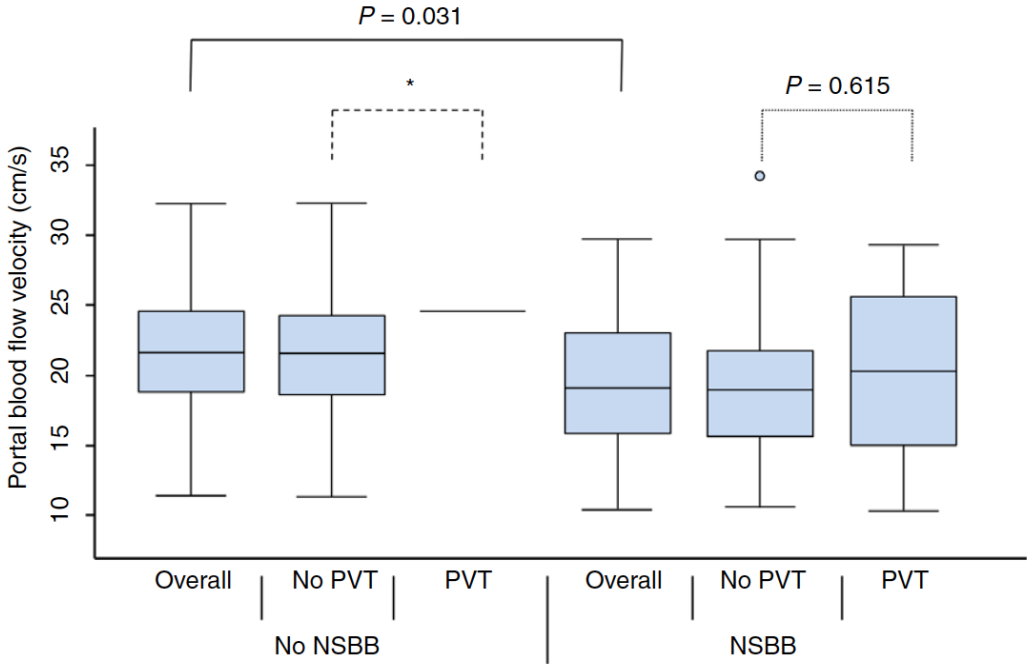
Study or Subgroup	NSBBs Events	NSBBs Total	No NSBBs Events	No NSBBs Total	Weight	Odds Ratio M-H, Random, 95% CI
Giannitrapani 2018	11	45	8	185	11.7%	7.16 [2.68, 19.11]
Gomez 2015	15	160	8	408	12.5%	5.17 [2.15, 12.46]
Menadier 2018	41	65	34	85	14.0%	2.56 [1.32, 4.98]
Nery 2015	40	282	78	961	15.6%	1.87 [1.25, 2.81]
Nery 2019	10	57	1	51	5.7%	10.64 [1.31, 86.34]
Pellicelli 2011	8	20	3	36	8.5%	7.33 [1.67, 32.29]
Tang 2015	7	16	13	135	10.6%	7.30 [2.33, 22.85]
Violi 2016	67	344	59	409	15.7%	1.43 [0.98, 2.11]
Zampino 2018	18	28	1	102	5.6%	181.80 [21.91, 1508.41]
Total (95% CI)		**1017**		**2372**	**100.0%**	**4.62 [2.50, 8.53]**
Total events	217		205			

Heterogeneity: Tau² = 0.59; Chi² = 40.24, df = 8 (P < 0.00001); I² = 80%
Test for overall effect: Z = 4.88 (P < 0.00001)



Xu X. et al, Hepatol Int 2019

Particular considerations - NSBB



Effect of NSBB over PVT development other than decrease in PBFV

Nery F. et al, Aliment Pharmacol Ther 2019

Particular considerations – Inflammation

Independent risk factors of portal vein thrombosis identified by univariate and multivariate analysis

Factors	Univariate			Multivariate		
	B	Odd ratio (95%)	*P* value	B	Adjusted odd ratio (95% confidence interval)	*P* value
Child grade	0.782	2.187 (1.220–3.920)	0.009	0.416	1.516 (0.672–3.420)	0.316
Splenectomy	1.814	6.138 (3.004–12.538)	<0.001	2.488	12.040 (4.748–30.533)	<0.001
D-Dimer	1.911	6.758 (3.775–12.101)	<0.001	1.935	6.925 (3.269–14.666)	<0.001
CRP	0.114	1.121 (0.660–1.904)	0.674			
IL-6	1.296	3.656 (2.113–6.324)	<0.001	0.945	2.574 (1.248–5.310)	0.011
IL-8	0.160	1.173 (0.698–1.972)	0.547			
TNF-α	0.442	1.556 (0.923–2.622)	0.097	0.249	1.282 (0.603–2.725)	0.518
IL-10	1.079	2.941 (0.988–8.758)	0.053	0.528	1.695 (0.419–6.848)	0.459

231 patients with cirrhosis and gastroesophageal varices: 103 with PVT and 128 without PVT

Blood samples collected 12h before endoscopic treatment but with an already documented PVT

Huang X. et al, Eur J Gastro Hepatol 2019

Particular considerations – Inflammation

	Did not develop PVT (*N*=96)	Developed PVT (*N*=11)	*P* value
Age (years)	54.1±11	57.8±8.5	0.28
Male gender	69 (71.9%)	6 (54.5%)	0.23
Etiology of cirrhosis			
Alcoholic	43 (44.8%)	4 (36.4%)	
Viral[a]	14 (14.6%)	1 (9.1%)	
Alcoholic+Viral[a]	11 (11.5%)	3 (27.3%)	
Metabolic[b]	12 (12.5%)	0 (0.0%)	
Autoimmune	12 (12.4%)	3 (27.3%)	
Cryptogenic	4 (4.2%)	0 (0.0%)	0.34
Current alcohol use	7 (7.3%)	2 (18.2%)	0.47
Current NSBB use	47 (49.0%)	10 (90.9%)	0.008
Ascites	19 (19.8%)	4 (36.4%)	0.21
Oesophageal varices (grade ≥2)	28 (28.9%)	8 (72.7%)	0.004
Child-Pugh			
A	74 (77.1%)	9 (81.8%)	
B	17 (17.7%)	2 (18.2%)	
C	5 (5.2%)	0 (0.0%)	0.74
MELD ≥13	19 (19.8%)	2 (18.2%)	0.90
Albumin (g/dL)	4.2±0.6	3.9 ±0.6	0.14
TB (mg/dL)	1.5± 1.4	1.5±0.6	0.96
AST (U/L)	44.2±31.7	44.2±19.8	1.00
ALT (U/L)	38.1±31.6	29.5 ±15.8	0.38
INR	1.25±0.24	1.26±0.19	0.90
Platelets (10^9/L)	109.3±57.4	84.4±37.7	0.16
Creatinine (mg/dL)	0.8±0.3	0.8±0.3	0.91
Current diuretics use	44 (45.8%)	6 (54.6%)	0.58
Decompensated cirrhosis	46 (47.9%)	5 (45.4%)	0.88
Leukocytes (10^9/L)	**5.2±2.1**	**4.3±2.1**	**0.16**
Neutrophils (10^9/L)	**3.2±1.3**	**2.7±1.8**	**0.30**
Lymphocytes (10^9/L)	**1.4±0.7**	**0.95±0.4**	**0.05**
NLR	**2.63±0.12**	**3.34±0.70**	**0.10**
Hs-CRP (mg/L)	**5.4±8.9**	**8.7±10.7**	**0.25**
Ferritin (ng/mL)	**290±279**	**237±302**	**0.65**
TNF-α (pg/mL)	*	*	*
IL-6 (pg/mL) [Median (P25–P75)]	**4.8 (1.6–9.9)**	**7.6 (5.8–19.3)**	**0.01**
Portosystemic collaterals	21 (21.9%)	3 (27.3%)	0.47
PBFV (cm/s)	20.4±5.0	20.6±6.1	0.88
Spleen size (cm)	15.1±3.4	16.1±3.3	0.34

Multivariate Cox proportional models of predictive factors for portal vein thrombosis development, adjusted for all potential confounders [Nonselective beta-blocker and alcohol current use; presence of portosystemic collaterals, oesophageal varices (grade ≥2) and ascites; model for end-stage liver disease ≥13 and spleen size]

	Hazard ratio	95% CI	*P* value
Interleukin-6 ≥ 5.5 pg/mL (vs < 5.5 pg/mL)[a]	5.66	1.05–30.54	0.044
Lymphocytes < 1.2 × 10^9/L (vs ≥ 1.2 × 10^9/L)[a]	8.58	1.34–54.73	0.023
NLR	1.39	0.86–2.26	0.18

All the patients developing PVT had at least one of the identified risk factors (IL-6 > 5.5 pg/mL and lymphocytes <1.2 x10^9/L): 36% had one of them and 64% had both.

Nery F. et al, Eur J Gastro Hepatol 2020

Particular considerations – Inflammation

Variables	PVT (n = 23)	No PVT (n = 287)	sHR (95	alue
Hemostatic proteins				
Primary hemostasis				
VWF (Ag,%)	120.9 ± 32	125.6 ± 27.3	0.99 (0.97–1.01)	0.54
VW ristocetin co-factor (functional,%)	108.8 ± 22.4	119.1 ± 26.3	0.98 (0.97–1)	0.051
ADAMTS13,%	98.6 ± 18.5	96.9 ± 17.3	1 (0.98–1.03)	0.69
Secondary hemostasis				
sTF,ng/ml	135.9 ± 25.5	143.5 ± 27.9	0.99 (0.98–1)	0.19
Factor II, %	52.8 ± 15	62.9 ± 16.6	0.96 (0.94–0.99)	**0.001**
Factor V, %	52 ± 12.9	62.2 ± 15.8	0.95 (0.93–0.98)	**0.001**
Factor VII, %	43.9 ± 12.6	52.6 ± 15.6	0.96 (0.95–0.99)	**0.002**
Factor VIII, %	125.8 ± 19.1	135.2 ± 23.3	0.981 (0.96–0.99)	**0.036**
Factor IX, %	57.5 ± 18.8	59.8 ± 19.1	0.99 (0.97–1.01)	0.49
Factor X, %	50.4 ± 12.1	61.2 ± 15.3	0.95 (0.92–0.97)	**<0.001**
Factor XI, %	62.5 ± 17	76.9 ± 19.6	0.96 (0.95–0.98)	**<0.001**
Factor XII, %	58.4 ± 14.4	65 ± 15.1	0.97 (0.95–0.99)	**0.024**
Factor XIIIa, %	61.2 ± 28.5	75.0 ± 36.1	0.99 (0.97–1.01)	0.18
Fibrinogen, mg/ml	2.24 ± 0.71	2.47 ± 0.84	0.68 (0.39–1.17)	0.16
Protein C, %	60.3 ± 20.7	79.0 ± 23.9	0.97 (0.95–0.98)	**<0.001**
Protein S, %	66.7 ± 17.9	81.5 ± 20.4	0.97 (0.95–0.98)	**<0.001**
Antithrombin, %	75.5 ± 17.9	84.1 ± 18.8	0.98 (0.96–0.99)	**0.02**
Fibrinolysis				
Plasminogen, %	53.7 ± 11.5	60.8 ± 13.1	0.96 (0.94–0.99)	**0.002**
PAI-1, ng/ml	26.7 ± 7.6	23.3 ± 7.1	1.05 (1.01–1.09)	**0.017**
Markers of activation of hemostasis				
Soluble P-Selectin, ng/ml	73.7 ± 18	63.3 ± 24.2	1.02 (1–1.03)	**0.012**
Soluble CD40L, ng/ml	98.3 ± 19.7	104.5 ± 21.9	0.98 (0.97–1)	0.14
Fragment 1+2, nmol/ml	1.8 ± 0.8	1.4 ± 0.5	2.51 (1.47–4.27)	**<0.001**
Factor VIIa, ng/ml	3.4 ± 1.8	2.4 ± 1.5	1.29 (1.11–1.51)	**0.001**
Factor XIIa, ng/ml	3.8 ± 1.7	3.3 ± 1.6	1.17 (0.96–1.43)	0.11
D-dimer, ng/ml	466.8 ± 225.8	460.9 ± 221.2	1 (0.99–1)	0.95
PAP, µg/ml	1024.1 ± 268.4	949.6 ± 338.46	1(1–1)	0.21
Microparticles	24.3 ± 10.4	18.0 ± 9.1	1.05 (1.02–1.08)	**<0.001**
Global functional tests				
ETP (without TM), nM IIa*min	322.9 ± 27.7	349.8 ± 60.6	0.98 (0.97–0.99)	**<0.001**
ETP (with TM), nM IIa*min	268.6 ± 24.2	282.9 ± 44.3	0.98 (0.97–0.99)	**0.009**
Clot lysis time, min	82 ± 40	71 ± 25	1.01 (0.99–1.02)	0.072
Permeability, Ks	$4.2 \times 10^{-9} \pm 1.9 \times 10^{-9}$	$4.7 \times 10^{9} \pm 8 \times 10^{-9}$	0.99 (0.95–1.03)	0.61
Clot weight, mg	55 ± 10	60 ± 9	0.95 (0.90–0.99)	**0.042**
Ratios				
Von Willebrand ratio (VWF co-factor/Ag)	0.96 ± 0.33	0.98 ± 0.27	0.76 (0.11–5.01)	0.78
Ratio FVIII/Protein C	2.34 ± 0.98	1.89 ± 0.75	1.58 (1.17–2.14)	**0.0028**
ETP ratio (with/without TM)	0.83 ± 0.08	0.81 ± 0.06	1.70 (0.77–3.72)	0.20
Inflammatory markers				
Cell-free DNA, ug/ml	0.89 ± 0.16	0.89 ± 0.22	0.97 (0.22–4.27)	0.97
MPO-DNA (AU)	0.21 ± 0.29	0.29 ± 0.46	0.68 (0.28–1.67)	0.40
IL-6, pg/ml	7.7 ± 7.9	8.4 ± 12.5	0.99 (0.97–1.02)	0.70
TNF-α,pg/ml	12.4 ± 5.1	11.6 ± 10.5	0.01 (0.99–1.03)	0.32
CRP, ng/ml	5315 ± 8044	3584 ± 6631	1 (1–1)	0.24

Subgroup of 310 patients, 23 with PVT

Turon F. et al, J Hepatology 2021

Particular considerations – Inflammation

	Normal value systemic circulation	Systemic circulation	Portal vein	Hepatic vein	*p*-value normal value SC vs SC/ PV/HV	*p*-value SC vs PV	*p*-value PV vs HV/ PV vs normal value	*p*-value SC vs HV/ HV vs normal value
Markers of inflammation								
LPS (pg/ml)	79.5 [64.5–109.5]	151 [76–222]	163 [96–259]	131 [68–236]	0.0069/0.0002/0.014	<0.0001	<0.0001	0.038
TNF-α (pg/ml)	0 [0–16.4]	11.9 [5.0–19.0]	11.9 [6.0–22.0]	11.5 [4.9–22.0]	0.0006/0.001/0.0006	n.s.	n.s.	n.s.
IL-6 (ng/ml)	3.5 [2.7–11]	10.3 [5.8–35.1]	17.2 [6.6–35.6]	8.6 [5.6–32.8]	0.0015/<0.0001/0.0082	0.014	0.0004	0.0063
TBARS (μM)	2.7 [1.5–3.4]	2.6 [1.9–3.8]	2.9 [2.0–4.1]	2.6 [1.9–3.8]	<0.0001/<0.0001/<0.0001	0.0003	0.0007	n.s.
cfDNA (μg/ ml)	1.0 [0.9–1.1]	1.0 [0.8–1.2]	1.0 [0.9–1.2]	1.0 [0.8–1.2]	n.s./n.s./n.s.	n.s.	n.s.	n.s.
MPO-DNA (AU)	0.1 [0–0.2]	0.2 [0.1–0.4]	0.2 [0.1–0.4]	0.1 [0.1–0.4]	0.0049/0.0096/0.01	n.s.	n.s.	n.s.
Markers of hemostasis								
VWF (%)	150 [102–204]	305 [211–426]	343 [227–452]	311 [218–461]	<0.0001/<0.0001/<0.0001	0.037	n.s.	n.s.
FVIII (%)	87 [70–103]	181 [147–244]	178 [143–244]	169 [136–211]	<0.0001/<0.0001/<0.0001	n.s.	n.s.	0.016
PF4 (ng/ml)	98 [75–143]	133 [92–283]	145 [89–281]	177 [88–289]	0.028/0.014/0.016	n.s.	n.s.	n.s.
TAT (μg/ml)	0.7 [0.4–1.2]	42 [12–118]	46 [29–79]	19 [7–35]	<0.0001/<0.0001/<0.0001	n.s.	0.005	0.0022
PAP (ng/ml)	191 [161–239]	876 [533–2173]	1075 [542–4296]	810 [533–1596]	<0.0001/<0.0001/<0.0001	0.044	0.0028	n.s.
D-dimers (ng/ ml)	107 [64–176]	3050 [1820–5440]	3650 [2230–6920]	2750 [1690–3730]	<0.0001/<0.0001/<0.0001	n.s.	0.0003	n.s.

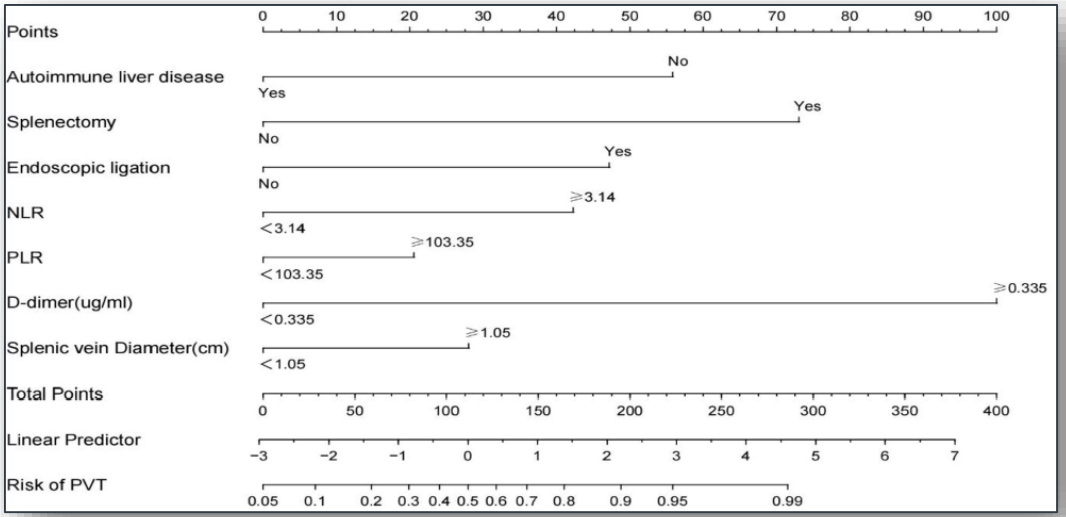
- 51 patients with cirrhosis and PH undergoing TIPS
- Decreased inflammatory and activation of coagulation factors in HV explained by hepatic clearance, rather than a true inflammatory or prothrombotic environment in PV

Driever EG. et al J Thromb Haemost 2022

Particular considerations – Inflammation

Variables	B	SE	Wald	*P*	OR	95% CI
NLR	1.061	0.297	12.72	<0.001	2.889	1.613–5.175
PLR	0.8	0.277	8.323	0.004	2.225	1.292–3.831
Endoscopic ligation	1.216	0.475	6.567	0.01	3.374	1.331–8.554
D-dimer (μg/ml)	2.627	0.284	85.74	<0.001	13.827	7.93–24.11
Splenic vein diameter (cm)	0.663	0.278	5.675	0.017	1.941	1.125–3.349
Splenectomy	1.847	0.406	20.741	<0.001	6.342	2.864–14.044
Autoimmune liver disease	−1.665	0.532	9.797	0.002	0.189	0.067–0.537

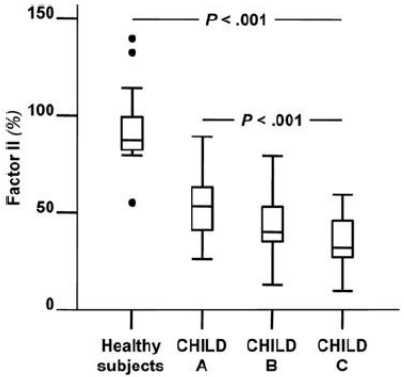
- Retrospective cohort of patients with cirrhosis 239 with/ 239 without PVT

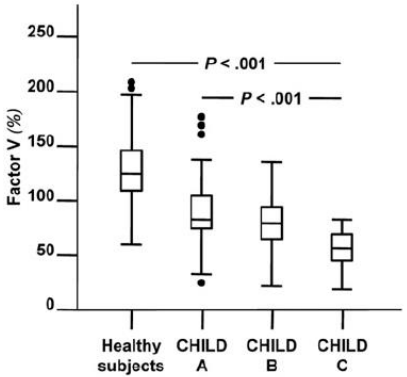


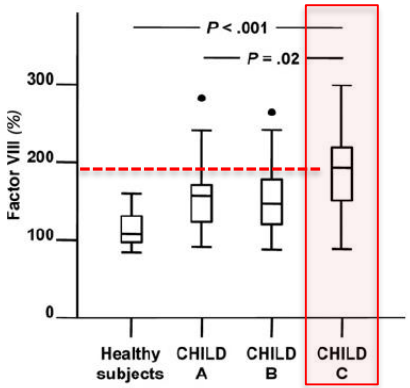
- Proposal of a nomogram to predict PVT based on NLR and PLR

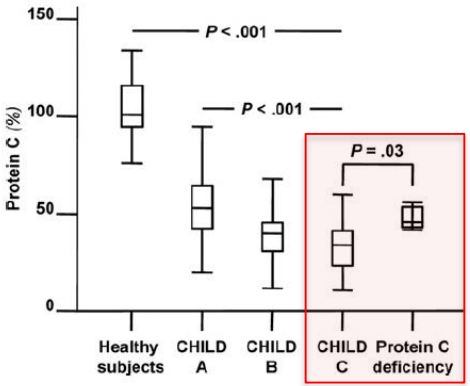
Xing Y. et al, Annals of Medicine 2022

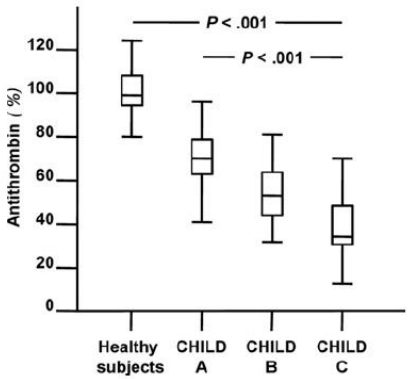
Particular considerations – Hypercoagulability

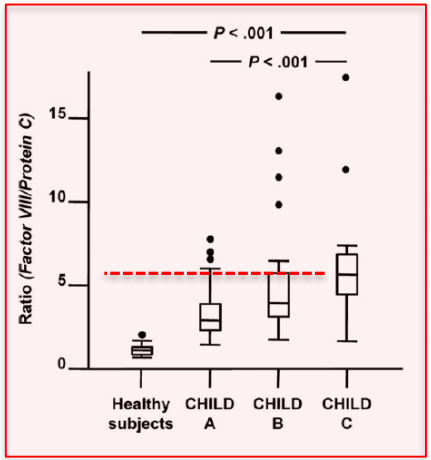












Tripodi A. et al, Gastroenterology 2009

Particular considerations – Hypercoagulability

Research Article
Cirrhosis and Liver Failure

JOURNAL OF HEPATOLOGY

Factor VIII/protein C ratio independently predicts liver-related events but does not indicate a hypercoagulable state in ACLD

Bernhard Scheiner[1,2,†], Lorenz Balcar[1,2,†], Rosa Johanna Nussbaumer[1], Johanna Weinzierl[1], Rafael Paternostro[1,2], Benedikt Simbrunner[1,2], Lukas Hartl[1,2], Mathias Jachs[1,2], David Bauer[1,2], Albert Friedrich Stättermayer[1,2], Georg Semmler[1,2], Matthias Pinter[1], Cihan Ay[3,4], Peter Quehenberger[5], Michael Trauner[1], Thomas Reiberger[1,2], Ton Lisman[6,*], Mattias Mandorfer[1,2]

[1]Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria; [2]Vienna Hepatic Hemodynamic Lab, Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria; [3]Clinical Division of Haematology and Haemostaseology, Department of Internal Medicine I, Medical University of Vienna, Vienna, Austria; [4]I. M. Sechenov First Moscow State Medical University, Moscow, Russia; [5]Department of Laboratory Medicine, Medical University of Vienna, Vienna, Austria; [6]Surgical Research Laboratory and Section of Hepatobiliary Surgery and Liver Transplantation, Department of Surgery, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Study group: 576 ACLD

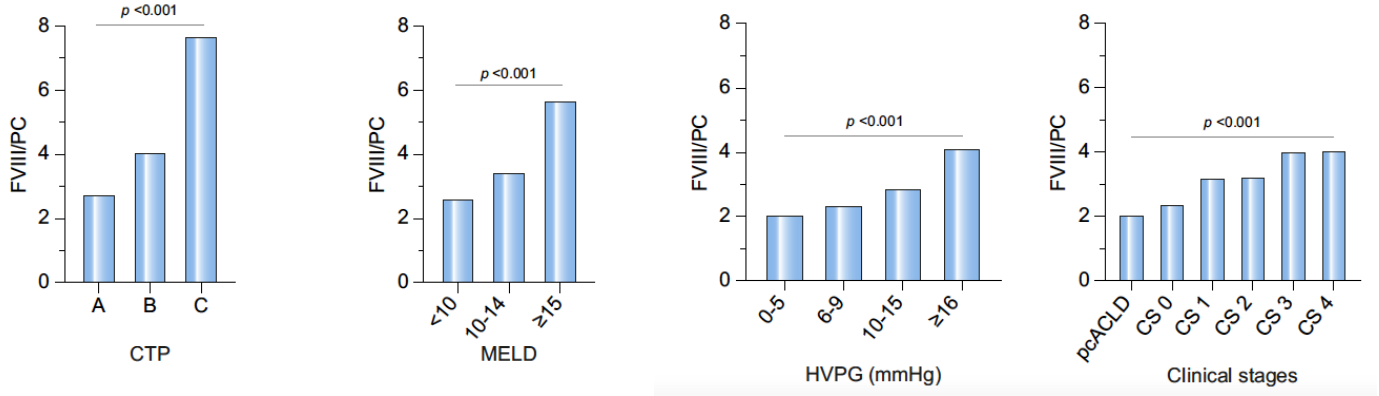
Control group: 122 healthy

Group TM-TGA: 142

Outcome-cohort – Clinical stages	n = 576
Probable cACLD (LSM ≥10 kPa and HVPG <6 mmHg)	n = 35
CS 0 (cACLD and 6-9 mmHg)	n = 88
CS 1 (cACLD and HVPG ≥10 mmHg)	n = 153
CS 2 (dACLD with variceal bleeding)	n = 47
CS 3 (dACLD with non-bleeding decompensation)	n = 139
CS 4 (≥2 decompensating events)	n = 114

CSPHT

Particular considerations – Hypercoagulability



- FVIII/PC and markers of severity of liver disease
- FVIII/ PC and relationship with decompensation and death
- **No relationship between FVIII/ PC with bleeding or thrombotic events** in the outcome or TM-TGA cohorts

Sheiner B. et al, J Hepatol 2022

Particular considerations – Hypercoagulability

Variables	PVT (n = 23)	No PVT (n = 287)	sHR (95	alue
Hemostatic proteins				
Primary hemostasis				
VWF (Ag,%)	120.9 ± 32	125.6 ± 27.3	0.99 (0.97–1.01)	0.54
VW ristocetin co-factor (functional,%)	108.8 ± 22.4	119.1 ± 26.3	0.98 (0.97–1)	0.051
ADAMTS13,%	98.6 ± 18.5	96.9 ± 17.3	1 (0.98–1.03)	0.69
Secondary hemostasis				
sTF,ng/ml	135.9 ± 25.5	143.5 ± 27.9	0.99 (0.98–1)	0.19
Factor II, %	52.8 ± 15	62.9 ± 16.6	0.96 (0.94–0.99)	**0.001**
Factor V, %	52 ± 12.9	62.2 ± 15.8	0.95 (0.93–0.98)	**0.001**
Factor VII, %	43.9 ± 12.6	52.6 ± 15.6	0.96 (0.95–0.99)	**0.002**
Factor VIII, %	125.8 ± 19.1	135.2 ± 23.3	0.981 (0.96–0.99)	**0.036**
Factor IX, %	57.5 ± 18.8	59.8 ± 19.1	0.99 (0.97–1.01)	0.49
Factor X, %	50.4 ± 12.1	61.2 ± 15.3	0.95 (0.92–0.97)	**<0.001**
Factor XI, %	62.5 ± 17	76.9 ± 19.6	0.96 (0.95–0.98)	**<0.001**
Factor XII, %	58.4 ± 14.4	65 ± 15.1	0.97 (0.95–0.99)	**0.024**
Factor XIIIa, %	61.2 ± 28.5	75.0 ± 36.1	0.99 (0.97–1.01)	0.18
Fibrinogen, mg/ml	2.24 ± 0.71	2.47 ± 0.84	0.68 (0.39–1.17)	0.16
Protein C, %	60.3 ± 20.7	79.0 ± 23.9	0.97 (0.95–0.98)	**<0.001**
Protein S, %	66.7 ± 17.9	81.5 ± 20.4	0.97 (0.95–0.98)	**<0.001**
Antithrombin, %	75.5 ± 17.9	84.1 ± 18.8	0.98 (0.96–0.99)	**0.02**
Fibrinolysis				
Plasminogen, %	53.7 ± 11.5	60.8 ± 13.1	0.96 (0.94–0.99)	**0.002**
PAI-1, ng/ml	26.7 ± 7.6	23.3 ± 7.1	1.05 (1.01–1.09)	**0.017**
Markers of activation of hemostasis				
Soluble P-Selectin, ng/ml	73.7 ± 18	63.3 ± 24.2	1.02 (1–1.03)	**0.012**
Soluble CD40L, ng/ml	98.3 ± 19.7	104.5 ± 21.9	0.98 (0.97–1)	0.14
Fragment 1+2, nmol/ml	1.8 ± 0.8	1.4 ± 0.5	2.51 (1.47–4.27)	**<0.001**
Factor VIIa, ng/ml	3.4 ± 1.8	2.4 ± 1.5	1.29 (1.11–1.51)	**0.001**
Factor XIIa, ng/ml	3.8 ± 1.7	3.3 ± 1.6	1.17 (0.96–1.43)	0.11
D-dimer, ng/ml	466.8 ± 225.8	460.9 ± 221.2	1 (0.99–1)	0.95
PAP, µg/ml	1024.1 ± 268.4	949.6 ± 338.46	1(1–1)	0.21
Microparticles	24.3 ± 10.4	18.0 ± 9.1	1.05 (1.02–1.08)	**<0.001**
Global functional tests				
ETP (without TM), nM IIa*min	322.9 ± 27.7	349.8 ± 60.6	0.98 (0.97–0.99)	**<0.001**
ETP (with TM), nM IIa*min	268.6 ± 24.2	282.9 ± 44.3	0.98 (0.97–0.99)	**0.009**
Clot lysis time, min	82 ± 40	71 ± 25	1.01 (0.99–1.02)	0.072
Permeability, Ks	$4.2 \times 10^{-9} \pm 1.9 \times 10^{-9}$	$4.7 \times 10^{9} \pm 8 \times 10^{-9}$	0.99 (0.95–1.03)	0.61
Clot weight, mg	55 ± 10	60 ± 9	0.95 (0.90–0.99)	**0.042**
Ratios				
Von Willebrand ratio (VWF co-factor/Ag)	0.96 ± 0.33	0.98 ± 0.27	0.76 (0.11–5.01)	0.78
Ratio FVIII/Protein C	2.34 ± 0.98	1.89 ± 0.75	1.58 (1.17–2.14)	**0.0028**
ETP ratio (with/without TM)	0.83 ± 0.08	0.81 ± 0.06	1.70 (0.77–3.72)	0.20
Inflammatory markers				
Cell-free DNA, ug/ml	0.89 ± 0.16	0.89 ± 0.22	0.97 (0.22–4.27)	0.97
MPO-DNA (AU)	0.21 ± 0.29	0.29 ± 0.46	0.68 (0.28–1.67)	0.40
IL-6, pg/ml	7.7 ± 7.9	8.4 ± 12.5	0.99 (0.97–1.02)	0.70
TNF-α,pg/ml	12.4 ± 5.1	11.6 ± 10.5	0.01 (0.99–1.03)	0.32
CRP, ng/ml	5315 ± 8044	3584 ± 6631	1 (1–1)	0.24

- Subgroup of 310 patients, 23 with PVT

- **None of the variables tested are independent risk factors for PVT**

Turon F. et al, J Hepatology 2021

Particular considerations – blood group type

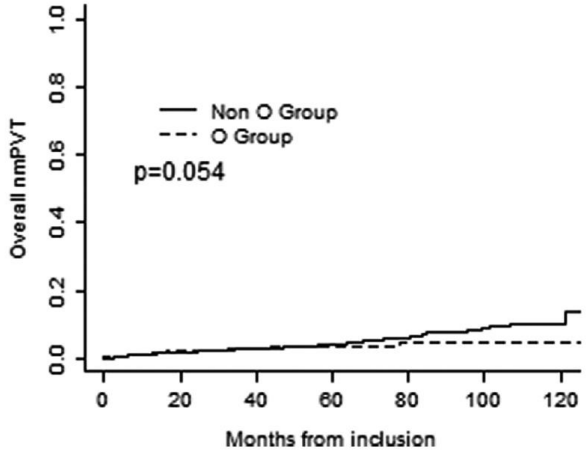
Rational:

- Non-O blood type is associated with an increased risk of arterial and venous thrombosis

- Patients wit non-O blood type have 25% higher concentration of VWF and factor VIII than O groups

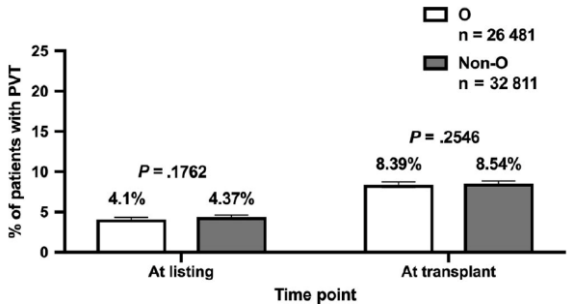
Particular considerations – blood group type

- "French cohort"
- 1789 Child-Pugh A patients
- 59.9% Non-O blood type
- 90 patients developed PVT



Ollivier-Hourmand I. et al, Liver Int 2022

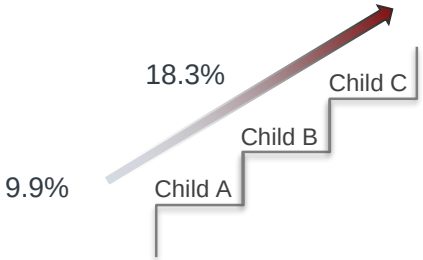
- "US cohort" – 59292 undergoing LT
- MELD at LT: 23.7±10.3



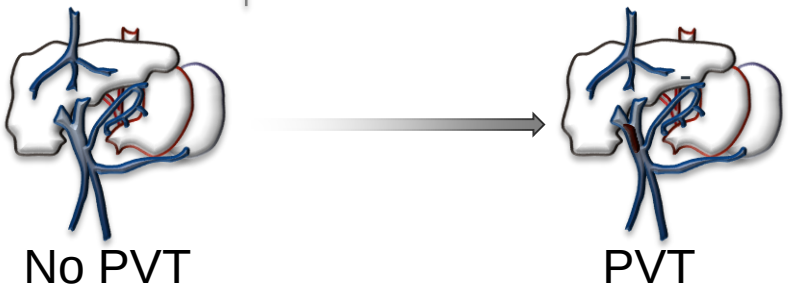
Sheiner B. et al, Liver Int 2020

No relationship between blood group type and PVT

Epidemiology → Risk factors → Risk factors for further progression

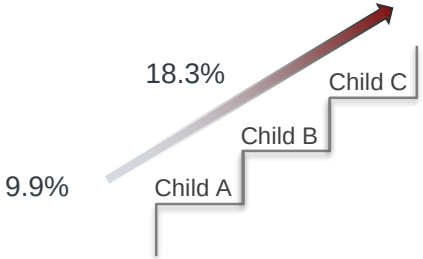


- Linked to increased PHT
- Linked to increased liver dysfunction

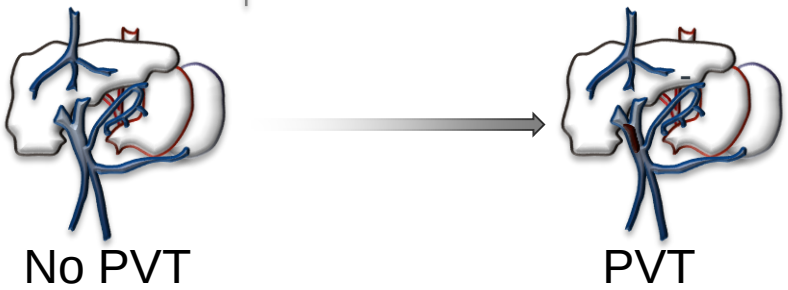


PVT? PV narrowing?

Epidemiology → Risk factors → Risk factors for further progression



- Linked to increased PHT
- Linked to increased liver dysfunction



PVT? PV narrowing?

- Spontaneous regression of PVT in up to 45-70% of patients
- Repermeabilization 28-84% under anticoagulation
- **Progression** of PVT in up to 37.5-71.4%

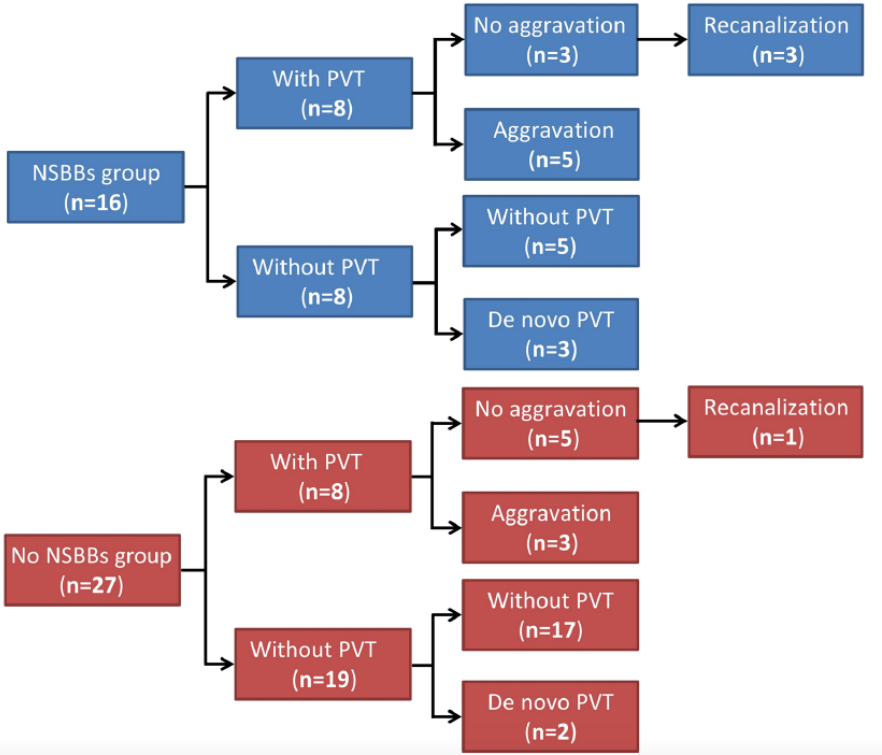
Gao Y. et al, Clin Res Hepatol Gastroenterol 2021; Nery F. et al, Hepatology 2015; Chen H. et al, Eur J gastroenterol Hepatol 2016; Senzolo M. et al, Liver Int 2012

- Spontaneous regression of PVT in up to 45-70% of patients
- Repermeabilization 28-84% under anticoagulation
- **Progression** of PVT in up to 37.5-71.4%

Is this progression linked to the same predisposal risk factors as for PVT?

Gao Y. et al, Clin Res Hepatol Gastroenterol 2021; Nery F. et al, Hepatology 2015; Chen H. et al, Eur J gastroenterol Hepatol 2016; Senzolo M. et al, Liver Int 2012

Role of NSBB

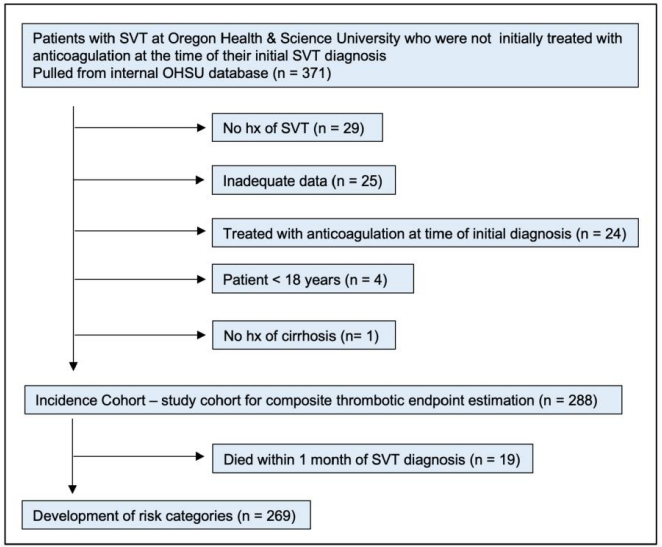


NSBB effect “mild”, expressed in univariate OR 4.4 (CI 95% 1.1-17.5; p=0.035), but not in multivariate analysis OR 4.1 (CI 95% 0.5-34.2; p=0.194)

NSBB group under >6M treatment. Info regarding the type, dosage, duration and adherence was acquired by telephone FU

Xu X. et al, Adv Ther 2020

Role of intraabdominal infection and pancreatitis

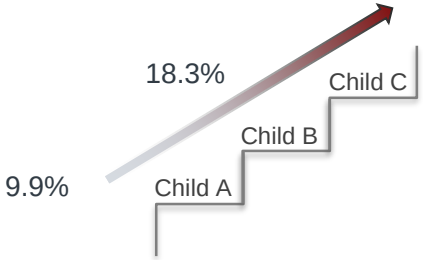


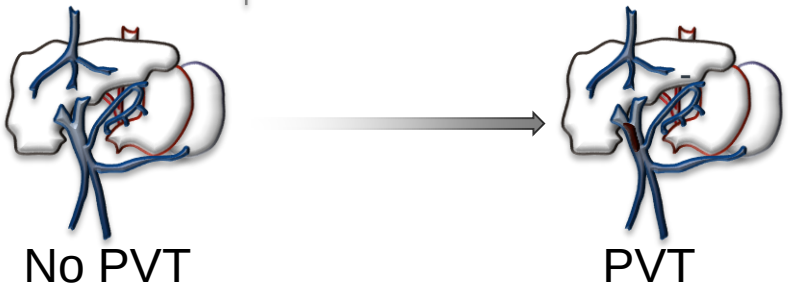
Event type	Count	% of events	% of cohort
Clot enlargement	56	52%	21%
Cavernous thrombosis	30	28%	11%
Progression to occlusion	25	23%	9%
Additional venous thrombosis	19	18%	7%
Arterial thrombosis	13	12%	5%
Intestinal ischemia	12	11%	4%
Portal cholangiopathy	12	11%	4%
Total	167[a]	–	–

Covariates	Adj OR	Unadj OR	95% CI		p
			Lower	Upper	
Age	1.00	0.99	0.97	1.03	0.92
Gender (female)	1.12	0.99	0.59	2.08	0.73
BMI	0.98	0.98	0.94	1.03	0.47
History of VTE	1.49	1.62	0.45	4.98	0.51
Aspirin use	1.78	1.38	0.68	4.65	0.24
Etiology					
Viral	0.61	0.88	0.21	1.76	0.36
Alcoholic	0.36	0.69	0.08	1.65	0.19
Multifactorial	0.43	0.75	0.16	1.14	0.09
Autoimmune	0.30	0.57	0.08	1.10	0.07
Other/unknown	0.75	1.56	0.29	1.89	0.54
Varices	1.81	1.72	0.94	3.47	0.07
Tumor-associated thrombus	1.30	1.15	0.60	2.79	0.50
Malignancy	0.87	0.91	0.43	1.76	0.69
Pancreatitis or intra-abdominal infection	3.61	3.23	1.21	10.71	0.02
Location					
Portal vein	0.38	0.39	0.04	3.81	0.41
Multiple splanchnic veins	1.11	1.49	0.53	2.35	0.77
Other	2.48	2.42	0.37	16.56	0.35
Obstructive clot	1.49	1.36	0.78	2.86	0.23
Ascites	0.98	1.22	0.52	1.87	0.96
Na	0.99	0.99	0.98	1.02	0.98
Cr	0.79	0.67	0.48	1.32	0.38
Total bilirubin	0.90	0.90	0.82	1.00	0.5

McMurry H. et al, Thrombosis research 2022

Epidemiology





Risk factors

- Linked to increased PHT
- Linked to increased liver dysfunction

PVT? PV narrowing?

Risk factors for further progression

- NSBB use?
- Intra-abdominal infections and pancreatitis (inflammation?)