International Congress on Coagulopathy in Liver Disease
Hemostasis and Thrombosis in Liver Disease
from Bench to Bedside

# HCC Development and the Thrombotic Microenvironment

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UOS Vascular Liver Diseases and Treatment of Portal Hypertension
Gastroenterology

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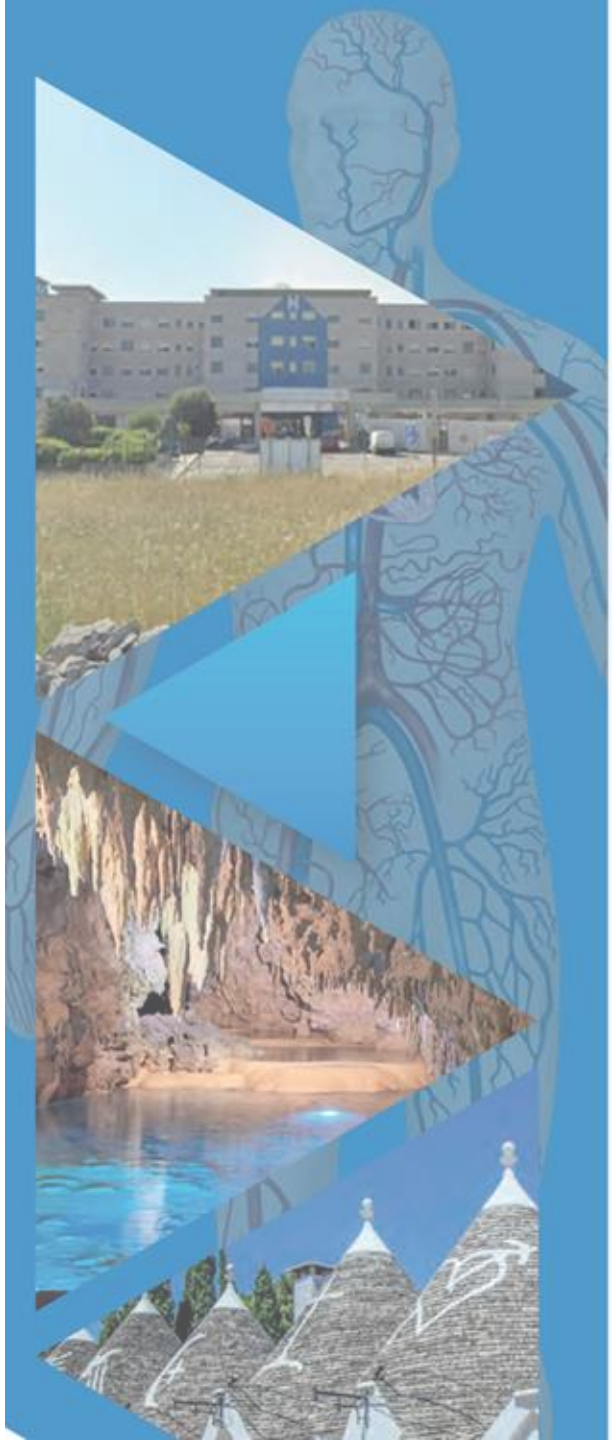
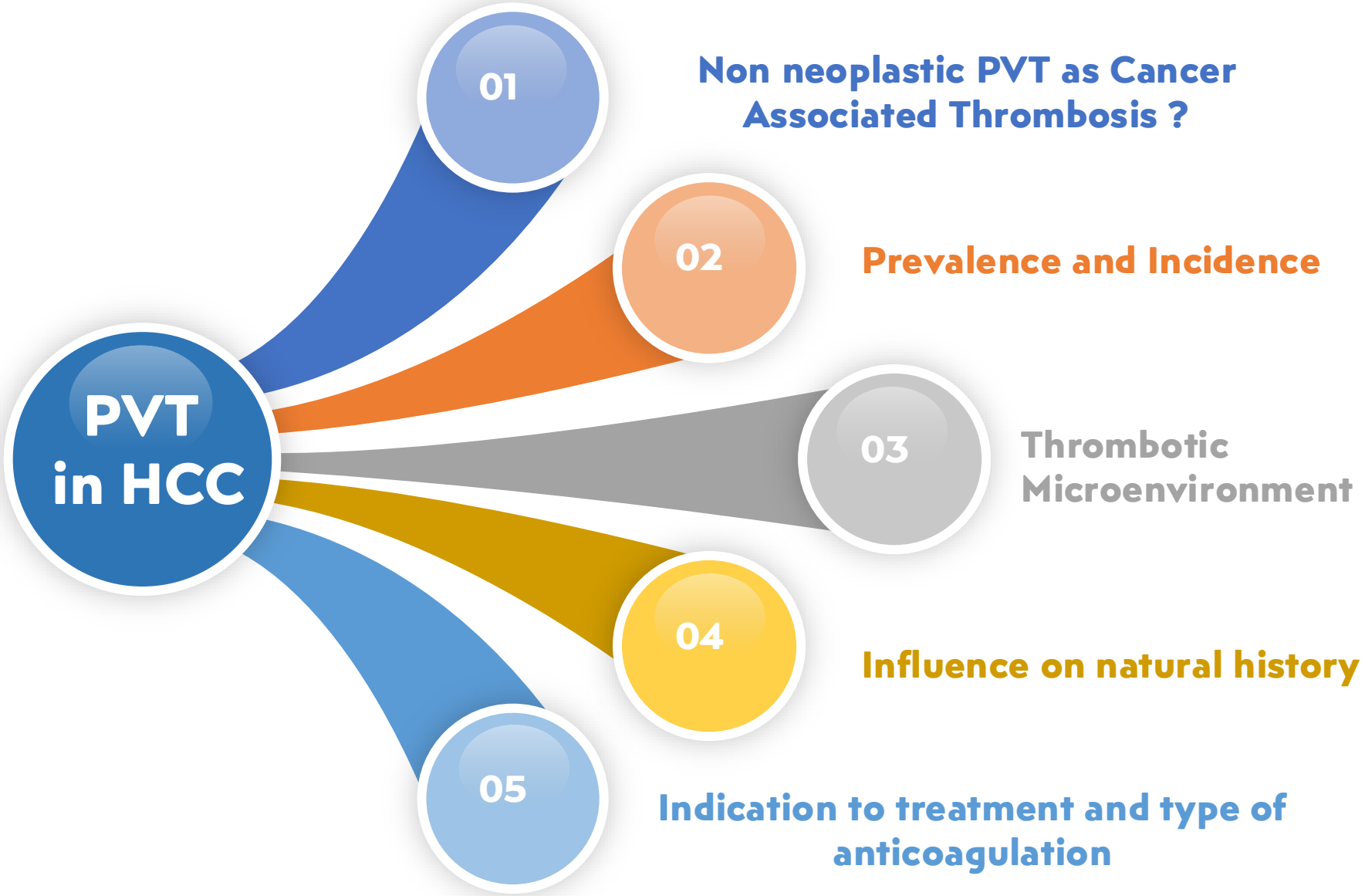


# OUTLINE

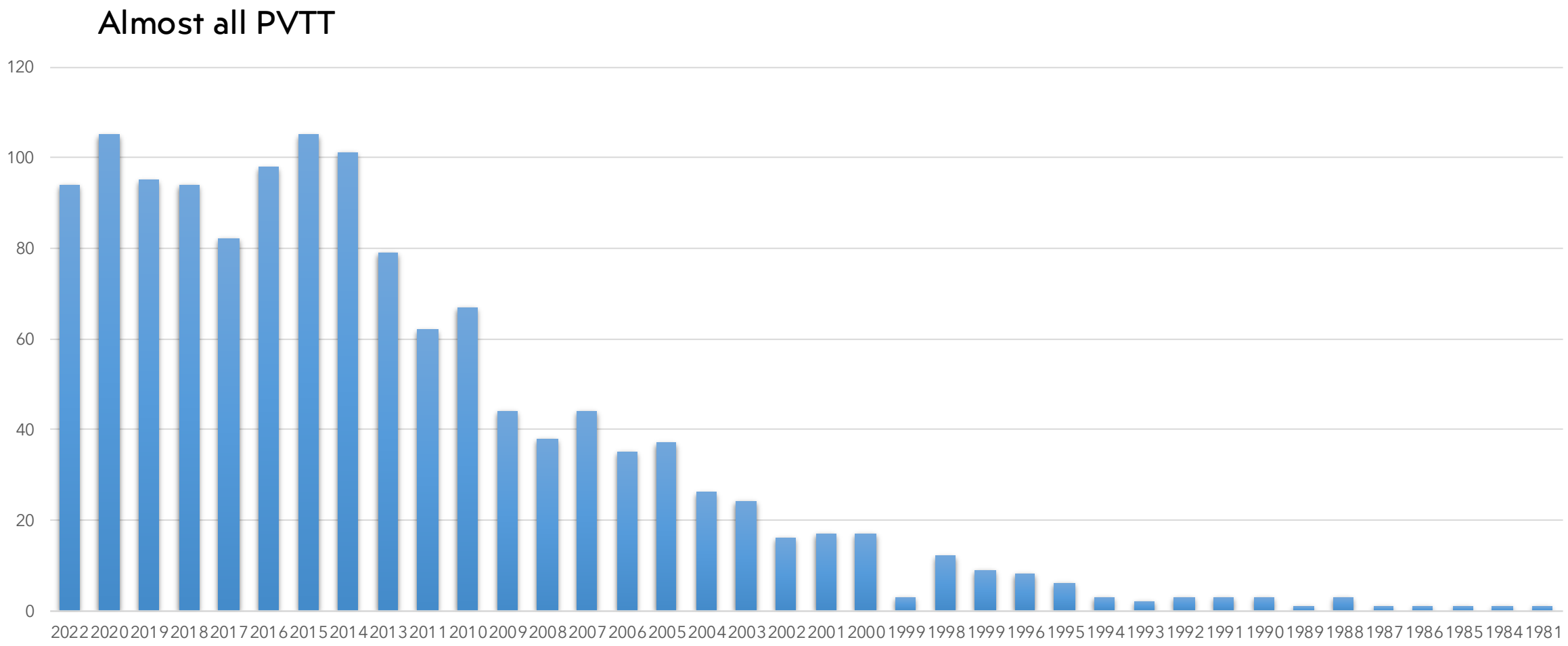

PVT in HCC
01
Non neoplastic PVT as Cancer Associated Thrombosis ?
02
Prevalence and Incidence
03
Thrombotic Microenvironment
04
Influence on natural history
05
Indication to treatment and type of anticoagulation

# Cancer Associated Venous Thrombosis (CAT)

- About 15% of patients with cancer will experience VTE - RR 15
- Prevalence of cancer in VTE patients is about 7%
- Incidence is increasing over time due to the improved survival and the use of targeted anti-cancer therapies (i.e. immune checkpoint inhibitors)
- Heterogeneity across various ethnic populations
- CAT mortality 1.9 per 100 pts-year (higher in recurrent VTE) – low CAT related mortality

Khorana et al, Nat Rev, Disease Primers 2022; Abdulla, Thromb Haemost 2020

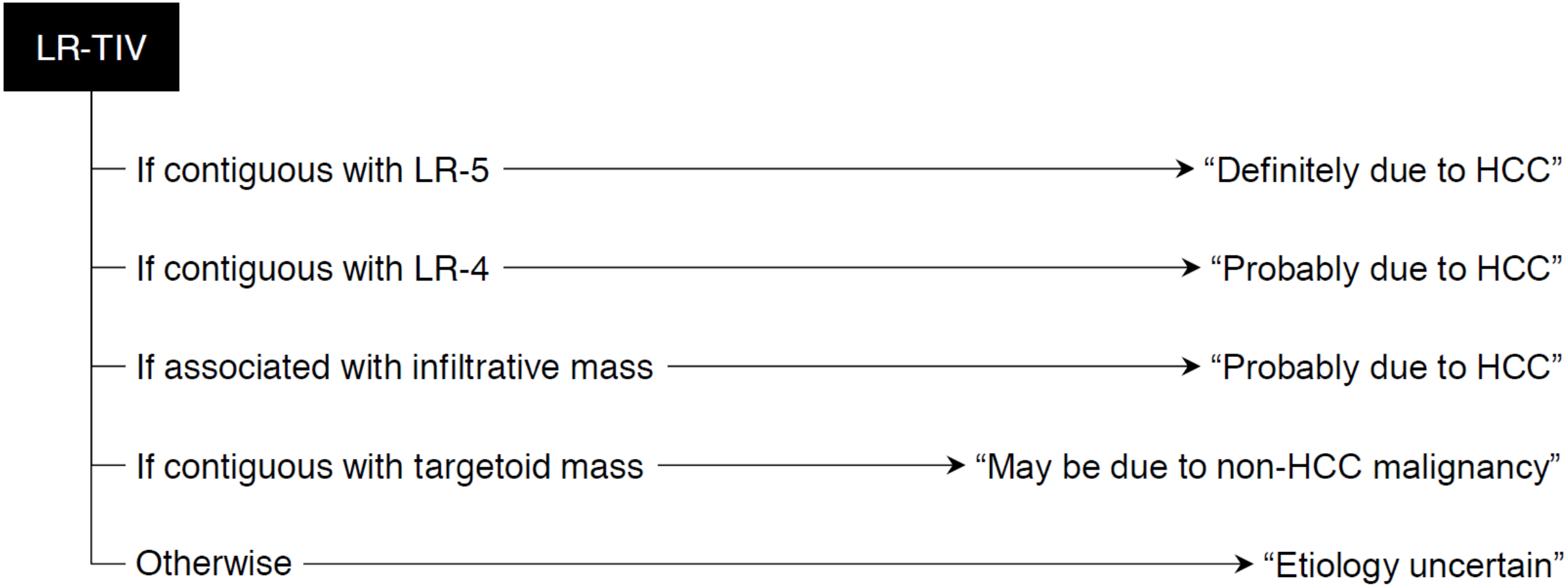
# CAT (PVT) in Cirrhosis with HCC: Highly Overlooked!



# Distinguish Portal Vein Tumor Invasion (PVTT) – LI-RADS

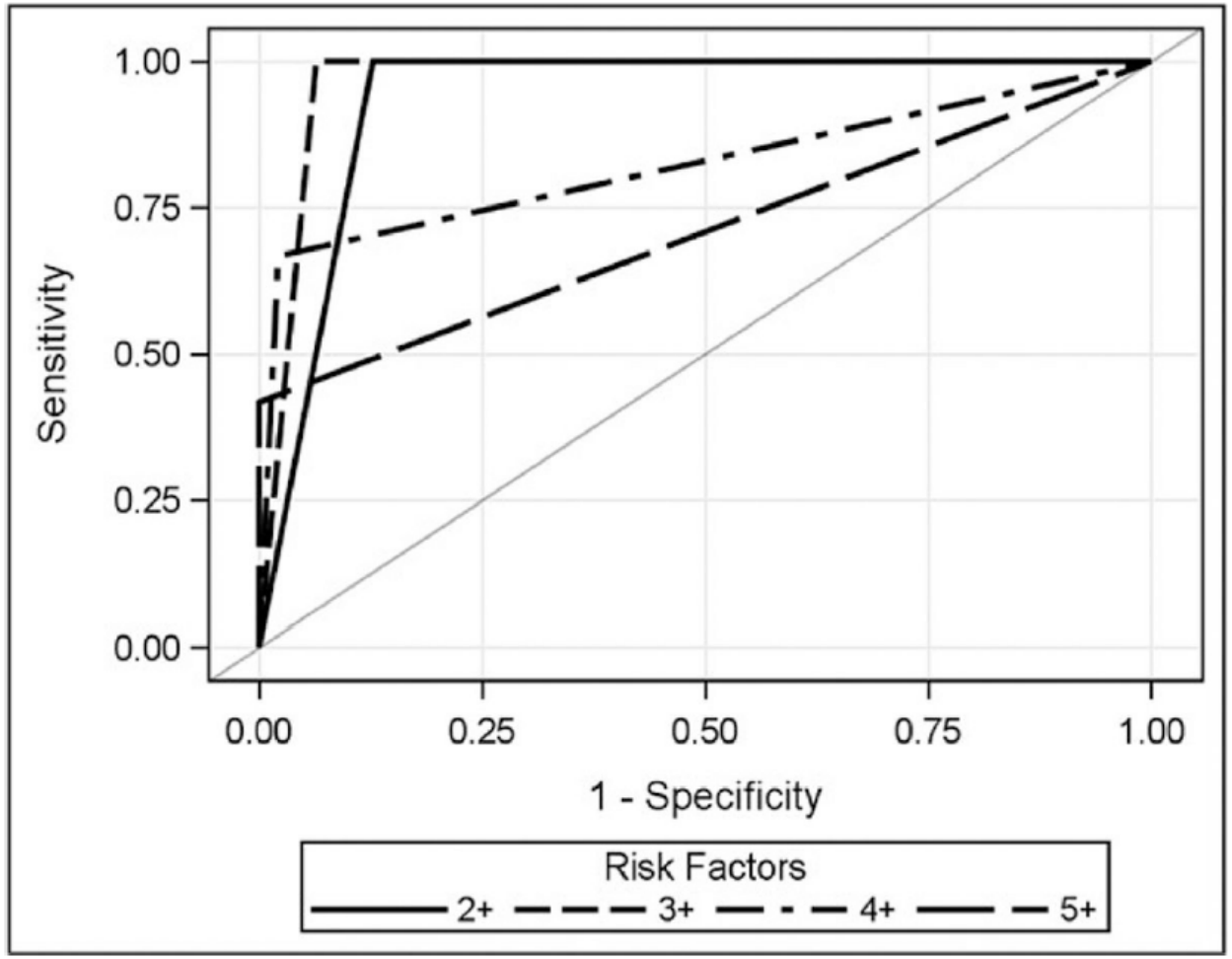
- Imaging features that suggest tumor in vein but do NOT establish its presence are listed below:
  - Occluded vein with ill-defined walls
  - Occluded vein with restricted diffusion
  - Occluded or obscured vein in contiguity with malignant parenchymal mass
  - Heterogeneous vein enhancement not attributable to artifact
  - Unequivocal enhancing soft tissue in vein, regardless of visualization of parenchymal mass

# Distinguish Portal Vein Tumor Invasion (PVTT) – LI-RADS



# Distinguish Portal Vein Tumor Invasion (PVTT) – AVENA Criteria

- Thrombus enhancement
- Venous expansion
- Neovascularity
- Being adjacent to HCC or prior treatment site
- (AFP) >1000 ng/dL




≥3 criteria best characterized tumor PVT

100% sensitivity, 93.6% specificity

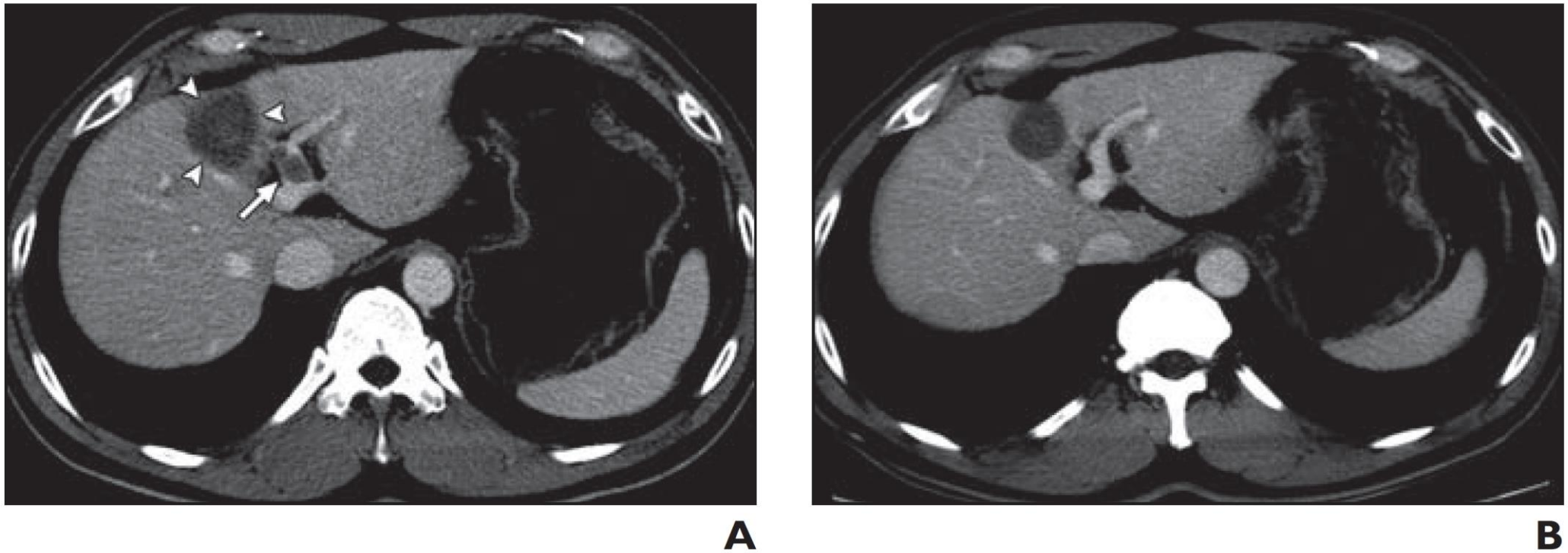
80% PPV, and 100% NPV

Sherman, Liver Transplant 2019

# Distinguish procedural related PVT

1%-3% incidence of local venous thrombosis

Spontaneous amelioration/repermeation in 70%



A B

Kim, Vascular Intervent Radiology 2010

# Trombosis and HCC

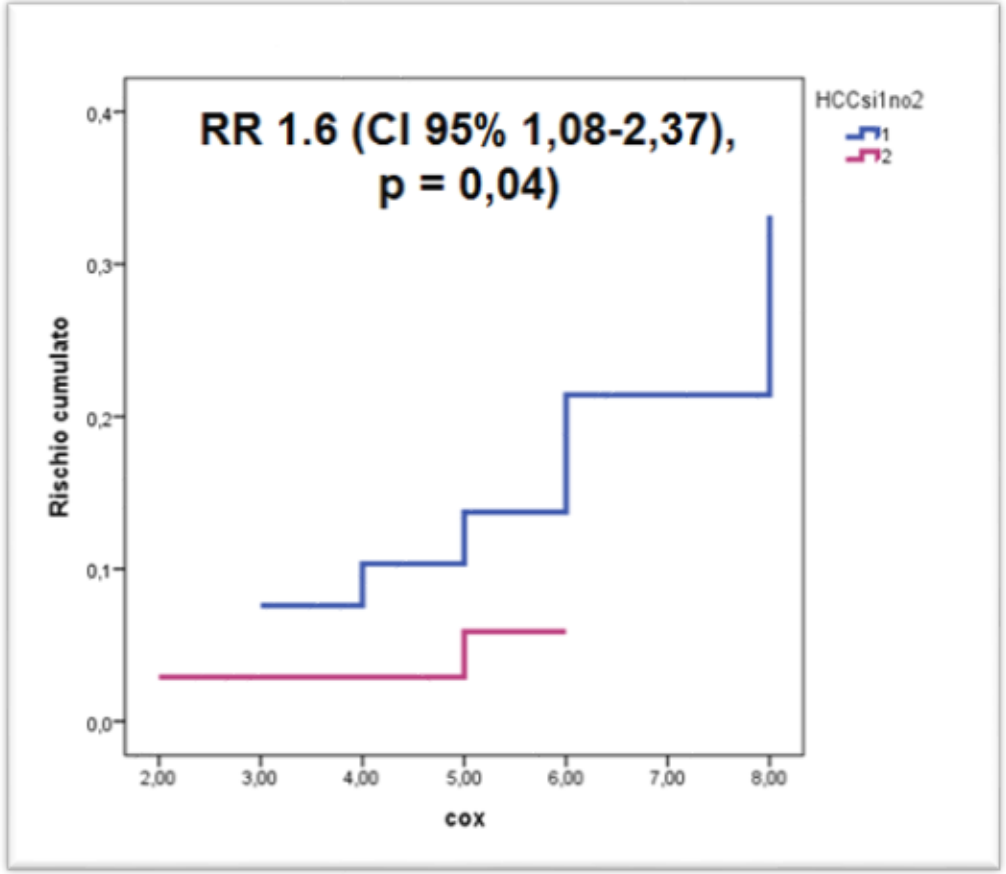
| Study | Population | Thrombosis Type | Key Findings |
|---|---|---|---|
| **Nonami 1991** | Cirrhosis ± HCC (LT) | PVT | Higher in HCC (34.8% vs 15.7%); severity also relevant |
| **Davidson 1994** | Cirrhosis ± HCC (LT) | PVT | Higher in HCC (27% vs 9%); more complete PVT |
| **Ravaioli 2001** | LT cohort | PVT | HCC independently associated with PVT |
| **Connolly 2008** | Cirrhosis + HCC | DVT/PE | VTE 6.7%; higher if PVT present |
| **Lesmana 2010** | Cirrhosis ± HCC | DVT | Similar VTE rates (≈4–5%) |
| **Zanetto 2017** | Prospective cirrhosis ± HCC | PVT | ↑ PVT in HCC (24.4% vs 11.4%); ROTEM predictive |
| **Wang 2018** | Cirrhosis + HCC | DVT/PE | VTE ~6%; linked to tumor burden & metastasis |
| **Ow 2021** | ICU cirrhosis | PVT + VTE | HCC predicts early & late thrombosis |
| **Senzolo 2024** | Cirrhosis + HCC | PVT | Linked to CSPH & tumor volume |

# Prevalence of Non-neoplastic Portal Vein Thrombosis in HCC

- HCC awaiting LT (**12%**) – AVENA
- HCC versus non-HCC LT patients (**27%** vs 9%)
- HCC versus non-HCC LT patients (**34.8%** vs 11.4%)
- HCC versus non-HCC LT patients (**40%** vs 30%)
- HCC awaiting locoregional treatment – concomitant diagnosis (**12%**)

Nonami, Hepatology 1992; Davidson, Transplantation 1994; Ravaioli Ann Surg 2011; Sherman, Liver Transplant 2019; Shalaby Hepatology 2024

# Incidence of Non-neoplastic Portal Vein Thrombosis in HCC




| Child Class (n) | Number of PVT during follow-up | PVT/cirrhotics with HCC | PVT/cirrhotics without HCC | Total |
|---|---|---|---|---|
| A | 29 | 5/20 [25%] | 0/9 [0%] | 5/29 [17.2%] |
| B | 29 | 3/12 [25%] | 1/17 [5.9%] | 4/29 [13.8%] |
| C | 18 | 2/9 [22.2%] | 3/9 [33.3%] | 5/18 [27.8%] |
| Total | 76 | 10/41 [24.4%] | 4/35 [11.4%] | 14/76 [18.4%] |

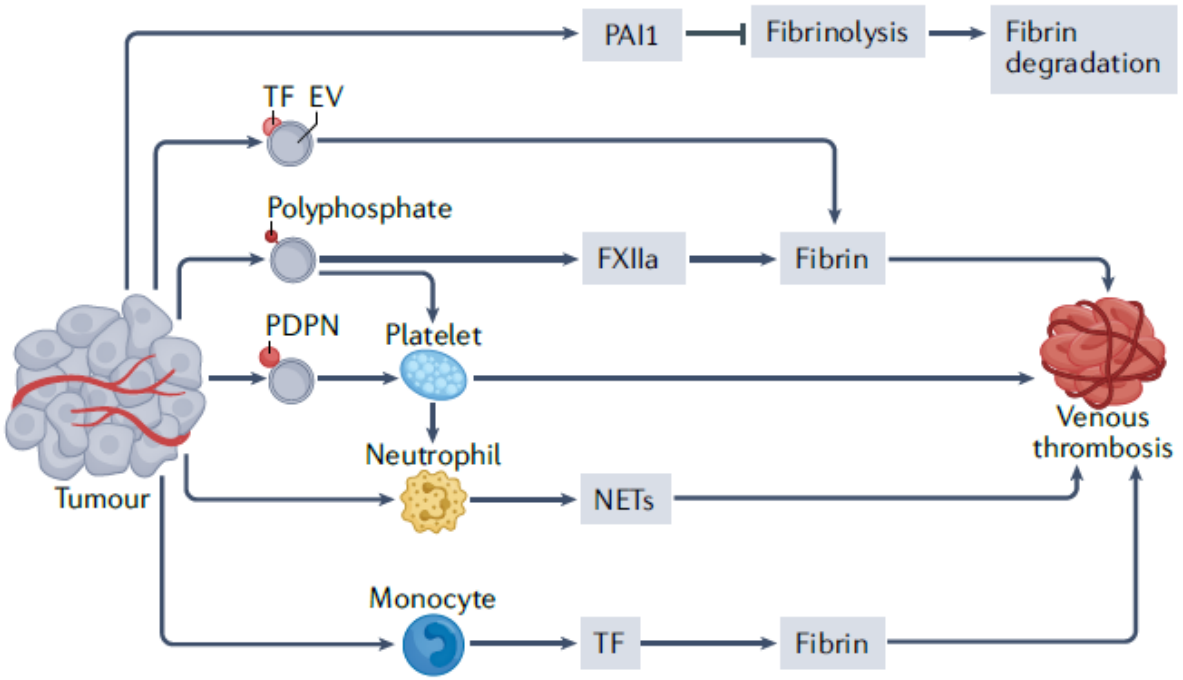
Zanetto, Liv Int 2017

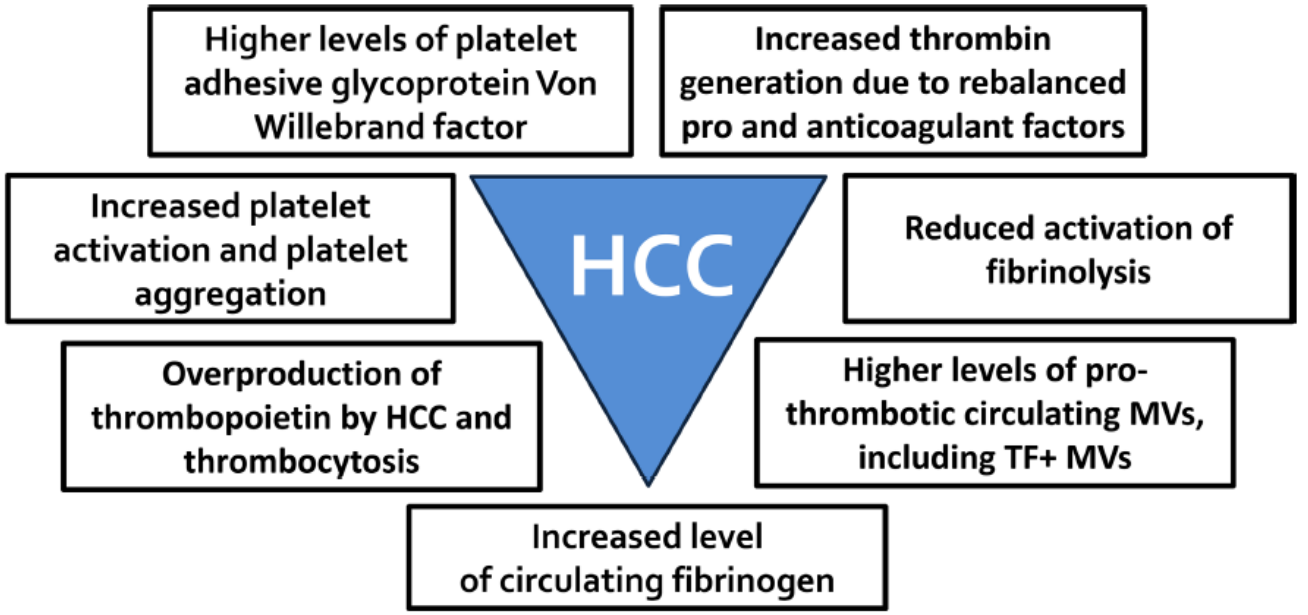
# Incidence of Non-neoplastic Portal Vein Thrombosis in HCC

- 623 retrospective patients with CLD non electively admitted to a specialist ICU
- VTE occurred in 125 (20%) patients – 80 previous diagnosis
- 39 pts < 48h (80% PVT); 45 pts > 48h (55%PVT)
- Previous and >48h VTE (HCC 30% vs 9%)
- Later > 48h VTE diagnosis (HCC 22% vs 12%)
- At multivariate analysis HCC remains a risk factor – OR 2.79

Tsai-Wing Ow, Thrombosis and Haemostasis 2022

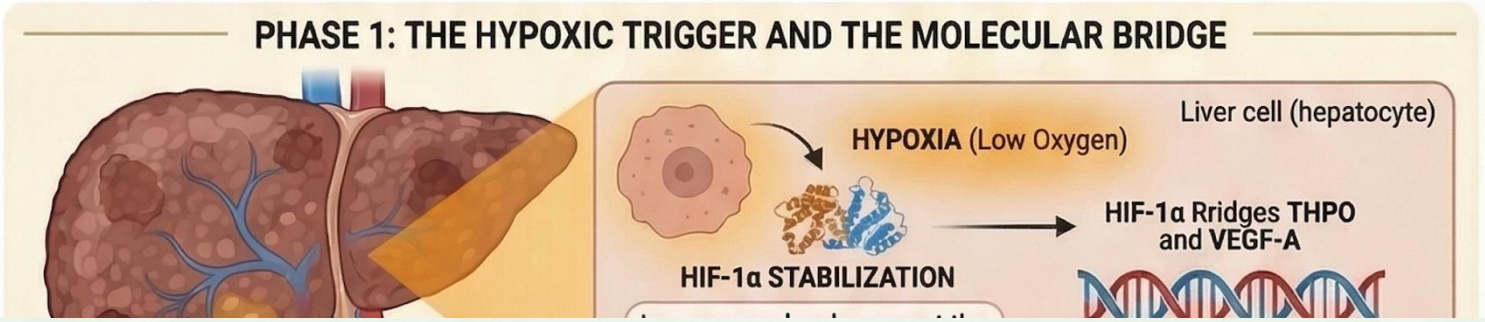
# Tumour-related pro-thrombotic changes

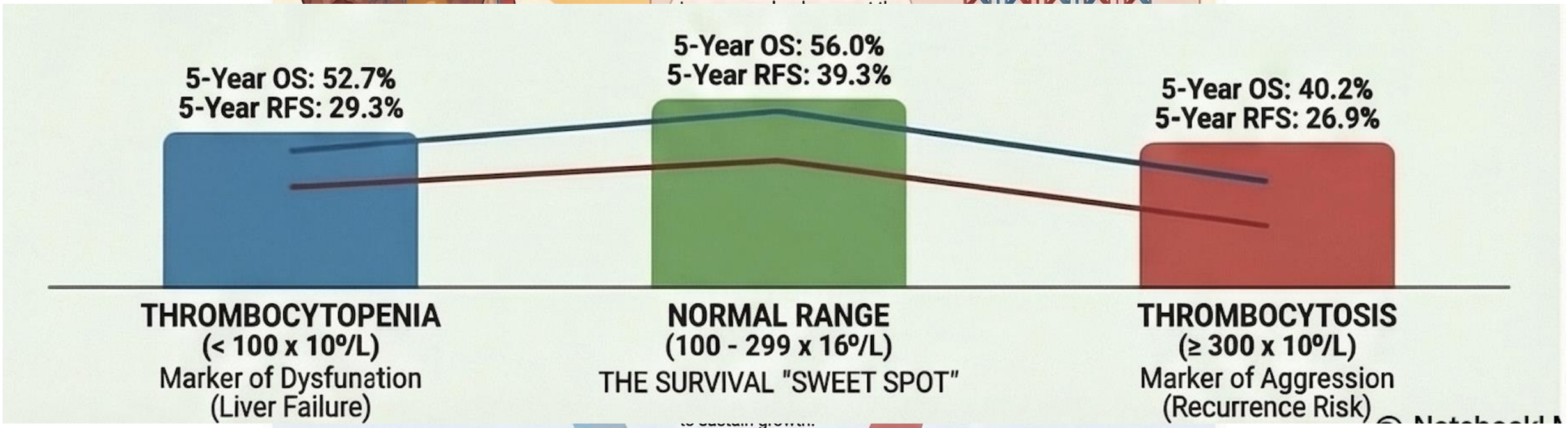


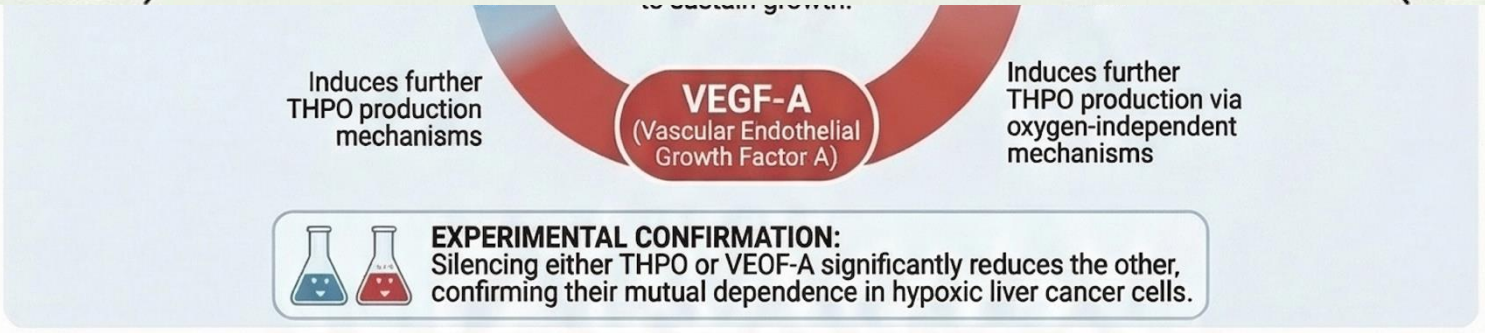




Khorana, DISEASE PRIMERS 2022; Zanetto, Liv Int 2022

# Platelets

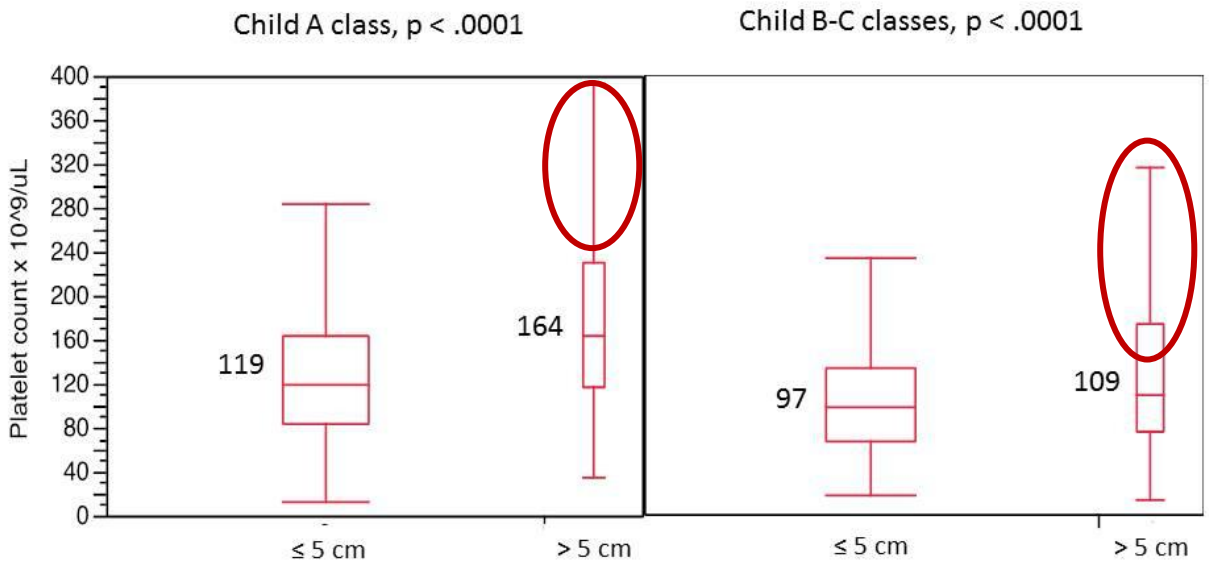

PHASE 1: THE HYPOXIC TRIGGER AND THE MOLECULAR BRIDGE
Liver cell (hepatocyte)
HYPOXIA (Low Oxygen)
HIF-1α STABILIZATION
HIF-1α Rridges THPO and VEGF-A


5-Year OS: 52.7%
5-Year RFS: 29.3%
5-Year OS: 56.0%
5-Year RFS: 39.3%
5-Year OS: 40.2%
5-Year RFS: 26.9%
THROMBOCYTOPENIA
(< 100 x 10⁹/L)
Marker of Dysfunation
(Liver Failure)
NORMAL RANGE
(100 - 299 x 16⁹/L)
THE SURVIVAL "SWEET SPOT"
THROMBOCYTOSIS
(≥ 300 x 10⁹/L)
Marker of Aggression
(Recurrence Risk)


Induces further THPO production mechanisms
VEGF-A
(Vascular Endothelial Growth Factor A)
Induces further THPO production via oxygen-independent mechanisms
EXPERIMENTAL CONFIRMATION:
Silencing either THPO or VEOF-A significantly reduces the other, confirming their mutual dependence in hypoxic liver cancer cells.

# Platelets

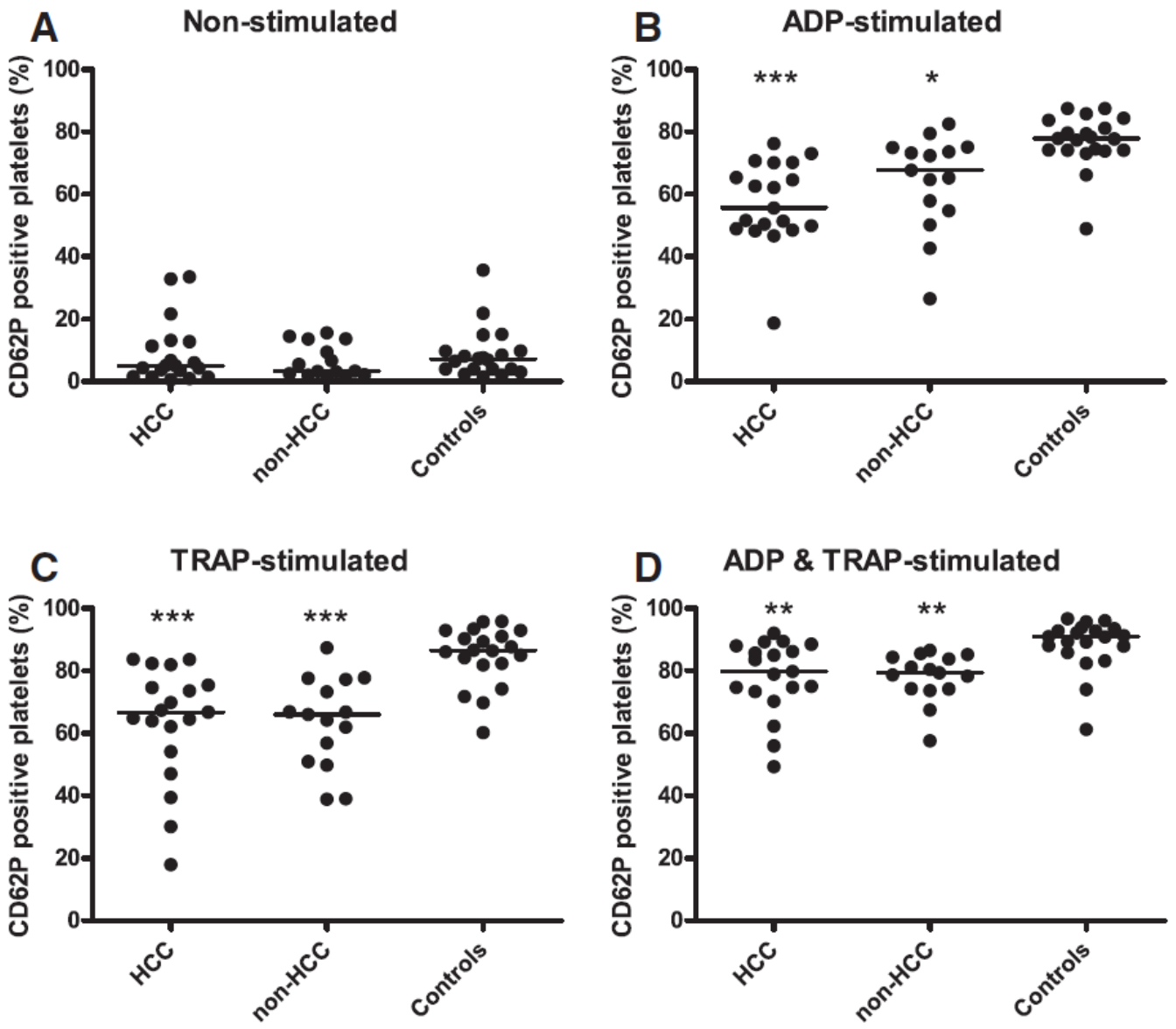
**Figure 2.** Platelet count stratified according to Child class and diameter of the largest nodule




## Mortality

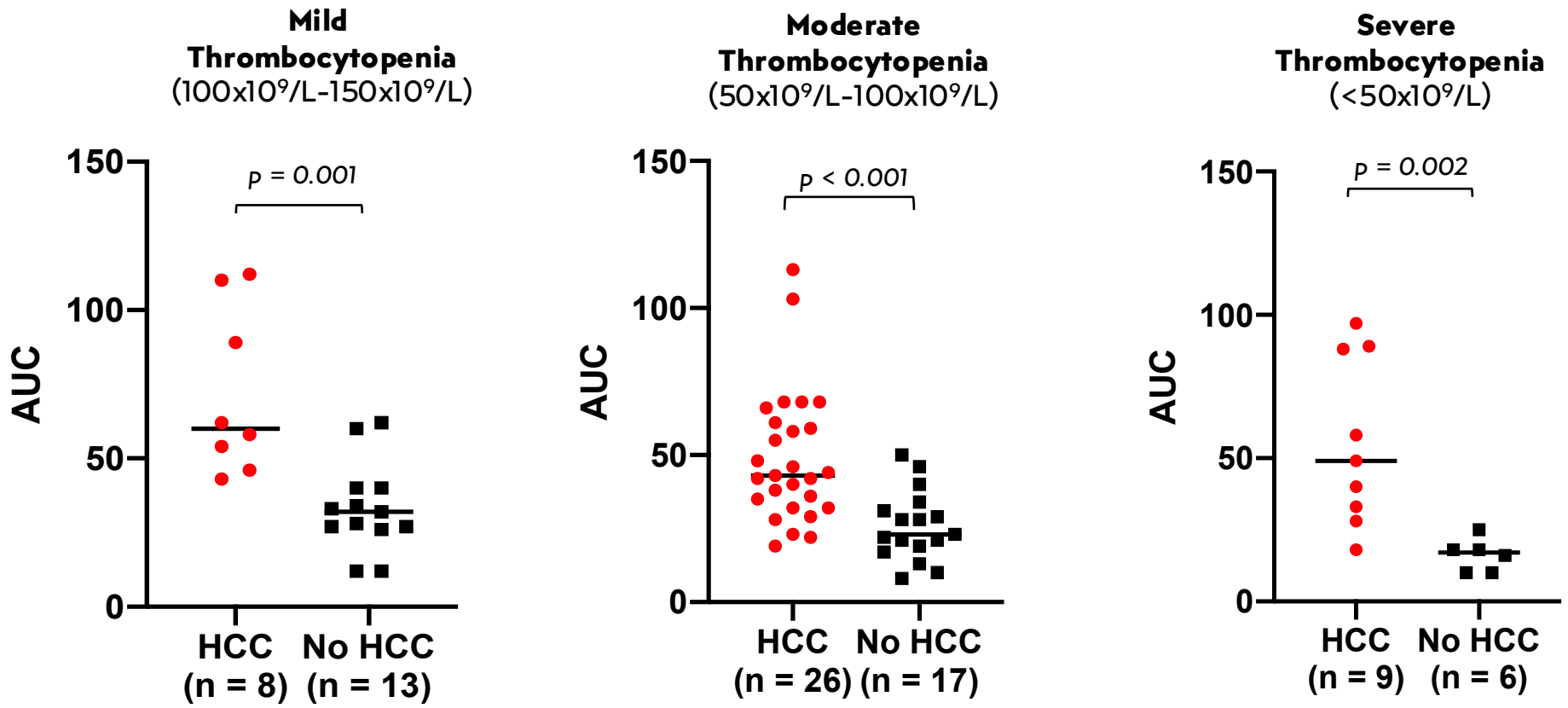
| | Study cohort Child A | | Study cohort Child B-C | |
|---|---|---|---|---|
| | RR (95%CI) | p | RR (95%CI) | P |
| PLT>140 x10$^9$ /uL | 0,9 (0,77-1,05) | .2 | 1,22 (1,02-1,46) | .02 |
| Multinodularity | 2,11 (1,7-2,56) | <.001 | 1,75 (1,46-2,09) | <.001 |
| Main HCC > 5cm | 1,4 (1,2-0,56) | | 1,46 (1,18-1,78) | <.001 |
| AFP > 16 ng/mL | 1,46 (1,25-1,70) | <.001 | 1,44 (1,22-1,69) | <.001 |
| Metastasis | 2,29 (1,52-3,31) | <.001 | 1,4 (0,95-2) | .08 |
| Neoplastic thombosis | 1,84 (1,45-2,32) | <.001 | 2,13 (1,75-2,57) | <.001 |
| | **Validation cohort Child A** | | **Validation cohort Child B-C** | |
| | RR (95%CI) | p | RR (95%CI) | P |
| PLT>140 x10$^9$ /uL | 0,93 (0,78-1,12) | .46 | 1,44 (1,15-1,80) | .001 |
| Multinodularity | 1,78 (1,46-2,15) | <.001 | 1,19 (1,96-1,48) | 0.1 |
| Main HCC > 5cm | 2,26 (1,85-2,74) | <.001 | 1,97 (1,51-2,56) | <.001 |
| AFP > 16 ng/mL | 1,82 (1,53-2,18) | <.001 | 1,28 (1-1,64) | <.04 |
| Neoplastic thombosis | 1,41 (1,16-1,72) | <.001 | 1,75 (1,37-2,24) | <.001 |

# Platelets' activation in HCC




Alkozai, Thrombosis Research 2015

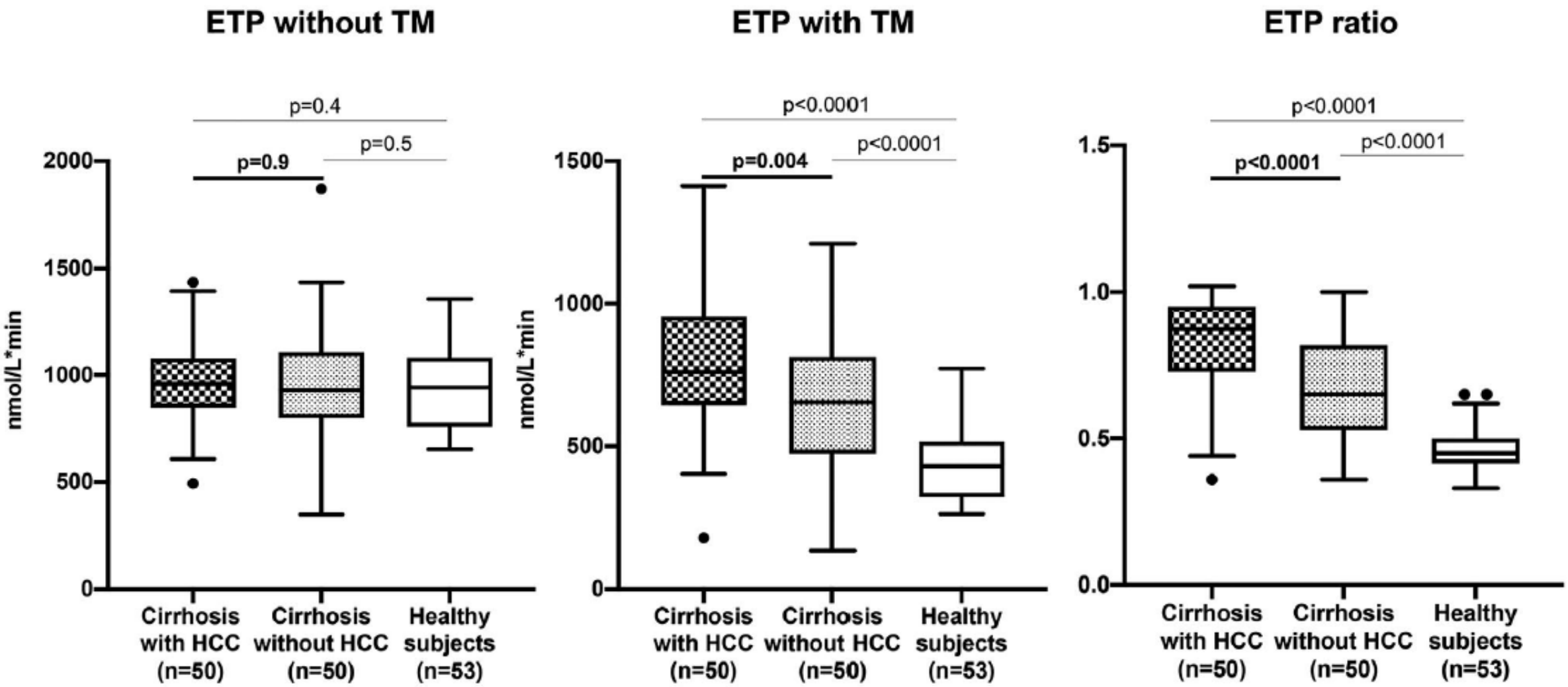
# Platelets' aggregation in HCC



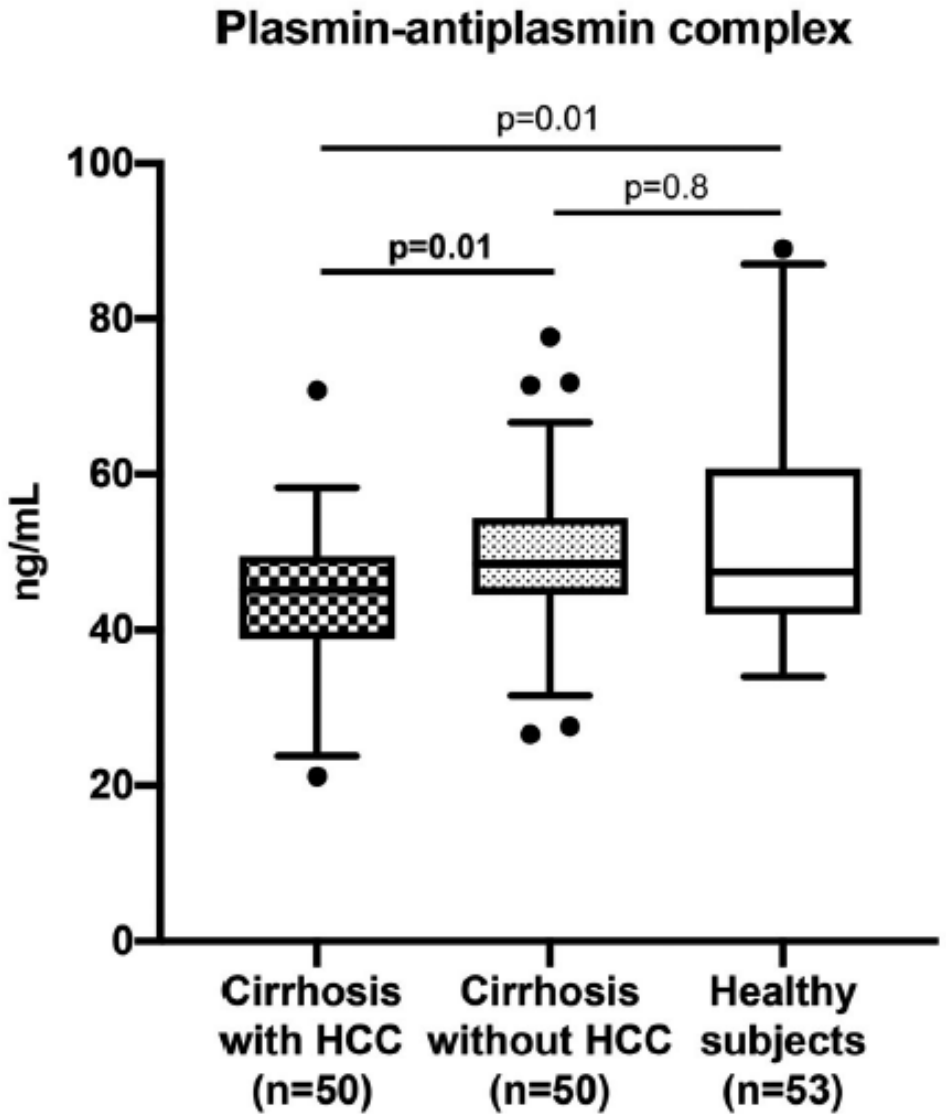

*ADP-induced aggregation

Zanetto, Cancers 2021

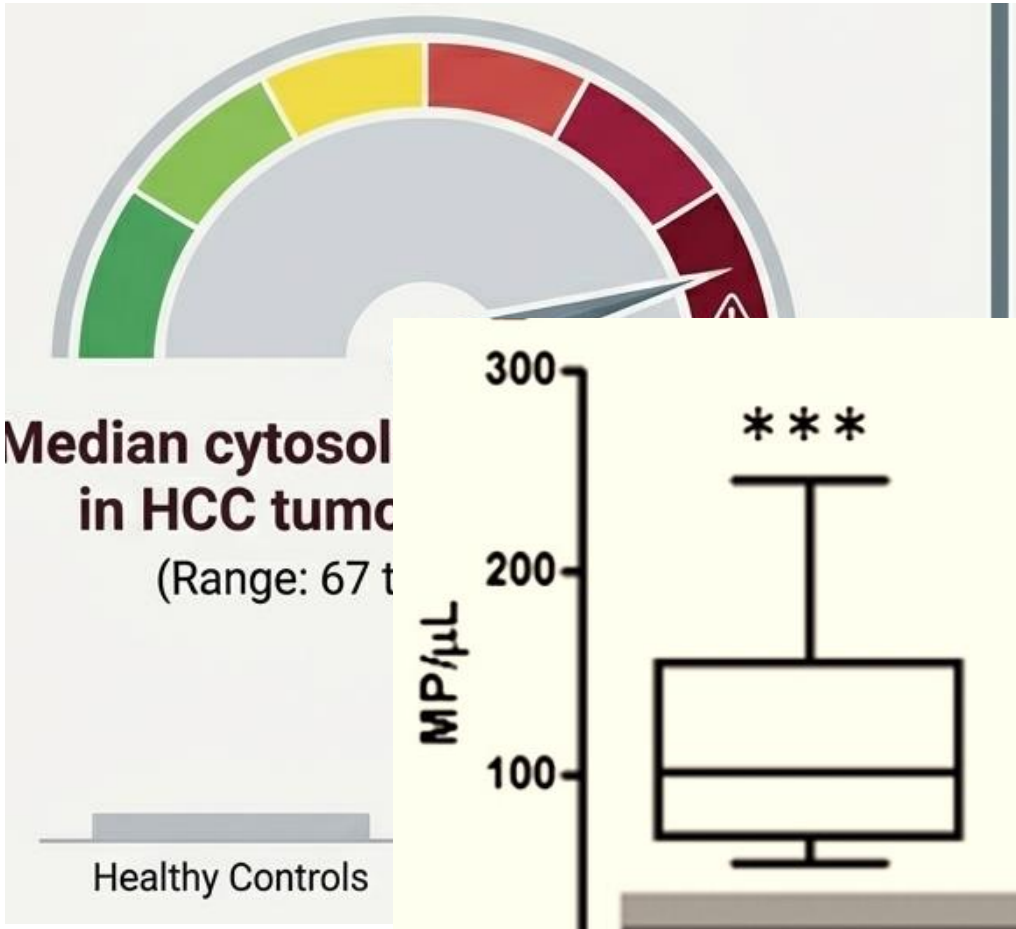
# Thrombin Generation in HCC



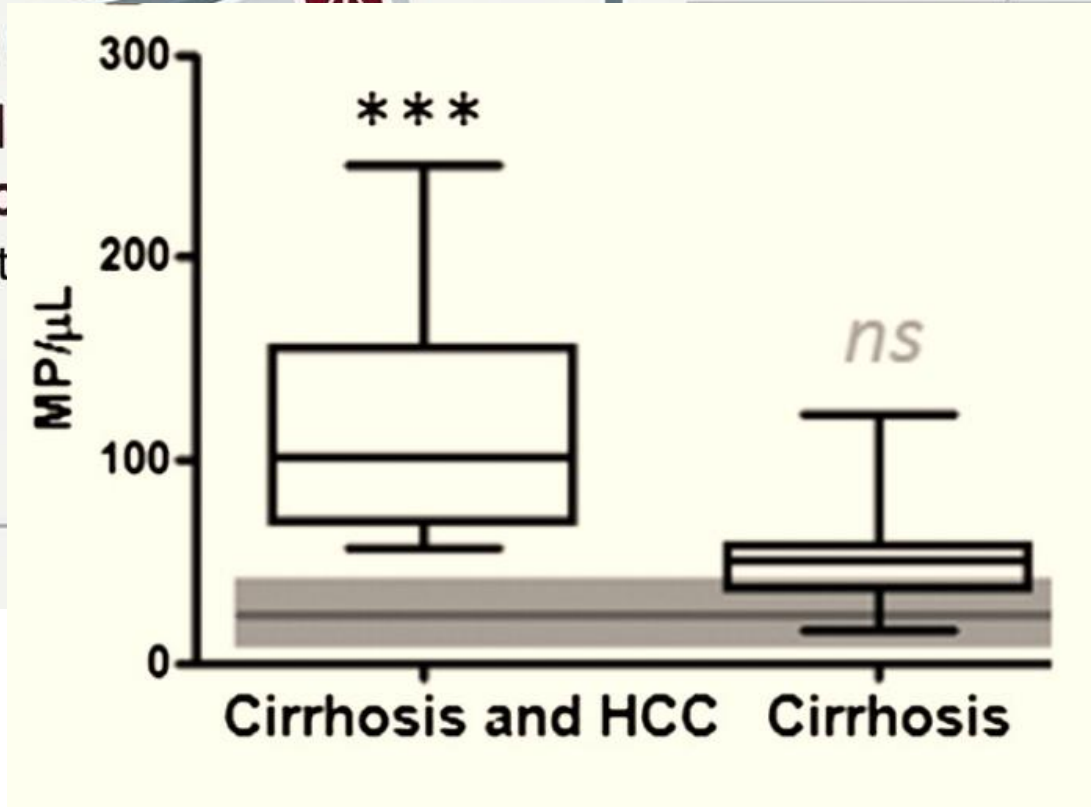
# Fibrinolysis in HCC



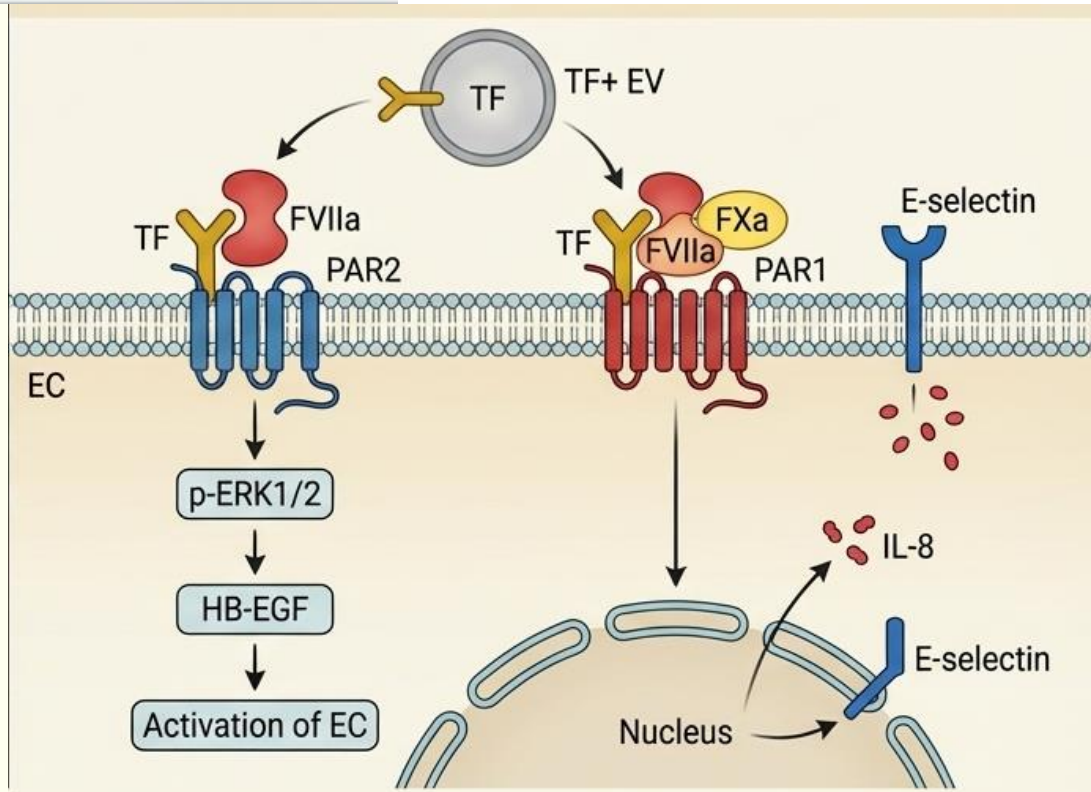
# Tissue Factor




| Clinical Dimension | Impact of High TF |
|---|---|
| Tumor Size | Accelerated growth and larger nodule diameters. |




**The Release & Transport:** HCC cell sheds Extracellular Vesicles loaded with TF (TF+ EVs) directly into the circulatory system.




**The Systemic Impact:** TF+ EVs bind to distant endothelial cells, inducing a pro-inflammatory, pro-adhesive state.

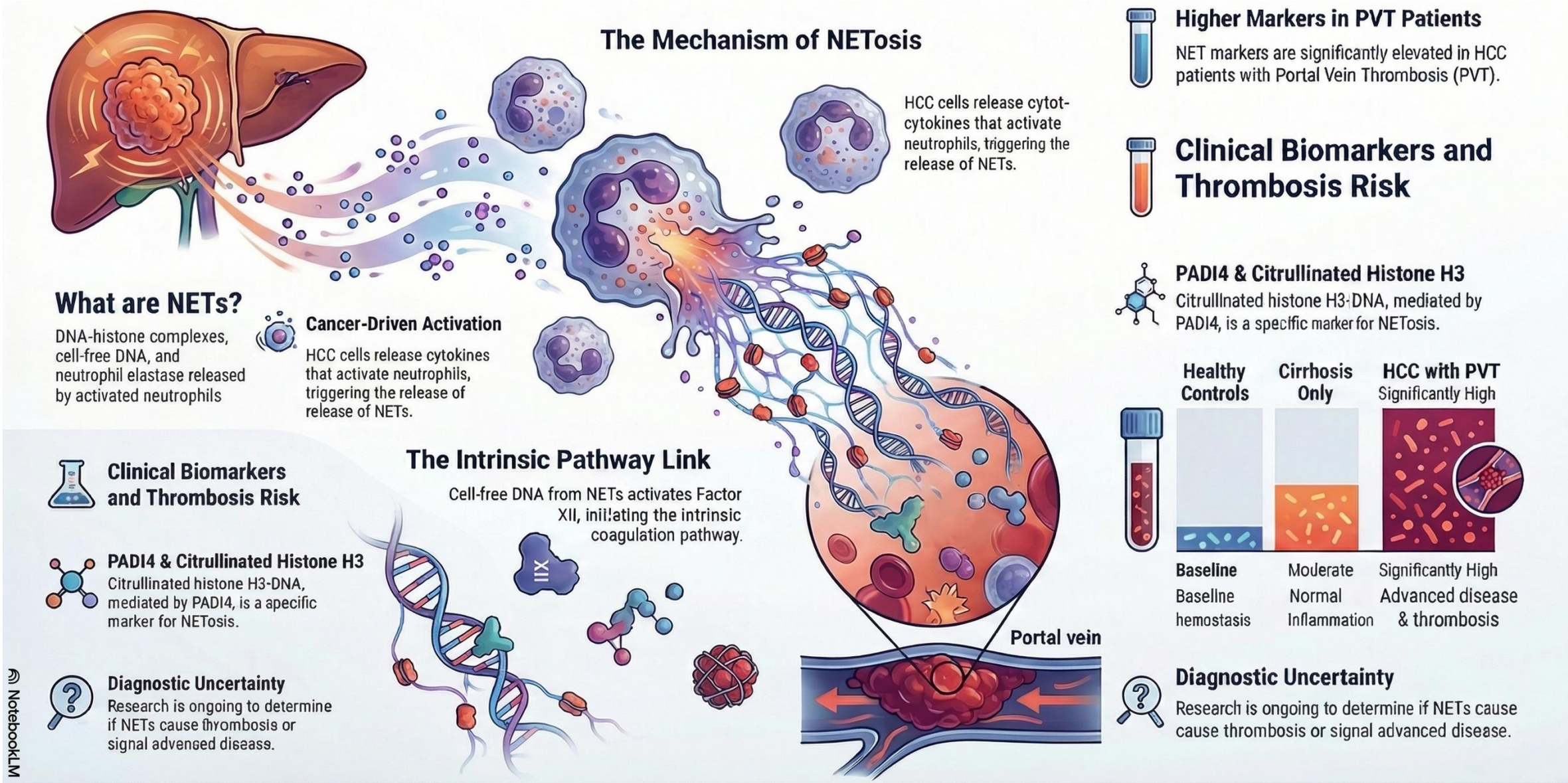
Campello, Thrombosis Research 2016, Hishada, Curr Opin Hematol 2019

# Pro inflammatory citokynes

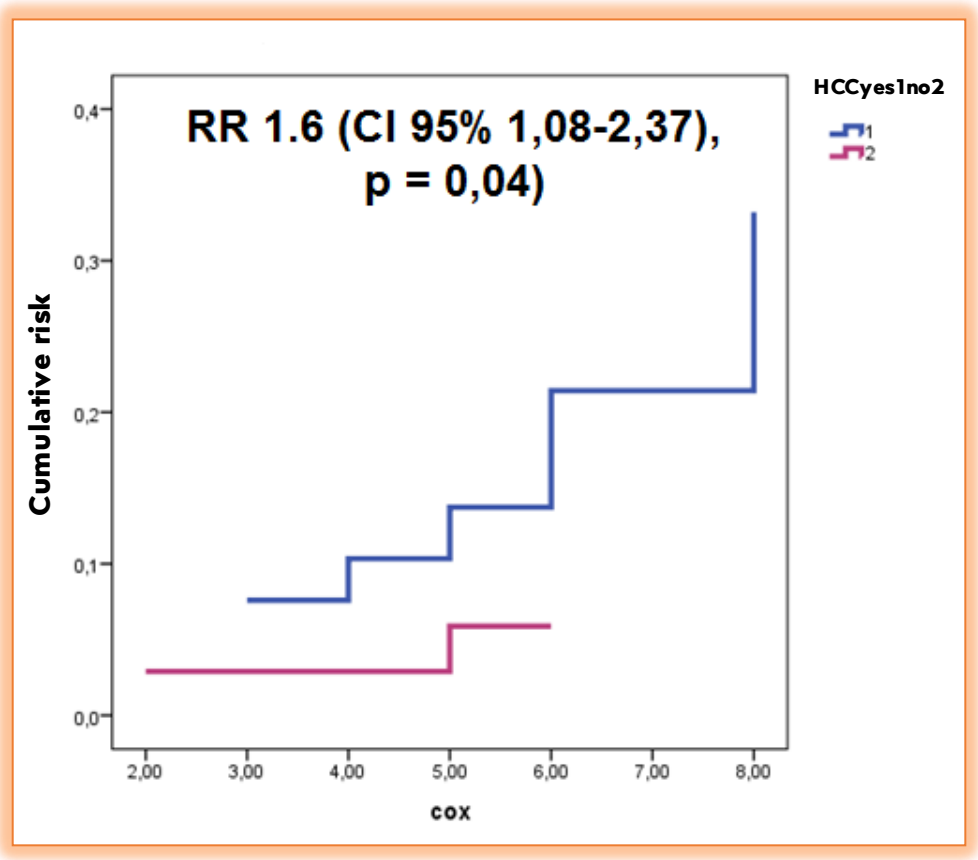
| Cytokine | Key Finding in HCC | Study Population | Clinical Significance |
|---|---|---|---|
| **IL-6** | Significantly elevated vs. controls; correlated with tumor stage, size, and Child-Pugh class | 192 HCC patients | Independent prognostic factor for OS; correlated with CRP (r = 0.667) |
| | Higher in HCC than cirrhosis/controls; activates STAT3 pathway | 144 HCC, 20 cirrhosis, 20 controls | Associated with poor survival via p-STAT3 activation |
| | Elevated in advanced HCC | 138 advanced HCC patients | High IL-6 associated with shorter OS (HR 1.79, P = 0.003) |
| | Pre-/post-radiotherapy levels measured | 60 HCC patients (phase II trial) | Post-RT IL-6 decrease associated with better PFS and OS with tislelizumab + anlotinib |
| **IL-8 (CXCL8)** | Independent prognostic factor | 555 HCC patients (prospective) | HR = 5.816 (P  0.001); incorporated into modified inflammation-based index |
| **IL-1β** | Significantly elevated vs. controls; inversely correlated with IL-12 | HCC, premalignant lesions, controls | Marker of immune dysregulation in hepatocarcinogenesis |
| **TNF-α** | Elevated pre- and postoperatively; higher in liver carcinoma than GI cancers | gruppen of surgical cancer patients | Postoperative TNF-α elevation associated with recurrence |
| **IL-10** | Elevated in HCC; associated with advanced features | 767 HCC patients (MD Anderson cohort) | High levels associated with worse OS and advanced clinicopathologic features |
| **IL-1R1, IL-15,, IL 16, IL-18, IL4** | Elevated in HCC | 767 HCC patients | Associated with advanced disease and inferior OS |
| **IL-4** | Elevated (Th2 shift) | HCC patients treated with TACE | Th2 dominance (↑IL-4, IL-10) associated with worse prognosis |
| **IFN-γ** | Decreased (Th1 suppression) | HCC patients treated with TACE | Post-TACE Th1 shift (↑IFN-γ/IL-10 ratio) associated with prolonged survival |
| **IL-2** | Included in peripheral blood inflammatory score (PBIS) | HCC patients on atezolizumab-bevacizumab | High PBIS (incorporating IL-2, IL-12, NLR, CRP) predicted poor OS, PFS, and ORR |
| **IL-12** | Decreased in HCC; inversely correlated with IL-1β | HCC, premalignant lesions, controls | Low IL-12 reflects impaired Th1 anti-tumor immunity |
| **CRP** | Elevated; downstream of IL-6/STAT3 | 192 HCC patients | Strongly correlated with IL-6; practical surrogate for systemic inflammation |

Jang, JW, Cytokines 2021, Chamnseddine, Oncology 2023, Beudeker, Cancers 2022, Zekri WJG 2018

# NET-Coagulation Axis



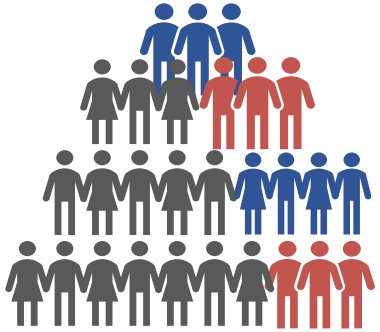
# Fibrinogen and HCC




| | HCC+PVT | HCC | p |
|---|---|---|---|
| MCF **FIB**TEM (mm) | 23,71±12,82 | 16,30±7,08 | 0,047 |
| AUC **FIB**TEM (mm) | 2359±1272,62 | 1535±640,20 | 0,022 |
| Fibrinogen (mg/dL) | 362±160,44 | 282,81±115,49 | 0,04 |

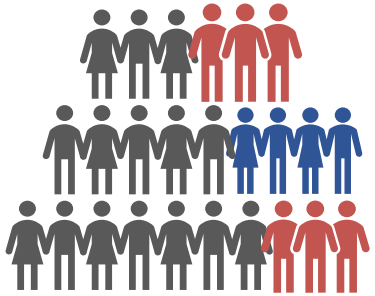
Zanetto, Liv Int 2017

# Risk factors for PVT in HCC



923 patients with cirrhosis and new HCC diagnosis
between January 2015 and December 2018

122 hepatic resection
3 transjugular portosystemic shunt
25 neoplastic PVT
15 chronic PVT
8 isolated thrombosis of SMV or SV



**750 patients with HCC listed for locoregional treament**

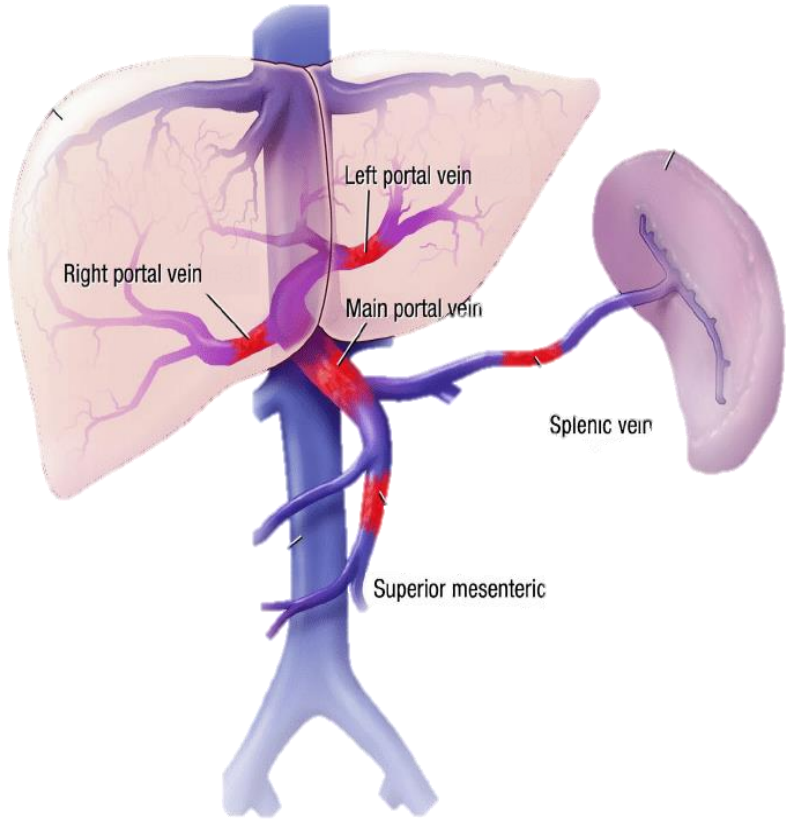
88 with PVT
at baseline

662 without PVT
at baseline

Senzolo et al. Hepatology 2024

# PVT extension


| | Partial | Complete | Total |
|---|---|---|---|
| MPV only | 20 | 4 | **24** |
| MPV + IHB | 8 | 3 | **11** |
| MPV + SMV | 17 | 2 | **19** |
| MPV + IHB + SMV | 4 | 5 | **9** |
| MPV + SMV + SV | 4 | 0 | **4** |
| MPV + IHB + SMV + SV | 4 | 1 | **5** |
| MPV + IHB + SV | 1 | 0 | **1** |
| IHB only | 11 | 4 | **15** |
| **Total** | **69** | **19** | **88** |

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# Risk factors for PVT in HCC

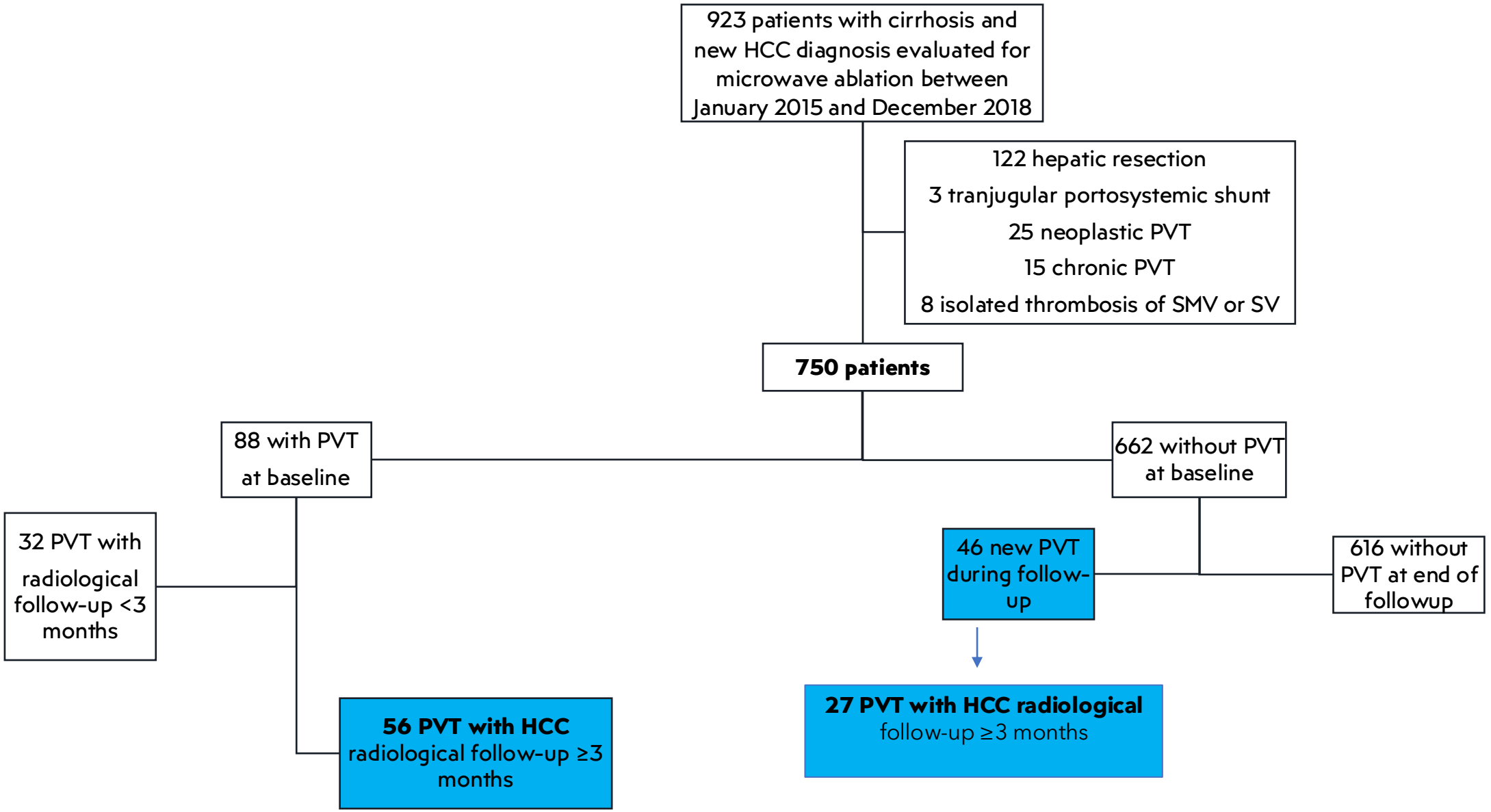
| | PVT number = 88 | No PVT number = 662 | p |
|---|---|---|---|
| **Age -** median ($q_3$- $q_1$) | 64 (59-69) | 67 (59-73) | NS |
| **Gender Female -** number (%) | 12 (14) | 100 (15) | NS |
| **Etiology of liver disease -** number (%): Viral/Alcoholic/N | | | NS |
| **Child-Pugh sco** A/B/C | | | **< .0001** |
| **MELD** - median | | | **< .0001** |
| **Clinically signif hypertesion** - number (%) | 78 (89) | 352 (53) | **< .0001** |
| **Total tumor volume** ($cm^3$) - median ($q_1$- $q_3$) | 16 (5.6-44) | 9.2 (4.2-22.9) | **.002** |
| **AFP (ng/ml)** - median ($q_1$- $q_3$) | 16.3 (5.9-275.3) | 5.9 (3.3-18.2) | **.058** |

**Multivariate analysis**

TTV (OR 1.2, p<.0001)

CSPH (OR 2.9, p=.007)

# Natural history of non-neoplastic Portal Vein Thrombosis in HCC

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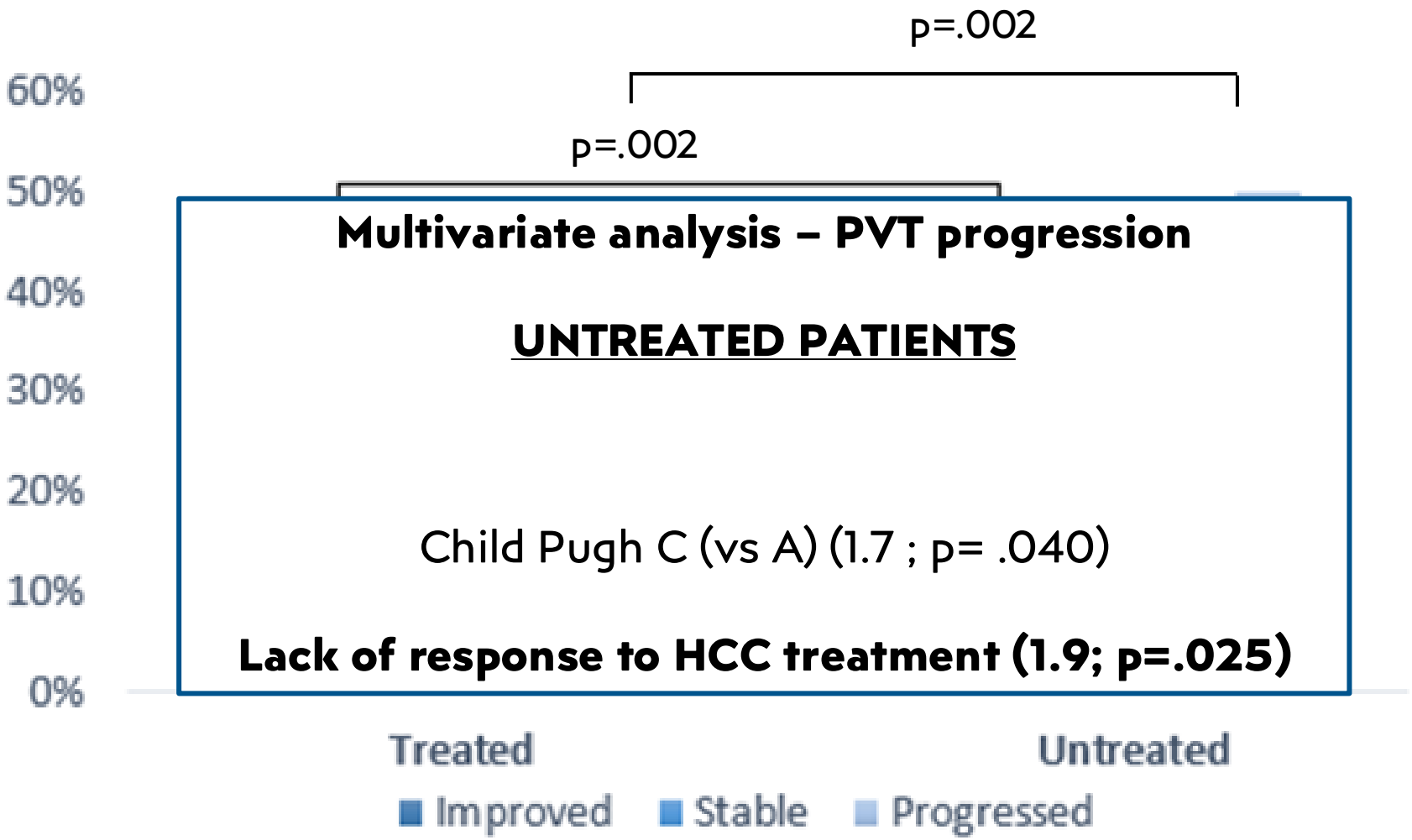
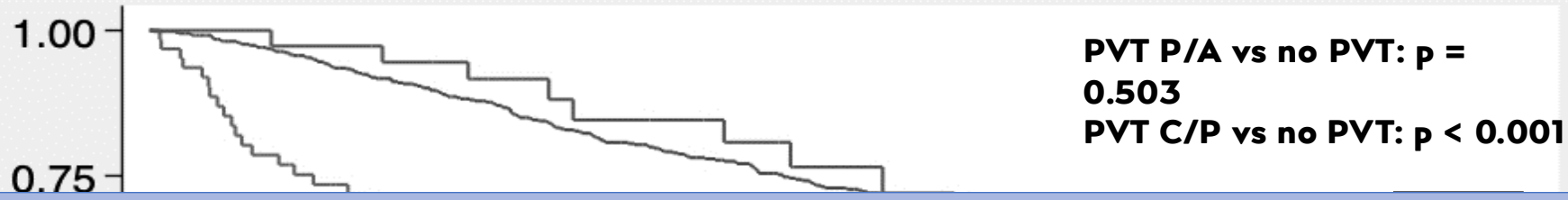
# Natural history of untreated PVT in HCC



# Survival analysis – PVT evolution




## Multivariate analysis

**Complete/progressive PVT vs no PVT** (HR 3.41, 95%CI 2.46-4.71, p= <.0001)

Child-Pugh score B/C vs A (HR 1.89, 95%CI 1.47-2.43, p= <.0001)

AFP (HR 1.24, 95%CI 1.1-1.39, p= <.0001)

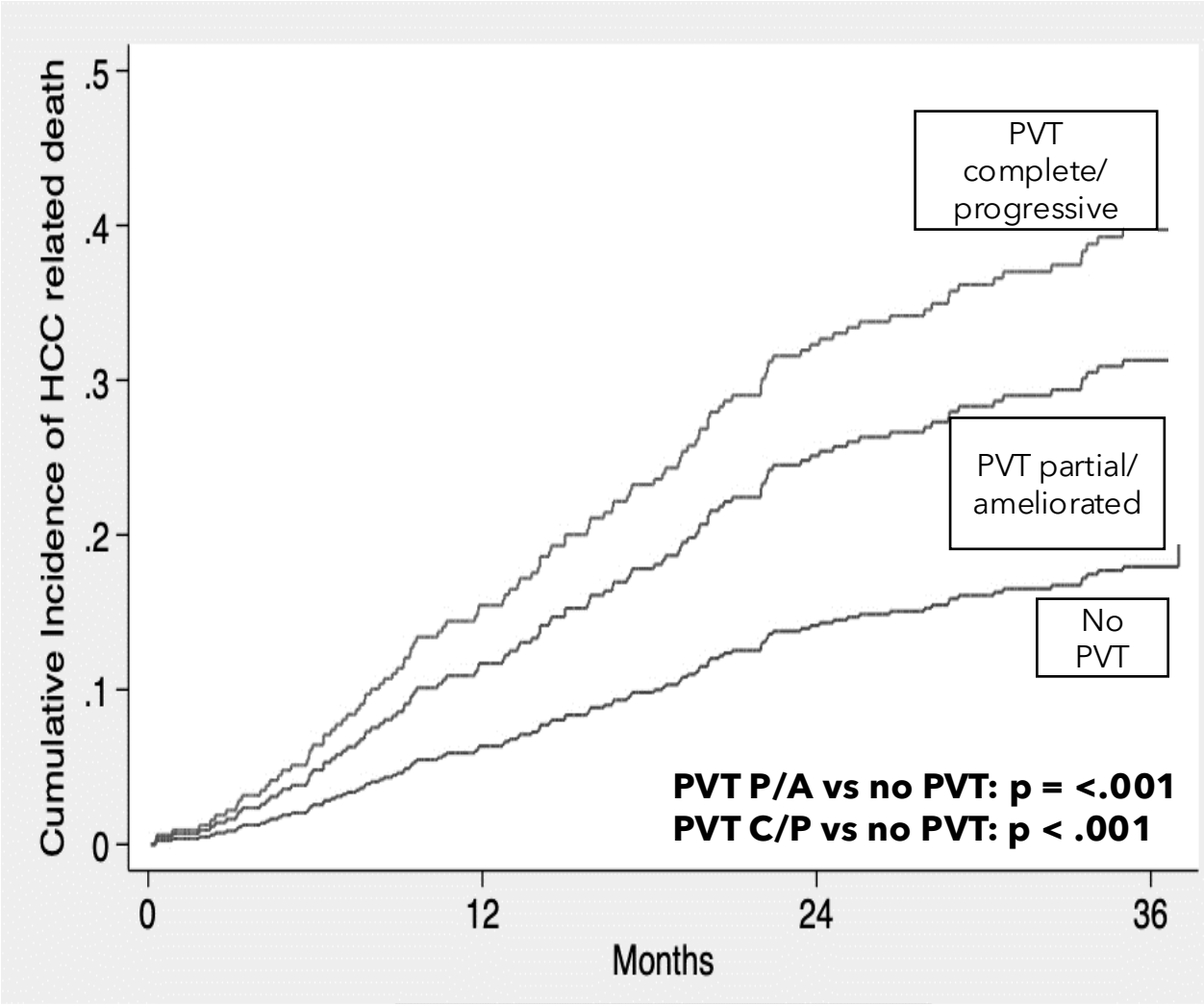
TTV at PVT diagnosis (HR 1.14, 95%CI 1.09-1.2, p= <.0001)

Number of nodules at PVT diagnosis (HR 1.23, 95%CI 1.1-1.39, p= <.0001)

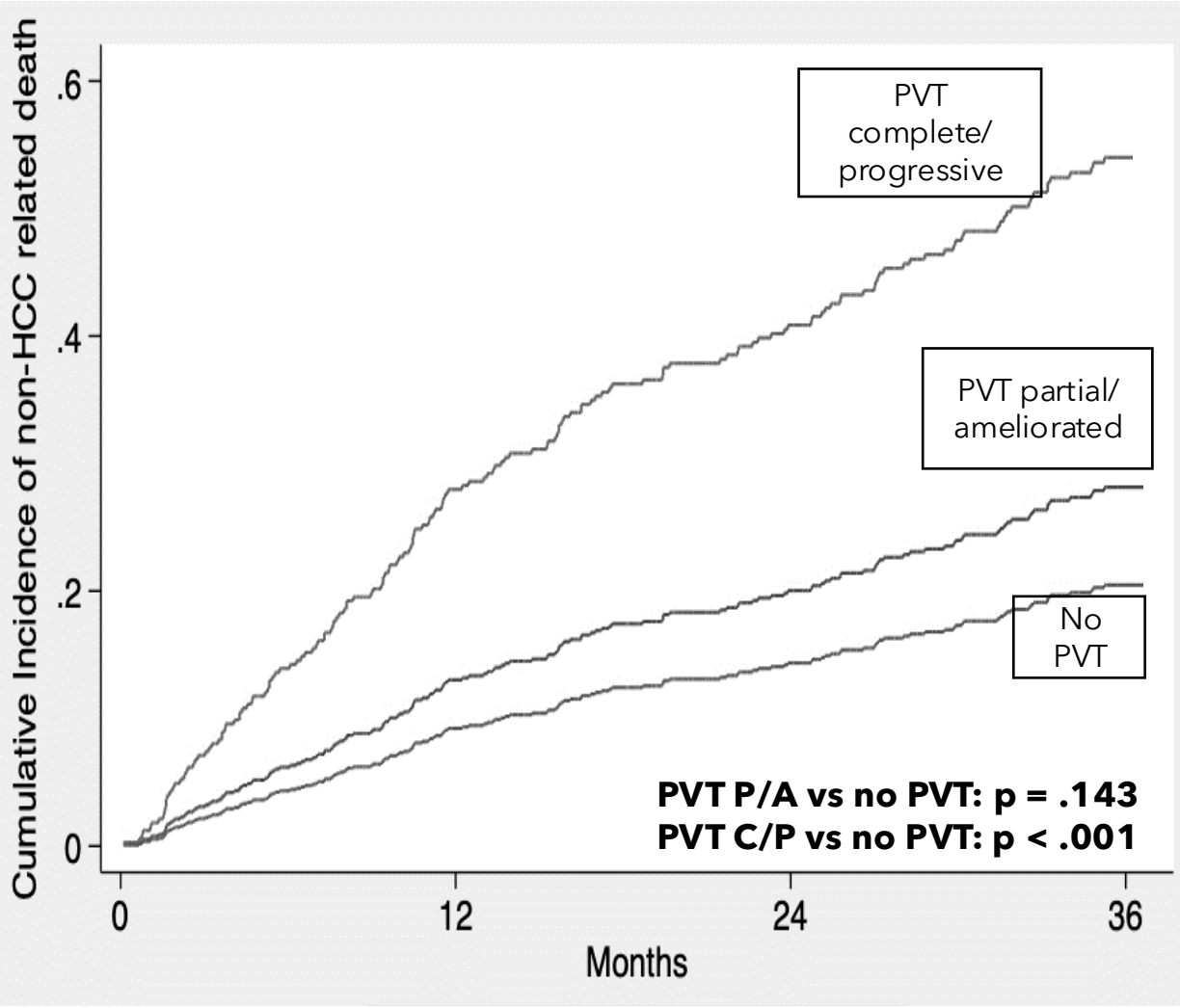
| Number at ris | | | | |
|---|---|---|---|---|
| **No PVT:** | | | | |
| **PVT Partial/Ameliorated:** | 65 | 26 | 13 | 2 |
| **PVT Complete/Progressive:** | 37 | 24 | 13 | 4 |

# Cumulative HCC and non-HCC related mortality – PVT evolution

**A)**




**B)**



# Thromboprophylaxys of Cancer Associated Thrombosis (CAT)- non cirrhosis

- Extending post-surgical prophylaxis to up to 4 weeks in patients who have undergone high-risk abdominal or pelvic surgery, again on the basis of randomized trials
- In in-patients, Khorana score of ≥2 is predictive of VTE
- Initial studies addressing this issue used LMWH in a population of patients with various solid tumours but without risk stratification
- The CASSINI and AVERT trials led to guideline recommendations, with consideration of primary outpatient prophylaxis with low dose rivaroxaban, apixaban

Khorana score

| Patient characteristics | | Risk score |
|---|---|---|
| Site of cancer | Very high risk (stomach and pancreas cancers) | 2 |
| | High risk (lung, lymphoma, gynaecological, bladder and testicular cancers) | 1 |
| Pre-chemotherapy platelet count ≥350×10⁹/l | | 1 |
| Haemoglobin level <10 mg/ml or use of red blood cell growth factors | | 1 |
| Pre-chemotherapy leukocyte count >11×10⁹/l | | 1 |
| BMI ≥35 kg/m² | | 1 |

Lyman, G. H, Blood Adv 2021

# Thromboprophylaxys of Cancer Associated Thrombosis (CAT)- non cirrhosis

The **NCCN** classifies **liver cancer as a "high thrombotic risk" malignancy** alongside pancreatic, biliary, lung, stomach, brain, and esophageal cancers

Other Specific risk factors

- **Advanced tumor stage and large tumor burden** — multinodular HCC and total tumor volume >3 $cm^3$ are particularly high-risk

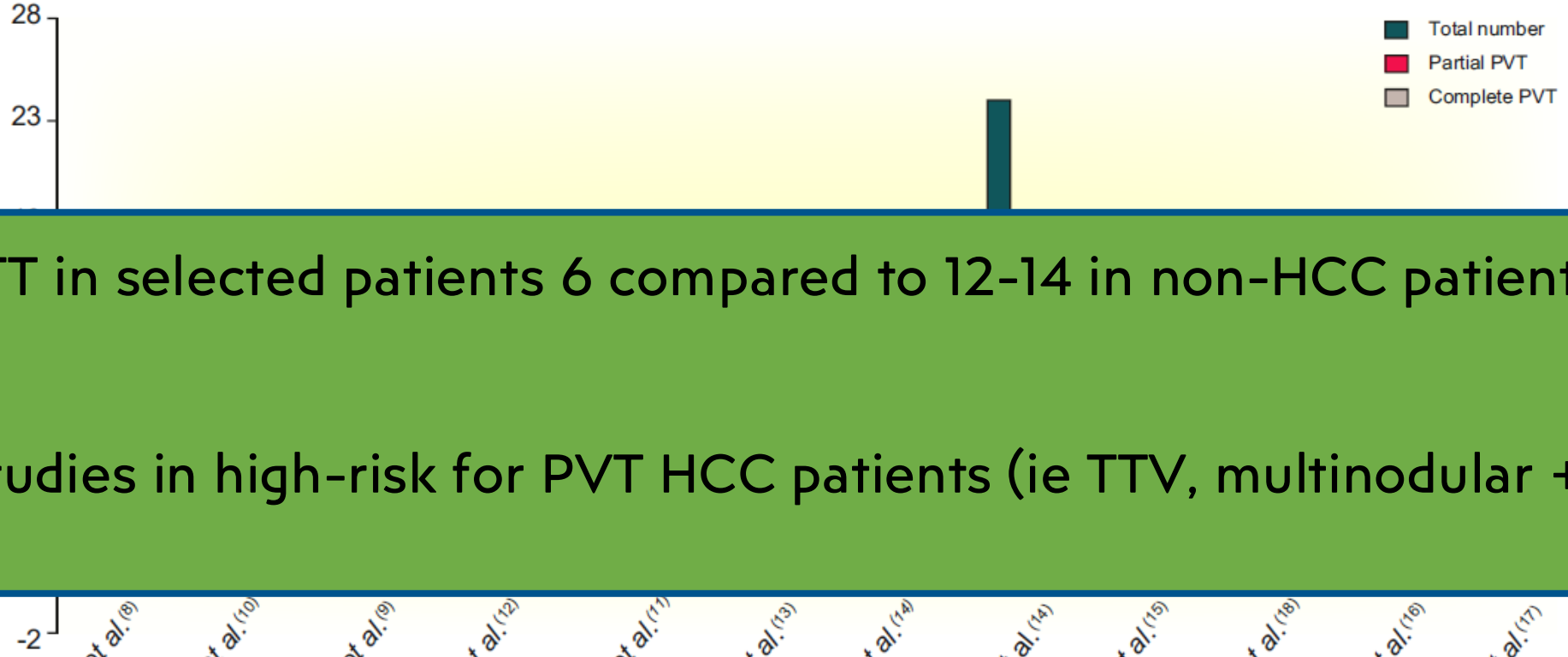
- **Higher Child-Turcotte-Pugh (CTP) class** reflecting more severe liver dysfunction [3]

- **Elevated serum AFP**

- **Low serum albumin**

- **Clinically significant portal hypertension**

# Thromboprophylaxys for HCC associated non-neoplastic PVT ?




| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patients (N) | 100 | 243 | 150 | 1,243 | 95 | 36 | 35 | 41 | 109 | 108 | 241 | 320 |
| Child-Pugh C (%) | 5 | NA | 12 | 0 | 30.5 | 11 | 25.7 | 22 | 0 | 4.6 | 10.8 | 6 |
| HCC (%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 100 | 0 | 0 | 0 | 0 |

NTT in selected patients 6 compared to 12-14 in non-HCC patients

Future studies in high-risk for PVT HCC patients (ie TTV, multinodular + CSPH)

Senzolo, J Hepatol 2021

# American Society of Hematology 2021 guidelines for management of VTE : prevention and treatment in patients with cancer

**BAVENO VIII**

Anticoagulation should be considered in patients with (i) recent partial (<50% remnant lumen) or complete thrombosis of the main portal vein (LoE3, strong), (ii) symptomatic PVT, independently of the extension (LoE3, strong), (iii) nontumoral PVT and HCC, especially in those with indication for locoregional therapy (LoE3, weak) **(changed)**

**CONSIDERATIONS IN CAT (PVT) IN HCC+CIRRHOSIS**

Progression of PVT seems to be higher than without HCC

HCC persistence/recidivism influence progression of PVT without AC

PVT could influence the natural history of the liver/HCC disease

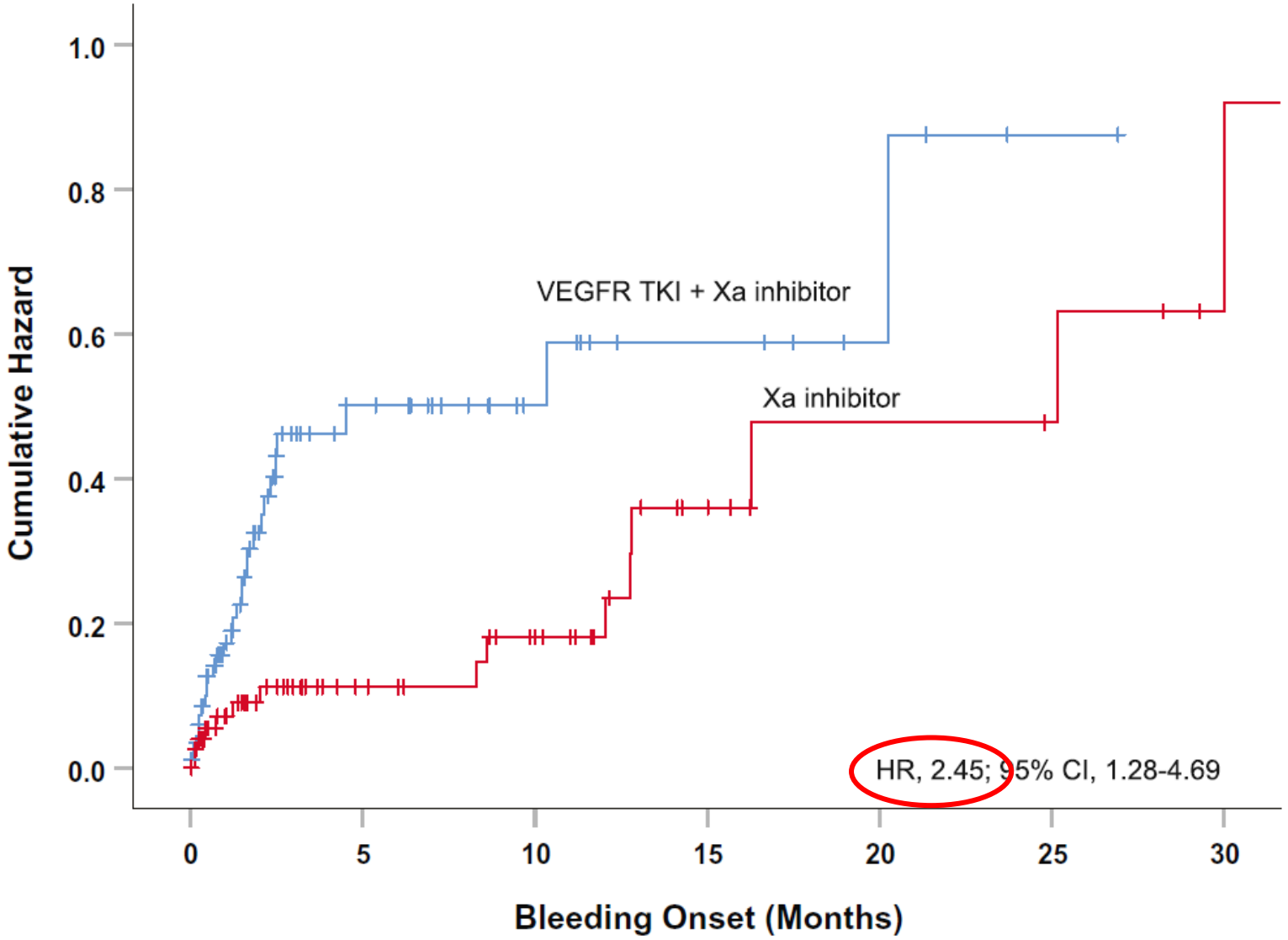
<u>Consideration for early treatment in all PVT with full AC dose</u>

Gary H. Lyman, Blood Advances 2021

# Caution with the risk of drugs interaction with AC

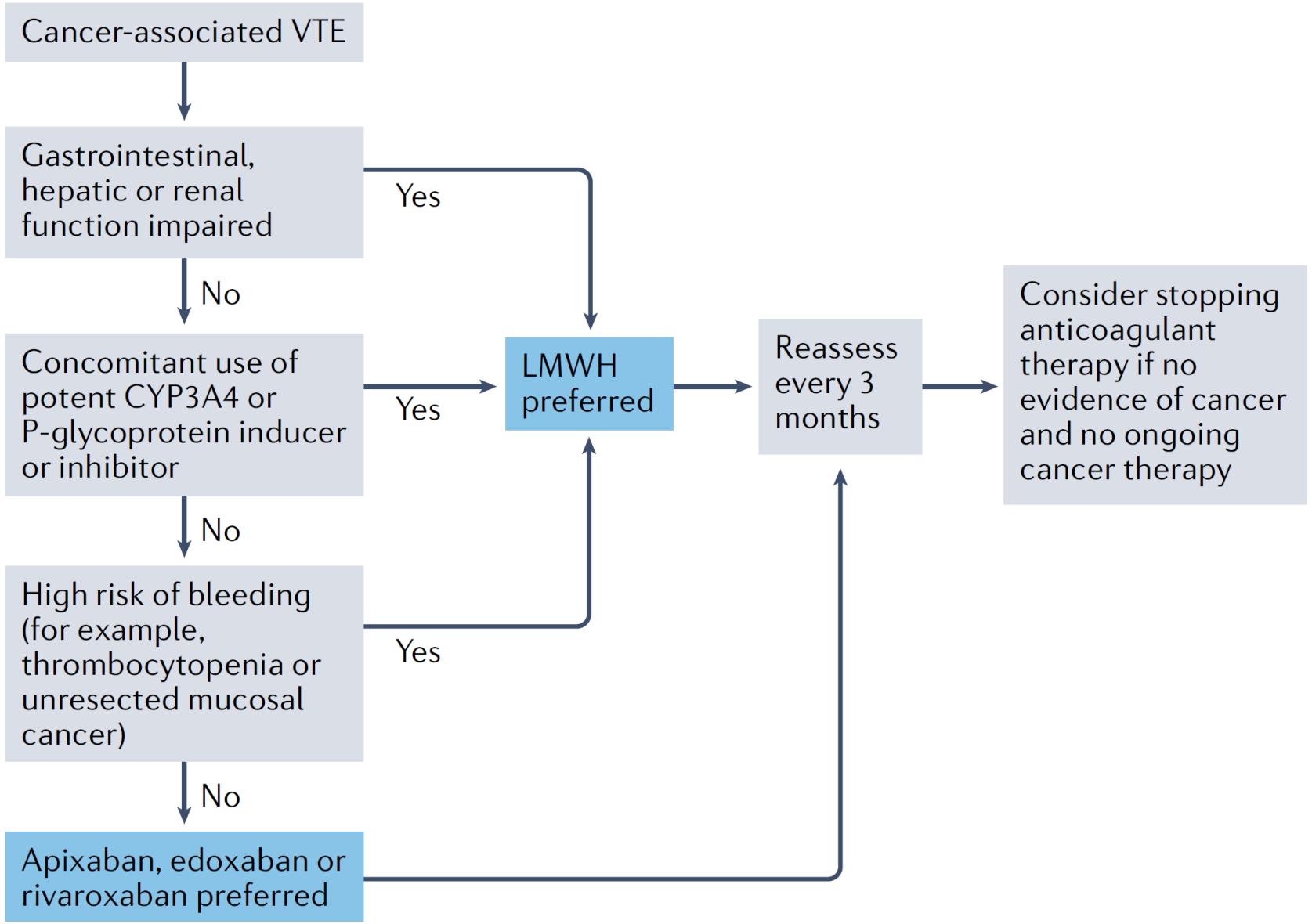
| | Anticoagulant Target | Protein Binding | Metabolism | Efflux Protein | Inducer/inhibitor of CYP/P-gp |
|---|---|---|---|---|---|
| **LMWH** | AntiXa/Antilla | - | Desulfation and depolymerisation | - | No |
| **Rivaroxaban** | AntiXa | 95% | CYP3A4/3A5/2J2 | P-gp, BCRP | No |
| **Apixaban** | AntiXa | 87% | CYP3A4/3A5 | P-gp, BCRP | No |
| **Edoxaban** | AntiXa | 42-59% | CYP3A4 | P-gp, BCRP | No |

# Bleeding risk with AC during concomitant TKI therapy



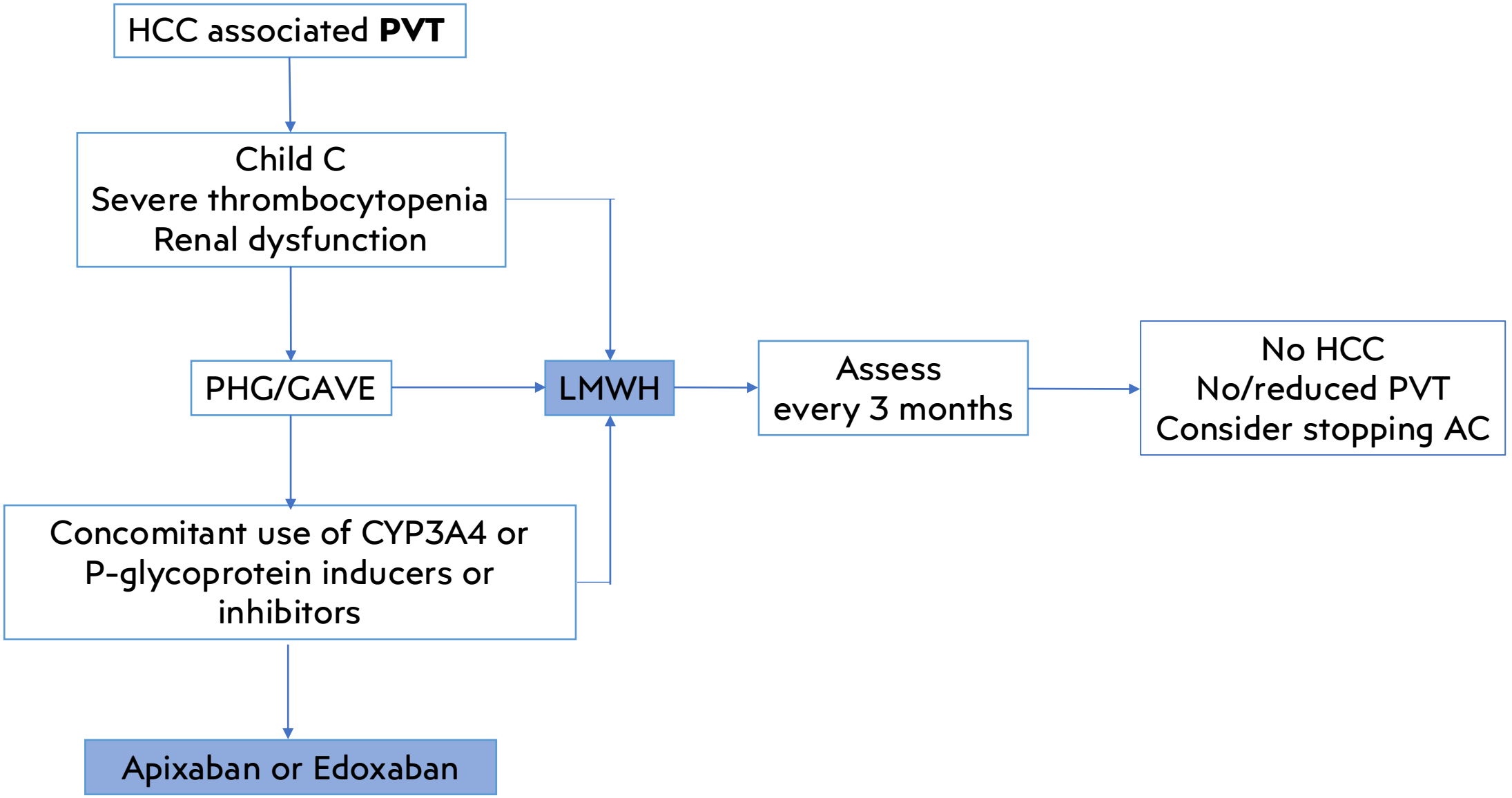

Patel, Cancer 2021

# Algorythm of AC for Cancer Associated Thrombosis (CAT)

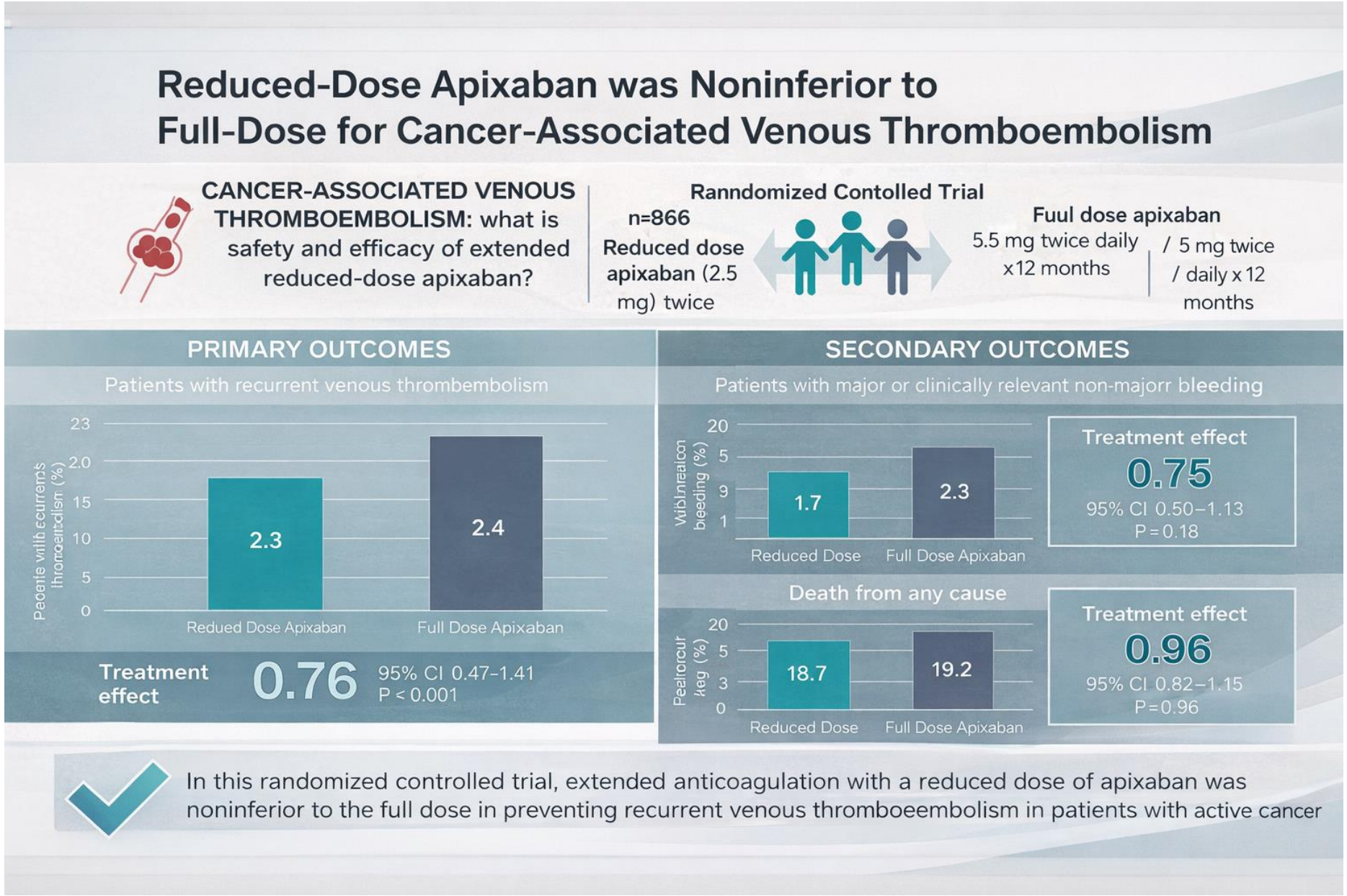



Lyman, G. H, Blood Adv 2021

# Possible Algorythm of AC for PVT in HCC



# Full-dose versus reduced-dose Apixaban for CAT




Mahè, NEJM 2025

# CONCLUSIONS

- HCC causes a prothrombotic microenvironment which nduces a shift in hemostasis in cirrhotic patients
- It constitutes an independent risk factor for the occurrence of PVT in patients with cirrhosis correlated with its biological activity
- PVT in HCC patients seems to have a different natural history and influence in survival compared to non-HCC cirrhotics
- Anticoagulation should be promptly considered in all patients
- Type of anticoagulation could be evaluated on the basis of liver function, risk of GI bleeding and concomitant anti-neoplastic drugs, preferring DOACs when possible
- Future study should aim to evaluate thromboprophylaxis in high-risk patients