

**MODELOS NO INVASIVOS PARA
LA PREDICCIÓN DE RIESGO DE HIPERTENSIÓN PORTAL
Y EVENTOS HEPÁTICOS EN PACIENTES
CON ENFERMEDAD HEPÁTICA CRÓNICA AVANZADA**

Juan Bañares Sánchez

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TESIS DOCTORAL

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LISTADO DE ABREVIATURAS

En el texto se utilizarán las siglas de las abreviaturas en inglés.

BMI = Índice de masa corporal.

cACLD = Enfermedad hepática avanzada compensada

CSPH = Hipertensión portal clínicamente significativa

HCC = Hepatocarcinoma

HVPG = Gradiente de presión venosa hepático

kPa = kilopascales

LRE = Eventos relacionados con la enfermedad hepática.

LSM = Medida de rigidez hepática

NPV = Valor predictivo negativo

NSBB = Beta-bloqueantes no selectivos

PPV = Valor predictivo positivo

VCTE = Elastografía de transición con velocidad controlada

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RESUMEN

RESUMEN

El depósito de fibrosis en el parénquima hepático conduce inicialmente a la enfermedad hepática crónica avanzada compensada (cACLD), posteriormente a la aparición de hipertensión portal clínicamente significativa (CSPH) y, finalmente, a la posibilidad de aparición de una descompensación hepática (LRE). La identificación de pacientes con CSPH es especialmente importante dada la posibilidad de prevención de descompensación con tratamiento con betabloqueantes. El avance de los métodos no invasivos, incluyendo la rigidez hepática (LSM) por elastografía, permite descartar y diagnosticar CSPH. Sin embargo, en pacientes con esteatosis por disfunción metabólica (MASLD) con obesidad, este diagnóstico es mucho menos preciso.

Por otro lado, tradicionalmente se ha usado la histología para predicción de eventos en pacientes con MASLD. Sin embargo, más allá de su naturaleza invasiva, esta técnica tiene problemas inherentes de interpretación y representatividad. Los modelos no invasivos ANTICIPATE -basados en LSM, plaquetas e índice de masa corporal (BMI)- permiten estimar el riesgo de CSPH y adicionalmente de LRE en pacientes MASLD.

Esta tesis pretende explorar la capacidad de los modelos no invasivos para, por un lado, mejorar el diagnóstico de CSPH con respecto a los criterios actualmente utilizados y, por otro, mejorar la predicción de LRE en pacientes con MASLD con respecto a la biopsia.

Con este fin, hemos desarrollado dos trabajos. El primero, un meta-análisis de datos individuales para validar los criterios de Baveno VII de CSPH. El segundo, un artículo original en el que hemos comparado la capacidad para la predicción de eventos del modelo ANITICIPATE con respecto a la biopsia en dos cohortes independientes y con dos definiciones de LRE ligeramente distintas.

Como consecuencia de estos dos trabajos podemos concluir que los criterios actuales para el descartar y diagnosticar CSPH son excelentes. Sin embargo, tanto como regla general como para la población de pacientes MASLD con obesidad, el criterio ANTICIPATE $\pm$ NASH $\geq 75\%$ parece ser superior. Por otro lado, el modelo ANTICIPATE-NASH es claramente superior para la predicción de eventos hepáticos en pacientes MASLD y, una vez conocido el valor no invasivo, conocer la histología no añade mayor precisión diagnóstico. Estos hallazgos podrían cambiar la forma de diseñar estrategias terapéuticas y ensayos clínicos en el futuro.

ABSTRACT

ABSTRACT

The accumulation of fibrosis in the liver leads initially to compensated advanced chronic liver disease (cACLD), then to the development of clinically significant portal hypertension (CSPH), and ultimately to the possibility of presenting a liver related event (LRE). The identification of patients with CSPH is particularly important given the possibility of preventing decompensation through treatment with beta-blockers. The advancement of non-invasive methods, including liver stiffness measurement (LSM) by elastography, allows CSPH to be ruled out and diagnosed. However, in patients with metabolic dysfunction-associated steatotic liver disease (MASLD) and obesity, this diagnosis is much less accurate.

On the other hand, histology has traditionally been used to predict events in patients with MASLD. However, beyond its invasive nature, this technique has inherent limitations related to interpretation and representativeness. The non-invasive ANTICIPATE models -based on LSM, platelet count, and body mass index (BMI)- allow estimation of the risk of CSPH and, additionally, of LRE in patients with MASLD.

This thesis aims to explore the ability of non-invasive models, on one hand, to improve the diagnosis of CSPH compared with currently used criteria, and, on the other hand, to improve the prediction of LRE in patients with MASLD compared with biopsy.

To this end, we developed two studies. The first is an individual patient data meta-analysis to validate the Baveno VII criteria for CSPH. The second is an original article in which we compared the event prediction performance of the ANTICIPATE model with that of biopsy in two independent cohorts using two slightly different definitions of LRE.

As a result of these two studies, we can conclude that current criteria for ruling out and diagnosing CSPH are excellent. However, both for all the etiologies and specifically in the MASLD with obesity population, the ANTICIPATE $\pm$ NASH $\geq 75\%$ criterion appears to be superior. On the other hand, the ANTICIPATE-NASH model is clearly superior for the prediction of hepatic events in patients with MASLD, and once the non-invasive value is known, histological information does not add further diagnostic accuracy. These findings could change the way therapeutic strategies and clinical trials are designed in the future.

INTRODUCCIÓN

1. INTRODUCCIÓN

1.1 CIRROSIS E HIPERTENSIÓN PORTAL

Independientemente de la causa inicial que lo produzca, como resultado del insulto inflamatorio crónico sobre el hígado se produce una respuesta de reparación del daño tisular con depósito de tejido fibroso en el parénquima [1]. Esta fibrosis gradual produce una distorsión de la arquitectura hepática que culmina en la aparición de la cirrosis hepática. La cirrosis, aunque en su origen es un concepto histológico, se puede diagnosticar clínicamente a través de una combinación de signos en la exploración física, pruebas de imagen, datos endoscópicos y análisis de laboratorio. Sin embargo, durante años la biopsia ha sido la prueba de referencia para el diagnóstico y la estadificación de la fibrosis (desde F0 sin fibrosis a F4 sinónimo de cirrosis). Aunque es un procedimiento seguro, no está exento de riesgos y en los últimos años se ha comenzado a cuestionar si la representatividad de un pequeño fragmento de hígado refleja el grado de fibrosis del resto del parénquima, en un proceso -la fibrosis- que puede no ser homogéneo [2]. Adicionalmente, el concepto de cirrosis es un concepto dicotómico que no termina de reflejar que la enfermedad se produce de forma gradual.

Como consecuencia directa de estos cambios arquitectónicos del parénquima, se produce un aumento de la resistencia intrahepática al flujo y un aumento de la presión en el sistema portal [3]. El desarrollo de hipertensión portal es fundamental para la aparición de eventos relacionados con la enfermedad hepática (LRE), fundamentalmente hemorragia digestiva de origen variceal, ascitis, encefalopatía hepática [4] y hepatocarcinoma (este último mucho más relacionado con la fibrosis e inflamación que no con la hipertensión portal). Tradicionalmente, el diagnóstico de la presencia de hipertensión portal se ha podido inferir también con pruebas diagnósticas: varices esofágicas en la endoscopia, colaterales o esplenomegalia en pruebas de imagen, trombocitopenia y otras, pero la prueba de referencia ha sido la medición del gradiente de presión venosa hepática (HVPG). Siendo un procedimiento seguro, se trata de un procedimiento invasivo por el que, tras acceder por vía generalmente transyugular y cateterizar selectivamente una vena suprahepática, se realiza una medida de presión venosa. Una diferencia de presión elevada entre la presión libre y la enclavada (HVPG) representa el mejor marcador subrogado de la presión portal directa en la hipertensión portal sinusoidal. La hipertensión portal clínicamente significativa (CSPH) se define cuando el HVPG es mayor a 10 mmHg y su presencia está claramente asociada con la aparición de LRE [5].

La detección de CSPH es actualmente de especial interés, dado que en pacientes que no han presentado descompensación hepática, el tratamiento con betabloqueantes no cardio selectivos (NSBB) previene la primera descompensación [6-8].

ENFERMEDAD HEPÁTICA ESTEATÓSICA ASOCIADA A DISFUNCIÓN METABÓLICA (MASLD)

Una de las principales transformaciones en la hepatología de los últimos años ha sido el cambio de la etiología predominante de las enfermedades hepáticas. Con la alta proporción de curación con los tratamientos dirigidos para el virus C [9] y el aumento progresivo de los factores de riesgo metabólicos [10], se ha producido un cambio de paradigma en las causas de enfermedad hepática. Los factores metabólicos (como diabetes mellitus tipo 2, obesidad,

hipertensión...) producen acumulación de grasa en el hígado (esteatosis) y la posibilidad de inflamación crónica (esteatohepatitis) con el depósito progresivo de tejido cicatricial desde la fibrosis mínima hasta la cirrosis [11]. Esta enfermedad hepática esteatótica secundaria a disfunción metabólica (MASLD) es en el momento actual, junto con la enfermedad relacionada con el consumo de alcohol (ALD), la causa más prevalente de enfermedad hepática [12].

En los pacientes con MASLD la progresión hacia enfermedad hepática avanzada parece más lenta y, globalmente, tienen menor riesgo de descompensación hepática en comparación con otras etiologías. Sin embargo, la presencia de CSPH también es un factor predictor relevante de la aparición de eventos [13]. Otra forma de clasificar a los pacientes con MASLD con respecto al riesgo de LRE ha sido mediante el estadio histológico. Los pacientes con categoría F0 a F2 tienen un riesgo bajo de presentar eventos y en contraposición, los pacientes F3 (puentes de fibrosis) y F4 (cirrosis) tienen riesgos crecientes [14]. La presencia de F3 o F4 ha sido criterio de inclusión para numerosos ensayos clínicos y la regresión de la categoría de fibrosis uno de los objetivos fundamentales de dichos estudios. Sin embargo, esta clasificación no está exenta de los problemas expuestos anteriormente, principalmente la representatividad de una muestra pequeña -la biopsia- de la totalidad del parénquima (Figura 1).

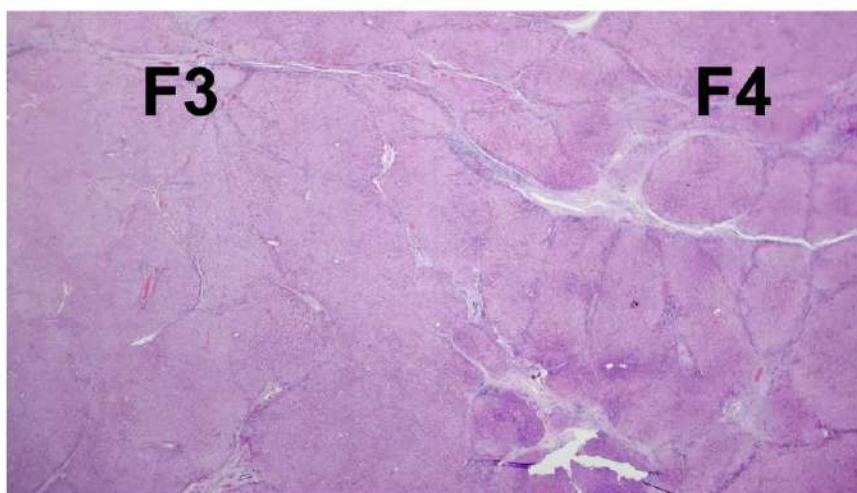


Figura 1. Biopsia hepática que muestra, en la misma pieza, la presencia de zonas con un grado de fibrosis interpretable como F3 y otro como F4, ilustrando gráficamente el problema de representatividad. Cortesía de la Dra. Salcedo-Allende.

ELASTOGRAFÍA HEPÁTICA Y ENFERMEDAD HEPÁTICA AVANZADA COMPENSADA

Otras de las grandes transformaciones en la práctica clínica en hepatología es la generalización de la elastografía hepática como método inicial en la aproximación diagnóstica a un paciente con sospecha de enfermedad hepática. Aunque originalmente diseñado para la industria de materiales y alimentaria, el Fibroscan© llega a la práctica médica [15] hace 20 años. La elastografía de transición (VCTE) estima la rigidez hepática (LSM) mediante el envío de un pulso de vibración de ultrasonido recogiendo la velocidad de propagación a través del tejido. La VCTE tiene una serie de ventajas con respecto a la biopsia: es repetible, no invasiva y recoge información más representativa de todo el parénquima hepático. Sin embargo,

también tiene también alguna desventaja: falsos positivos en situaciones especiales, la necesidad de una máquina específica para realizarlo y que no proporciona información específica acerca del diagnóstico etiológico. En los últimos años se ha venido construyendo progresivamente una sólida base científica que consolida la VCTE como una de las herramientas fundamentales para la estimación no invasiva de la fibrosis hepática [16, 17]. Actualmente, el LSM se ha convertido en una herramienta central en la práctica clínica del hepatólogo.

Durante el seguimiento de un paciente en la consulta de hepatología, existe la posibilidad de que un individuo en el que clínicamente no hay una sospecha de cirrosis, presente una enfermedad avanzada con hipertensión portal y riesgo de desarrollar descompensación hepática [18]. ¿Cómo podemos identificar precozmente a estos pacientes? El término enfermedad hepática crónica avanzada compensada (cACLD) se introduce en la conferencia de consenso sobre hipertensión portal de Baveno VI [19] para reflejar el continuo de fibrosis avanzada hasta cirrosis en paciente con enfermedad hepática crónica. En la siguiente conferencia de Baveno VII [20] el modelo se consolida con el establecimiento de unos umbrales prácticos de LSM en forma de la “regla de los 5” [20, 21] ligándose directamente con la posibilidad de tener CSPH y con el riesgo progresivo de presentar eventos hepáticos. Los pacientes con LSM por debajo de 10 kPa no tienen una enfermedad hepática avanzada ni riesgo de presentar eventos hepáticos. A partir de un LSM de 15 kPa la presencia de una enfermedad / fibrosis avanzada es altamente probable y existe la posibilidad de CSPH y descompensación (Figura 2).

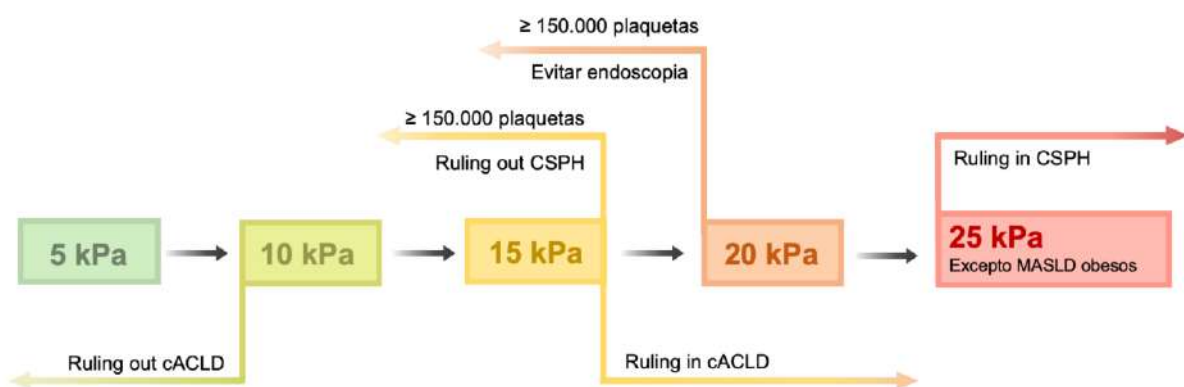


Figura 2. Adaptación de la “regla de los 5” de [20, 21]. En paralelo al aumento progresivo de LSM aumenta el riesgo de enfermedad avanzada e hipertensión portal. Los pacientes con < 10 kPa no tienen cACLD. Con ≤ 15 kPa y ≥ 150.000 plaquetas se descarta CSPH. A partir de LSM ≥ 25 kPa se puede establecer el diagnóstico de CSPH excepto en pacientes MASLD.

DETECCIÓN DE CSPH Y PREDICCIÓN DE EVENTOS CON MÉTODOS NO INVASIVOS

En un estudio multicéntrico, Pons et al [21] identificaron puntos de corte para descartar y diagnosticar CSPH. En una cohorte de más de 800 pacientes en los que se disponía de medidas simultáneas de HVP, plaquetas y LSM, se consiguió establecer: 1) que la combinación de un LSM menor de 15 kPa y plaquetas de más de 150.000 era un excelente criterio de exclusión (rule out) de CSPH con un valor predictivo negativo (NPV) alto ($>90\%$) y 2) que un LSM mayor de 25 kPa era un criterio apropiado para confirmar (rule in) CSPH con un valor predictivo positivo (PPV) alto ($>90\%$). Sin embargo, este último criterio era válido

para todas las etiologías excepto en pacientes MASLD con obesidad ($\text{BMI} \geq 30 \text{ kg/m}^2$). Estos criterios se han validado posteriormente [22-27] y han pasado a formar parte del documento de consenso de Baveno VII [20 véase también Figura 2).

Además del problema del bajo PPV para los pacientes MASLD con obesidad, estos criterios de Baveno VII dejan a un porcentaje importante de pacientes donde no podemos determinar si el paciente tiene o no tiene CSPH (Figura 2) por lo que recientemente se han desarrollado estudios encaminados a reducir esta zona intermedia o indeterminada con distintas estrategias, destacando el uso de parámetros de laboratorio [25] y la elastografía esplénica [28]. Además, el desarrollo del modelo ANTICIPATE [29] y la posterior adaptación del modelo (ANTICIPATE-NASH) a pacientes con MASLD [21], permite la estimación individual para cada paciente del riesgo de presentar CSPH, utilizando parámetros sencillos (LSM, plaquetas y añadiendo el BMI para pacientes MASLD). Adicionalmente, este modelo fue adaptado y validado (ANTICIPATE-NASH-LRE) para la predicción individual de LRE, definidos como descompensación hepática más carcinoma hepatocelular y muerte de causa hepática, a 3 años [30], con un sencillo nomograma o una calculadora online (<https://www.bcn-liverhuvh.com/resources>).

Ambos modelos ANTICIPATE permiten realizar una predicción individual del riesgo de CSPH, de modo que se pueden plantear diferentes preguntas con relevancia clínica. ¿Es posible encontrar un punto de corte que permita realizar un diagnóstico de CSPH con un alto PPV, especialmente en pacientes con MASLD y obesidad? Por otro lado, utilizando el modelo ANTICIPATE-NASH se puede predecir el desarrollo de LRE a 3 años. ¿Podría ser el modelo mejor que la biopsia como predictor de eventos?

HIPÓTESIS

2. HIPÓTESIS

Los modelos ANTICIPATE podrían mejorar tanto el diagnóstico no invasivo de CSPH para todas las etiologías como la predicción de eventos en pacientes con MASLD.

OBJETIVOS

3. OBJETIVOS

Objetivo principal:

Mejorar los criterios diagnósticos de CSPH propuestos usando los modelos ANTICIPATE y comparar el rendimiento del ANTICIPATE-NASH-LRE con la histología en pacientes MASLD.

Objetivos secundarios:

- Validar los criterios de Baveno VII para el diagnóstico y exclusión de CSPH
- Evaluar el rendimiento del modelo ANTICIPATE±NASH por centro.
- Evaluar si una vez se conoce el valor de ANTICIPATE-NASH-LRE añadir la categoría histológica mejora la predicción de eventos.

COMPENDIO DE PUBLICACIONES

4. COMPENDIO DE PUBLICACIONES

4.1. ARTÍCULO 1

Bañares J, Pons M, Reiberger T, Mandorfer M, Jachs M, Semmler G, Colecchia A, Colecchia L, Dajti E, Bureau C, Larrue H, Grgurević I, Kujundžić PD, Fortea JI, Puente A, Berzigotti A, Tsochatzis E, Bosch J, Abraldes JG, Genesca J; a study by the Baveno Cooperation: an EASL consortium. Refining the Baveno VII criteria for clinically significant portal hypertension: An individual patient data meta-analysis. J Hepatol. 2025 Oct 24:S0168-8278(25)02565-6. doi: 10.1016/j.jhep.2025.10.014. Epub ahead of print. PMID: 41138818.

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Title: Refining the Baveno VII criteria for clinically significant portal hypertension: an individual-patient data meta-analysis

Short title: Baveno VII criteria for CSPH: a meta-analysis

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Abstract

Background and Aims: Clinically significant portal hypertension (CSPH) in compensated advanced chronic liver disease (cACLD) has therapeutic consequences. CSPH may be assessed with the Baveno VII criteria with lower performance in patients with obesity (body mass index ≥ 30 kg/m²) and metabolic dysfunction-associated steatotic liver disease (MASLD). The ANTICIPATE $\pm$ NASH models predict the risk of CSPH. We aimed to validate Baveno VII criteria and refine them with the ANTICIPATE $\pm$ NASH models.

Methods: Systematic review of studies validating Baveno VII criteria of CSPH (hepatic venous pressure gradient as reference) with search strategy of “CSPH” (AND) “Baveno VII”, from Baveno VII consensus until June 2024. A meta-analysis of Baveno VII criteria (ruling in: LSM (liver stiffness measurement) ≥ 25 kPa and ruling out: LSM ≤ 15 kPa + platelets $\geq 150 \times 10^9$ /L) was performed. Using a risk threshold of CSPH by the ANTICIPATE $\pm$ NASH for a positive predictive value (PPV) of $\geq 90\%$ was explored. Individual patient data was used to assess model performance by center.

Results: Five studies with 1433 cACLD patients (CSPH 34% to 62%) of different etiologies were identified. LSM ≥ 25 kPa had an excellent PPV (92%) pooled by studies and etiologies, except MASLD with obesity. A $\geq 75\%$ risk of CSPH by the ANTICIPATE $\pm$ NASH models improved PPV to 95%, including MASLD with obesity (PPV 0.67 to 0.83; $p < 0.001$). The pooled NPV for ruling out was 99% for all etiologies. ANTICIPATE $\pm$ NASH showed an excellent performance across centers.

Conclusion: Baveno VII criteria for CSPH adequately classify patients across etiologies, except MASLD with obesity. Using a $\geq 75\%$ risk threshold by ANTICIPATE models to detect CSPH improves global performance, including MASLD with obesity, supporting it can be a simpler way of predicting CSPH in clinical practice.

Impact and implications: This systematic review and meta-analysis confirm the validity for ruling out and ruling in CSPH in cACLD patients with the Baveno VII criteria. Using a threshold of $\geq 75\%$ of the ANTICIPATE $\pm$ NASH models, the global performance for detecting CSPH improves regardless of etiology. This represents a very practical approach for general hepatologists to select patients for prophylactic β -blocker therapy as its calculation relies on BMI, liver stiffness and platelet count with an online calculator.

Introduction

Compensated advanced chronic liver disease (cACLD) encompasses a heterogeneous group of patients with different risk of portal hypertension [1]. In the last Baveno VII consensus, new non-invasive criteria for detecting clinically significant portal hypertension (CSPH), defined as a hepatic venous pressure gradient (HVPG) ≥ 10 mmHg, in the cACLD population were proposed [2]. The need to identify patients with a high probability of CSPH is now more important, as the evidence for the use of non-selective β -blockers to prevent first decompensation is increasing [3-5]. CSPH could be ruled in with a liver stiffness measurement (LSM) by transient elastography (TE) of ≥ 25 kPa and ruled out with an LSM of ≤ 15 kPa plus platelet count of $\geq 150 \times 10^9/L$ with a very good classification accuracy.

Although the proposed ruling in threshold performed optimally for viral hepatitis, alcohol related (ALD) and metabolic dysfunction-associated steatotic liver disease (MASLD) patients without obesity, it was suboptimal for MASLD patients with obesity (body mass index-BMI ≥ 30 kg/m²) with a positive predictive value (PPV) below 90%. Furthermore, by using these classification rules, a very high proportion of patients (40-50%) remained unclassified, with a mean prevalence of CSPH around 50%. This intermediate zone is an unresolved current challenge for which different alternatives have been proposed, such as the AASLD criteria [6], predictive models for CSPH [2, 7-9], and an upper endoscopy searching for varices [10]. The risk for decompensation of not detecting and treating CSPH in this unclassified population is unknown. In addition, with the current non-invasive strategy, 5 to 10% of patients will be misclassified and might receive β -blockers without having CSPH. If these patients

have progressive disease, CSPH will probably develop in the short-term and initiating therapy would be acceptable.

The ANTICIPATE and the ANTICIPATE-NASH models (ANTICIPATE $\pm$ NASH models) using LSM plus platelet count with or without BMI were developed for a continuous risk prediction of the probability of having CSPH for patients with viral hepatitis and ALD, and with MASLD, respectively [7-8]. Both models have been validated several times in additional cohorts [11-13], present numerous advantages for clinicians (simple, repeatable, at point-of-care), and have been recommended by the Baveno VII consensus and hepatology societies [2, 6, 14].

Baveno VII recommendations for CSPH were based on a preliminary analysis of a multicenter sample specifically collected to inform the symposium. An expanded version was subsequently published as a full manuscript [8]. Since then, several studies have specifically evaluated Baveno VII criteria with a different composition of etiologies and distinct performance for ruling in and out CSPH [15-21]. On the other hand, it might be possible that by using a different approach utilizing thresholds of predicted values of CSPH by the models, the ruled in group could be improved, especially for MASLD patients, and the indeterminate zone diminished.

We have conducted a systematic review and meta-analysis of the studies published after Baveno VII specifically designed at: 1) validating the consensus recommended criteria for ruling in and ruling out CSPH and assessing their performance of the in the different etiologies of cACLD patients; 2) providing additional improved criteria for ruling in CSPH using the predicted risk of CSPH of the ANTICIPATE $\pm$ NASH models; and 3) evaluating the robustness of the performance of ANTICIPATE $\pm$ NASH models taking into account the clustering by center.

Materials and methods

This study was designed to evaluate the performance of Baveno VII criteria to rule out and rule in CSPH. The review and meta-analysis are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [22]. The study included patients who had previously given informed consent to participate in each study.

Search strategy and eligibility criteria

The search strategy was designed and conducted by JG and JB. This meta-analysis was designed to pool the data of individual cACLD patients who had never been decompensated with suspected CSPH who underwent both HVPG measurement (reference test) and LSM (index test) evaluated by TE (FibroScan, Echosens, Paris, France), in studies designed to evaluate the Baveno VII recommendations for CSPH [2]. Using the databases MEDLINE, EMBASE, Google Scholar and Web of Science [23], we performed the search from October 2021 (date of the Baveno VII workshop) to June 30, 2024. Briefly, the key terms for the search were “clinically significant portal hypertension” and “Baveno VII” (full search strategy is shown in Supplementary Table 1). Cross-sectional studies reporting data on adults (≥ 18 years) with HVPG and LSM were eligible, including conference abstracts and letters. Only studies with at least 50 patients included were eligible. Excluded studies were case-control studies, case reports, or other non-original work (reviews, expert opinions, or practice guidelines). Further research was conducted through a manual check of references. Regarding

etiologies, in patients with hepatitis C only studies with untreated patients were included.

Study identification, selection and data extraction

Criteria for study identification and selection, and the methodology for data extraction are detailed in Supplementary Text 1.

Quality assessment

Two authors (JGA and JB) independently assessed the methodological quality of the included studies using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool [24]. The assessed domains of study quality were patient selection, index test, reference standard, and flow and timing. A study was considered at high risk of bias when at least one of the domains of QUADAS-2 showed this risk. Any disagreements were resolved through discussion with a third author (JG).

Definitions and outcome

The criterion to rule in CSPH was LSM of ≥ 25 kPa, while the criterion to rule out CSPH was a LSM of ≤ 15 kPa and platelet count $\geq 150 \times 10^9/L$. If CSPH could be neither ruled in nor ruled out, patients were in an indeterminate (also called “grey”) zone. The main outcome was to assess the performance of the diagnostic algorithms using the individual data from each study for providing positive predictive values (PPV) and negative predictive values (NPV) of $\geq 90\%$. According to Baveno consensus and

current recommendations, these targets were considered adequate [2, 25]. In this study, we prioritize selecting patients with CSPH in most of them (90%) to make sure that they are the correct candidates for receiving β -blockers; in other words, we want to avoid false positives, prioritizing a test that predicts a high chance of having CSPH, versus a test with high diagnostic accuracy.

Statistical analysis

Contingency tables were constructed with true positives, true negatives, false positives and false negatives with individual patient data from each study. Sensitivity, specificity, PPV, NPV and their 95% CIs were calculated. With these data, we performed a univariate quantitative meta-analysis of proportions to pool PPVs (for ruling in criteria) and NPVs (for ruling out criteria). In the meta-analysis of studies, two analyses were performed, excluding and including the original paper by Pons, et al. [8]. We used the Freeman-Tukey double arcsine transformation, and a random-effects model with the inverse variance method for pooling the proportions. We did not use bivariate models (which consider the covariance of sensitivity and specificity) in our meta-analysis because bivariate models require continuity correction, which adds a 0.5 to cells with zero value; since the number of zero cells was high in this study, we thought this would substantially bias the estimators. Also, the ruling in and ruling out criteria are very different and were developed to have a high PPV and NPV respectively. It has been argued that prevalence has a major impact on PPV and NPV. This is the case also for sensitivity and specificity [26]. We addressed the issue of the impact of prevalence of CSPH on NPV and PPV in two ways, described in Supplementary Text 2.

Further, in trying to simplify predictions for all etiologies we assessed whether the use of the ANTICIPATE±NASH (<https://www.bcn-liverhuvh.com/resources>) with a threshold probability of 0.75 of CSPH could be a general threshold to rule in CSPH in all etiologies of cACLD, as explained in Supplementary Text 2 .

We also analyzed the performance in the intermediate zone (patients not ruled in or out) of the AASLD criteria for assuming CSPH published after the Baveno VII consensus [6]. Specifically, CSPH can be presumed if LSM ≥ 20 and < 25 kPa plus platelets $< 150 \times 10^9/L$ or if LSM > 15 and < 20 kPa plus platelets $< 110 \times 10^9/L$. In addition, in a small subset of 216 patients from which we had an upper endoscopy performed at the same time as the other procedures, we analyzed the effect of detecting varices to reclassify patients for CSPH on the intermediate zone, as reported by Dajti, et al. [10].

Finally, since adequate calibration is essential for decision making [27] and considering the proposed use of ANTICIPATE±NASH for clinical practice, there is a need for testing the performance of these models in different centers. The methodological approach for this analysis is explained in Supplementary Text 2.

All analyses were performed in R / R Studio Version 2024.12.1+563 (2024.12.1+563) with the *dplyr*, *pROC*, *ggplot 2*, *randomForest*, *metafor*, *meta*, and *rms* packages [28-35].

Results

Study selection process and quality assessment

Our search strategy identified 801 potential records. Then we proceed with the automatic removal of duplicates, reviewing titles and abstracts and full-text assessment for some studies (Supplementary Figure 1). Of note, four poster abstracts and one published study [15] were included for full review but were finally excluded because of overlapping data with the final selected studies and another study [21] did not have LSM paired with HVPG in all patients (only 49 patients). After manual search of references, we identified and included another relevant work [16]. Six studies [8, 16-20] were eligible and all corresponding authors were contacted; however, no response was received from one author after three attempts. The remaining five authors [8, 16-19] agreed to share their data and participate in the analysis. All studied samples were retrospective. One of them included prospectively collected data for the validation cohort [8], while another one was a retrospective analysis of prospectively collected data [18]. All studies were performed in a hospital setting.

The methodological quality of the studies assessed with the QUADAS-2 tool and the characteristics of the studies are summarized in Supplementary Tables 2 and 3.

Patient characteristics

The total sample comprised 1433 patients from five studies. The distribution of etiologies and general characteristics of the patients included in the studies are shown

in Table 1. Mean LSM in the overall sample was 26.9 ± 17.2 kPa. The mean value of ANTICIPATE $\pm$ NASH was 60.1 (SD 31.7). The prevalence of CSPH in the included studies correlating HVPG and LSM by TE was close to 60% with a mean HVPG of 11.8 (6.1) mmHg. The characteristics and distribution of patients by etiology is shown in Supplementary Table 4 and 5.

Meta-analysis of the ruling in criterion for CSPH of Baveno VII

Figure 1 A and B show the PPVs for ruling in CSPH (LSM ≥ 25 kPa) corresponding to the analysis excluding and including the original paper by Pons, et al., with similar results. With all studies included, the pooled PPV was 0.92 (0.89-0.94) with low heterogeneity. The lowest PPV was seen in the Odraizola, et al. cohort (0.73), which presented the lowest prevalence of CSPH. The performance of the ruling in criterion for the aggregated data from all studies is shown in Supplementary Table 6.

The forest plot of the same ruling in criterion by etiology of cACLD is depicted in Figure 1C. As seen, for each etiology the pooled PPV was greater than 0.90, except in MASLD patients with obesity (0.67). Supplementary Table 7 shows the performance metrics of the raw data pooled for each etiology. Here additional and mixed etiologies not individually represented in the meta-analysis are analyzed, showing a very high PPV for metabolic dysfunction and increased alcohol intake (MetALD), cholestatic diseases and HCV combinations with other etiologies.

Figure 2 shows the result of meta regression (or moderator analysis) to test the contribution of etiology and prevalence to explain the variation in PPV for CSPH of the

ruling in criteria. Meta-regression showed that cohorts with higher CSPH prevalence tended to have higher PPV (coefficient 0.57, 95% CI 0.20–0.95; p-value= 0.003, Figure 2A). After accounting for etiology, however, this association was attenuated (coefficient 0.20, 95% CI –0.34–0.73, p-value=0.477, Figure 2B).

Meta-analysis of a new ruling in criterion based on ANTICIPATE±NASH values

To provide an etiology-agnostic ruling in prediction for CSPH, we tested the performance of a prediction rule based on a risk of CSPH by the ANTICIPATE±NASH model $\geq 75\%$. Figure 3A shows the pooled results of PPVs for ruling in CSPH with this criterion. The pooled PPV was 0.95 (0.93-0.97), higher than LSM ≥ 25 kPa with also low heterogeneity. The performance of this ruling in criterion for the aggregated data from all studies is shown in Supplementary Table 8.

The forest plot of the ANTICIPATE±NASH model $\geq 75\%$ criterion by etiology of cACLD is depicted in Figure 3B. As observed, the PPV for MASLD patients with obesity notably increased from 0.67 to 0.83 ($p < 0.001$). Supplementary Table 9 shows the performance metrics for the raw data pooled for each etiology, including etiologies not individually represented in the meta-analysis, all of them with very high PPVs.

Finally, in Supplementary Figure 2 we show in a meta regression analysis that with the use of the ANTICIPATE±NASH $\geq 75\%$ criteria there is no association between the prevalence of CSPH and the PPV for CSPH even without adjusting by etiology, suggesting that this new prediction rule is truly etiology agnostic.

Meta-analysis of the ruling out criteria for CSPH of Baveno VII

Figure 4A shows the pooled results of NPV for ruling out CSPH (LSM ≤ 15 kPa + platelets $\geq 150 \times 10^9/L$). The pooled NPV was 0.99 (0.97-1) with low heterogeneity. The performance of this ruling out criterion for the aggregated data from all studies is shown in Supplementary Table 10.

The forest plot of the same ruling out criteria by etiology of cACLD is depicted in Figure 4B. As seen, for each etiology the pooled NPV was excellent. Supplementary Table 11 shows the performance metrics of the raw data pooled for each etiology. As shown in Supplementary Figure 3, NPVs are not influenced by etiology of cACLD.

We provide at the end of Supplementary Data all contingency tables for all previous analysis.

Intermediate zone and AASLD criteria or endoscopy for CSPH

Table 2 summarizes the distribution of patients and the prevalence of CSPH in the different subgroups determined by the distinct ruling in criteria, including the AASLD classification criteria for the intermediate zone. As seen, patients selected by the AASLD criteria present CSPH prevalences of less than 81%.

Also, in Supplementary Table 12, the results of performing an endoscopy searching for varices in the subset of 216 patients are shown. Using both classification criteria

the percentage of patients with varices in the intermediate zone is similar (22-24%), representing a reduction of 10% in the unclassified patients (from 46% to 36%).

Calibration of the ANTICIPATE±NASH model to predict CSPH clustered by centers

As reported in methods, we tested the robustness of the prediction performance of the ANTICIPATE±NASH across centers. Supplementary Table 13 outlines the general characteristics of all patients available after the addition of the patients provided by two corresponding authors (ED and TR). Figure 5A shows the calibration-in-the-large of the ANTICIPATE±NASH model divided by center. There was an excellent agreement between mean predicted and observed probabilities of CSPH. Furthermore, discrimination (assessed by the C-statistic) was excellent within each center (see Supplementary Table 14). We then used a 2-step meta-analytic approach to test the moderate calibration of ANTICIPATE±NASH considering center clustering. Figure 5B shows the meta-analytic calibration curve, again showing excellent agreement between predicted and observed probabilities of CSPH across all levels of risk.

Discussion

Preventing first decompensation is now a cornerstone of treatment in at-risk patients with cACLD [2-5]. Since patients with CSPH will have the highest benefit from preventive therapies, their identification is becoming increasingly important [3-5]. Screening for CSPH is now possible with non-invasive tests that are simple, repeatable, usable at point-of-care, and recommended by the Baveno VII consensus [2]. In this study, we conducted a systematic review and IPD meta-analysis from data-independent cohorts validating the performance of Baveno VII criteria for detecting CSPH while improving the ruling in criteria with the ANTICIPATE±NASH model.

Baveno VI introduced the possibility to rule in CSPH in virus related cACLD [1] and Baveno VII consolidated a solid recommendation for non-invasive CSPH diagnosis across different etiologies [2], changing clinical decision making in hepatology. The combined LSM ≤ 15 kPa and platelets $\geq 150 \times 10^9/L$ and the LSM ≥ 25 kPa thresholds, confidently divide patients into two groups regarding the presence of CSPH: extremely unlikely and highly probable, respectively. The high performance of these classification rules comes with two drawbacks: First, the ruling in criterion is valid for most etiologies of cACLD except for MASLD patients with obesity, losing the ability to predict CSPH with high BMI. Second, many patients (40-50%) [8, 16-20] fall into an area of uncertainty, the intermediate or gray zone, in which CSPH cannot be excluded or affirmed. Many efforts have been made since the advent of these recommendations to narrow this gap, and some promising tools have risen in the field.

The first key finding of this study is the validation of the Baveno VII criteria. First, the ruling out criterion presents a nearly unbeatable pooled NPV (0.99) with only 4 patients

(out of 203, 1.97%) having CSPH in this group. For this reason, no attempt was made to improve the classification rule. Second, the ruling in criterion ($\text{LSM} \geq 25$) has an excellent PPV (0.92) but, as expected, fails to accurately classify MASLD patients with obesity. In the cohort of Odraizola, et al. a study with a high proportion of MASLD patients and obesity- the PPV fell to 0.73 and, when analyzing the PPV by etiology, MASLD patients with obesity had a poor pooled PPV (0.67). This low PPV was not seen in MASLD patients without obesity (0.96).

Improving the ability to detect CSPH in MASLD patients with obesity is needed. The ANTICIPATE models provide an individual risk assessment of CSPH [8] and are currently recommended [2, 6, 14] as valuable diagnostic tools in the increasing population of cACLD patients. Moreover, the ANTICIPATE-NASH model was specifically developed for MASLD patients, considering BMI an important variable. In this study, we propose an $\text{ANTICIPATE} \pm \text{NASH} \geq 75\%$ threshold for ruling in CSPH. First, the overall pooled PPV is greater with the $\text{ANTICIPATE} \pm \text{NASH} \geq 75\%$ (0.95) than with the $\text{LSM} \geq 25$ kPa criterion (0.92). Second, in the population of MASLD patients with obesity, the PPV improved notably from 0.67 to 0.83. Third, the $\text{ANTICIPATE} \pm \text{NASH}$ criteria render etiology less critical for the prediction of CSPH (as shown in the scatter plots in Figure 2 and Suppl. Figure 2). Fourth, with the new criteria there is a marginal reduction of patients left in the intermediate zone (from 45% to 43%). Lastly, changing from LSM to the ANTICIPATE models does not complicate the process since by using the online tool, the information can be still obtained rapidly at point-of-care by imputing platelet count (in all patients) and BMI (in MASLD patients).

It is worth mentioning that the compilation of the present large sample of patients has provided the opportunity of analyzing the performance of these different classification criteria for CSPH in other etiologies generally underrepresented in large studies. In that sense, the classification criteria perform very well in all of them, including MetALD, cholestatic diseases and combination of HCV and other etiologies, supporting the universal utility of these classification rules. In addition, we were able to test a potential “center effect”, which shows that the performance of the ANTICIPATE±NASH model is robust across the centers involved in the study, both in terms of calibration and discrimination. Finally, we show that the AASLD criteria for classifying CSPH in the intermediate zone present in our study an observed prevalence of CSPH lower than 81%, and that by performing an upper endoscopy in patients in this intermediate zone, 22% of them present gastro-esophageal varices, reducing the proportion of unclassified patients.

There have been other steps forward to improve the detection of CSPH in patients with cACLD since Baveno VII. Notably, the von Willebrand factor antigen to platelet ratio (VITRO) as a non-invasive test alone or applying it sequentially to Baveno VII criteria [18] can detect patients with CSPH with a similar diagnostic accuracy and reduce significantly the intermediate zone. In the last few years, spleen stiffness measurement (SSM) has been establishing its role in the field of noninvasive assessment of portal hypertension. Recently, Jachs, et al. showed that the use of SSM 100Hz in detecting CSPH comparing a combination of SSM, LSM platelet and BMI (NICER model) directly with the ANTICIPATE±NASH, yielded a slightly higher AUC for prediction of CSPH [9], though the new model did not improve the AUC in MASLD

patients. In the classification algorithm proposed by these authors, the performance for MASLD patients with obesity was similar to other etiologies. However, using this algorithm, there is still an intermediate (unclassified) group of patients of 35%, not far from our 43%.

Our study has several strengths. This is an individual patient data meta-analysis of a large cohort of more than 1400 patients with representation of various etiologies of liver disease. Notably 25% of the total cohort are MASLD patients and nearly 20% ALD patients. The IPD approach provides high consistency in collecting the data, more precise estimation, harmonization across studies and stratified subgroup analysis. We validate Baveno VII criteria and further explore the utility of ANTICIPATE $\pm$ NASH in diagnosing CSPH. The new ruling in criteria using an ANTICIPATE $\pm$ NASH $\geq 75\%$ threshold will be a valuable addition to the algorithm of the “rule of five” (Figure 6). In addition, it is important to remark that detecting or not CSPH by these non-invasives rules is clinically relevant since the different subgroups determined by the algorithms carry very different clinical outcomes as evidenced in several reports [36, 37]. Furthermore, the IPD approach allows us to conduct new exploratory analyses and find a relationship between ANTICIPATE $\pm$ NASH values and HVPG. Our study has some limitations. The analysis is based on a limited number of retrospective studies. Also, any classification rule that includes LSM is a limitation for centers that do not have access to the device, and it might be problematic the performance and interpretation of LSM in patients with important obesity, in which LSM often fails. The new proposed algorithm for ruling in CSPH using the 75% threshold of ANTICIPATE $\pm$ NASH obtained by using our whole dataset might be affected by overfitting and will need further validation.

In conclusion, Baveno VII criteria have excellent performance in screening in and out CSPH in cACLD patients of different etiologies. Using an ANTICIPATE±NASH value $\geq 75\%$ as ruling in threshold, the global performance improved, especially in MASLD patients with obesity. Finally, we show stability of the performance of ANTICIPATE±NASH across different centers, suggesting that it can be used as a validated tool to guide clinical practice.

Abbreviations:

ALD = Alcohol-related liver disease

BMI = Body mass index

cACLD = Compensated advanced chronic liver disease

CSPH = Clinically significant portal hypertension

HBV = Hepatitis B virus

HCV = Hepatitis C virus

HVPG = Hepatic venous pressure gradient

IPD-MA = Individual patient data meta-analysis

kPa = Kilopascals

LSM = Liver stiffness measurement

MetALD = MASLD and increased alcohol intake

MASLD = Metabolic dysfunction-associated steatotic liver disease

NPV = Negative predictive value

PPV = Positive predictive value

PRISMA = Preferred reporting Items for Systematic Reviews and Meta-Analyses

QUADAS-2 = Quality assessment of diagnostic accuracy studies 2

SSM = Spleen stiffness measurement

TE = Transient elastography

WoS = Web of Science

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Tables:

Table 1. General characteristics of the overall cohort and of the individual studies

	Pons [8]	Jachs [18]	Dajti [17]	Podrug [16]	Odraizola [19]	Overall
Patients (n)	835	276	195	71	56	1433
Age (mean $\pm$ SD)	57.1 $\pm$ 11.2	54.2 $\pm$ 11.5	58.6 $\pm$ 12.7	59.3 $\pm$ 10.3	60.2 $\pm$ 7.5	57 $\pm$ 11.4
Male (%)	533 (63.8%)	191 (69.2%)	134 (68.7%)	55 (77.5%)	56 (66.1%)	950 (66.3%)
Etiology (n, %)						
HCV*	358 (42.8%)	114 (41.3%)	73 (37.4%)	3 (4.2%)	0	548 (38.2%)
HBV	27 (3.2%)	14 (5.1%)	11 (5.6%)	3 (4.2%)	1 (1.8%)	56 (3.9%)
ALD	167 (20%)	47 (17%)	18 (9.2%)	28 (39.4%)	11 (19.6%)	271 (18.9%)
MASLD†	222 (26.6%)	41 (14.8%)	31 (15.9%)	23 (32.4%)	43 (76.8%)	360 (25.1%)
• MASLD with obesity (BMI $\geq$ 30 kg/m ²)	121 (14.5%)	24 (8.7%)	10 (5.13%)	11 (15.49%)	39 (69.6%)	205 (14.3%)
• MASLD without obesity	87 (10.4%)	17 (6.2%)	21 (10.8%)	12 (16.9%)	4 (7.1%)	141 (9.8%)
Other **	61 (7.3%)	60 (21.7%)	62 (31.8%)	14 (19.7%)	1 (1.8%)	198 (13.8%)
LSM (kPa) (mean, SD)	28.72 $\pm$ 18.8	26.51 $\pm$ 16	22.83 $\pm$ 10	24.71 $\pm$ 17	18.72 $\pm$ 13.7	26.9 $\pm$ 17.2
Platelet count (10 ⁹ /L) (mean, SD)	141.8 $\pm$ 72.9	130.9 $\pm$ 69.4	130.3 $\pm$ 67.8	166.9 $\pm$ 72.3	183.8 $\pm$ 84.1	141 $\pm$ 72.9
ANTICIPATE $\pm$ NASH (%) (mean, SD)	61.2 $\pm$ 32.3	63.3 $\pm$ 28.7	61.5 $\pm$ 27.6	52.1 $\pm$ 36.5	32.2 $\pm$ 29.4	60.1 $\pm$ 31.7
HVPG (mmHg) (mean, SD)	12.2 $\pm$ 6.6	11.8 $\pm$ 5.6	11.7 $\pm$ 4.3	10.5 $\pm$ 6	7.7 $\pm$ 4.5	11.8 $\pm$ 6.1
CSPH (n, %)	493 (59%)	167 (60.5%)	121 (62%)	38 (53.5%)	19 (33.9%)	838 (58.5%)

* All HCV patients had active infection and were assessed prior to therapy

† 14 MASLD patients missed BMI information all in Pons et al [4]

** Other included patients with the following etiologies: MetALD, HCV and ALD, HCV and MASLD, PBC, PSC and other underrepresented etiologies (see Supplementary table 4).

CSPH = Clinically significant portal hypertension, HCV = Hepatitis C virus, HBV = Hepatitis B virus, ALD = Alcohol-related liver disease, MASLD = Metabolic dysfunction-associated steatotic liver disease, LSM = Liver stiffness measurement, HVPG = Hepatic venous pressure gradient, BMI = body mass index

Table 2. Distribution of patients and prevalence of clinically significant portal hypertension (CSPH) in the subgroups based on different classification criteria, including the AASLD criteria for the intermediate zone. In (A) ruling in CSPH with Baveno VII criteria of LSM ≥ 25 kPa. In (B) ruling in CSPH with ANTICIPATE $\pm$ NASH $\geq 75\%$

(A) RULING IN CSPH WITH LSM ≥ 25 kPa		
RULING OUT CSPH LSM ≤ 15 kPa + platelets ≥ 150.000	INTERMEDIATE ZONE*	RULING IN CSPH LSM ≥ 25 kPa
203 (14.2%) CSPH: 1.97%	646 (45.1%) CSPH: 46.9%	584 (40.75%) CSPH: 90.92%
	**LSM 20-25 kPa + < 150.000	
	134 (CSPH 80.6%)	
	**LSM 15-20 kPa + <110.000	
	80 (CSPH 71.25%)	

(B) RULING IN CSPH ANTICIPATE $\pm$ NASH $\geq 75\%$		
RULING OUT CSPH LSM ≤ 15 kPa + platelets ≥ 150.000	INTERMEDIATE ZONE*	RULING IN CSPH ANTICIPATE $\pm$ NASH $\geq 75\%$
203 (14.2%) CSPH: 2%	616 (43.1%) CSPH: 42.7%	610 (42.7%) CSPH: 93.5%
	**LSM 20-25 kPa + < 150.000	
	53 (CSPH 71.7%)	
	**LSM 15-20 kPa + <110.000	
	61 (CSPH 67.2%)	

* Intermediate zone refers to patients not ruled in or out.

** Classification criteria based on AASLD recommendations.

LSM = Liver stiffness measurement

Figure legends:

Figure 1. Forest plots for ruling in CSPH with LSM ≥ 25 kPa criteria. (A)

Performance excluding the study by Pons et al., (B) Performance including all studies and (C) Performance by etiology.

Figure 1 footnotes: LSM = Liver stiffness measurement, CSPH = Clinically significant portal hypertension, PPV = Positive predictive value, Prev = Prevalence, HCV = Hepatitis C virus, HBV = Hepatitis B virus, ALD = Alcohol-related liver disease, MASH = Metabolic dysfunction-associated steatohepatitis, Other etiologies include patients classified as such in Table 1 and Supplementary Table 4.

Figure 2. Meta regression showing the association between the prevalence of CSPH (in different etiologies) and the PPV of the Baveno VII ruling in criteria (LSM ≥ 25 kPa).

In univariable meta-regression, higher prevalence was associated with higher PPV (coefficient 0.57, 95% CI 0.20–0.95) (A), but this association was no longer significant after adjustment for etiology (coefficient 0.20, 95% CI –0.34–0.73) (B).

Figure 2 footnotes: PPV = Positive predictive value, CSPH = Clinically significant portal hypertension, ALD = Alcohol-related liver disease, HBV = Hepatitis B virus, HCV = Hepatitis C virus, MASH = Metabolic dysfunction-associated steatohepatitis.

Figure 3. Forest plots for ruling in CSPH with ANTICIPATE $\pm$ NASH $\geq 75\%$ criteria.

(A) Performance including all studies and (B) Performance by etiology.

Figure 3 footnotes: LSM = Liver stiffness measurement, CSPH = Clinically significant portal hypertension, PPV = Positive predictive value, Prev = Prevalence, HCV = Hepatitis C virus, HBV = Hepatitis B virus, ALD = Alcohol-related liver disease, MASH

= Metabolic dysfunction-associated steatohepatitis, Other etiologies include patients classified as such in Table 1 and Supplementary Table 4.

Figure 4. Forest plots for ruling out CSPH the LSM ≤ 15 kPa + platelet count $\geq 150 \times 10^9/L$ criterion. (A) Performance by study and (B) by etiology.

Figure 4 footnotes: LSM = Liver stiffness measurement, CSPH = Clinically significant portal hypertension, NPV = Negative predictive value, Prev = Prevalence, HCV = Hepatitis C virus, HBV = Hepatitis B virus, ALD = Alcohol-related liver disease, MASH = Metabolic dysfunction-associated steatohepatitis. Other etiologies include patients classified as such in Table 1 and Supplementary Table 4.

Figure 5. Calibration of the ANTICIPATE $\pm$ NASH model to predict CSPH clustered by centers. A) Calibration-at-large across the centers providing patients for the present study. Due to the low numbers, the two centers contributing less patients (Bern and London) were pooled as a single center. The size of the circles represents the number of patients contributed by each center. The plot shows an excellent agreement between the mean predicted risk of CSPH (by ANTICIPATE $\pm$ NASH) and observed proportion of patients with CSPH. B) 2-step meta-analytic calibration plot. The dark pink area represents the 95% confidence interval of the average calibration curve (CI). The lighter pink areas represent the 95% confidence interval of the prediction intervals (PI) at each level of estimated probability of CSPH.

Figure 6. Updated algorithm for the “rule of 5” for non-invasive determination of cACLD and CSPH.

Figure 6 footnotes: cACLD = compensated advanced chronic liver disease; CSPH = clinically significant portal hypertension; MASLD = metabolic dysfunction-associated steatotic liver disease.

Figures:

Figure 1A

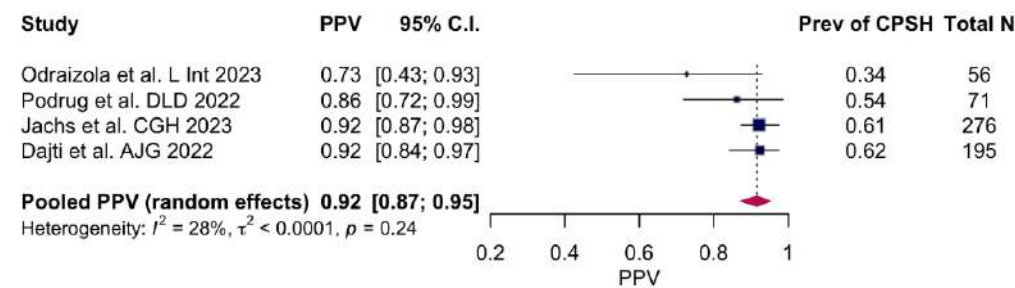


Figure 1B

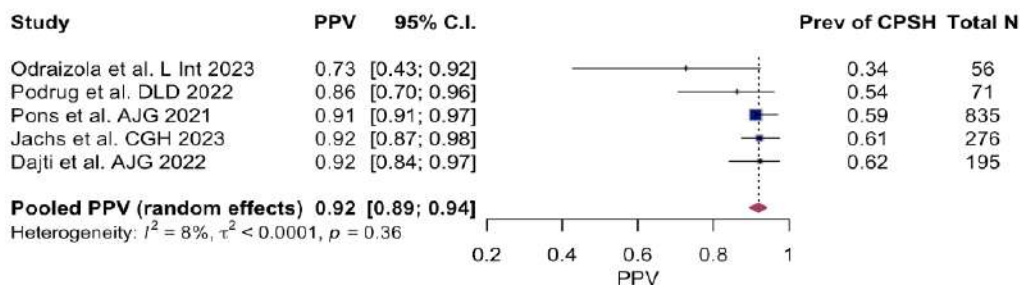


Figure 1C

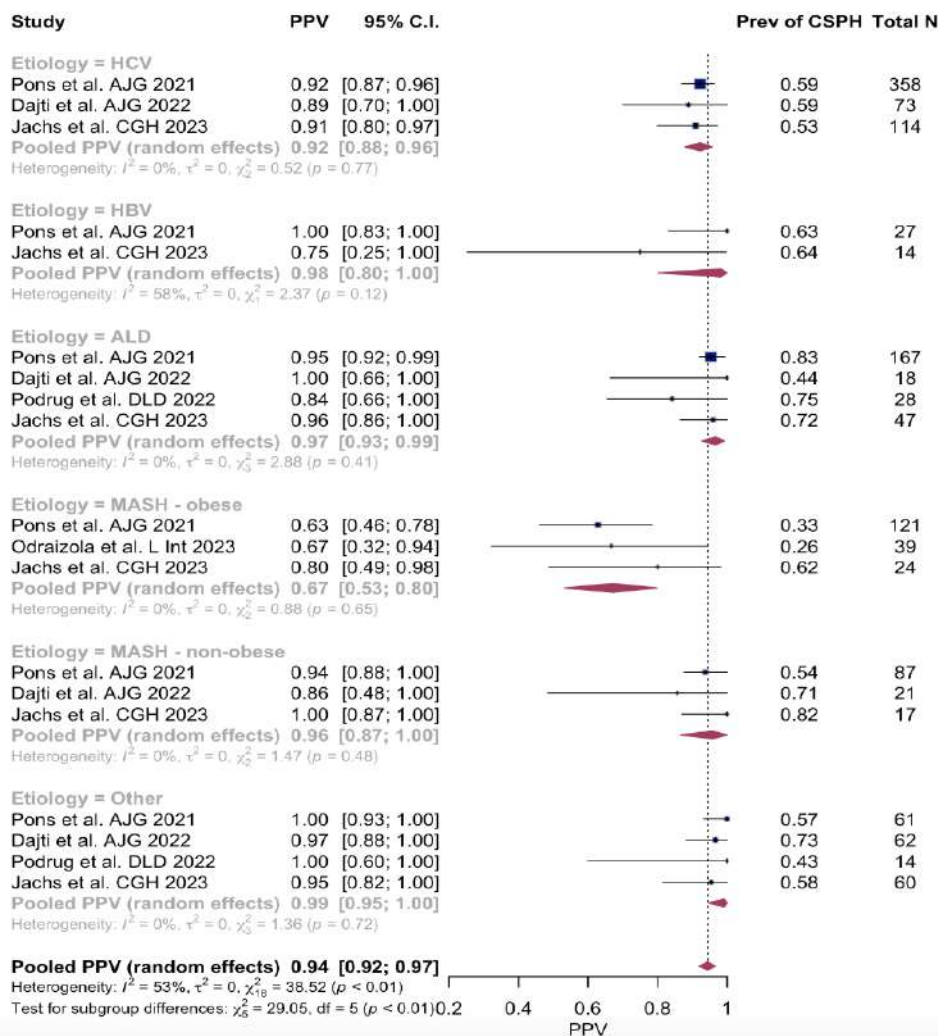


Figure 2A

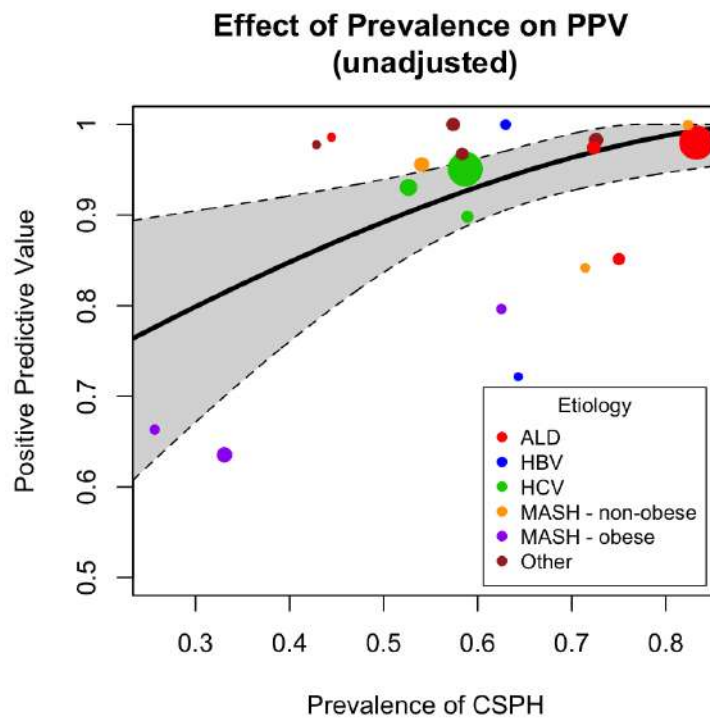


Figure 2B

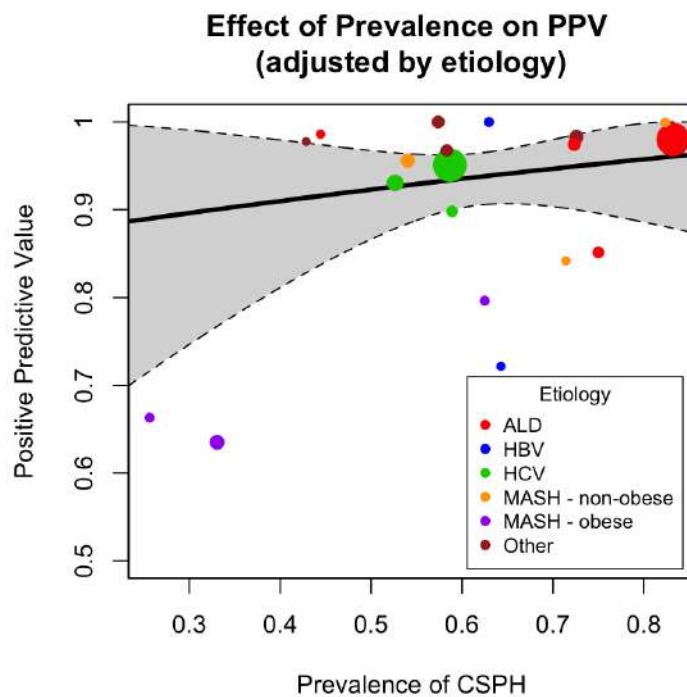


Figure 3A.

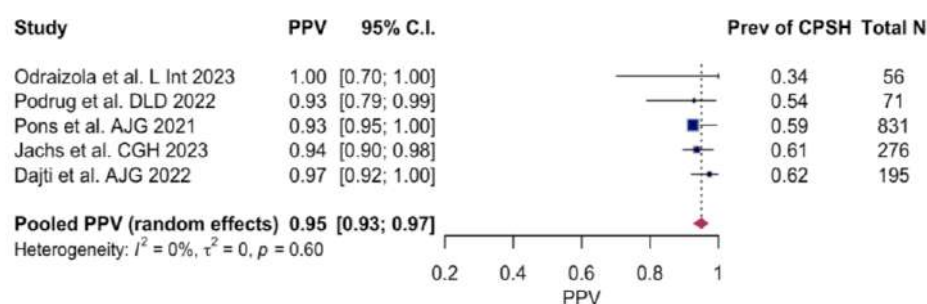


Figure 3B.

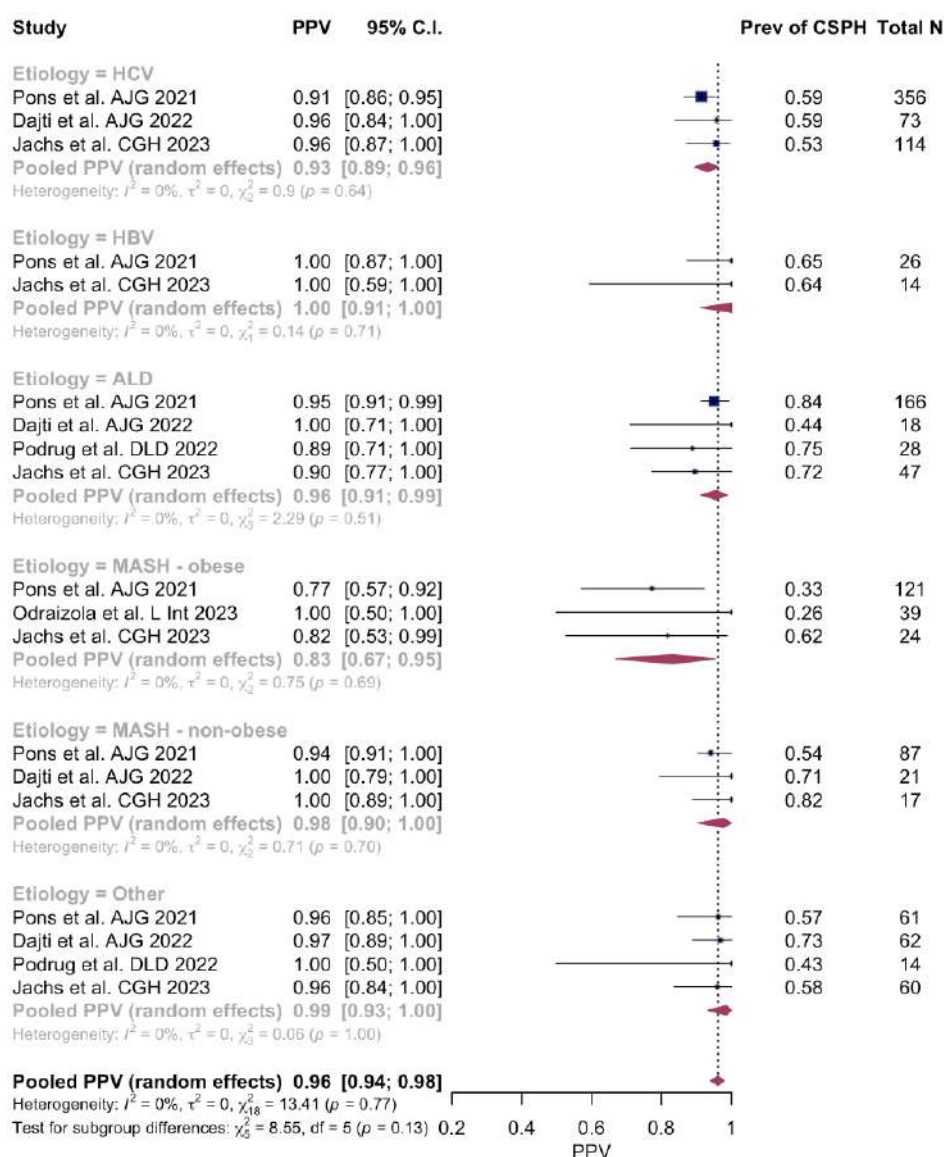


Figure 4A

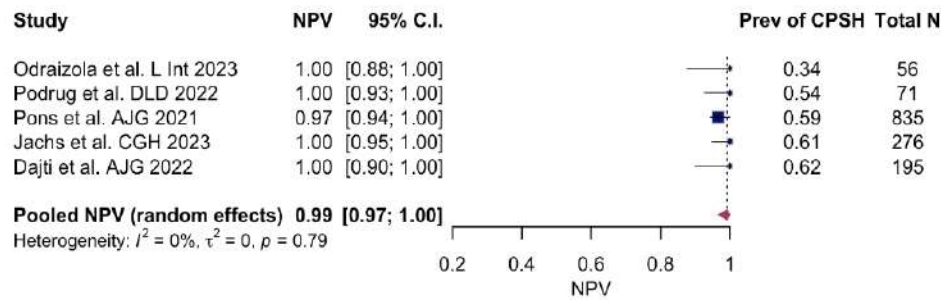


Figure 4B

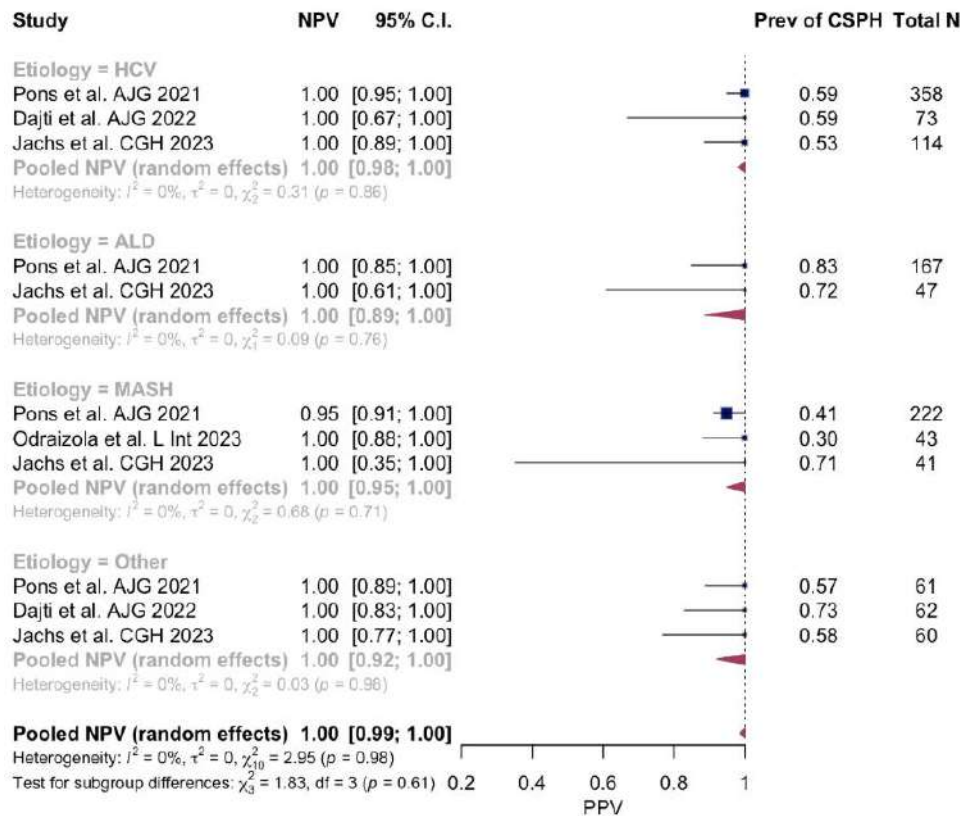


Figure 5

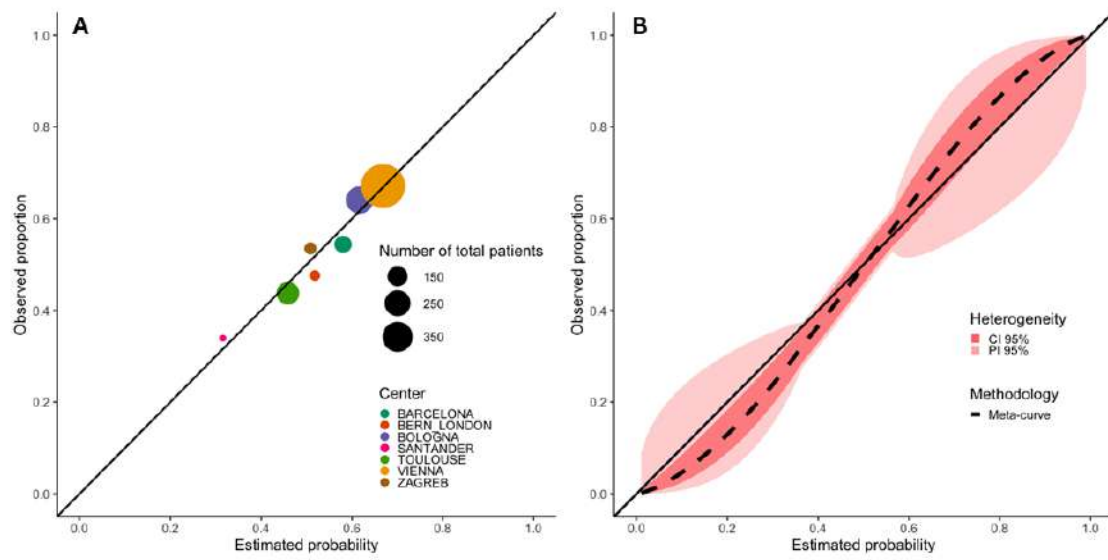
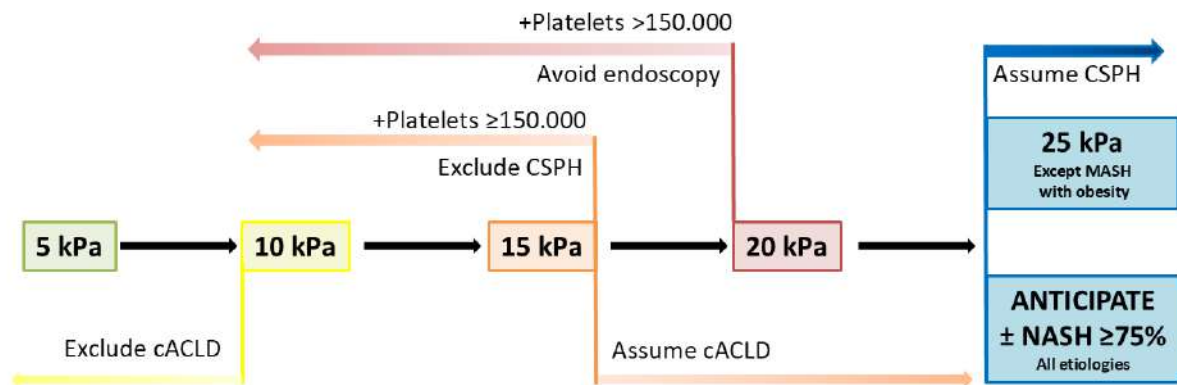


Figure 6



4.2. ARTÍCULO 2

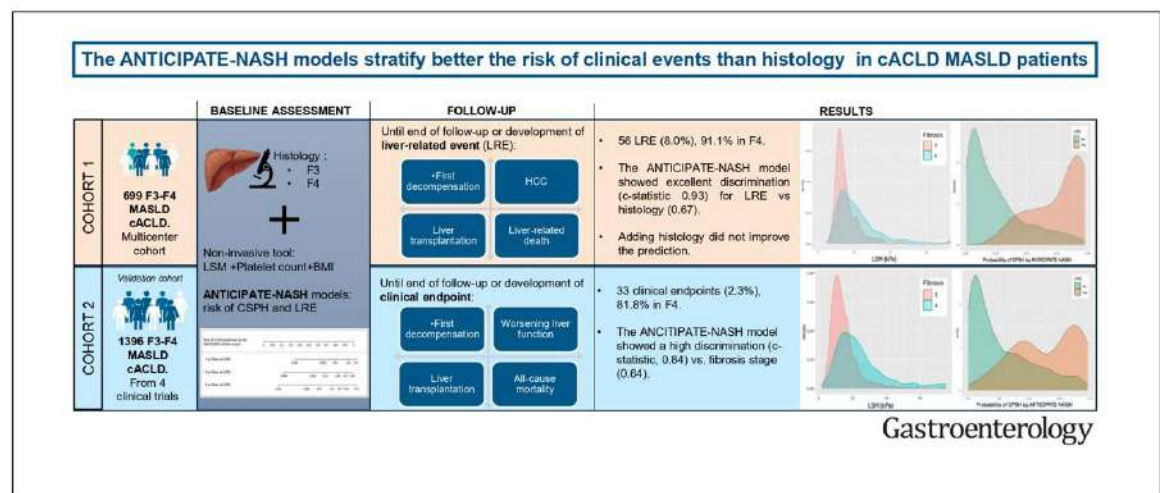
Aceituno L, Bañares J, Pons M, Rivera-Esteban J, Sabiote C, Cammà C, Ciancimino G, Pennisi G, Tulone A, Ma MM, Liu X, Watkins TR, Billin AN, Petta S, Pericàs JM, Abraldes JG, Genescà J. The ANTICIPATE-NASH Models Stratify Better the Risk of Clinical Events Than Histology in Metabolic Dysfunction-Associated Steatotic Liver Disease Patients With Advanced Chronic Liver Disease. *Gastroenterology*. 2025 Nov 10:S0016-5085(25)05905-0. doi: 10.1053/j.gastro.2025.08.020. Epub ahead of print. PMID: 41212130.

DOI: 10.1053/j.gastro.2025.08.020

The ANTICIPATE-NASH Models Stratify Better the Risk of Clinical Events Than Histology in Metabolic Dysfunction-Associated Steatotic Liver Disease Patients With Advanced Chronic Liver Disease

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BACKGROUND & AIMS: The reference for risk stratification and clinical trial selection of metabolic dysfunction-associated steatotic liver disease (MASLD) patients is fibrosis degree by histology. The noninvasive ANTICIPATE-NASH models have been validated for risk prediction of clinically significant portal hypertension (CSPH) and liver-related events (LRE). We assessed whether these models provide better risk stratification of events than histology. **METHODS:** A multicenter cohort 1, including 699 biopsy specimen-proven F3-F4 patients with MASLD was evaluated. The end point was LRE (hepatic decompensation, hepatocellular carcinoma, transplantation, or liver-related death). We assessed (Cox regression) whether histology provided added value to ANTICIPATE-NASH and whether model predictions differed in F3/F4 patients. Results

were validated in cohort 2 (1396 F3-F4 patients) from 4 clinical trials using the clinical regulatory end point. **RESULTS:** In cohort 1, F3 and F4 were equally distributed. There were 56 LREs (8.0%) during follow-up, concentrated in F4 (51 LREs). The ANTICIPATE-NASH model showed excellent discrimination (C statistic, 0.93) for LRE, higher than histology (C statistic, 0.67). Model calibration was excellent. Adding histology did not improve model prediction. Thresholds of ANTICIPATE-NASH above which F3 patients developed LREs and below which F4 patients did not were identified. Results were reproduced in cohort 2 with the regulatory end point, with higher model discrimination (C statistic, 0.84) compared with histology (C statistic, 0.64). **CONCLUSIONS:** In MASLD patients with F3/F4, the noninvasive ANTICIPATE-NASH models

provide better risk stratification of clinical events than histologic classification. These models could be very useful for clinical trials by selecting patients at risk of clinical events and patients with higher chances of observed cirrhosis regression.

Keywords: Predictive Models; Clinical Events; Steatotic Liver Disease.

Predicting the risk of having a clinical condition or clinical events related to that condition is essential for clinical practice. Very often, patients are classified in subgroups with different risks of presenting events (risk stratification) based on characteristics or parameters related to the disease.¹ Then these subgroups, frequently based on numerical thresholds, provide an average estimate of the risk of events. The lower the number of subgroups, the less accurate is the prediction for an individual patient.² By contrast, predictive models can provide individual prediction for the whole spectrum of the disease condition. These models to be successful should be validated, easy to use, clinically sound, and if possible, applied to a clinical situation in which interventional or therapeutic decisions must be taken.

Metabolic dysfunction-associated steatotic liver disease (MASLD)³ is one of the most common causes of chronic liver diseases, currently affecting ~30% of the worldwide adult population.⁴ It has emerged as one of the leading causes of cirrhosis and hepatocellular carcinoma in middle- and high-income countries.⁵ MASLD includes a continuum of hepatic lesions from steatosis, with or without inflammation, to fibrosis and ultimately, cirrhosis. A liver biopsy specimen has served as the primary tool for risk stratification and selection of patients for clinical trials in MASLD patients. It has been established that only fibrosis stages F3 and F4 are associated with death due to liver disease.⁶ However, histologic classification is invasive, with a high degree of misclassification,⁷ and importantly, very inaccurate in predicting an individual risk, because the variability of risks inside each subgroup (F3 or F4) is considerable.

The development of clinically significant portal hypertension (CSPH) is a key driver and a surrogate marker of decompensation and liver-related events (LREs) in patients with compensated advanced chronic liver disease (cACLD),^{8,9} including MASLD patients.¹⁰ The development of CSPH and LREs in cACLD MASLD patients seems to follow a more subtle and slow progression than with other etiologies,^{6,11} complicating predictions regarding disease outcomes and clinical trial design.¹²

Among the noninvasive tests to predict the presence of CSPH, liver stiffness measurement (LSM), alone or combined with other markers, has been proposed as a preferred tool to identify patients at risk of LRE. The ANTICIPATE model, based on LSM by transient elastography and platelet count, is a validated tool for predicting CSPH in cACLD patients of different etiologies.^{13–15} By adding body mass index (BMI) to the model, the ANTICIPATE-NASH model was constructed and validated

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Stratification of the risk of clinical events and selection of patients for clinical trials with clinical end points in metabolic dysfunction-associated steatotic liver disease patients is usually done by assessing fibrosis degree by histology. Validated predictive models for assessing the risk of clinically significant portal hypertension and clinical events could potentially provide better and more granular risk stratification.

NEW FINDINGS

In metabolic dysfunction-associated steatotic liver disease patients with advanced fibrosis (F3 and F4 fibrosis degree), the ANTICIPATE-NASH models that include liver stiffness, platelet count, and body mass index, stratify the risk of clinical events much better than liver biopsy specimen. Once prediction of events by the model was known, histology was unable to improve it.

LIMITATIONS

The cohorts used were retrospective and partially used in prior studies. Central liver biopsy specimen reading was not available in all patients. The number of clinical events was low.

CLINICAL RESEARCH RELEVANCE

The use of the ANTICIPATE-NASH models for risk stratification and clinical trial selection of metabolic dysfunction-associated steatotic liver disease patients could facilitate risk assessment at point-of-care and reduce sample size and duration of clinical trials with clinical endpoints.

BASIC RESEARCH RELEVANCE

Liver fibrosis and portal hypertension can be reliably assessed by noninvasive methods sparing direct liver tissue analysis.

for predicting CSPH in MASLD patients.¹⁴ Both models are currently recommended in daily clinical practice according to Baveno VII guidelines.¹¹ Finally, the ANTICIPATE-NASH-LRE model was a subsequently validated adaptation of the original model to predict 3-year risk of LREs in MASLD patients.¹⁶

We hypothesized that by using the ANTICIPATE-NASH models, a more accurate prediction of LREs compared with liver histology (F3 vs F4) would be achieved in MASLD patients, providing better risk stratification and an

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Abbreviations used in this paper: BMI, body mass index; cACLD, compensated advanced chronic liver disease; CSPH, clinically significant portal hypertension; LRE, liver-related event; LSM, liver stiffness measurement; MASLD, metabolic dysfunction-associated steatotic liver disease; NASH, nonalcoholic steatohepatitis.

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improved patient selection for clinical trials. Further, we hypothesized that once ANTICIPATE-NASH is known, histology does not provide additional refinement in risk prediction. Finally, we aimed at testing whether ANTICIPATE-NASH predictions have a different interpretation when coming from patients with F3 and F4. To this end, 2 large cohorts of MASLD patients with F3/F4 fibrosis were consecutively evaluated.

Materials and Methods

Study Cohorts

The first cohort (cohort 1) was a multicentered retrospective cohort composed of MASLD patients from Vall d'Hebron University Hospital in Barcelona and patients from a multicenter international cohort from different European centers, plus 1 each from China and Canada, that had been published before.¹⁷ The patients from Barcelona were part of MASLD patients enrolled from January 2016 to December 2021 and monitored to July 2023 as outpatients, as previously published.¹⁶ During this period, 358 MASLD patients underwent a liver biopsy, and 149 showed F3/F4 fibrosis (Supplementary Figure 1). All patients had MASLD based on current criteria, no decompensation, LSM, and blood tests obtained within 3 months of the liver biopsy.

The multicenter international patients of cohort 1 were MASLD patients with F3/F4 fibrosis on histology or LSM ≥ 10 kPa.¹⁷ In this study, LSM was obtained within 6 months of the histology assessment. The initial cohort included 1039 patients recruited in the different centers from 2004 to 2019, of which 550 with a liver biopsy specimen showing F3/F4 fibrosis were selected. All patients in these 2 studies were monitored at 6-month intervals with laboratory tests and abdominal ultrasound imaging; LREs were recorded during follow-up visits. These 2 sets of patients were merged due to similar origin, composition, and clinical characteristics.

The second large cohort (cohort 2) was used to validate the results obtained by using a slightly different definition of LREs. This cohort was built with F3/F4 biopsy specimen-proven MASLD patients included in 4 different trials already reported in several publications (GS-US-321-0105; GS-US-321-0106; GS-US-384-1943/Safety and Efficacy of Selonsertib in Adults With Nonalcoholic Steatohepatitis [NASH] and Bridging [F3] Fibrosis [STELLAR-3]; GS-US-384-1944/Safety and Efficacy of Selonsertib in Subjects with Compensated Cirrhosis due to Nonalcoholic Steatohepatitis [NASH] STELLAR-4).^{18,19} A summary of the main characteristics of these 4 trials is described in Supplementary Table 1.

The 4 trials accounted for 2153 patients, from which 1396 could be included in the present analysis because they had LSM available to calculate the ANTICIPATE-NASH models. Length of follow-up and clinical end point rates were similar between patients with or without LSM (Supplementary Table 2). Additional information regarding cohort composition and overlapping is in the Supplementary Material.

Study Design and Definitions

We aimed to demonstrate the superior capability of the ANTICIPATE-NASH models to predict LREs and the higher

accuracy to stratify the risk of LREs in MASLD patients compared with liver histology. Specifically, we wanted to show that once the risk of LREs by the ANTICIPATE models is known, the information of whether the patient presents F3 or F4 in the liver biopsy specimen is irrelevant.

The first cohort with 699 F3/F4 patients from 2 different studies was used to again validate the ANTICIPATE-NASH-LRE model in this histology-driven population and compare the performance of both the model and fibrosis degree for predicting LREs and classifying subgroups of patients at different risk of LRE. For this, we used the LREs definition that was used in the original publication of the model,¹⁶ a composite of liver decompensation (ascites, portal hypertensive bleeding, and hepatic encephalopathy) and hepatocellular carcinoma. Liver transplantation and liver-related death are also included, but they rarely present as primary events. In every case, only the first LRE was considered.

The second cohort with 1396 F3/F4 patients from the clinical trials was used to prove that the same results could be achieved in a very selected population of MASLD patients with a different follow-up time and by using a different clinical event definition. The United States Food and Drug Administration regulatory composite end point was used, defined as hepatic decompensation (as previously defined), liver transplantation, worsening liver function with qualification for transplantation (Model for End-Stage Liver Disease ≥ 15), or all-cause mortality. The use of a similar but different end point or definition of clinical events was intentional to prove the adaptability and high predictability of the ANTICIPATE-NASH models.

Also, to demonstrate the ability of the models to reclassify F3 and F4 patients based on the predicted (and observed) risk of clinical events, we used the median values of ANTICIPATE-NASH of F3 and F4 patients to analyze F4 and F3 patients, respectively.

Finally, we explored the ANTICIPATE-NASH values of the following subgroups of the STELLAR 3 and 4 trials: (1) 84 F3 patients who improved ≥ 1 fibrosis stage at the 48-week follow-up liver biopsy specimen; (2) 88 F3 patients who progressed to F4 at the 48-week follow-up liver biopsy specimen; and (3) 122 F4 patients who improved ≥ 1 fibrosis stage at the 48-week follow-up liver biopsy specimen.¹⁸ Comparisons were made with F3 and F4 patients who changed fibrosis stage.

Assessments

Transient elastography by FibroScan (Echosens, Paris, France) was performed by using the standards of quality and the devices and procedures described in each of the different publications.¹⁶⁻¹⁹ LSM values from all studies were optimized by assuring a $<30\%$ (interquartile range/median ratio) variability among the different measures. Test-retest variability was not assessed in the present study.

Histology assessments were performed according to the usual standards, being also extensively described in the different publications.¹⁷⁻¹⁹ For the Barcelona patients, histology was reviewed by our expert liver pathologist, and patients were classified as F3 or F4 according to the NASH Clinical Research Network. Liver biopsy specimens from patients from the multicenter cohort¹⁷ were not centrally assessed, and the histologic information was based on the report from each

participating center. Specimens from patients from the 4 clinical trials of cohort 2 were centrally read as is usually performed in these studies.

The ANTICIPATE-NASH and ANTICIPATE-NASH-LRE values were calculated by using the original formulas as described in the publications,^{14,16} also available as online calculators (<https://www.bcn-liverhuvh.com/resources>).

Statistical Analysis

Analysis in cohort 1 was conducted in R (R Foundation for Statistical Computing) using the packages rms (Harrell Jr FE [2022] rms: Regression Modeling Strategies. R package 6.3-0) and Hmisc (Harrell Jr F [2022]. Hmisc: Harrell Miscellaneous. R package 4.7-1). We used Cox regression to develop risk-prediction models for LREs. We used a time horizon limit of 3 years as in our previous study.¹⁶ The added value of fibrosis to ANTICIPATE-NASH was tested by quantifying the contribution of each variable to the model with the χ^2 test and by comparing models with and without the fibrosis stage with the likelihood ratio, as previously described (<https://www.fharrell.com/post/addvalue/>).

To assess whether fibrosis stage modifies ANTICIPATE-NASH predictions, we tested the interaction of both variables. Discrimination of the models, which reflects how predictions separate high-risk from low-risk patients (patients with an earlier LRE time should exhibit a higher risk and those with later LRE time or no event a lower risk) was assessed with the C statistic, that was derived from the Somers' Dxy rank correlation (for a censored response variable) computed with the formula $C \text{ statistic} = Dxy/2 + 0.5$. Calibration of the model was tested graphically by plotting a smooth calibration curve of the observed event rates against the predicted risks at 3 years. Predicted risk was calculated based on the formulas provided in Pons et al.¹⁶ To quantify calibration we provide (1) the integrated calibration index (mean absolute difference between smoothed observed proportions and predicted probabilities) and (2) the E50 and E90 (median and 90th percentile absolute difference between observed and predicted probabilities of the outcome), using methods and code described in McLernon et al.²⁰

The analysis of cohort 2 was conducted in-house by the Gilead statistical team, following a similar strategy. Calibration could not be assessed in this cohort, because follow-up was much shorter than 3 years, and definition of the end point was more inclusive in cohort 2 than the one used to construct ANTICIPATE-NASH-LRE.

Results

Cohort 1 Evaluation

The main characteristics and LRE prevalence during follow-up for the 699 MASLD patients in cohort 1 are shown in [Supplementary Table 3](#). The proportion of F3 and F4 patients was 46.5% vs 53.5%, respectively. As expected, F3 patients were different from F4 patients in many epidemiologic and clinical characteristics. LREs developed during follow-up in 56 patients. Most LREs occurred in F4 patients (51 of 56). [Figure 1](#) shows the distribution of LSM values in F3 and F4 patients. F4 patients presented higher mean LSM values, but with considerable overlap with F3 patients. Accordingly, the predicted risk of CSPH by the ANTICIPATE-NASH model was higher in F4 patients ([Supplementary Table 3](#)), but also with high overlap with F3 patients ([Figure 1](#)).

Finally, the 56 patients who developed an LRE during follow-up compared with patients who did not, presented higher LSM (34.4 kPa vs 18.1 kPa, $P < .001$), and higher predicted risks of CSPH (62.6% vs 23.32%, $P < .001$) and 3-year LREs (17.7% vs 3.43%, $P < .001$). [Figure 2](#) shows the distribution of ANTICIPATE-NASH in patients with and without LRE within 3 years of follow-up, showing a markedly different distribution of ANTICIPATE-NASH values in patients with and without LREs.

Cohort 1 ANTICIPATE-NASH Models Performance and Added Value of Fibrosis Stage

The ANTICIPATE-NASH-LRE model showed excellent discrimination (C statistic, 0.93) ([Table 1](#)) and calibration

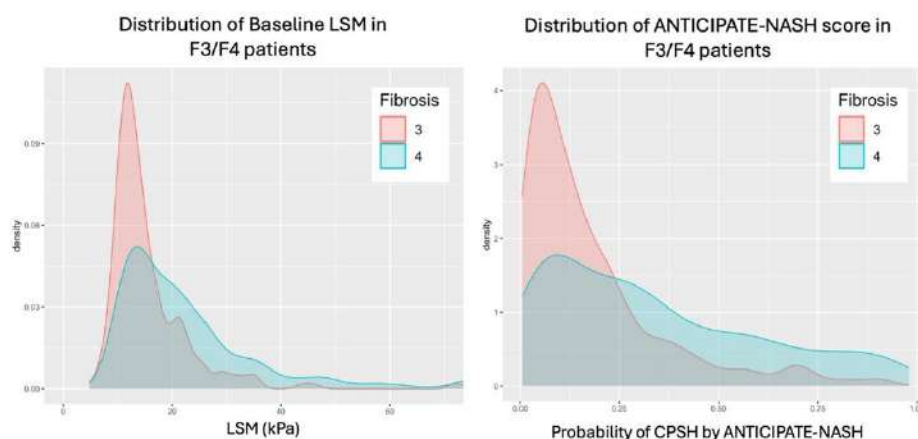


Figure 1. Distribution of (left) LSM and (right) ANTICIPATE-NASH model values (probability of CSPH) in F3 and F4 patients from cohort 1.

Distribution of ANTICIPATE-NASH score in patients with or without LRE

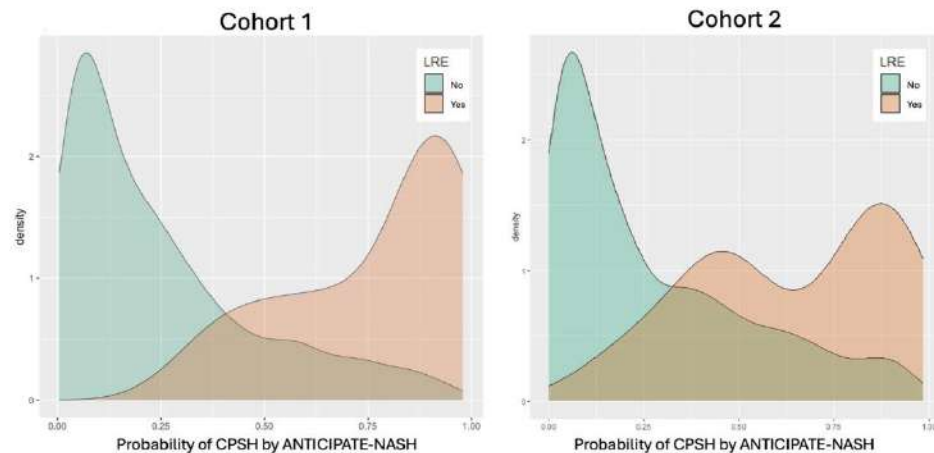


Figure 2. Distribution of the ANTICIPATE-NASH values (probability of CPH) in patients with and without clinical events (LRE) during follow-up from (left) cohort 1 and (right) cohort 2.

for LRE at 3 years (Supplementary Figure 2). In contrast, the C statistic for fibrosis stage (F4 vs F3) was 0.67. Supplementary Figures 3, 4, and 5, respectively, show that the model performs well in the subgroup of patients with BMI ≥ 35 kg/m², equally in men and women, and better than other noninvasive tests, although the sample size was limited.

We then tested the added value of fibrosis stage to the ANTICIPATE-NASH model by including both in a Cox regression model and comparing them with a model including only ANTICIPATE-NASH. Fibrosis stage did not add relevant information to the ANTICIPATE-NASH model (likelihood ratio tests for the comparison, $P = .55$). Table 1 summarizes the relative contribution of fibrosis stage and ANTICIPATE-NASH to the model.

Next, we tested whether predictions of ANTICIPATE-NASH were affected by fibrosis stage (ie, whether the association between ANTICIPATE-NASH and LREs would

change by knowing if it comes from a patient with F3 or F4 stage), by testing the interaction of both in a Cox regression model. Again, neither fibrosis stage ($P = .77$) nor its interaction with ANTICIPATE-NASH ($P = .63$) added value to ANTICIPATE-NASH predictions (Table 1).

Finally, F3 patients with an ANTICIPATE-NASH value of $>25\%$ (68 of 324 [20%]), that was the median value of F4 patients, accounted for the 5 LREs seen in F3 patients (Figure 3). By contrast, F4 patients with an ANTICIPATE-NASH value of $<12\%$ (104 of 375 [28.5%]), that was the median value of F3 patients, presented no LREs during follow-up. In summary, the ANTICIPATE-NASH model was able to reclassify, based on outcomes, an important number of F3 patients who behaved as F4 patients and reclassify F4 patients who behaved as F3. Supplementary Table 4 compares patients reclassified by the model with patients not reclassified based on ANTICIPATE-NASH values and LRE.

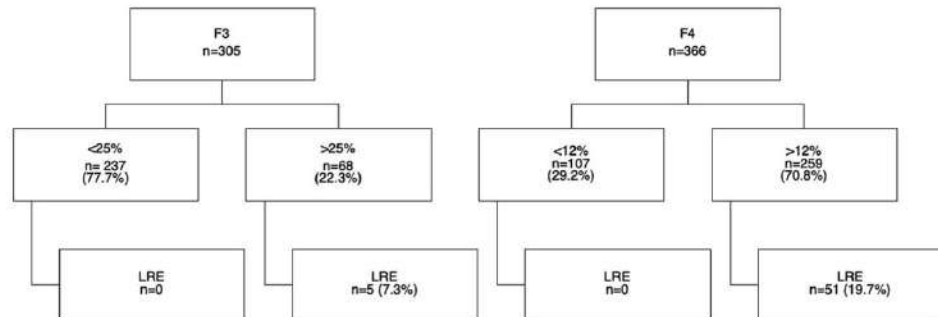
Table 1. Cox Regression Models for the Prediction of Liver-Related Events Up to 3 Years in Cohort 1

Variable	C statistic	Variables	Information contributed by each variable (χ^2) ^a	P value
ANTICIPATE-NASH	0.93	ANTICIPATE-NASH	39.8	<.0001
ANTICIPATE-NASH and fibrosis stage	0.93	ANTICIPATE-NASH	35.0	<.0001
		Fibrosis stage	0.4	.55
ANTICIPATE-NASH and fibrosis stage (model with interaction)	0.93	ANTICIPATE-NASH	35.2	<.0001
		Fibrosis stage	0.5	.77
		Interaction	0.2	.63
Fibrosis stage	0.67	Fibrosis stage	7.52	.0061

NOTE. The added value of fibrosis stage (F3/F4) to the noninvasive ANTICIPATE-NASH score was tested. An additive model and a model with interaction were both tested.

^aThe χ^2 statistic quantifies the contribution of information to each parameter in the model.

Cohort 1:



Cohort 2:

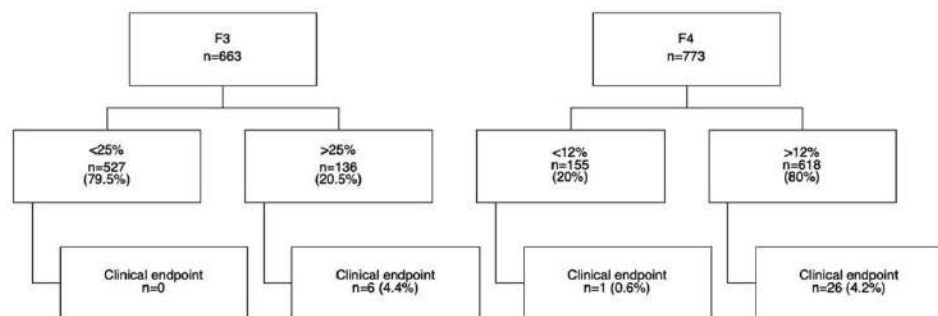


Figure 3. Risk stratification for clinical events of both cohorts, divided by the fibrosis degree (F3 and F4 fibrosis), based on ANTICIPATE-NASH thresholds expressed as the risk (percentage) of having CSPH. Clinical end point: the United States Food and Drug Administration regulatory end point for clinical events.

Cohort 2 Validation

Cohort 2 included 1396 MASLD patients enrolled in the 4 clinical trials. As shown in [Supplementary Figure 6](#), the composite end point developed in 33 patients (2.3%). The median follow-up of this cohort was 16.1 months (interquartile range, 13.8–18.7 months). The distribution of F3 and F4 patients was similar to cohort 1 (47.5% F3 vs 52.5% F4).

Similar to cohort 1, most end points concentrated in F4 patients (27 of 33). The distribution of LSM and ANTICIPATE-NASH values between F3 and F4 patients ([Figure 4](#)) was similar to that of cohort 1 ([Figure 1](#)). The ANTICIPATE-NASH values were very different between patients with and without the composite end point ([Figure 2](#)).

The ANTICIPATE-NASH model also showed a high discrimination for the composite end point in this cohort (C statistic, 0.84), although the C statistic for fibrosis stage (F4 vs F3) was lower (0.64). Similar to what was observed in cohort 1, adding fibrosis stage to the ANTICIPATE-NASH model did not improve performance (C statistic, 0.84).

In addition, as presented in [Figure 3](#), by using the same ANTICIPATE-NASH thresholds for cohort 1, F3 patients with a value >25%, concentrated the 6 clinical events observed in F3 patients, whereas F4 patients with a value <12% developed only 1 of the 27 events in this group.

Finally, [Table 2](#) summarizes the median ANTICIPATE-NASH values of patients from the STELLAR trials according to the occurrence of fibrosis stage changes at the 48-week follow-up liver biopsy specimen. As seen, patients with F3 at baseline who progressed had higher baseline ANTICIPATE-NASH values than patients who remained F3 or who improved to F0–2 in the follow-up biopsy specimen. On the other hand, in patients with F4 at baseline, those regressing to F3 or lower, had a much lower ANTICIPATE-NASH score than those that showed again an F4 biopsy specimen in the follow-up.

Discussion

The results of the present study confirmed our original hypothesis showing that by using the ANTICIPATE-NASH models, a more accurate prediction of LRE compared with liver histology can be achieved in MASLD patients. These models, therefore, could be considered a preferred tool for risk assessment and candidate selection for clinical trials in the setting of cACLD with clinical outcomes as the main end point. Also, our results have shown robustness, considering that they were reproduced in 2 different large cohorts, with different lengths of follow-up, and by using 2 comparable but slightly different end point definitions. Hepatocellular carcinoma was part of our LREs definition

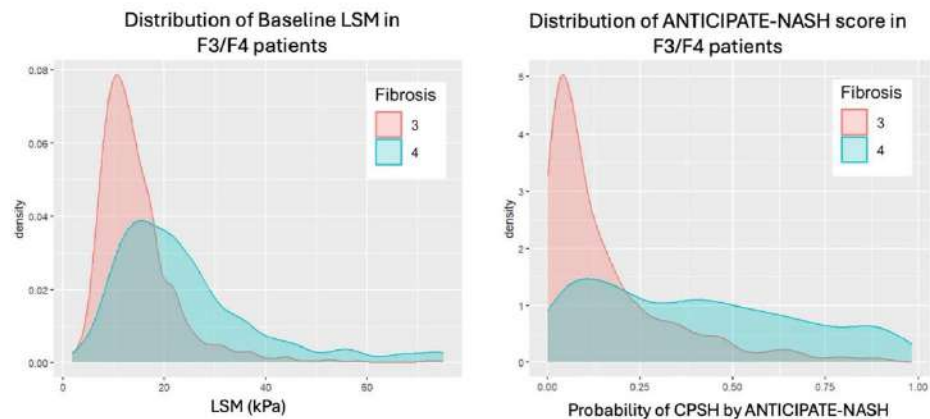


Figure 4. Distribution of (left) LSM and (right) ANTICIPATE-NASH model values (probability of CSH) in F3 and F4 patients from cohort 2.

used in cohort 1,¹⁶ whereas it was absent in the regulatory outcome used in cohort 2. Similarly, the regulatory end point included Model for End-Stage Liver Disease ≥ 15 and all-cause mortality, excluded in our LREs definition. This, in our opinion, reflects the adaptability and versatility of the ANTICIPATE-NASH models in predicting clinical events in ACLD MASLD patients.

The increasing use of noninvasive tools in the assessment and monitoring of chronic liver disease is causing a profound change in its management. Many different noninvasive tools have been developed and applied to assess the stage and prognosis of MASLD patients.²¹

Table 2. ANTICIPATE-NASH Median Values of the Risk of Clinically Significant Portal Hypertension in F3 and F4 Patients

Patient group	No.	ANTICIPATE-NASH values
		(%)
STELLAR-3	619	9.2 (3.9-22)
(a) F3 to F0-2	84	5.5 (2.6-10.9)
(b) F3 unchanged	412	9.3 (4-19.4)
(c) F3 to F4	88	20.9 (8.1-43.4)
STELLAR 4	693	36.8 (15.3-60.2)
(a) F4 to F0-3	122	16.4 (5.6-34.3)
(b) F4 unchanged	507	39.6 (18.8-63.9)

NOTE. Data are presented as the median (25th–75th percentiles). Patients are from the Safety and Efficacy of Selonsertib in Adults With Nonalcoholic Steatohepatitis (NASH) and Bridging (F3) Fibrosis (STELLAR 3) and Safety and Efficacy of Selonsertib in Subjects with Compensated Cirrhosis due to Nonalcoholic Steatohepatitis (NASH) (STELLAR 4) studies. Subgroups indicate improved, unchanged, or progressive fibrosis stage. STELLAR-3: a vs b, $P = .0001$; b vs c, $P < .0001$; STELLAR 4: a vs b, $P < .0001$. All P values were obtained using Wilcoxon's rank sum test.

Although most of them were originally built to stage the liver disease, trying to identify patients with steatohepatitis and fibrosis of different degrees, many have also been adapted to evaluate the risk of clinical events. The Fibrosis 4 (FIB-4) score, nonalcoholic fatty liver disease fibrosis score, and Aspartate Aminotransferase to Platelet Ratio Index score showed good accuracy for predicting LREs in a systematic review including 13 studies,²² and these results have been repeated in other series. Agile 3+ and Agile 4 are a combination of noninvasive parameters^{23,24} developed to detect advanced fibrosis or cirrhosis in MASLD patients, having demonstrated similar accuracy compared with LSM alone to predict LREs. The enhanced liver fibrosis panel has demonstrated a good accuracy for predicting LREs in different etiologies²⁵; the <9.8 cutoff identifies a subgroup of patients with a very low risk of LREs.

The ability of LSM for predicting LREs is known since 2011, when Robic et al²⁶ showed a similar performance of LSM compared with the hepatic venous pressure gradient. Since then, LSM by transient elastography has been validated as a very useful tool to assess prognosis in patients with chronic liver disease.^{27–29} The risk of LREs increases in parallel to LSM; however, as shown in 2 meta-analyses^{30,31} and by Pons et al,¹⁶ the relationship between LSM and the risk of LREs is not linear, and the slope of the risk of LREs flattens above LSM values of 20 kPa. This indicates that the discriminative capacity for LREs decreases but does not completely disappear, as shown by recent studies.³²

The ruling-in and ruling-out thresholds of the Baveno VII recommendations for detecting CSH have also been explored for predicting the risk of LREs with good performance.^{33–35} Spleen stiffness measurement alone can also be used for predicting liver decompensation, and by combining Baveno VII criteria with spleen stiffness measurement, it was possible to better classify all the decompensation events in the rule-in group.^{33,36} Another approach using the VITRO score (von Willebrand factor/

platelet count), in combination with the Baveno VII criteria, achieved an adequate classification of patients at risk of decompensation.³⁷

As explained, risk prediction models might explain better what could be expected for an individual patient based on a parameter or a combination of them rather than subgroups of risk strata. Examples of prognostic models for MASLD patients, include the ABIDE (albumin, bilirubin, international normalized ratio, diabetes, and esophageal varices), that uses varices by endoscopy as a variable and the NAFLD outcomes score (NOS).^{38,39} The NOS is a validated model in MASLD patients that showed a good accuracy (area under the curve, 0.90) for predicting LREs at 5 years.

In this regard, our ANTICIPATE-NASH model is a validated tool with good accuracy that can predict both CSPH and LREs at 3 years in MASLD patients. One of the properties of the model is its simplicity, with only 3 easy-to-obtain variables that can be calculated by a nomogram or an online tool. Indeed, one of the important findings of the present work was the ability of the ANTICIPATE-NASH model to reclassify patients. By simply using a binary stratification with certain ANTICIPATE-NASH value thresholds in both F3 and F4 patients and based on clinical events, ~30% of F4 patients behaved as F3, and 20% of F3 might be classified as F4. The low accuracy and reproducibility of liver biopsy specimen is also evidenced by showing that patients who changed fibrosis stage during follow-up possessed a very different baseline risk of CSPH.

Those who improved fibrosis stage (either F3 or F4) presented lower risk than those who did not change or progressed, whereas patients progressing from F3 to F4 already showed higher risk of CSPH. This probable misclassification of liver biopsy specimen both at baseline and during follow-up might explain why patients from these trials with baseline F4⁴⁰ who had cirrhosis regression at follow-up presented many fewer clinical events than patients who maintained F4 stage. Our results suggest that those patients were already different at baseline, with a much lower risk of CSPH and therefore much earlier in the natural history of the disease.

Our study has several strengths. It includes 2 large cohorts of biopsy specimen-proven F3/F4 MASLD patients and results from cohort 1 were reproducible in cohort 2, despite differences in follow-up and clinical end points. We provide enough evidence to demonstrate the superior capacity of the ANTICIPATE-NASH models over liver biopsy for risk stratification, considering, in addition, the easiness, availability, and repeatability of the model compared with the invasiveness of liver biopsy. Although in unselected cACLD MASLD patients, the risk of LREs at 3 years of follow-up is low, ANTICIPATE models may identify a subgroup of patients with higher-risk LREs at 3 years. Indeed, this tool could be used instead of histology to better select patients for the evaluation of clinical events in phase 3 MASLD clinical trials, sensibly decreasing sample size and length of follow-up by entering patients at higher risk of events. An example of the effect on sample size of using the

model to enrich patients at higher risk of events is shown on [Supplementary Table 5](#). On the other hand, it could serve to select the F4 patients in whom observing regression to F3 is more likely.

Limitations of our study include that our cohorts have been retrospectively analyzed and recruited from other studies or from ongoing databases not specifically designed for the present study. In most of the cohort 1 patients, central biopsy specimen reading was lacking, and information regarding portal hypertension data (esophageal varices and portal pressure) was not available. The number of events is relatively low. The use of LSM is always an inconvenience for settings or countries lacking this tool, requiring adequate training and dedicated personnel.

Patients from cohort 2 were enrolled in clinical trials for MASLD treatments that were considered ineffective, although a possible effect on the natural history of the disease cannot be excluded. Future studies are needed to prospectively evaluate the use of the ANTICIPATE-NASH models for risk prediction in relation to changes in BMI or the other parameters included in the model. Adaptability in repeated assessments to changes after interventions is an important part of the process of clinical validation of a model.

Conclusion

The ANTICIPATE-NASH model is a noninvasive, point-of-care, accessible method for individual LRE prediction in cACLD-MASLD patients. Knowledge of fibrosis stage (F3 vs F4) does not add relevant prognostic information to ANTICIPATE-NASH. This model could be considered a valuable tool for risk assessment in daily clinical practice and for patient selection or risk stratification in clinical trials.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at <https://dx.doi.org/10.1053/j.gastro.2025.08.020>.

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Conflicts of interest

These authors disclose the following: Joan Genescà has received consulting fees from Boehringer Ingelheim and speaking fees from Echosens. Mònica Pons reports speaking fees from CSL Behring and consulting fees from Takeda. Juan G. Abalde consults for Boehringer Ingelheim, Agomab, 89bio, Boston Pharmaceuticals, AstraZeneca, and Novo Nordisk, and received personal speaker fees from Terumo and grants from Gilead and Cook, paid to the University of Alberta. Juan M. Pericás has received consulting fees from Madrigal, Novo Nordisk, Boehringer-Ingelheim, and MSD, has received speaking fees from Madrigal, Novo Nordisk, Boehringer-Ingelheim, Novartis, and Gilead, travel support from Madrigal, Novo Nordisk and Boehringer-Ingelheim, and educational and research support from Siemens, Gilead, Pfizer, Astellas, Accelerate, Novartis, AbbVie, ViiV, and MSD. Jesús Rivera-Esteban has received consulting and speaking fees from Novo Nordisk. Xiangyu Liu, Timothy R. Watkins, and Andrew N. Billin are employees and shareholders of Gilead Sciences, Inc. The remaining authors disclose no conflicts.

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Data Availability

The data underlying this study are protected by research agreements between the involved institutions and can only be made available through new agreements with the study investigators. Data from the Gilead trials are the property of Gilead, and sharing these data would require a separate agreement with Gilead. The analytic methods are described in detail within the paper to facilitate reproducibility. The authors are willing to share the analysis code upon request, subject to the necessary terms and conditions.

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RESUMEN GLOBAL DE LOS RESULTADOS

5. RESUMEN GLOBAL DE LOS RESULTADOS

El meta-análisis de datos individuales confirma que los criterios de Baveno VII para la exclusión y diagnóstico de CSPH son excelentes. Con respecto al criterio de diagnóstico (LSM ≥ 25 kPa) el PPV agregado para todos los estudios es de 0.92. Haciendo un análisis para cada etiología, el PPV se mantenía a excepción de los pacientes MASLD con obesidad donde caía hasta 0.67 (Figura 3A). Utilizando un punto de cohorte ANTICIPATE $\pm$ NASH $\geq 75\%$ el PPV global se mantiene (PPV 0.95) y el PPV de pacientes MASLD aumenta hasta 0.83 (Figura 3B).

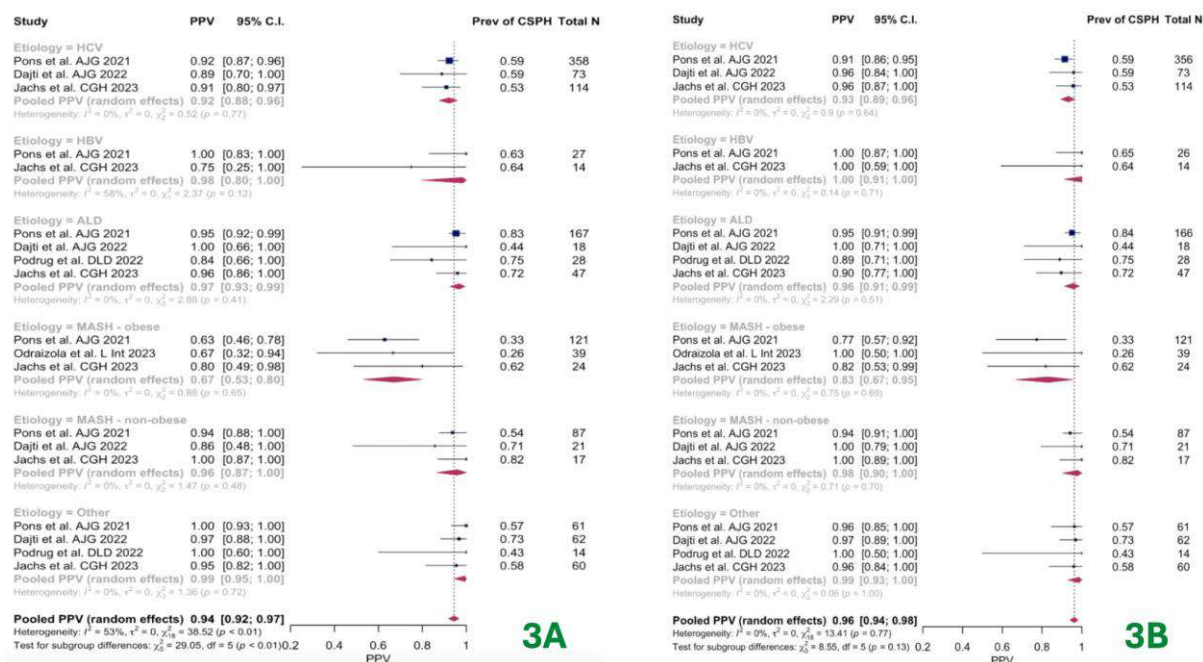


Figura 3. Diagramas de bosque para el diagnóstico de CSPH por etiología utilizando el criterio LSM ≥ 25 kPa (3A) y utilizando el criterio ANTICIPATE $\pm$ NASH $\geq 75\%$ (3B)

Con respecto al criterio de descarte (LSM ≤ 15 kPa + > 150.000 plaquetas) el NPV fue de 0.99. El rendimiento diagnóstico del modelo ANTICIPATE se mantuvo en todos los centros.

De forma importante, el modelo ANTICIPATE-NASH-LRE es superior a la histología para predicción de eventos hepáticos en ambas cohortes y con las dos distintas definiciones de eventos clínicos (c-statistic 0.93 vs. 0.67 para los eventos definidos como LRE; y c-statistic 0.84 vs. 0.64 para los eventos definidos por el criterio regulatorio de la FDA). En ambas cohortes, el modelo presentaba una calibración excelente. Además, una vez se conoce el valor de ANTICIPATE-NASH, añadir la histología no mejoraba la capacidad para predecir eventos. (Tabla 1).

Tabla 1. Modelos de regresión Cox para la predicción de eventos hepáticos (LRE) a 3 años en la cohorte 1.

Variable	c-statistic	Variables	Información contribuida por cada variable (χ^2)	p value
ANTICIPATE-NASH	0.93	ANTICIPATE-NASH	39.8	<.0001
ANTICIPATE-NASH y estadio de fibrosis	0.93	ANTICIPATE-NASH Estadio de fibrosis	35.0 0.4	<.0001 0.55
ANTICIPATE-NASH y estadio de fibrosis (modelo con interacción)	0.93	ANTICIPATE-NASH Estadio de fibrosis Interacción	35.2 0.5 0.2	<.0001 0.77 0.63
Estadio de fibrosis	0.67	Estadio de fibrosis	7.52	0.0061

Nota. Se evaluó el peso que añadía el estadio de fibrosis (F3/F4) a la estimación con el modelo no invasivo ANTICIPATE-NASH. Se testó con un modelo aditivo y con modelo de interacción. El estadístico χ^2 cuantifica la contribución de información de cada parámetro al modelo.

Las categorías histológicas F3-F4 tienen un importante solapamiento con respecto a valores de LSM y del modelo ANTICIPATE-NASH. Por el contrario, los pacientes que presentaron eventos tenían valores más elevados de ANTICIPATE-NASH que los pacientes que no presentaban eventos (Figura 4).

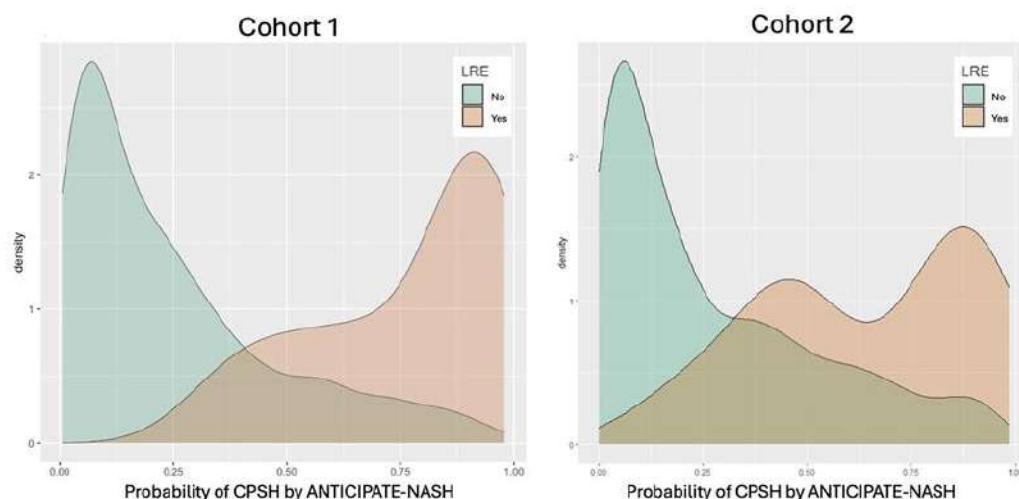


Figura 4. Distribución de los valores de ANTICIPATE-NASH en pacientes sin (en verde) y con (en rojo) eventos en la cohorte 1 (izquierda) y en la cohorte 2 (derecha).

Los pacientes F3 que presentaron todos los eventos tenían valores más elevados de ANTICIPATE-NASH (>25%, la mediana de los pacientes F4). Por otro lado, ningún paciente F4 con valores bajos de ANTICIPATE-NASH (<12%, la mediana de las pacientes F3) presentaron eventos. En la cohorte de ensayos clínicos, los pacientes F3 basal que progresaron a F4 tenían valores basales de ANTICIPATE-NASH más altos. Por el contrario, los pacientes F4 que mejoraron durante el ensayo clínico, tenían valores de ANTICIPATE-NASH más bajos.

RESUMEN GLOBAL DE LA DISCUSIÓN

6. RESUMEN GLOBAL DE LA DISCUSIÓN

El uso creciente de métodos no invasivos para el diagnóstico y monitorización de la enfermedad hepática ha transformado la Hepatología. Aunque se han desarrollado numerosas herramientas, la LSM se distingue por encima de todas por su fácil aplicabilidad y capacidad de clasificar con precisión a los pacientes dentro del espectro de la enfermedad hepática crónica y en concreto en la fase de cACLD. Los modelos ANTICIPATE (basados en LSM, plaquetas y BMI) son capaces de identificar el riesgo individual de cada paciente de presentar CSPH y la posibilidad de presentar descompensación en pacientes MASLD.

En el momento actual, es posible realizar un diagnóstico de CSPH con estos métodos no invasivos. La combinación de $LSM \leq 15$ kPa con ≥ 150.000 plaquetas y $LSM \geq 25$ kPa permite de forma certera excluir y diagnosticar CSPH, respectivamente. El meta-análisis que forma parte de esta tesis y que incluye datos individuales de 1433 pacientes valida de forma definitiva el criterio de exclusión (NPV 0.99). Con respecto al criterio de confirmación, el PPV era de 0.92 de forma global pero, como esperábamos, en los pacientes MASLD con obesidad el PPV caía a 0.67. Utilizando un punto de corte de $ANTICIPATE \pm NASH \geq 75\%$ el PPV mejoraba globalmente (0.95) pero especialmente en pacientes MASLD con obesidad (hasta 0.83). Pese a esta mejoría en la precisión diagnóstica, este criterio sólo conseguía reducir la zona intermedia o indeterminada del 45 al 43%.

Adicionalmente, el modelo ANTICIPATE-NASH predice de forma más precisa que la histología, en dos cohortes distintas y con dos definiciones de eventos clínicos ligeramente diferentes, el riesgo de eventos relacionados con la enfermedad hepática. El modelo parece sobrepasar uno de los principales problemas de la biopsia hepática: la representatividad de una pequeña muestra. Los pacientes F3 con valores de ANTICIPATE-NASH elevado tenían más riesgo de eventos y de ser clasificados como F4 en la siguiente biopsia dentro de ensayo, y los pacientes F4 que mejoraron presentaban valores más bajos de ANTICIPATE-NASH y menos riesgo de eventos. Con estos resultados, el modelo podría ser usado para el diseño de ensayos clínicos seleccionando una población más homogénea y con una estimación de riesgo de eventos más precisa.

CONCLUSIONES

7. CONCLUSIONES

Los modelos ANTICIPATE son métodos no invasivos, accesibles y repetibles que permiten:

- El diagnóstico de CSPH con un punto de cohorte de $\text{ANTICIPATE} \pm \text{NASH} \geq 75\%$, mejorando la precisión diagnóstica en pacientes MASLD con obesidad y globalmente el criterio actual de ≥ 25 kPa de Baveno VII.
- La estimación de eventos hepáticos en pacientes MASLD con mayor precisión que la biopsia hepática.

LÍNEAS DE FUTURO

8. LÍNEAS DE FUTURO

El trabajo desarrollado en esta tesis deja abierta la posibilidad de expandir el uso de los modelos ANTICIPATE para la estimación de eventos hepáticos en otros escenarios.

En primer lugar, uno de los siguientes pasos es validar el modelo ANTICIPATE para la predicción de eventos en otras etiologías como por ejemplo la enfermedad hepática relacionada con el alcohol u otras menos frecuentes como las enfermedades colestásicas.

En segundo lugar, expandiendo el primer trabajo de esta tesis, exploraremos las diferencias en la evolución de los pacientes en la zona intermedia (no clasificados con los criterios expuestos de CSPH) con respecto a los pacientes en los que sí se realiza un diagnóstico de CSPH. En un análisis preliminar los pacientes MASLD de la zona intermedia con CSPH presentaban valores de ANTICIPATE $\pm$ NASH más bajos (IQR 40-65%) que aquellos pacientes diagnosticados de CSPH (IQR 80-100%). Extrapolando estos datos a una cohorte de MASLD independiente con seguimiento longitudinal, los pacientes con valores ANTICIPATE $\pm$ NASH 40-65% tuvieron un riesgo de eventos (1.99% a 1 año y 7.8% a 3 años) frente a los pacientes con un ANTICIPATE $\pm$ NASH 80-100% (10.9% a 1 año y 23.4% a 3 años). Los pacientes no clasificados en la zona intermedia, por lo tanto, parecen tener un riesgo bajo de eventos al año.

En tercer lugar, el modelo ANTICIPATE-NASH-LRE predice tanto eventos directamente relacionados con la hipertensión portal (ascitis, hemorragia digestiva alta, encefalopatía...) como carcinoma hepatocelular. Parte de la línea de investigación irá dirigida a la adaptación del modelo para la predicción únicamente de eventos hepáticos excluyendo el tumor hepático y así poder adaptar el modelo a los tratamientos dirigidos a disminuir la hipertensión portal como los NSBB. Sin embargo, por otro lado, se intentará explorar a partir de qué punto de corte es coste-efectivo comenzar con el cribado de carcinoma hepatocelular en una población de pacientes cACLD, especialmente MASLD.

En cuarto lugar, durante el transcurso de la tesis estamos desarrollando un ensayo clínico aleatorizado a doble ciego en pacientes con cACLD con el objetivo principal de evaluar si el tratamiento con acexamato de zinc mejora el pronóstico. El diseño metodológico del estudio incluye como variable principal un objetivo combinado que incluye la reducción del número de eventos y la reducción del riesgo estimado por ANTICIPATE de desarrollarlos. Más allá del potencial beneficio del medicamento, el estudio ofrecerá el análisis de la historia natural de 300 pacientes compensados seleccionados con métodos no invasivos.

En definitiva, se espera que la exploración de estas líneas de trabajo permita, no solo mejorar y ampliar estos resultados, si no expandir el uso de métodos no invasivos en el mundo de la enfermedad hepática avanzada.

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ANEXOS

10. ANEXOS

10.1. OTRAS PUBLICACIONES DERIVADAS DE LA TESIS

10.1.1. PUBLICACIÓN 1

Bañares J, Aceituno L, Ruiz-Ortega L, Pons M, Abrales JG, Genescà J. Zinc supplementation to improve prognosis in patients with compensated advanced chronic liver disease: a multicenter, randomized, double-blind, placebo-controlled clinical trial. *Hepatol Commun*. 2024 Oct 10;8(11):e0524. doi: 10.1097/HC9.0000000000000524. PMID: 39392768; PMCID: PMC11469812.

DOI: 10.1097/HC9.0000000000000524

PROTOCOL PAPER

OPEN

Zinc supplementation to improve prognosis in patients with compensated advanced chronic liver disease: a multicenter, randomized, double-blind, placebo-controlled clinical trial

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Abstract

Zinc homeostasis could play a role in compensated advanced chronic liver disease, and its supplementation has been linked to improvement in liver function, a decrease of hepatic complications, and reduction in HCC incidence. Compensated advanced chronic liver disease encompasses a heterogeneous group of patients with variable risks of clinically significant portal hypertension and clinical events. The ANTICIPATE model is a validated model for stratifying these risks. Our aim is to demonstrate that zinc administration can reduce the rate and risk of presenting clinical events (first decompensation, HCC, death, and liver transplantation). This study protocol describes an ongoing phase III, national, multicenter, randomized, double-blind clinical trial that will enroll 300 patients to receive either the trial treatment (zinc acexamate) or placebo. An inclusion period of 42 months is planned, with a minimum follow-up of 2 years. Our principal hypothesis is that zinc could modify the natural history of patients with compensated advanced chronic liver disease, with an overall improvement in prognosis.

Key Words: cirrhosis, first decompensation, hepatocellular carcinoma, portal hypertension, zinc

INTRODUCTION

Existing research and trial rationale

Zinc is a crucial trace element for essential biological functions mainly related to cell division, growth, and

development. Many of the proteins and enzymes that use zinc as a cofactor are involved in beneficial antioxidant, anti-inflammatory, and apoptotic effects. A significant amount of evidence suggests that zinc homeostasis may play a role in liver diseases. In patients with cirrhosis, there is a high prevalence of zinc deficiency, probably

Abbreviations: ACLD, advanced chronic liver disease; ACZ, zinc acexamate; AEMPS, Agencia Española de Medicamentos y Productos Sanitarios; cACLD, compensated advanced chronic liver disease; CSPH, clinically significant portal hypertension; EudraCT, European Union Drug Regulating Authorities Clinical Trials.

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owing to a multifactorial cause.^[1–3] There is a direct correlation between blood zinc levels and the worsening of advanced chronic liver disease, with a good correlation with the Child-Pugh score.^[4,5] Furthermore, in patients with HCC, intracellular zinc levels in tumor tissue are consistently and markedly low.^[6]

Several nonrandomized clinical studies have suggested that oral zinc supplementation may have a positive impact on the progression of advanced chronic liver disease (ACLD) differently assessed by (1) raising blood levels of zinc in patients with cirrhosis^[7–10]; (2) improving liver function, evaluated by the Child-Pugh score^[7,8,10,11]; (3) decreasing serum ammonia levels^[7–9]; (4) decreasing the development of complications in ACLD (ascites and encephalopathy)^[8]; and (5) reducing incidence of HCC.^[10,12] Thus, zinc supplementation has the potential impact to modify the natural history and prognosis of patients with ACLD.

Compensated ACLD (cACLD) encompasses a heterogeneous group of patients at risk of developing clinically significant portal hypertension (CSPH) with a variable risk of clinical events. Of note, even when selecting patients with a high risk of events (HVPG > 10 mm Hg, presence of varices, or increased Child-Pugh score), the estimated cumulative incidence of clinical events after a 2–3-year follow-up period is relatively low (20%–30%).^[13,14] This incidence is even lower in patients with metabolic dysfunction–associated steatotic liver disease.^[15] Nevertheless, developing a first decompensating event has a marked survival impact on these patients.^[16] One of the main drawbacks in designing a clinical trial with clinical events in this compensated population is the need for large sample sizes, which might be unrealistic to accrue.^[17,18]

Recently, the ANTICIPATE model (which includes liver stiffness by transient elastography (Fibroscan and platelet count) has been developed to predict the risk of having CSPH.^[19] This model has now been externally validated.^[15,20] A nomogram based on this model is shown in [Figure 1](#).

The ANTICIPATE model allows the estimation of the risk of CSP, which has a marked prognostic value for clinical events in patients with cACLD.^[21] Furthermore, liver stiffness measured using transient elastography is independently associated with clinical events in these patients.^[13]

Endpoints based on ordinal scales have been proposed to capture more granularity in describing the clinical outcomes of patients in randomized trials while making them more efficient by substantially reducing the required sample size. This approach has been routinely used, for example, in stroke randomized trials (using the Rankin scale)^[22] and COVID trials (using the WHO scale of severity).^[23] We postulated that in trials of patients with compensated cirrhosis, we could add efficiency in detecting the effect of an intervention

based on the distribution of patients according to an ordinal scale.^[17] This scale would have the highest severity level defined by the development of clinical events but would also add granularity by ranking the patients not developing clinical events according to their risk of CSPH and clinical events (based on the ANTICIPATE model).

Therefore, we decided to conduct a clinical trial to investigate the efficacy of oral administration of zinc in the form of zinc acexamate (ACZ) (a soluble, well-tolerated salt) to improve prognosis in patients with cACLD. As this randomized trial will test an approved therapy (already on the market), the lack of constraints of a defined path for regulatory approval allowed us to use an innovative design based on the use of 2 co-primary endpoints. One would be the classic endpoint used in compensated cirrhosis trials, which is the “time to clinical events” (decompensation, HCC, transplantation, and liver death). The innovative contribution is the use of a co-primary endpoint (in which we based the sample size calculation) based on the distribution of patients on a 6-point ordinal scale of severity at the 2-year mark, which could potentially detect a similar given effect size with a much smaller sample size. This design will also allow us to test (if the trial shows benefit) if the effect size observed on the ordinal outcome is predictive of the effect size estimated from the traditional time to clinical events endpoint.

Study objectives

Main objective

The main objective of this clinical trial is to evaluate whether the oral administration of ACZ at a dose of 600 mg/d (equivalent to 100 mg/d of zinc element) to patients with cACLD improves prognosis by reducing the number of expected clinical events and the estimated risk of developing these events (evaluated with the ANTICIPATE model) during the study.

Secondary objective

As secondary objectives, we aim to evaluate whether the administration of ACZ (1) decreases the risk of having the first decompensation; (2) decreases the risk of CSPH estimated by the ANTICIPATE model; (3) reduces the risk of HCC; (4) reduces the risk of bacterial infections; (5) improves overall transplant-free survival and the risk of liver-related death; and (6) improves liver function as measured by Child-Pugh and MELD scores. In addition, we aim to evaluate the possible association between blood zinc levels and the study outcomes, as well as the possible adverse effects of treatment ([Table 1](#)).

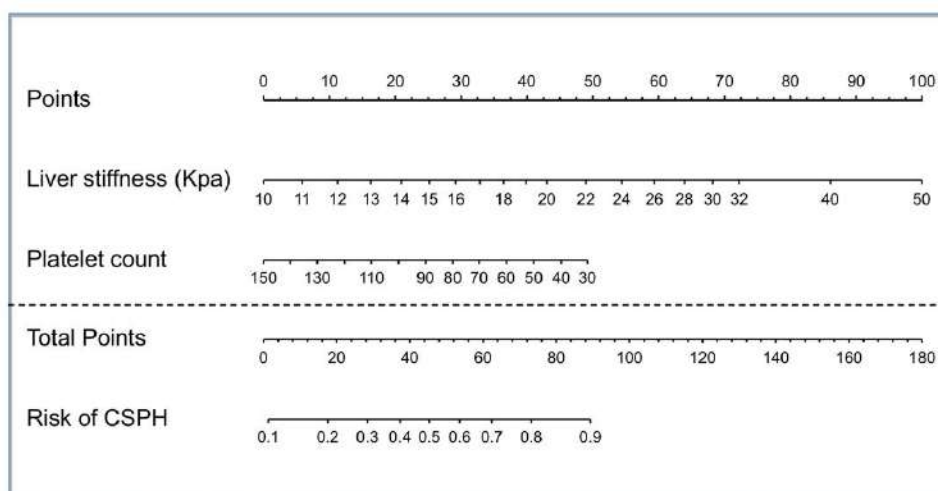


FIGURE 1 Nomogram for calculating the risk of CSPH using liver stiffness and platelet count, estimated by the ANTICIPATE model.

METHODS

Study design and setting

This is a phase III, randomized, double-blind clinical trial with 2 parallel groups, controlled with a placebo. This is a low-level intervention clinical trial since the experimental drug is an authorized medication. This is a multicenter national study with 15 Spanish centers recruiting patients.

Participants recruitment and eligibility criteria

Eligible participants may be identified and recruited at all sites over the course of the study period, both from general cirrhosis outpatient clinics and from monographic consultations for the different causes of chronic liver disease, such as metabolic dysfunction-associated steatotic liver disease and alcohol-associated liver disease. Detailed inclusion and exclusion criteria are presented in Figure 2.

Study population and total number of patients

The study will be conducted on a total of 300 patients who will be randomly distributed into 2 arms.

The sample size was calculated based on the predicted distribution of patients on an ordinal scale with 6 levels (Table 2). This ordinal scale captures both the development of clinical events (level 6) and the risk of presenting them based on the ANTICIPATE model (levels 1–5 as defined in Table 2). Considering the sum of expected clinical events at 24 months of follow-up according to the PREDESCI study^[14] and other studies on the natural history of liver cirrhosis^[24–27] with the added effect of decompensation, HCC, and death, a total of 20% of clinical events are expected at 2 years of follow-up (16% decompensations, 2% HCCs, and 2% deaths). To estimate the distribution of liver-related events according to the ordinal scale (for those not developing a clinical event), we used data from Pons et al.^[15]

The hypothesized effect of ACZ will be an OR of 0.55, which would result in a reduction in clinical events from 20% to 12% in the treated group and a shift in the

TABLE 1 Summary of the main and secondary objectives of the study

Main objective:

- Evaluate whether the oral administration of zinc in patients with cACLD improves prognosis, reducing the number of clinical events and the estimated risk of developing these events.

Secondary objectives:

- Evaluate if the administration of zinc decreases the risk of having the first decompensation.
- Evaluate if the administration of zinc decreases the risk of CSPH estimated by the ANTICIPATE model.
- Evaluate if the administration of zinc reduces the risk of HCC.
- Evaluate if the administration of zinc reduces the risk of bacterial infections.
- Evaluate if the administration of zinc improves overall transplant-free survival and the risk of liver-related death.
- Evaluate if the administration of zinc improves liver function as measured by Child-Pugh and MELD score.
- Evaluate the possible association between blood zinc levels and the study outcomes.
- Evaluate possible adverse effects of treatment.

Abbreviations: cACLD, compensated advanced chronic liver disease; CSPH, clinically significant portal hypertension.

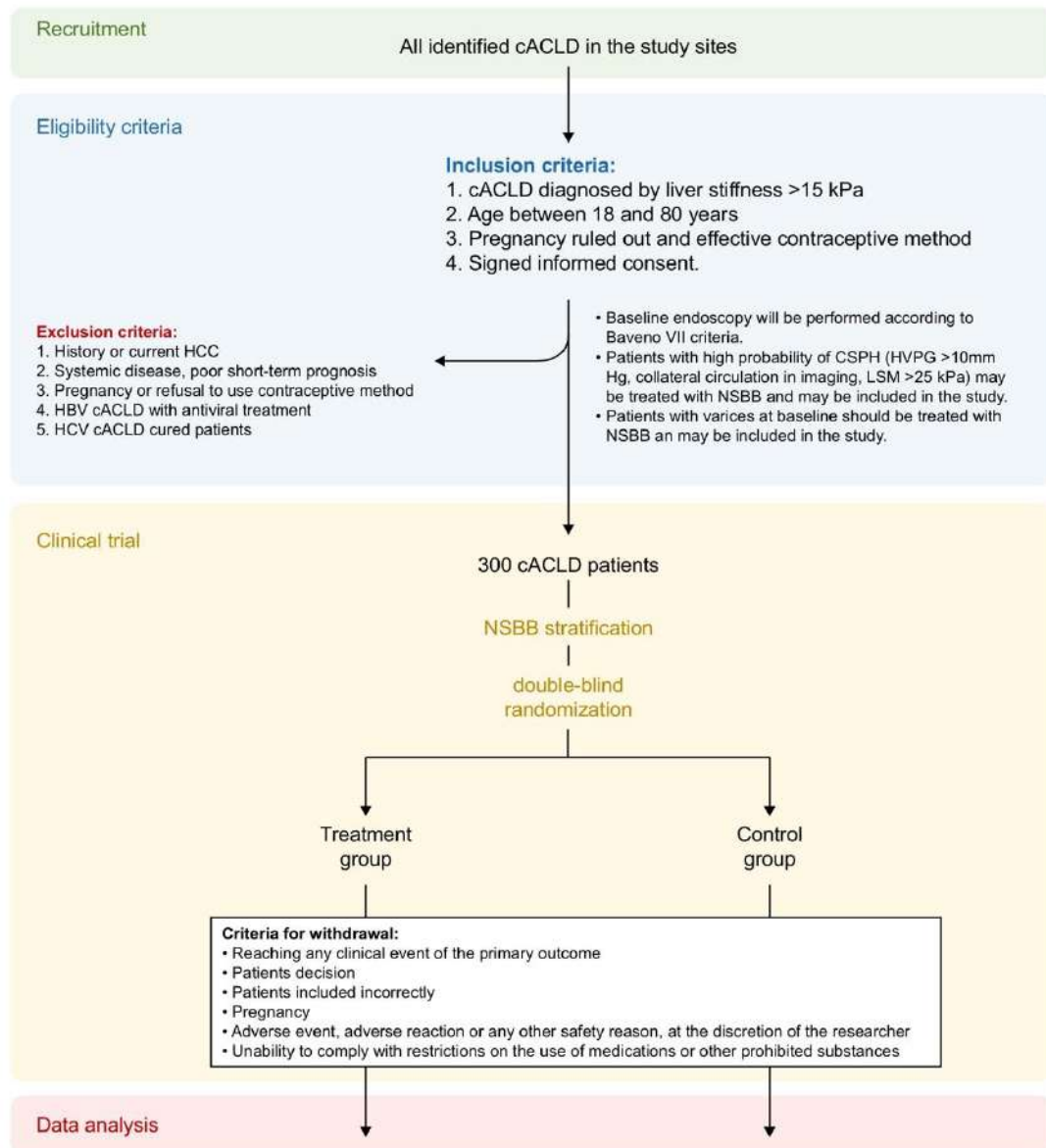


FIGURE 2 Workflow of the trial including inclusion/exclusion criteria and treatment arms.

TABLE 2 Ordinal scale to assess the efficacy of the intervention

Ordinal scale	1 ANTICIPATE < 0.30	2 ANTICIPATE 0.30–0.45	3 ANTICIPATE 0.45–0.60	4 ANTICIPATE 0.60–0.85	5 ANTICIPATE > 0.85	6 Clinical event
Placebo (%)	2	8	10	21	39	20
Treatment (%)	4	13	14	25	32	12

Note: This table also includes the expected distribution of patients on the ordinal scale in the placebo group at the 2-y mark, and the expected distribution of patients under a treatment with an effect size of an OR of 0.55.

distribution of the CSPH risk category, as shown in Table 2. This effect was a conservative estimation of a more than 60% reduction of clinical events in patients with cirrhosis treated with zinc for 3 years, as observed by Hosui et al.^[10] Under these assumptions, 143 patients would be required per arm (with an α error of 0.05) to achieve a 0.80 power. Considering a 5% loss during follow-up, a total sample size of 300 patients will be included.

Randomization

Patients will be randomly assigned to the experimental or placebo groups. This randomization will be stratified according to the use of nonselective beta-blockers when entering the study. This process will be performed on a 1:1 ratio using a centralized network-based system with double-blind allocation through computer-generated electronic code (Figure 2).

Trial treatment and control

The experimental group will receive ACZ at a daily dose of 600 mg, equivalent to 100 mg of elemental zinc (1 hard gelatin capsule of 300 mg of ACZ twice a day). Treatment will be stopped when the patient presents with any of the events that define the main endpoint of the study.

ACZ is a soluble, well-tolerated salt that is commercialized and approved in Spain for the treatment of gastroduodenal ulcers. The dose chosen for the trial was based on the published clinical studies performed in patients with cirrhosis,^[7–12] in which 33–150 mg per day of zinc element in different compositions were administered once or 3 times per day.

The control group will receive hard gelatin capsules orally twice a day, identical to those of ACZ, in color, weight, and nature, but containing an inert preparation (isomaltose).

Compliance assessment (adherence to treatment)

To assess compliance, the medication count method will be used at each of the control visits, recording the number of capsules consumed and the expected number of capsules consumed, thereby obtaining a ratio or compliance percentage (current number of capsules consumed/expected number $\times$ 100). Adherence will be considered good when at least 70% of capsules are consumed.

Adverse events and reactions

All adverse events will be recorded, regardless of their possible association with the study treatment. Degrees of

a causal relationship between adverse events and study medication will be established (from no relationship to very likely related). A specific record will be included in the clinical report form to register all the possible adverse events and the imputability criteria at every scheduled visit. Suspected serious and unexpected adverse reactions will be reported to the Spanish Agency of Drugs and Sanitary Products (AEMPS). The AEMPS qualified the study of a low level of intervention and a Data Safety Monitoring Board was not needed. Copper deficiency might be caused by zinc treatment; the risk in patients seems to be very low.^[7,11] Copper levels will be assessed several times during follow-up.

Criteria for withdrawal of study subjects

Every patient may suspend participation in the study at any time without needing additional explanation and without prejudice to optimal subsequent treatment. Other criteria for withdrawal of the study are detailed in Figure 2.

OUTCOMES MEASURES AND STUDY PROCEDURES

Primary endpoint

The primary endpoint will be assessed at the 2-year mark as the distribution of patients on the 6-value ordinal scale shown in Table 2. The most severe category (level 6) will be the development of clinical events. These clinical events are defined as follows:

(1) First decompensation:

- (a) Ascites, are defined by clinical signs within the physical examination and confirmation by ultrasound or paracentesis. The sole presence of malleolar edema or the detection of i.p. fluid only by imaging techniques (subclinical ascites) will not be considered an event.
- (b) Gastrointestinal bleeding due to portal hypertension, defined as any episode of hematemesis or melena (or both) and endoscopic criteria according to Baveno consensus.
- (c) Overt HE, according to the West Haven criteria (equal or greater than grade II).

(2) HCC.

(3) Liver-related death (non–liver-related deaths will be considered as non-events).

(4) Liver transplantation.

Patients free of a liver-related event at 2 years will be classified according to the risk of CSPH and clinical

events estimated by the ANTICIPATE model value (Figure 1), distributing the patients on an ordinal scale with ascending hierarchy of CSPH risk (Table 2): level 1, <0.30 risk; level 2, 0.30–0.45 risk; level 3, 0.45–0.60 risk; level 4, 0.60–0.85 risk; and level 5, >0.85 risk.

Since patients will be followed up for clinical events until the study termination, there will be a co-primary outcome defined as the time to occurrence of the composite endpoint of clinical events. Superiority in any of the co-primary outcomes will define the success of the study intervention.

Secondary outcomes

The secondary outcomes will consist of the evolutionary development of each of the secondary objectives (Table 1).

Expected duration of inclusion period and treatment

An inclusion period of 42 months is planned, with a minimum of 24 months of follow-up for the last patient included. Therefore, the minimum follow-up would be 24 months, with a maximum of 66 months. Patients will receive their assigned treatment for the entire duration of the study. The expected median follow-up would be 45 months. The first patient was included in June 2022, and the predicted recruitment of the last patient will be in December 2025, with the last follow-up at the end of 2027. As of June 2024, 136 patients had already been randomized.

Schedule of assessments

The schedule of assessment is detailed in Table 3.

DATA ANALYSIS PLAN

Statistical considerations

A final detailed statistical analysis plan will be finalized before the lock of the database. All data will be collected in an electronic format (clinical report form) in an anonymized form. We will consider a type I error of 5%. For each variable, a descriptive analysis will be carried out, expressing the qualitative variables as the absolute number of cases and percentage of each of the categories in each group and overall. For the quantitative variables, means (standard deviations), medians (interquartile range), minimum, and maximum will be calculated.

Primary outcome measures

Both co-primary endpoints will be analyzed simultaneously at the end of the trial without adjustment for multiplicity. The superiority of the intervention will be declared with a p value <0.05 in any of the 2 co-primary outcomes.

The primary inferential analysis for the primary outcome based on the distribution of patients on the ordinal scale at 2 years will be conducted using a proportional odds model, in which the effect of the ACZ will be adjusted by the randomization strata (treatment with nonselective beta-blockers) and baseline ANTICIPATE model value. A single OR with a 95% CI will be used as a summary of treatment efficacy.

A sensitivity analysis of the main variable will be carried out, in which the proportional odds assumption will be relaxed, using a Bayesian constrained partial proportional odds model as described in <https://www.fharrell.com/post/yborrow/>. This analysis will assess a special OR for the treatment effect on the highest level of the ordinal scale (level 6). In addition, it will assess the departure from the proportional odds assumption (represented by the log of the ratio of the OR for clinical events to the OR for the general effect of treatment), using a skeptical prior (0.9 chance that is in the interval 0.5–2). This analysis assesses how likely it is for the effect of the treatment on clinical events (level 6) to be different from the effect on the levels defined by the ANTICIPATE-CSPH (levels 1–5). We will provide the probability of an overall effect, a treatment effect on clinical events, and the probability that the differential treatment effect on clinical events versus overall is by more than a factor of 1.2.

For the co-primary outcome (time to a clinical event across all follow-ups), we will use a Cox proportional hazards model (stratified by baseline beta-blocker treatment).

Secondary outcomes measures

The analysis of secondary outcomes will be based on a time-to-event analysis, using Kaplan-Meier curves for description, and analyzing treatment effects using the Cox proportional hazards model. In addition, a complementary analysis of competitive risks will be carried out using the Fine and Gray method. Specifically, we will assess (a) the effect of treatment in preventing mortality from liver causes and transplantation, considering nonhepatic mortality as a competing risk, and (b) the effect on decompensation/transplant or death, considering the development of HCC as a competing risk.

TABLE 3 Schedule of assessments

	Minimal duration of treatment											Extended follow-up till the end of the study				
	Baseline	3 mo	6 mo	9 mo	12 mo	15 mo	18 mo	21 mo	24 mo	30 mo	42 mo	54 mo	36 mo	48 mo	60 mo	End of follow-up (66 mo)
Confirm eligibility	✓															
Information /informed consent	✓															
Randomization	✓															
Medical history	✓															
Physical examination	✓															
Signs and symptoms	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Standard care blood test	✓		✓		✓		✓		✓		✓		✓		✓	✓
Blood Zn, Cu, and Fe levels	✓		✓		✓		✓		✓		✓		✓		✓	✓
Child-Pugh/MELD	✓															✓
Liver ultrasound ^a	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Endoscopy ^b	✓															✓
Liver stiffness with Fibroscan	✓								✓						✓	✓
Control of alcohol consumption	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Control of contraceptive measures ^c	✓		✓		✓		✓		✓		✓		✓		✓	✓
Dispense trial medication	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse event evaluation		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adherence		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Note. In case of event development, nonprogrammed visits will be conducted. If there is an abandonment during the study, there will be an intent to arrange an end of a follow-up visit with a blood test and liver stiffness measurement.

^aIncluding ultrasound performed in a 3-month period before the visit.

^bEndoscopy will be performed according to Bavero VII consensus recommendations.

^cOnly women of childbearing age.

Planned analysis of abandonments, missing data, and sensitivity analysis

In principle, no imputation of missing data will be performed. As this is a survival analysis, the management of lost patients is controlled in the analysis as long as the censoring is not informative. The main reasons for censoring will be losses to follow-up.

Patients who abandon treatment voluntarily, present serious deviations from the protocol, lack of compliance (adverse effects, change of residence, and loss of interest), and those lost to follow-up will be analyzed by intention to treat. In the event of patient withdrawal due to the appearance of adverse reactions or events, an assessment of imputability will be carried out, and follow-up will be attempted.

An analysis of missing cases will be performed depending on the treatment. Missing data > 10% in the relevant variables will not be allowed, in which case the results will be considered invalid. All analyses will be performed on an intention-to-treat basis. A sensitivity analysis will be performed in the final analysis. First, the results will be compared by assigning the worst and the best results to all the lost cases. Second, the best result will be assigned to the untreated and the worst to the treated group to compare the differences in the effects of the treatment.

ETHICS, CLINICAL TRIAL REGISTRATION, AND DISSEMINATION

Ethical consideration

The trial will be conducted in accordance with the ethical requirements expressed in the Declaration of Helsinki (Edinburgh revision, Scotland, October 2000), the current Spanish regulations on Clinical Research, and the European Union (EU) Good Clinical Practice standards and the ethical approval of the Ethics Committee of the participants' centers.

Candidate patients will be proposed to voluntarily participate in the trial after being informed (both orally and with an informative sheet) about the trial procedures, possible adverse events, detailed information on scheduled assessments, and the possibility of withdrawing at any time during the study. Written consent will be provided in writing to all subjects, and signing will be held after they have read and understood the trial information.

The data will be codified and strictly confidential (the anonymity of the subjects participating in the trial will always be maintained). The promoter and the center will comply with the data protection regulations of Spain and the EU regarding data protection.

Clinical trial versions and registration

The first version of the protocol was approved by the AEMPS on August 28, 2021, and registered in the EU Clinical Trials Register (EudraCT Number: 2021-000680-74). This version included clinical events during follow-up as the only primary endpoint. Version 2.0 was approved by the AEMPS on April 25, 2022. In this first amendment, the primary endpoint was switched to the ordinal 1–6 scale, as described in the Methods section. The second amendment (current version 3.0) was approved by the AEMPS on April 14, 2024, and registered in ClinicalTrials.gov (NCT06434753). This amendment included the co-primary endpoints (the ordinal scale at 2 y, and the time to event during the full follow-up).

AUTHOR CONTRIBUTIONS

Juan Bañares and Laia Aceituno contributed equally to the drafting of this manuscript. Lourdes Ruiz-Ortega and Mònica Pons were responsible for revising the final manuscript and contributing with important intellectual content. Joan Genescà and Juan G. Abraldes were responsible for the original idea, study design, revising the final manuscript, and contribution with important intellectual content.

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CONFLICTS OF INTEREST

Joan Genescà has received consulting fees from Boehringer Ingelheim, speaking fees from Echosens and travel expenses from Gilead and Abbvie. MP reports CSL Behring speaking fees and consulting fees from Takeda. Juan G. Abraldes consults for 89bio, Boehringer Ingelheim, Astra-Zeneca, AMGEN, Boston Pharmaceuticals, and Novo Nordisk and received consulting fees from Boehringer Ingelheim, Agomab, 89bio, Boston Pharmaceuticals, Astra-Zeneca, and Novo Nordisk. He received grants from Gilead and Cook, paid to the University of Alberta. The remaining authors have no conflicts to report.

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10.1.2. PUBLICACIÓN 2

Bañares J, Aceituno L, Pons M, Genescà J. Noninvasive Assessment of Portal Hypertension. Clin Liver Dis. 2024 Aug;28(3):401-415. doi: 10.1016/j.cld.2024.03.010. Epub 2024 May 8. PMID: 38945634.

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