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Endpoints for clinical studies in PSVD

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MVF CENTRE DE RÉFÉRENCE MALADIES VASCULAIRES DU FOIE

Instituts thématiques Inserm

Institut national de la santé et de la recherche médicale

CRI CENTRE DE RECHERCHE SUR L'INFLAMMATION

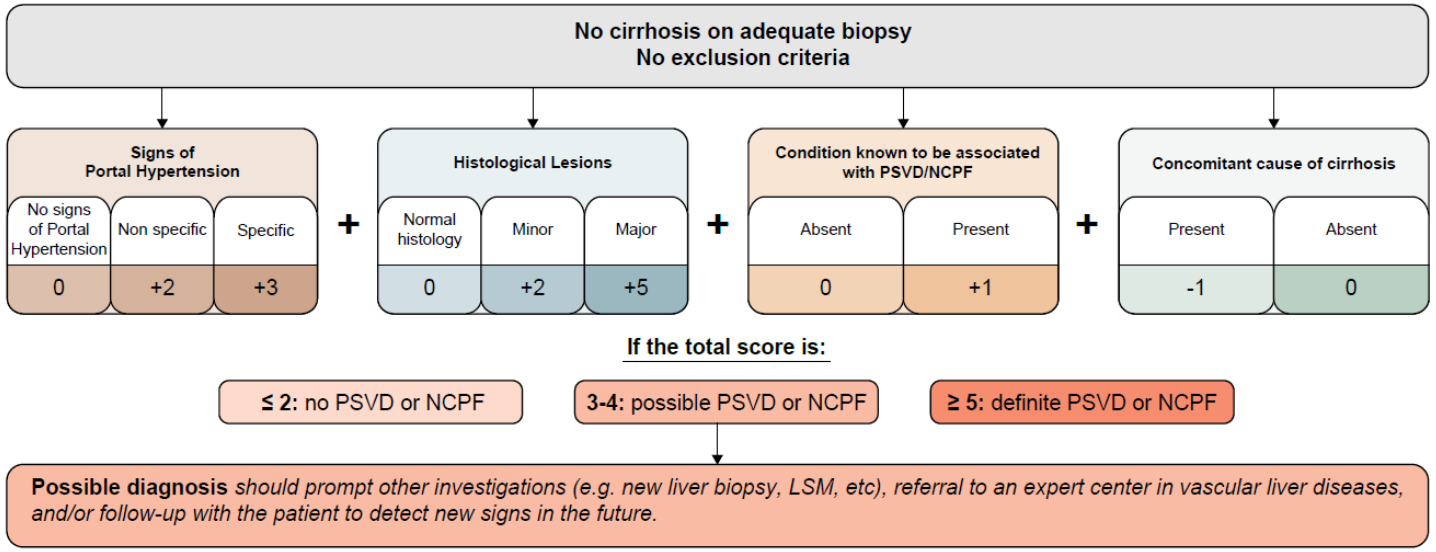
VALDIG
VASCULAR LIVER DISEASE GROUP

EURO VALDINET

One objective:
New therapies for patients with PSVD

New therapies in PSVD: what we need

- A common diagnosis ✓



Hernandez-Gea, *et al*. J Hepatol 2026

New therapies in PSVD: what we need

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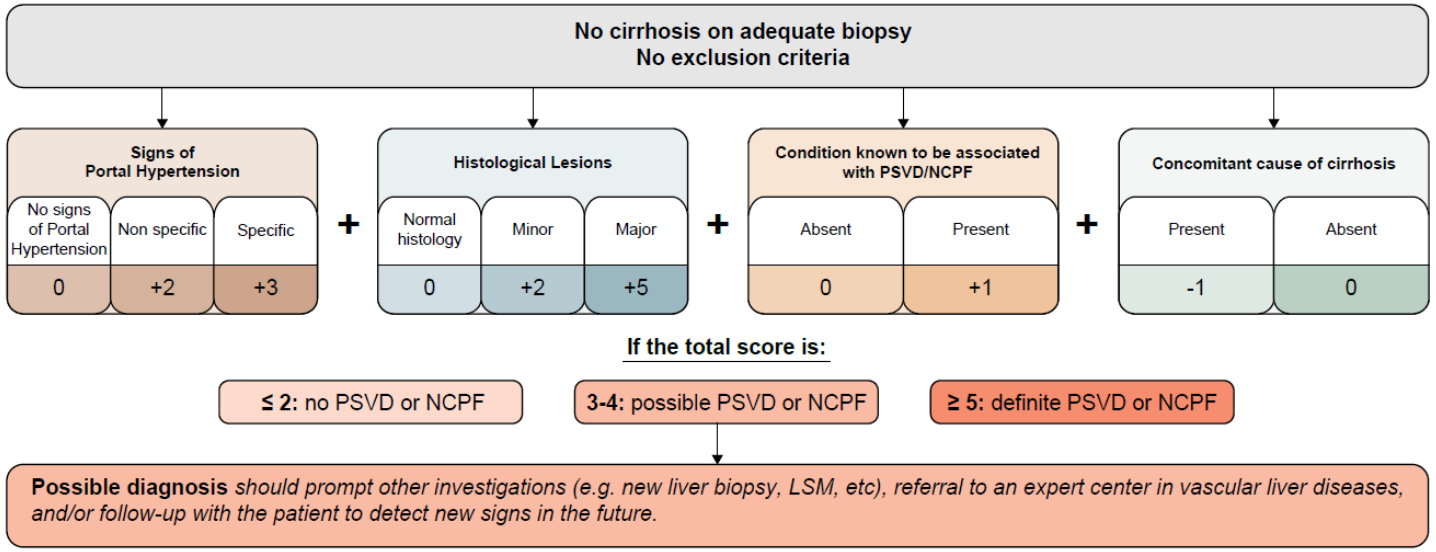

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- Drug candidates ⏳

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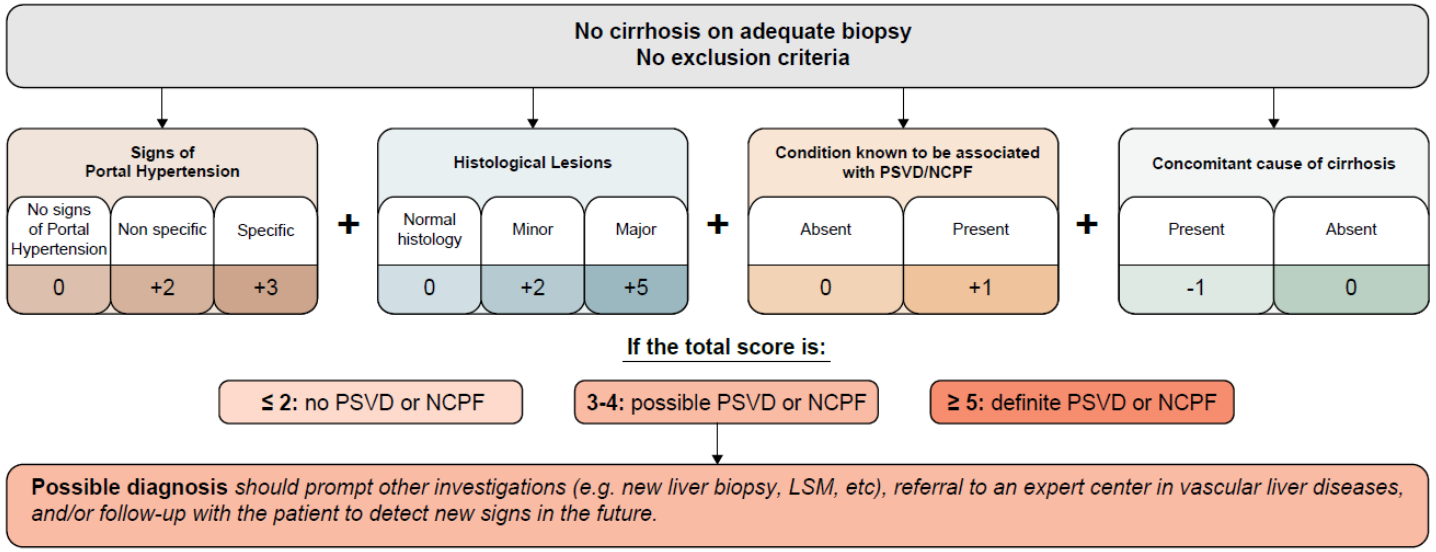

Hernandez-Gea, *et al*. J Hepatol 2026

- Drug candidates ⏳

- **Common endpoints**

Endpoints in PSVD: Methods

1) **Paris PSVD meeting (Dec 2025): 3 working groups**
   - ➔Inclusion criteria
   - ➔Surrogate endpoints
   - ➔Hard endpoints

   } 26 statements

Endpoints in PSVD: Methods

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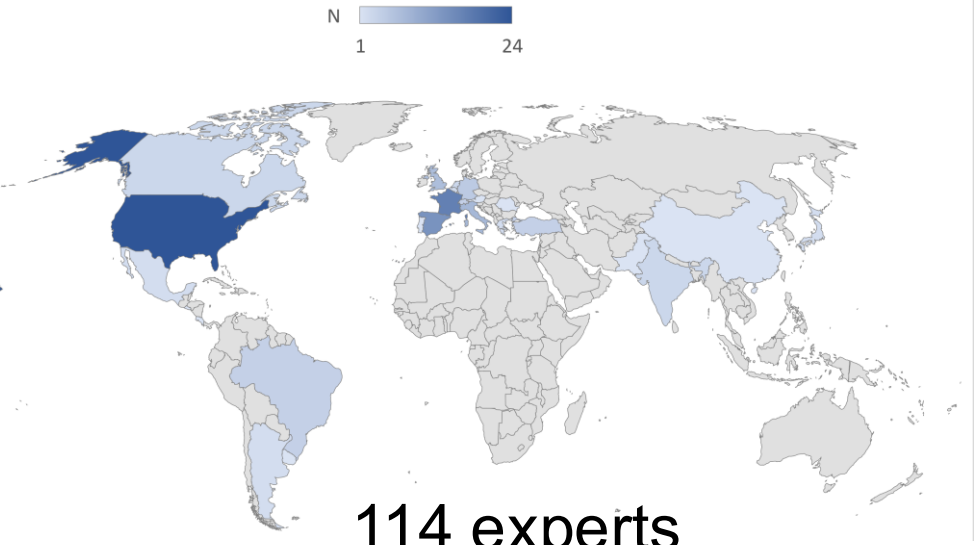
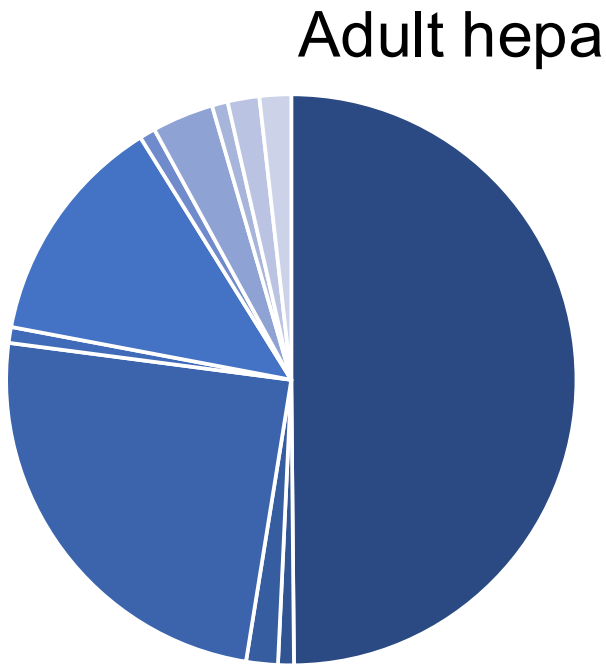
➔Surrogate endpoints
➔Hard endpoints

} 26 statements

2) Survey: 2 rounds



114 experts
25 countries, 11 specialties



Haematology, Patient advocate, Public health researcher, Radiology, Surgery, Translational Researcher, Internal medicine

Endpoints in PSVD: Results

Nomenclature in studies on PSVD

Do not use

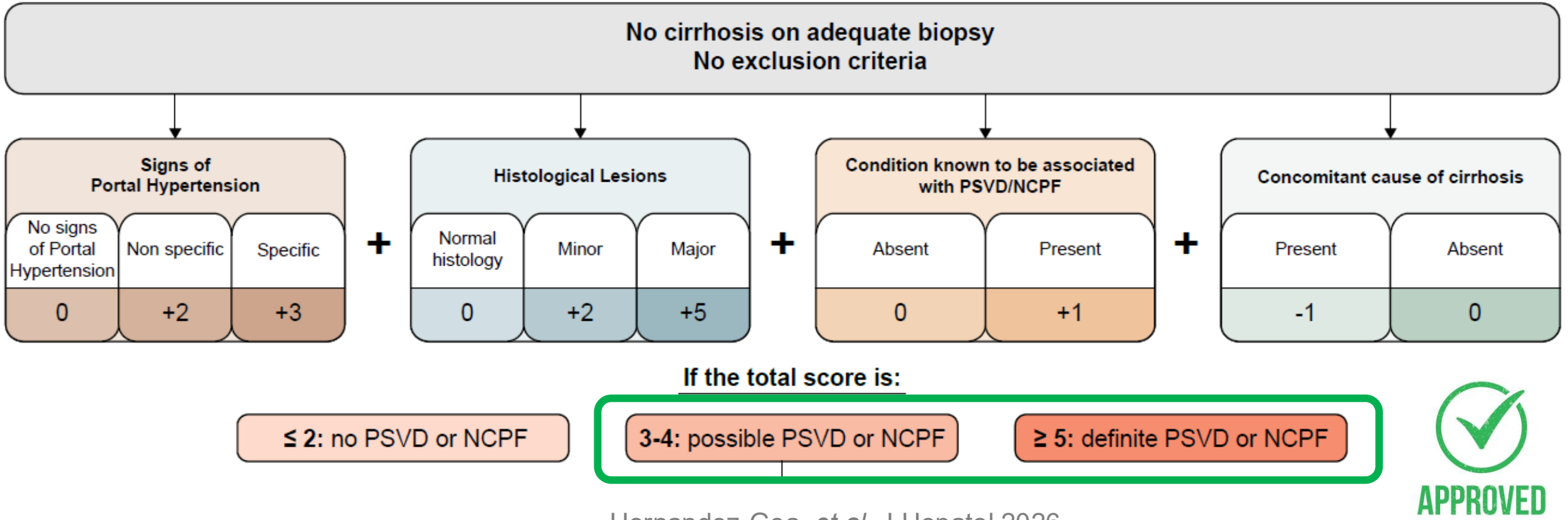
- Compensated
- Decompensated
- Recompensated
- Clinically significant portal hypertension

Use

Current or past liver-related complication

APPROVED

Inclusion criteria: possible or definite PSVD



Hernandez-Gea, *et al*. J Hepatol 2026

Adequate liver biopsy: 15 mm long with at least one fragment 10 mm long

de Broucker C, *et al.* JHEP Rep. 2025

Inclusion criteria in studies on PSVD: what to do if biopsy is smaller than 15 mm?

- **Derivation:** 106 PSVD *vs.* 170 cirrhosis
- **Validation:** 65 PSVD *vs.* 43 cirrhosis

} specific signs of portal hypertension

	Derivation n=276	Validation n=108
Specificity of < 10 kPa to rule out cirrhosis	0.988	0.977

Inclusion possible when combination of:
(i) minor or major histological criteria for PSVD
(ii) specific signs of portal hypertension
(iii) **2 LSM < 10 kPa (as a way to rule out cirrhosis)**
(iv) condition associated with PSVD and/or no cause for cirrhosis

Collab: Beaujon, France; Vienna, Austria; Hospital Clínic Barcelona, Spain

Ma A, *et al.* Poster THU-467

Stratified randomization in RCT

- On **severe associated condition** ➔ **should** be considered
  determined by a dedicated committee
- On **history of liver-related complications** ➔ **should** be considered
- On **other factors** according to the intervention and the outcome of interest (*e.g.* concomitant treatments, PVT) ➔ **may** be considered

Magaz, *et al*. J Hepatol 2025

Central reading of liver biopsies: 2026 criteria

- For clinical trials on PSVD ➔ should be considered
- When evaluation criteria rely on histology ➔ **is recommended**

Surrogate endpoints in clinical trials on PSVD without signs of portal hypertension

Appearance of:

Small varices	✗
Thrombocytopenia	✗
Splenomegaly	✓
Medium / large esophageal varices	✓
Gastric varices	✓
Portosystemic shunt at imaging	✓
Spleen stiffness ≥ 40 kPa in the absence of MPN	✓
↑ in HVPG	✗
↑ in direct portal pressure gradient (no deep sedation)	✓

Surrogate endpoints in clinical trials on PSVD with signs of portal hypertension

↓ in porto-systemic gradient assessed using direct portal pressure measurement in the absence of deep sedation,

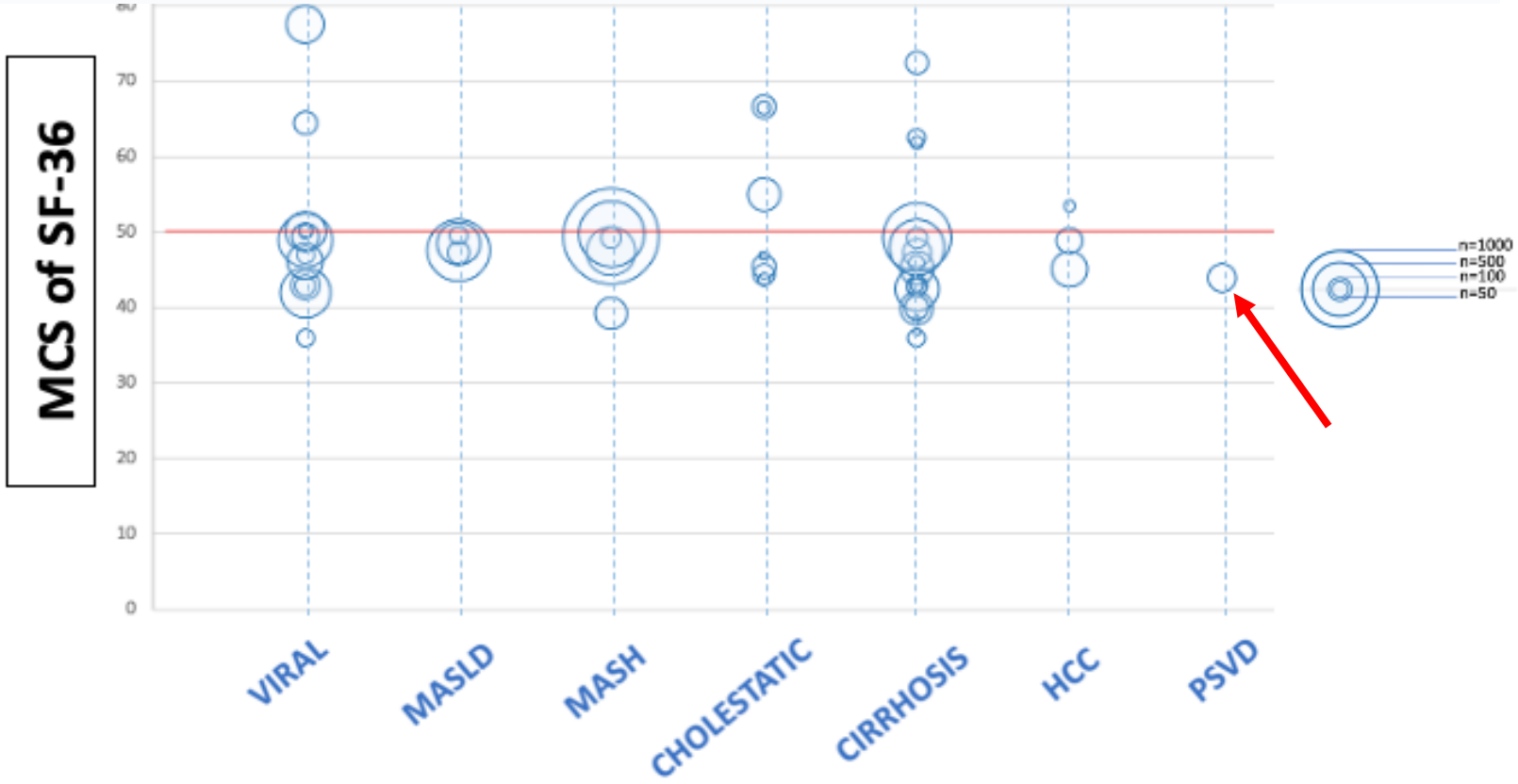
➔ can be considered as a marker of treatment response

Olivas, *et al.* JHEP Rep 2024

Quality of life impaired in PSVD

- PSVD (n=166)
- General population (n=26,095)

➔ SF36
➔ **Mental & physical components impaired in PSVD**



Torrao-Gomes M, *et al.*; EASL congress 2025; Alary, THY 415 EASL congress 2026

HRQoL (health-related quality of life) and PROs (Patient reported outcomes)

- **HRQoL** and **PROs** ➔ can be considered meaningful endpoints

- **Minimal Clinically Important Difference*** ➔ should be considered for analysis

  ** smallest change in an outcome that patients perceive as meaningful*

Hard endpoints in PSVD

Major adverse liver outcomes (MALOs) include

- Clinical **ascites** ✓
- Portal hypertension related **bleeding** ✓
- Overt hepatic **encephalopathy** ✓
- Hepatopulmonary syndrome (**HPS**) ✓
- Portopulmonary hypertension (**PoPH**) ✓
- Primary liver **cancer** ✓
- Portal vein **thrombosis** ✓
- Tranjugular intrahepatic portosystemic shunt (**TIPS**) ✓
- Liver **transplantation** ✓
- Liver-related **death** ✓

Hard endpoints in PSVD: analysis

- **Traditional approaches** (*i.e.* unique or composite endpoint)

➔ can be considered

- **Hierarchical approaches** (such as the Win ratio or the DOOR method)

➔ can be considered for analysis

1. Death
2. MALOs
3. Progression of portal hypertension
4. Portal vein thrombosis
5. Serious adverse events related to treatment
6. HRQoL

Conclusion & Next step

New therapies

- A common diagnosis ✓
- **Drug candidates** ⏳
- Common endpoints ✓

Global vision

Global PSVD or NCPF Study

Objective: understand diversity of PSVD worldwide

Thanks a lot

VALDIG
VASCULAR LIVER DISEASE GROUP

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MALADIES RARES DU FOIE DE L'ADULTE ET DE L'ENFANT
FILIÈRE DE SANTÉ

cost
EUROPEAN COOPERATION IN SCIENCE & TECHNOLOGY

ERN RARE-LIVER

Société Nationale Française de Gastro-Entérologie
SNFGE

AFEF
SOCIÉTÉ FRANÇAISE D'HÉPATOLOGIE

EASL
The Home of Hepatology

EUS-portal pressure in cirrhosis

Effect of sedation?

21 patients with cirrhosis
Mean HVPG without sedation: **14 ± 5 mmHg**
vs **12 ± 5 mmHg** under general anesthesia

Pressure threshold	≥10 mmHg	≥16 mmHg
HVPG & local anesthesia	17/21 (81%)	9/21 (43%)
HVPG & **general** anesthesia	16/21 (76%)	3/21 (14%)
EUS-PPG & **general** anesthesia	14/21 (67%)	3/21 (14%)

Vanderschueren *et al.*, JHEP Reports 2025