VALDIG
VASCULAR LIVER DISEASE GROUP

PARIS PORTAL VEIN THROMBOSIS MEETING

# WHEN AND HOW TO TREAT PVT IN A PATIENT WITH SIMULTANEOUS HCC (EXCLUDING PV INVASION)

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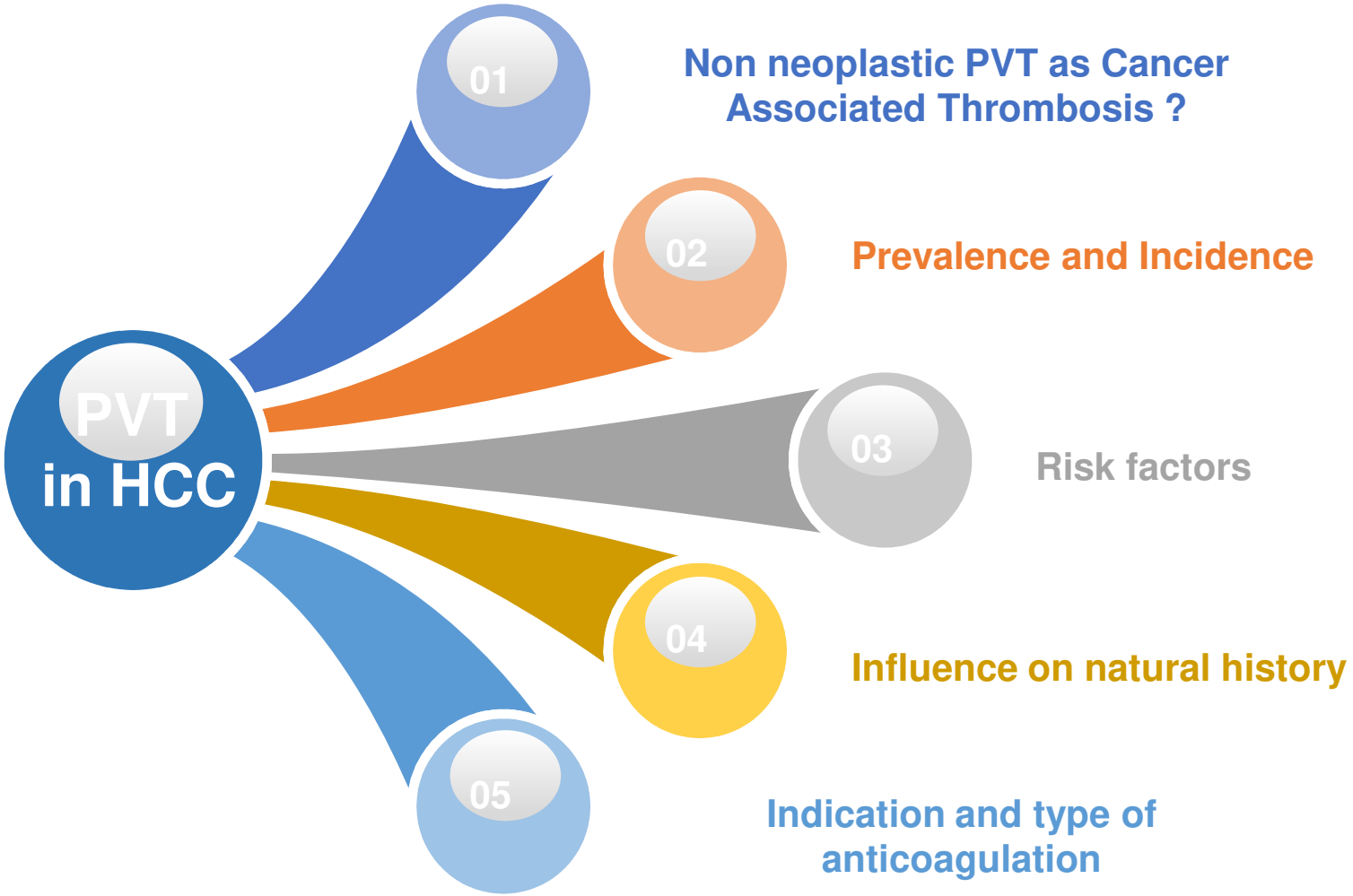
# OUTLINE

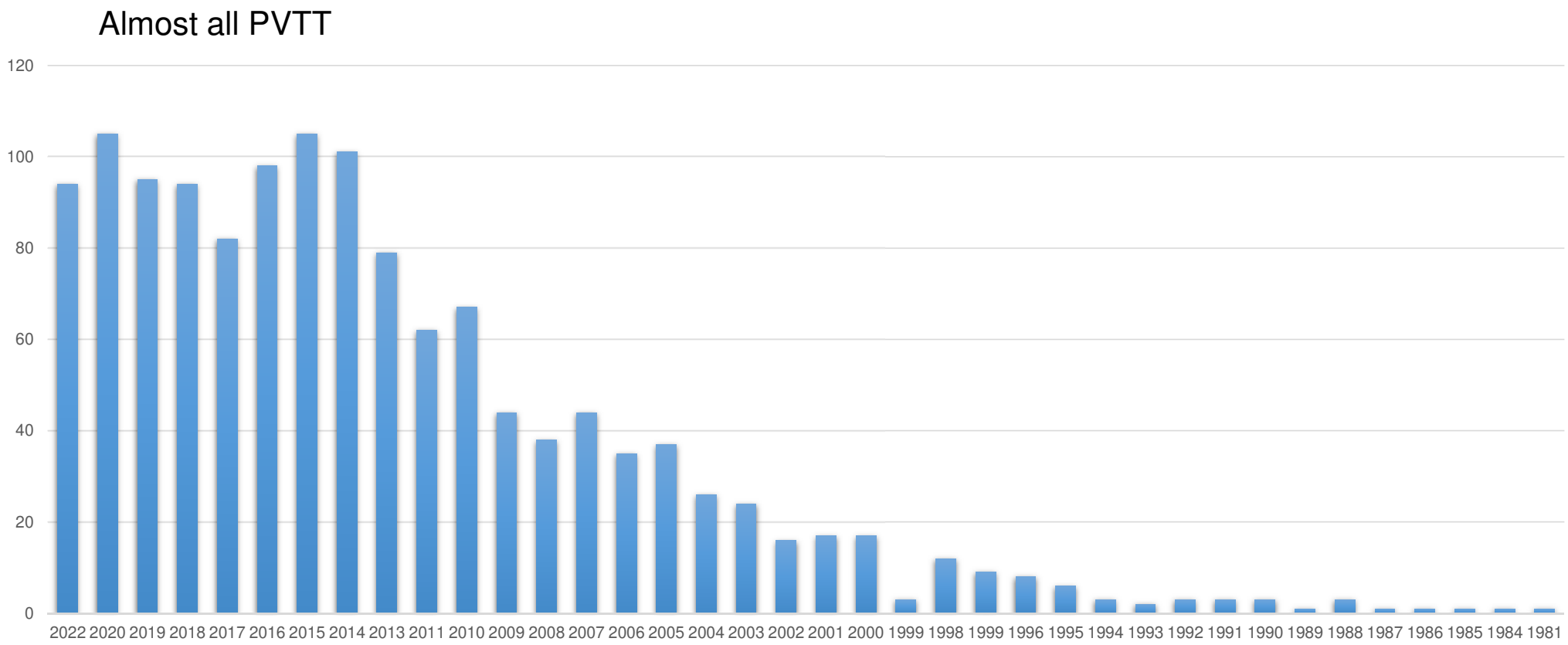

PVT
in HCC
01
Non neoplastic PVT as Cancer Associated Thrombosis ?
02
Prevalence and Incidence
03
Risk factors
04
Influence on natural history
05
Indication and type of anticoagulation

# 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

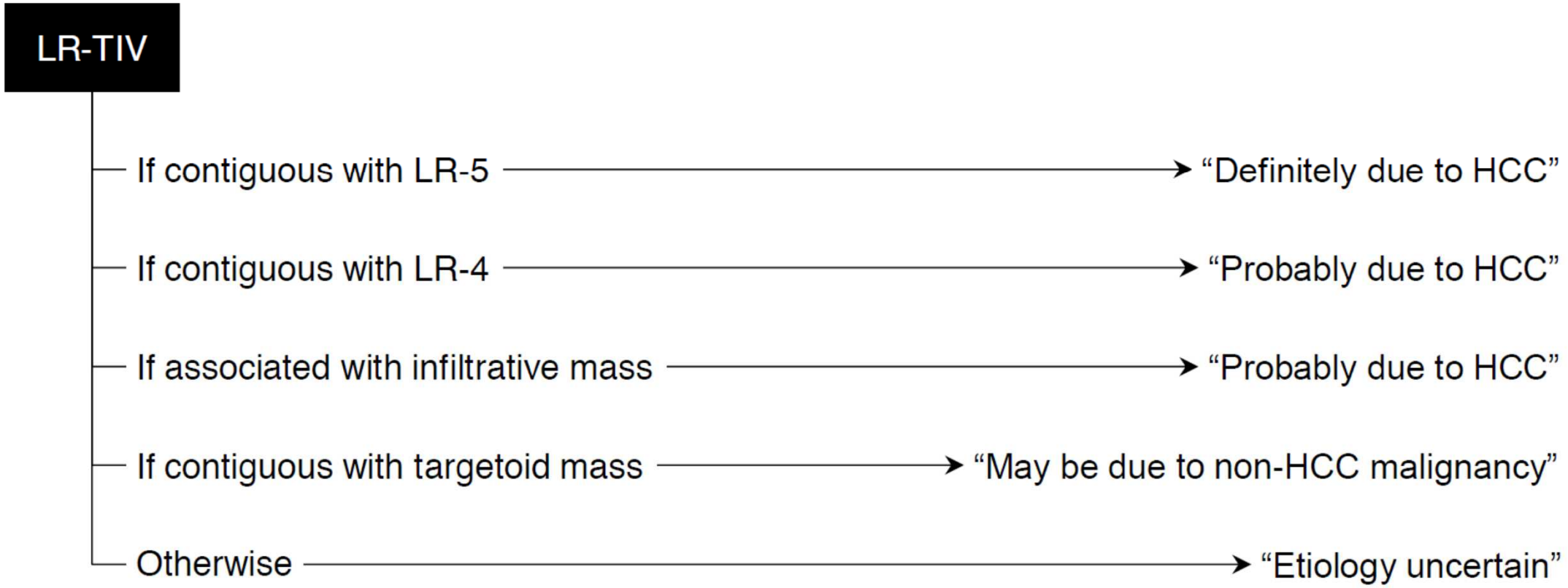
# CAT (PVT) in Cirrhosis with HCC: Highly Overlooked!



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

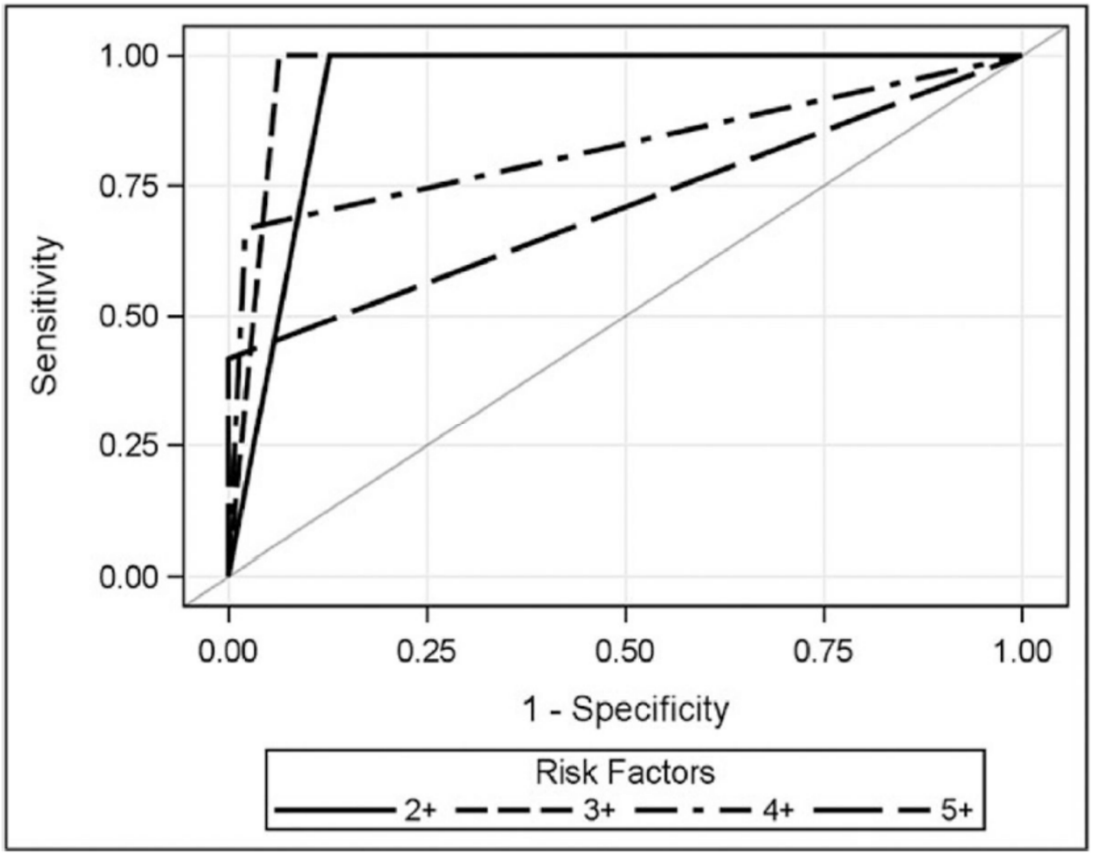
- Imaging features that suggest tumor in vein but do NOT establish its presence are listed below:
  - Occluded vein with ill-defined walls
  - Occluded vein with restricted diffusion
  - Occluded or obscured vein in contiguity with malignant parenchymal mass
  - Heterogeneous vein enhancement not attributable 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

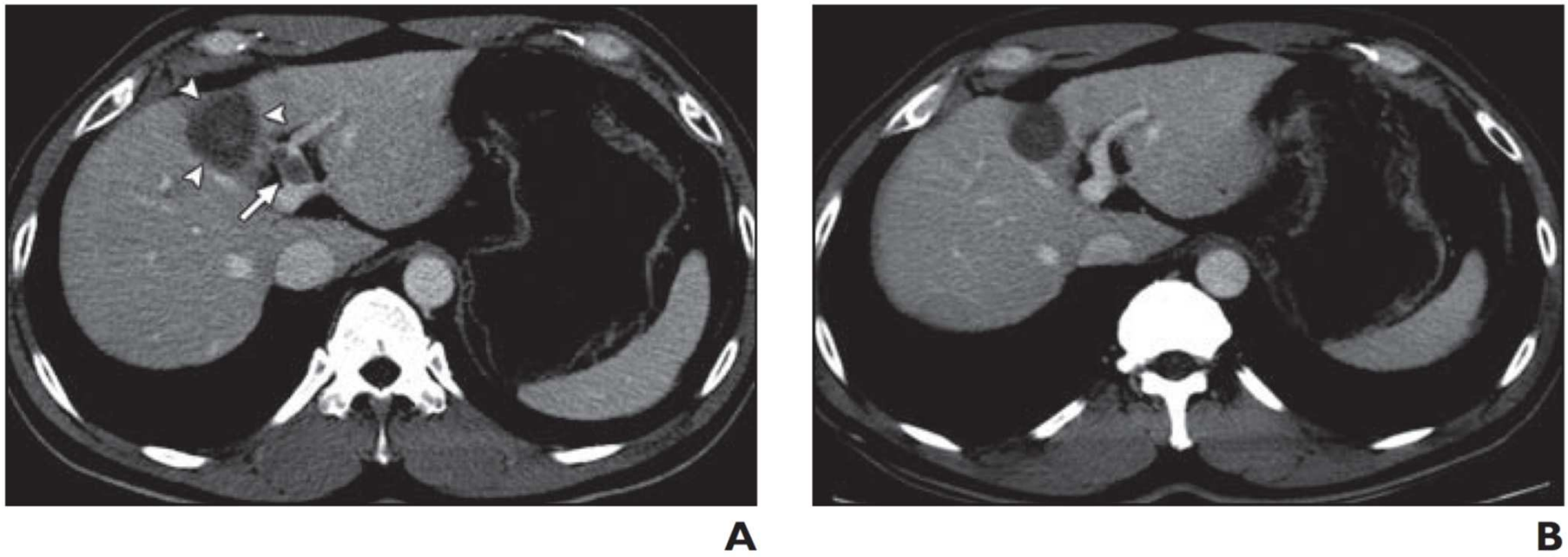
80% PPV, and 100% NPV

Sherman, Liver Transplant 2019

# Distinguish procedural related PVT

1%-3% incidence of local venous thrombosis

Spontaneous amelioration/repermeation in 70%



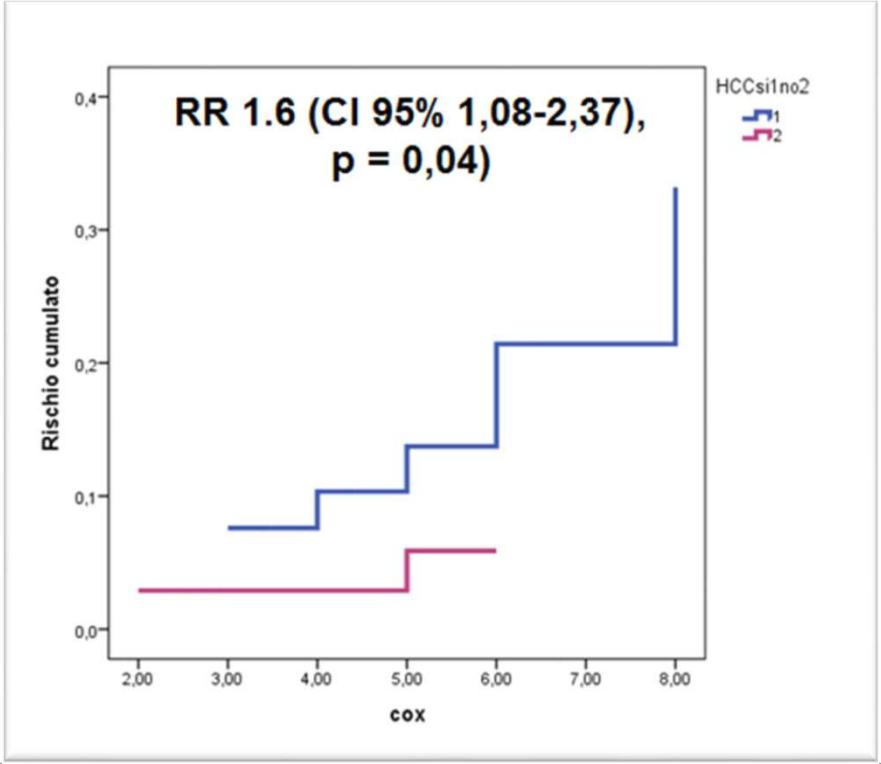

Kim, Vascular Intervent Radiology 2010

# 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; Grasso, DLD 2021

# Incidence of Non-neoplastic Portal Vein Thrombosis in HCC



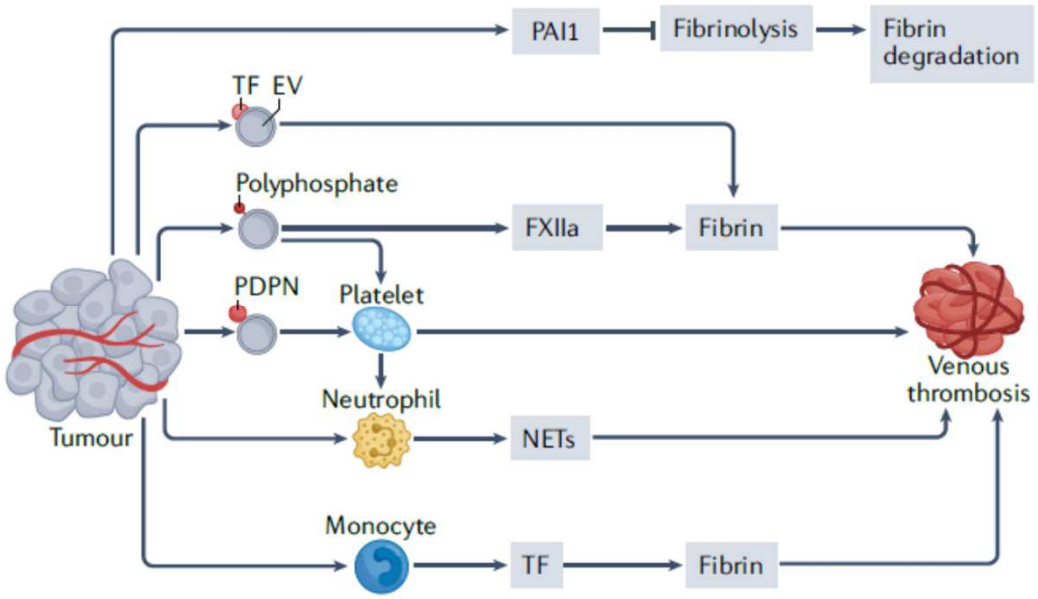

| Child Class (n) | Number of PVT during follow-up | PVT/cirrhotics with HCC | PVT/cirrhotics without HCC | Total |
|---|---|---|---|---|
| A | 29 | 5/20 [25%] | 0/9 [0%] | 5/29 [17.2%] |
| B | 29 | 3/12 [25%] | 1/17 [5.9%] | 4/29 [13.8%] |
| C | 18 | 2/9 [22.2%] | 3/9 [33.3%] | 5/18 [27.8%] |
| Total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

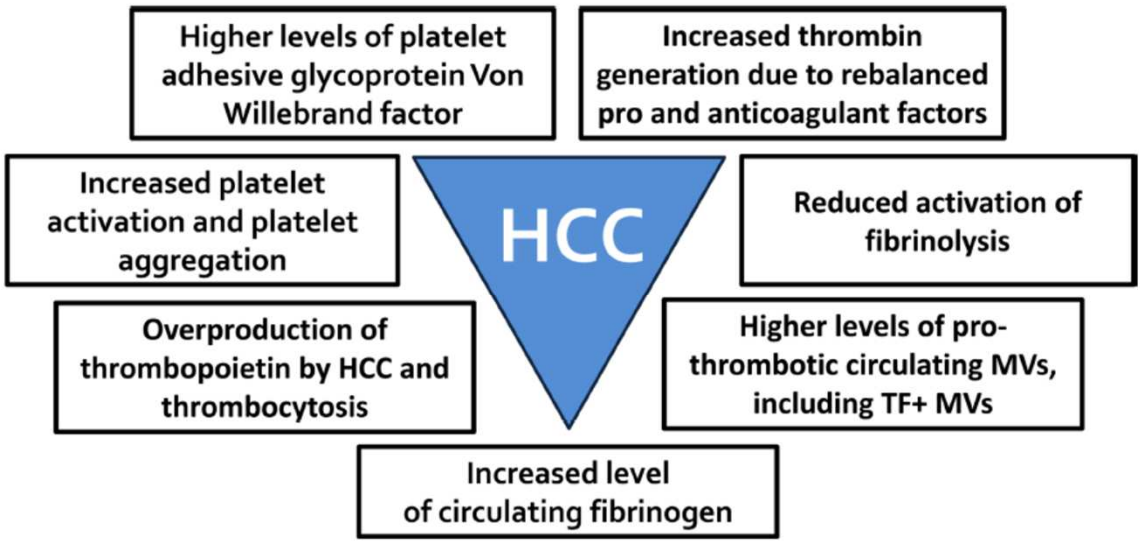
Zanetto, Liv Int 2017

# 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

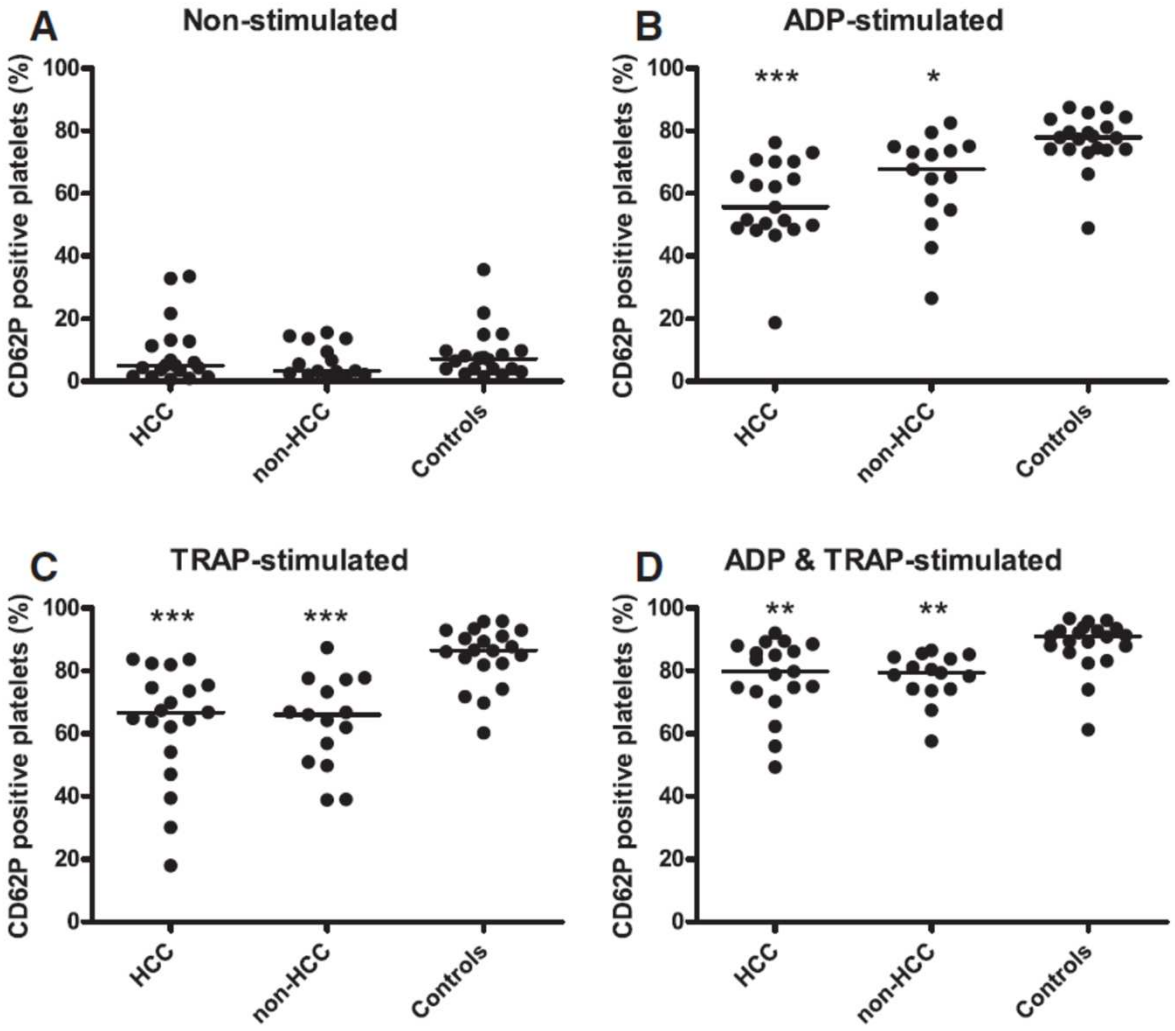
# Tumour-related pro-thrombotic changes



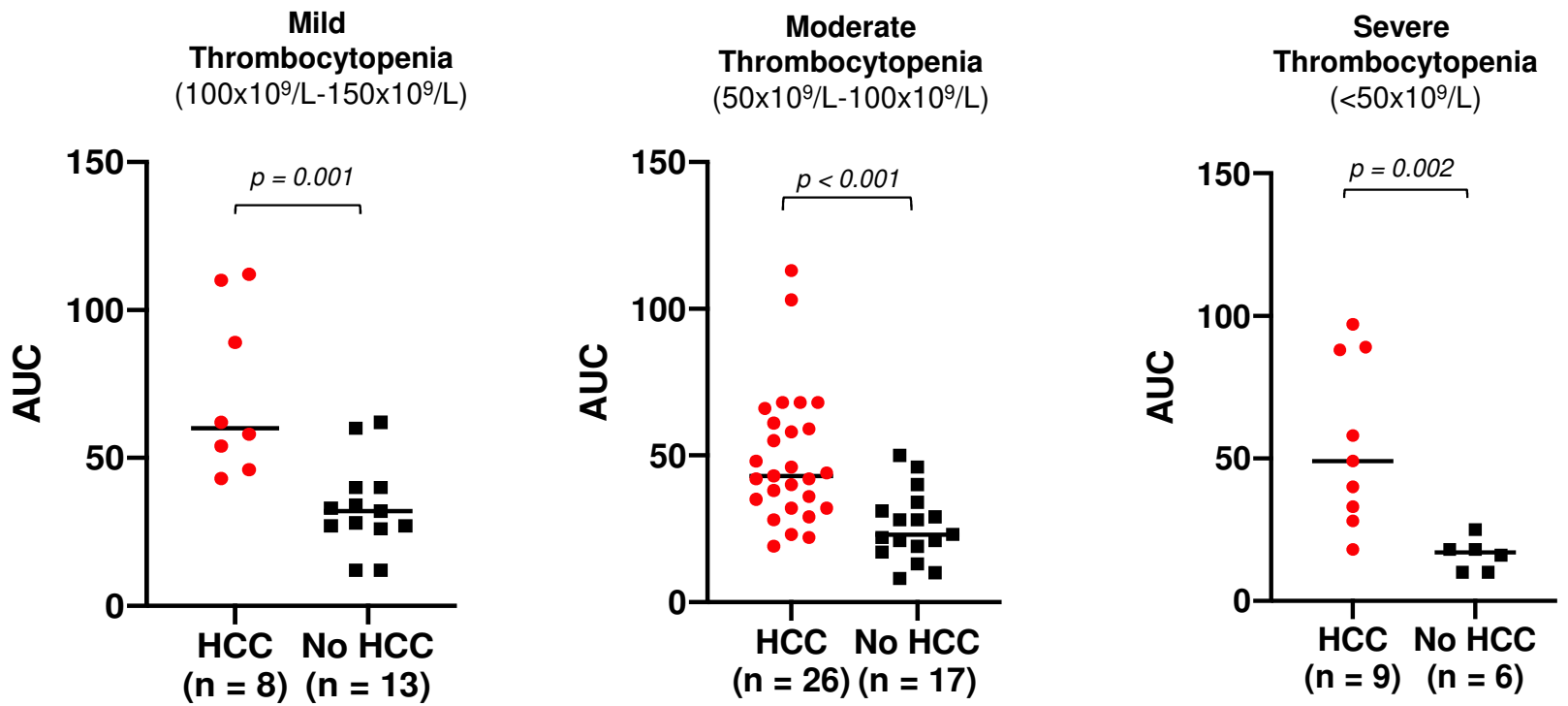

Khorana, DISEASE PRIMERS 2022; Zanetto, Liv Int 2022

# Platelets' activation in HCC



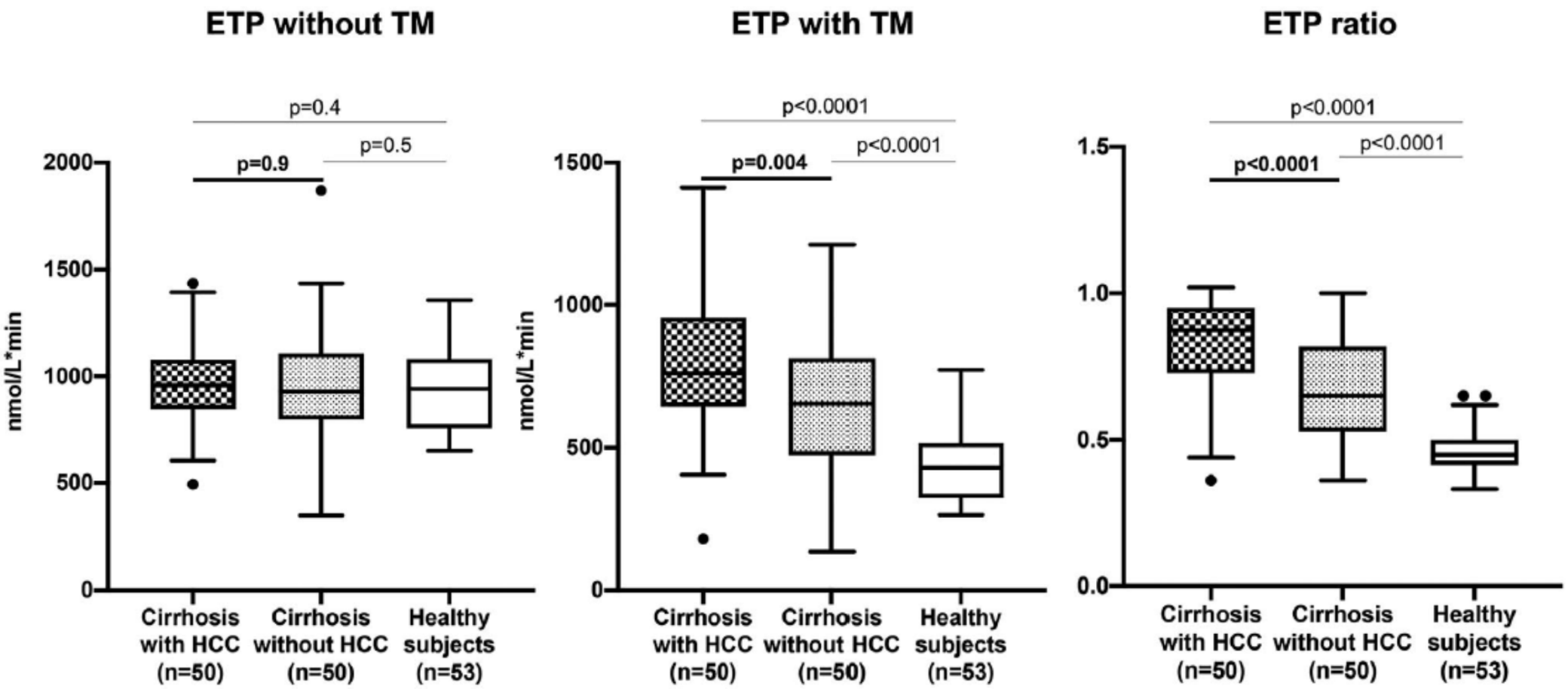

Alkozai, Thrombosis Research 2015

# Platelets' aggregation in HCC



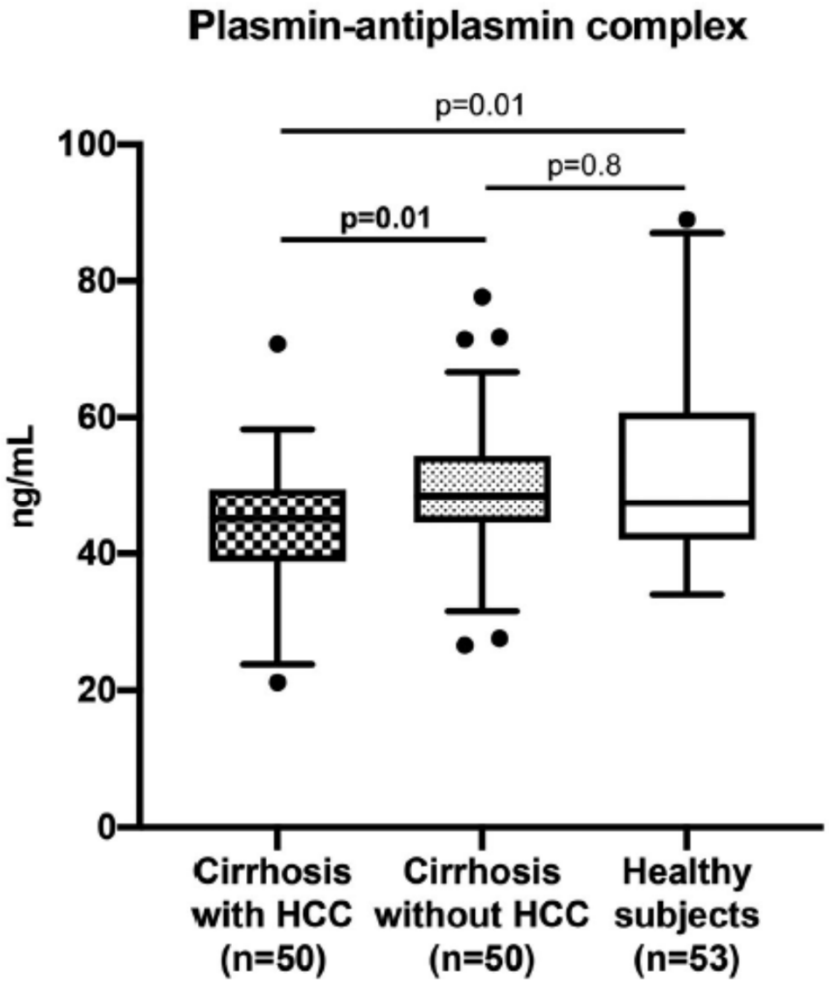

*ADP-induced aggregation

# Thrombin Generation in HCC

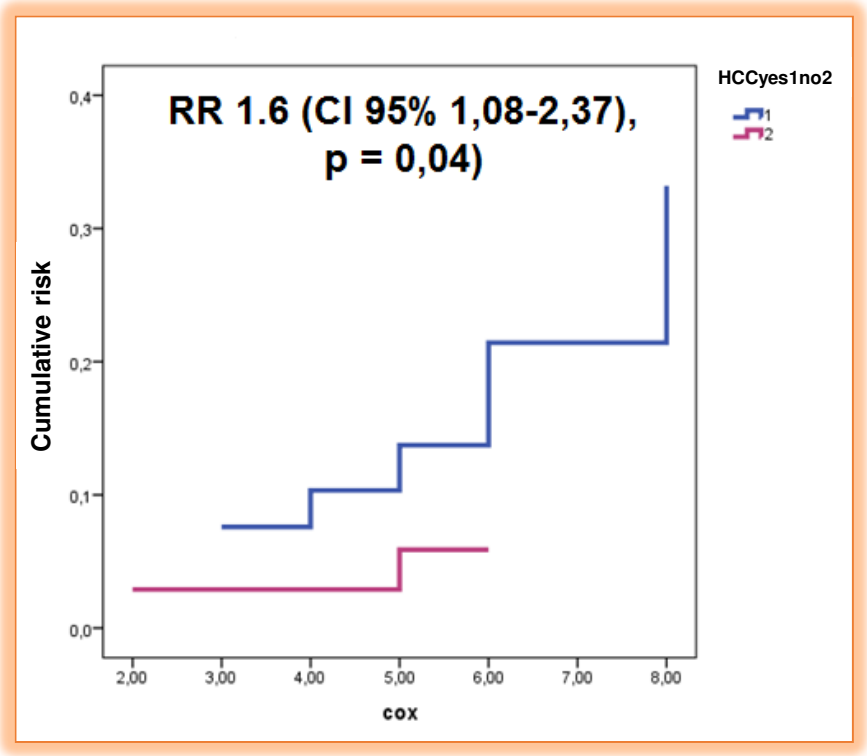



Zanetto, Hepatology Communications 2021

# Fibrinolysis in HCC



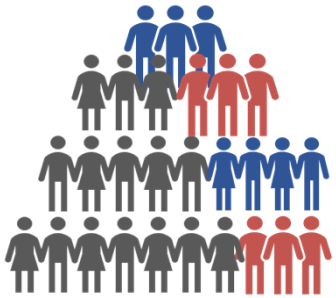
# Fibrinogen and HCC




| | 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 |

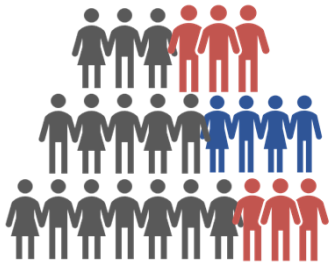
Zanetto, Liv Int 2017

# 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**

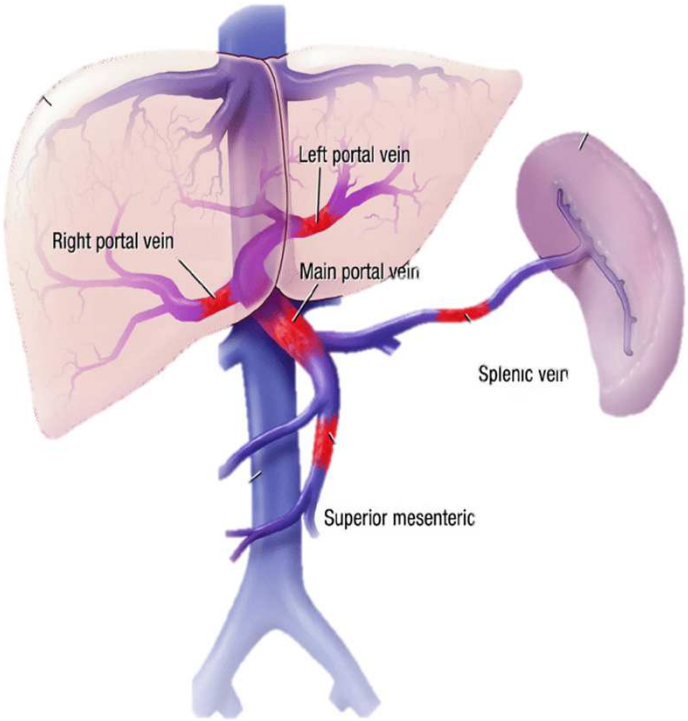
88 with PVT at baseline

662 without PVT at baseline

Senzolo et al. manuscript in preparation

# 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** |



# Risk factors for PVT in HCC

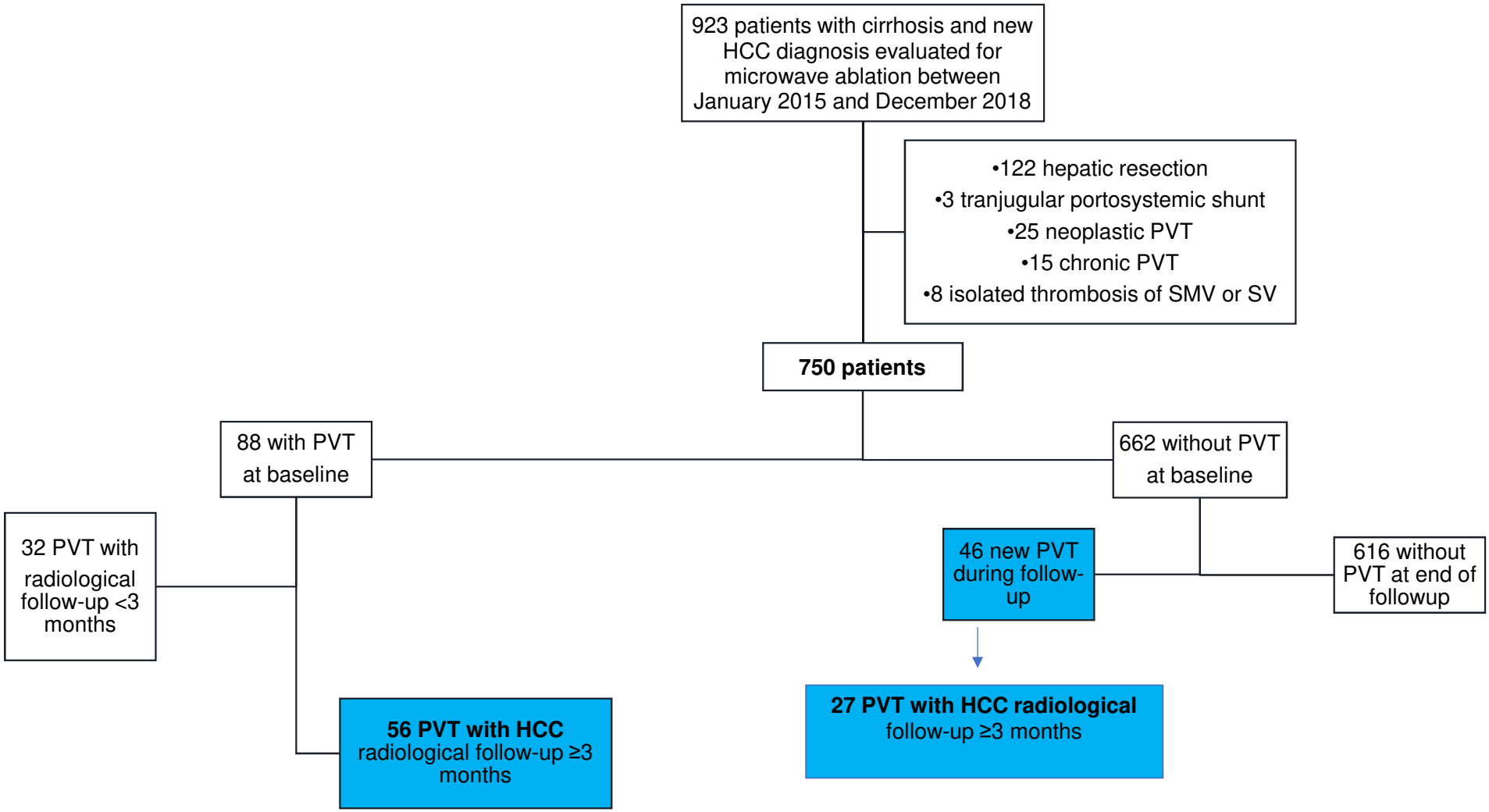
| | PVT number = 88 | No PVT number = 662 | p |
|---|---|---|---|
| **Age -** median ($q_3$- $q_1$) | 64 (59-69) | 67 (59-73) | NS |
| **Gender Female -** number (%) | 12 (14) | 100 (15) | NS |
| **Etiology of l** number (%): Viral/Alcoholic/M | | | NS |
| **Child-Pugh sco** A/B/C | | | **< .0001** |
| **MELD** - median | | | **< .0001** |
| **Clinically significant portal 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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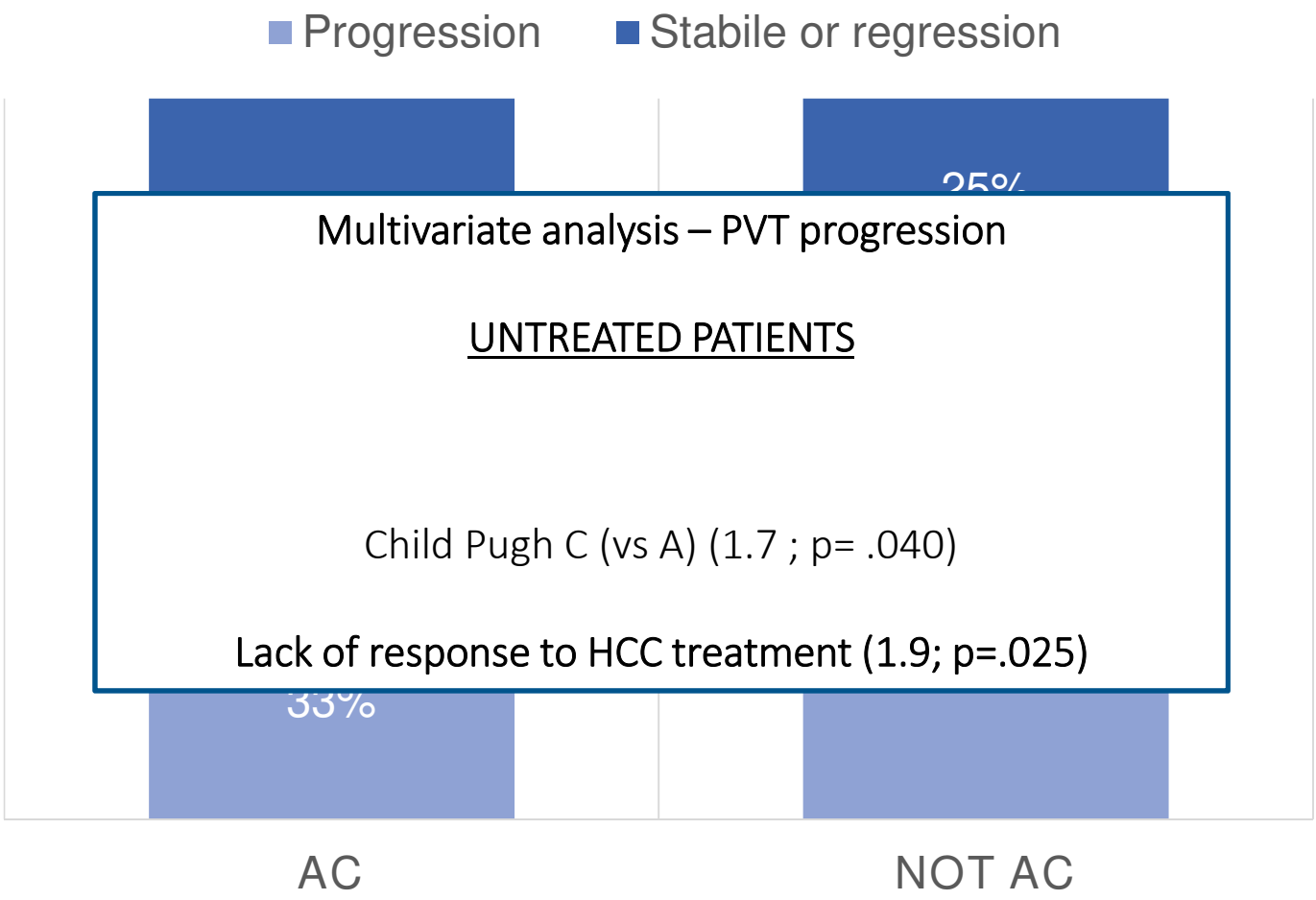
# Natural history of untreated PVT in HCC

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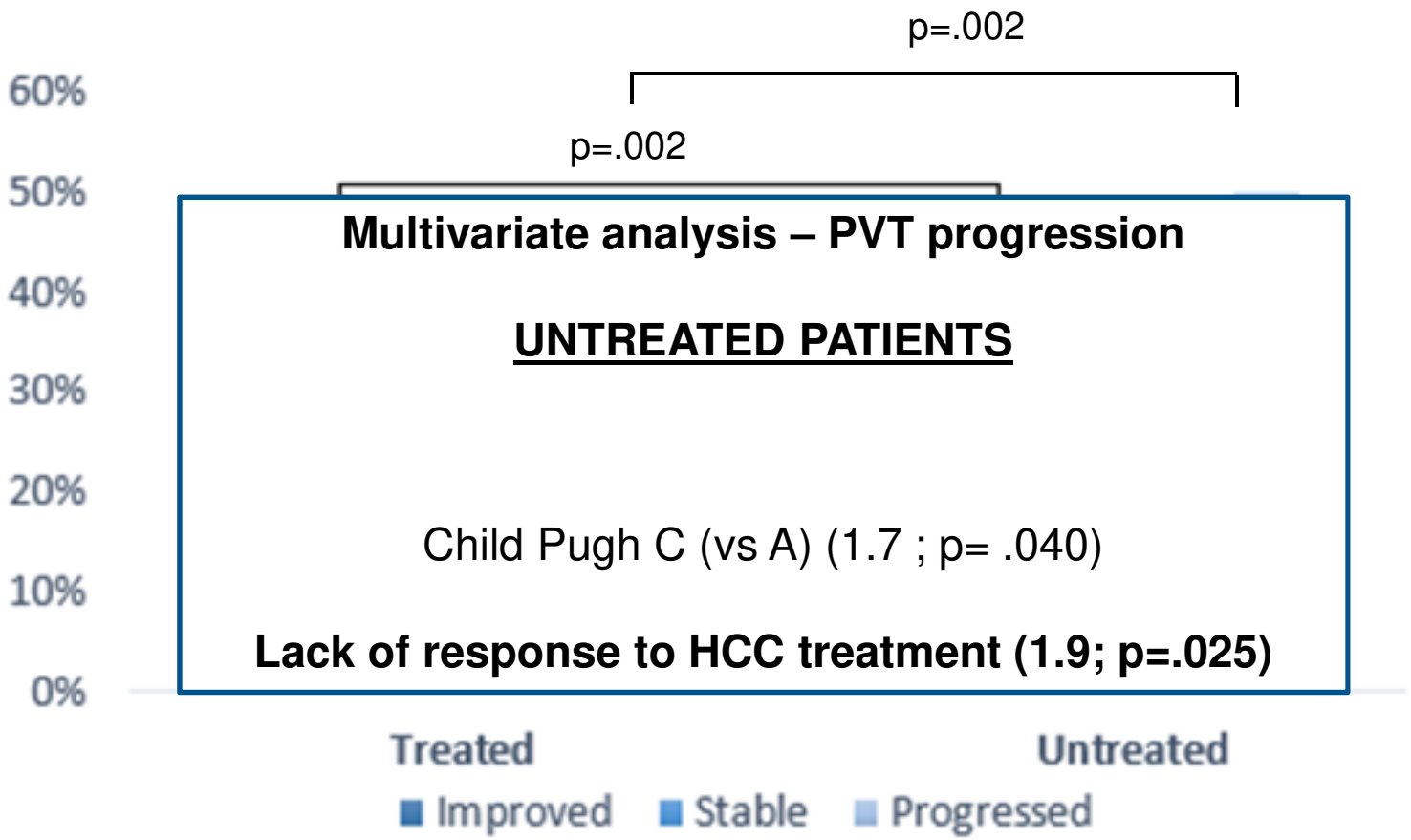
# Natural history of untreated PVT in HCC

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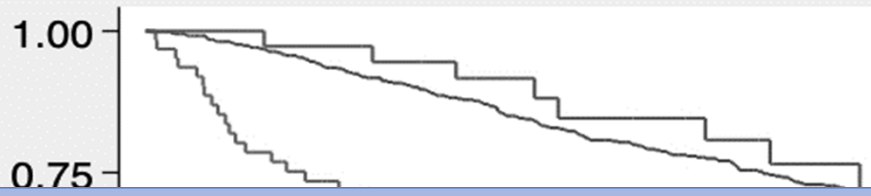
# Survival analysis – PVT evolution




**PVT P/A vs no PVT: p = 0.503**
**PVT C/P vs no PVT: p < 0.001**

## 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)

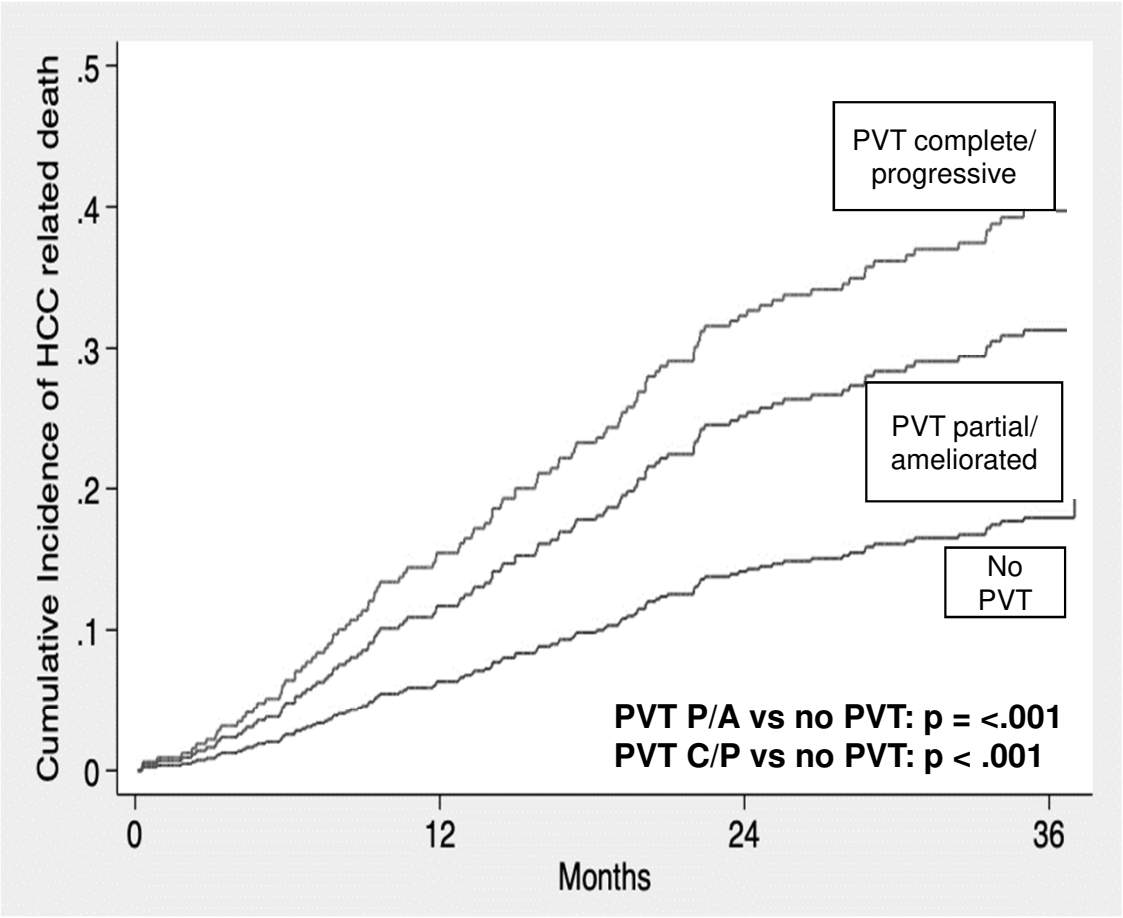
TTV at PVT diagnosis (HR 1.14, 95%CI 1.09-1.2, p= <.0001)

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

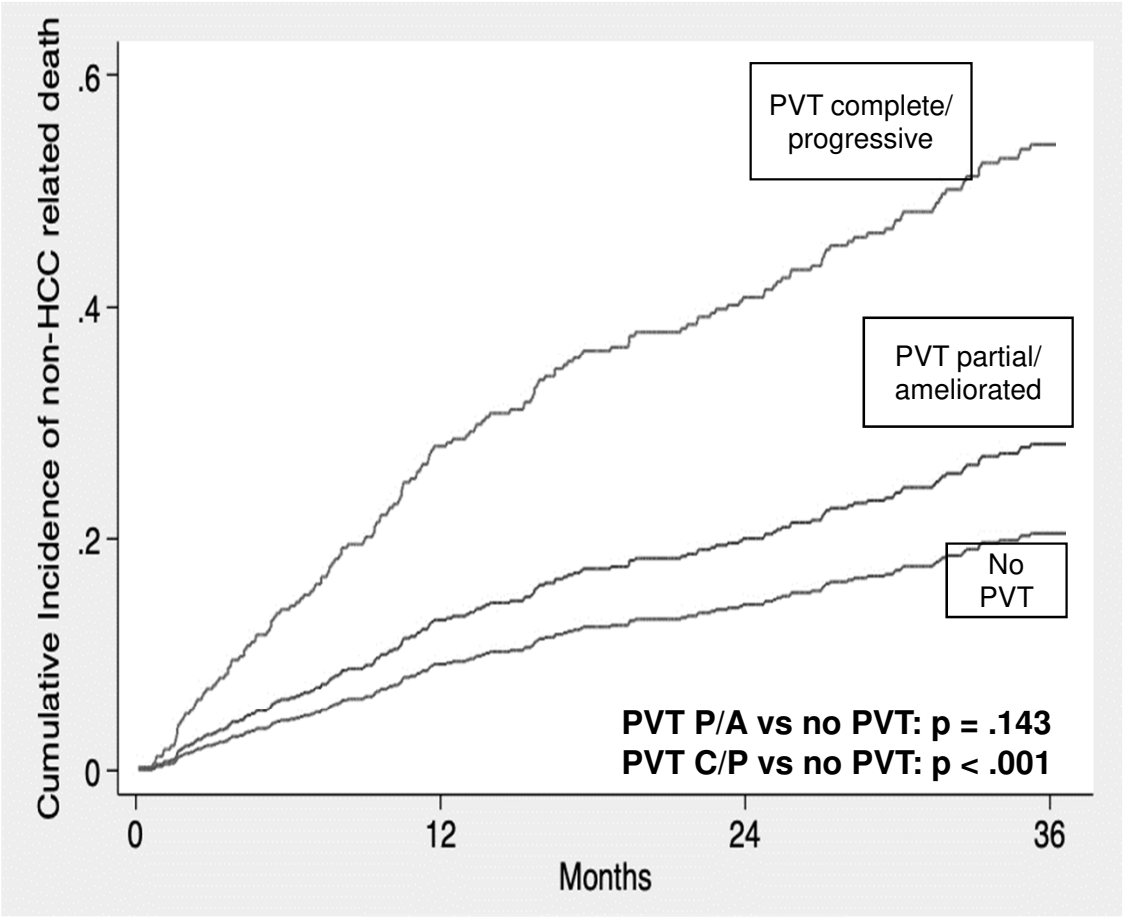
| Number at ris | | | | |
|---|---|---|---|---|
| **No PVT:** | | | | |
| **PVT Partial/Ameliorated:** | 65 | 26 | 13 | 2 |
| **PVT Complete/Progressive:** | 37 | 24 | 13 | 4 |

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

A)




B)



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

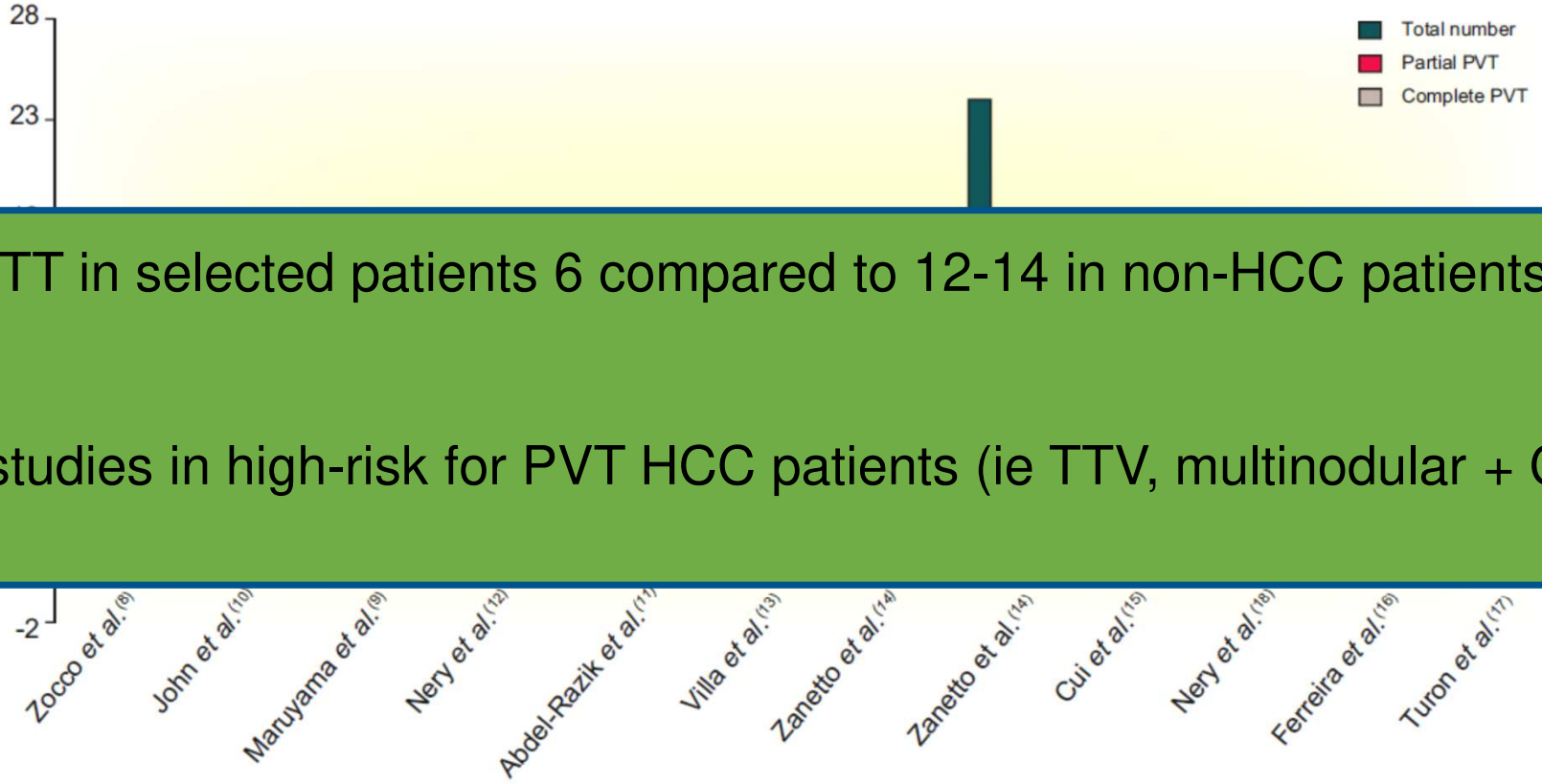
- Extending post-surgical prophylaxis to up to 4 weeks in patients who have undergone high-risk abdominal or pelvic surgery, again on the basis of randomized trials
- In in-patients, Khorana score of ≥2 is predictive of VTE
- Initial studies addressing this issue used LMWH in a population of patients 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×$10^9$/l | | 1 |
| Haemoglobin level <10 mg/ml or use of red blood cell growth factors | | 1 |
| Pre-chemotherapy leukocyte count >11×$10^9$/l | | 1 |
| BMI ≥35 kg/$m^2$ | | 1 |

Lyman, G. H, Blood Adv 2021

# 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)

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

RECOMMENDATION 28. For patients with cancer and visceral/splanchnic vein thrombosis, the ASH guideline panel *suggests* treating with short-term anticoagulation or observing (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

**CONSIDERATIONS IN CAT (PVT) IN 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

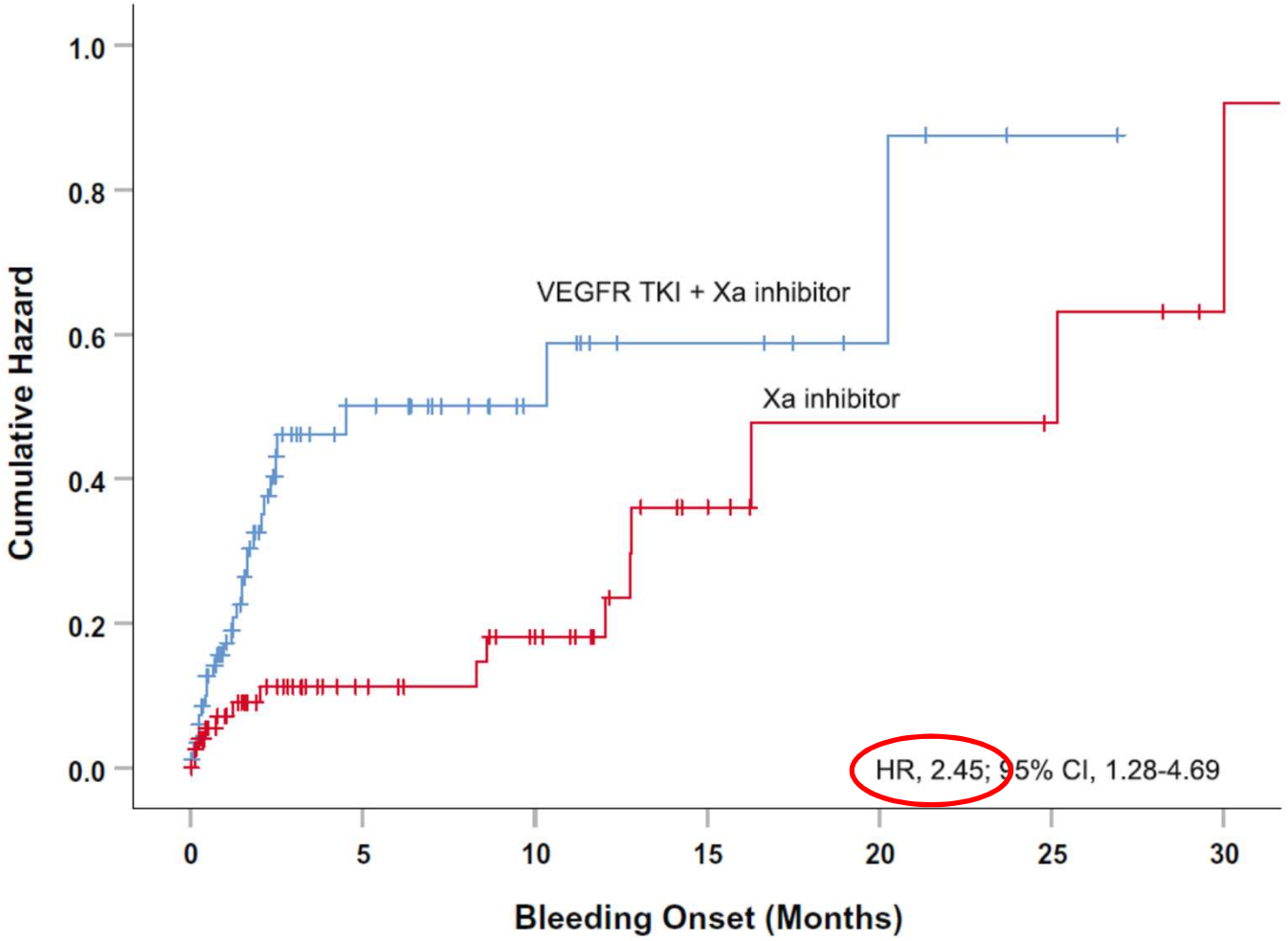
<u>Consideration for early treatment in all PVT with full AC dose</u>

Gary H. Lyman, Blood Advances 2021

# Caution with the risk of drugs interaction with AC

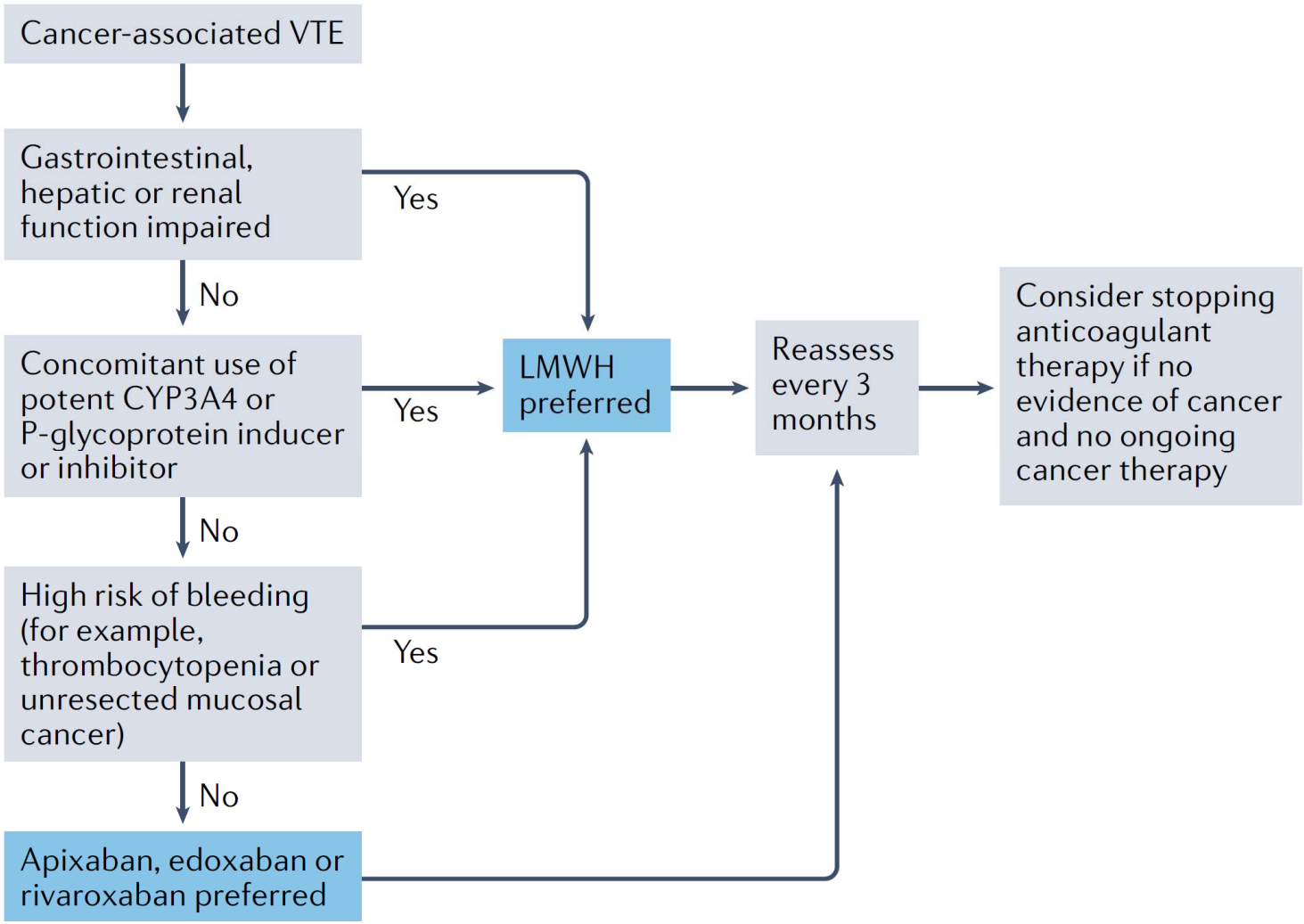
| | Anticoagulant Target | Protein Binding | Metabolism | Efflux Protein | Inducer/inhibitor of CYP/P-gp |
|---|---|---|---|---|---|
| **LMWH** | AntiXa/AntiIIa | - | Desulfation and depolymerisation | - | No |
| **Rivaroxaban** | AntiXa | 95% | CYP3A4/3A5/2J2 | P-gp, BCRP | No |
| **Apixaban** | AntiXa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

# Bleeding risk with AC during concomitant TKI therapy



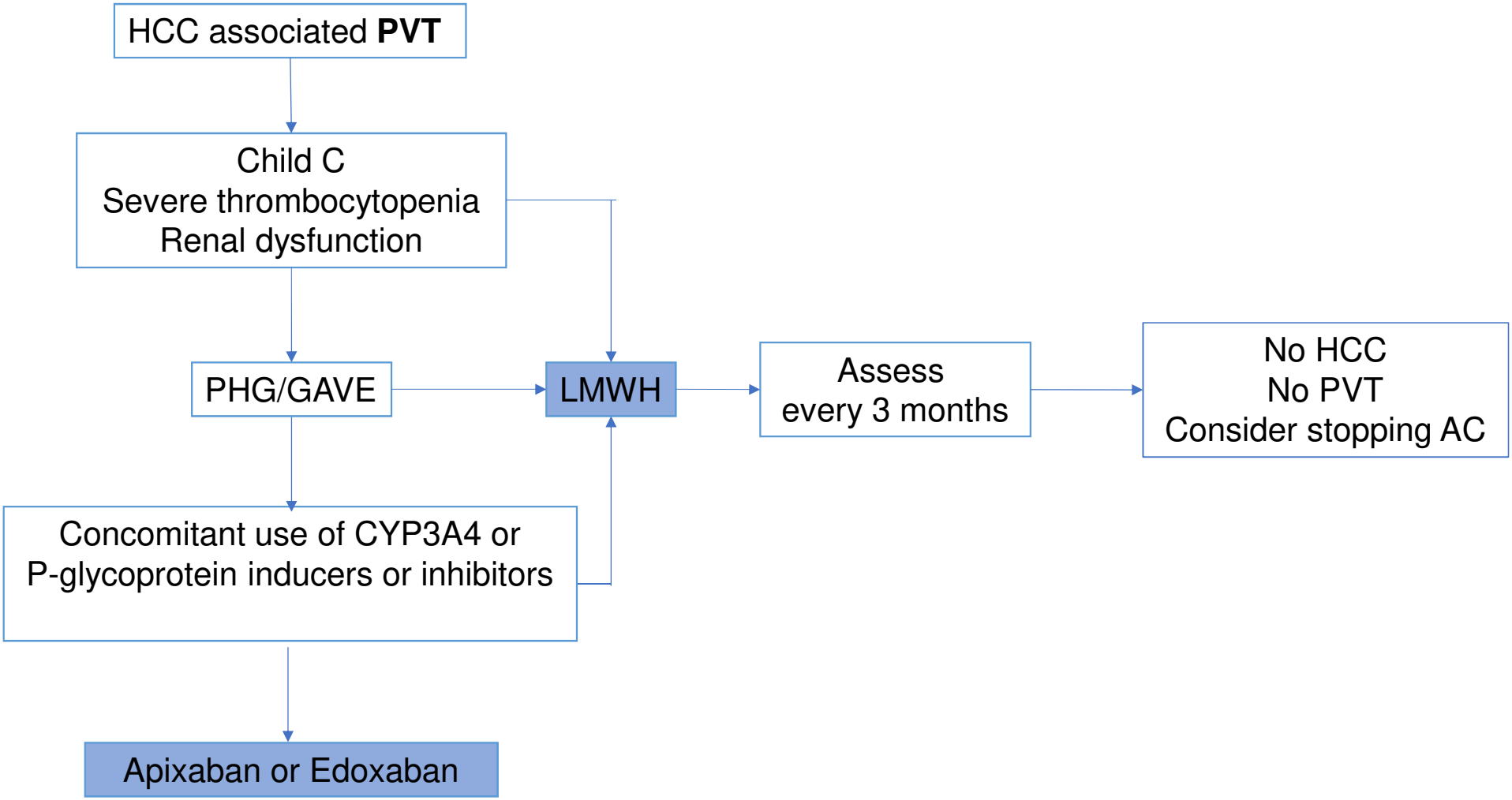

Patel, Cancer 2021

# Algorythm of AC for Cancer Associated Thrombosis (CAT)




Lyman, G. H, Blood Adv 2021

# Proposed Algorythm of AC for PVT in HCC



# CONCLUSIONS

- HCC appears to be an independent risk factor for the occurrence of PVT in patients with cirrhosis correlated with its biological activity – important distinguish PVTT and associated treatment thrombosis
- 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

# ACKNOWLEDGMENTS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