Hipertensión portal: Avances en su diagnóstico e impacto en el riesgo quirúrgico

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Hipertensión portal: Avances en su diagnóstico e impacto en el riesgo quirúrgico.

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INFORME DE LOS DIRECTORES DE LA TESIS

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La Dra. Virginia Hernández Gea, Especialista del Servicio de Hepatología del Hospital Clínic de Barcelona, y el Dr. Juan Carlos García Pagán, Profesor Asociado de la Facultad de Medicina de la Universidad de Barcelona, Jefe de Sección y Consultor Sénior del Servicio de Hepatología del Hospital Clínic de Barcelona

CERTIFICAN:

Que la tesis doctoral titulada "Hipertensión portal: Avances en su diagnóstico e impacto en el riesgo quirúrgico", realizada por JOSÉ ALBERTO FERRUSQUÍA ACOSTA para optar al grado de Doctor en Medicina e Investigación Traslacional ha sido elaborada bajo nuestra dirección y cumple todos los requisitos necesarios para ser defendida ante el Tribunal de evaluación correspondiente.

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CONTENIDO

ABREVIATURAS

HTP: Hipertensión portal

GPP: Gradiente de presión portosistémica

PP: Presión portal

PSE: Presión suprahepática enclavada

GPVH: Gradiente de presión venosa hepática

PSL: Presión suprahepática libre

EHGNA: Enfermedad hepática grasa no alcohólica

VHC: Virus de la hepatitis C

ASA: American Society of Anesthesiologists

HTPI: Hipertensión portal idiopática

TIPS: Transjugular intrahepatic porto systemic shunt

MELD: Model for End-stage Liver Disease

IMC: Índice de masa corporal

R: Coeficiente de correlación de Pearson

CCI: Coeficiente de correlación intraclase

OR: Odds ratio

HR: Hazard ratio

ARTÍCULOS QUE COMPONEN LA TESIS

La presente tesis doctoral fue realizada en formato de compendio de artículos y consta de dos artículos, los cuales se citan a continuación:

1. **Ferrusquía-Acosta J**, Bassegoda O, Turco L, Reverter E, Pellone M, Bianchini M, Pérez-Campuzano V, Ripoll E, García-Criado A, Graupera I, García-Pagán JC, Schepis F, Senzolo M, Hernández-Gea V. Agreement between wedged hepatic venous pressure and portal pressure in non-alcoholic steatohepatitis-related cirrhosis. *Journal of Hepatology*. 2020 Oct. Online ahead of print. PMID: 33068638. DOI: 10.1016/j.jhep.2020.10.003. Artículo publicado en una revista científica con un factor impacto de 20.582, perteneciente al primer cuartil del área de Hepatología según las clasificaciones del Journal Citation Report y del Scimago Journal Rank.

2. Elkrief L*, **Ferrusquía-Acosta J***, Payancé A, Moga L, Tellez L, Praktiknjo M, Procopet B, Farcau O, De Lédinghen V, Yuldashev R, Tabchouri N, Barbier L, Dumortier J, Menahem B, Magaz M, Hernández-Gea V, Albillos A, Trebicka J, Spahr L, De Gottardi A, Plessier A, Valla D, Rubbia-Brandt L, Toso C, Bureau C, García-Pagán JC, Rautou PE for VALDIG, an EASL consortium. Abdominal surgery in patients with idiopathic noncirrhotic portal hypertension: A multicenter retrospective study. *Hepatology*. 2019;70(3):911-924. PMID: 30924941. DOI: 10.1002/hep.30628. Artículo publicado en una revista científica con un factor impacto de 14.679, perteneciente al primer cuartil del área de Hepatología según las clasificaciones del Journal Citation Report y del Scimago Journal Rank.

** Ambos autores son considerados primeros autores*

RESUMEN

La hipertensión portal es un síndrome clínico que consiste en el aumento patológico y sostenido de la presión en el territorio venoso portal. Su relevancia se ve determinada por las graves complicaciones que produce, las cuales condicionan una elevada morbilidad y mortalidad en pacientes con enfermedades crónicas del hígado. El gradiente de presión venosa hepática, la diferencia entre la presión suprahepática enclavada y la presión suprahepática libre, es la técnica de elección para evaluar la hipertensión portal en pacientes con cirrosis, ya que proporciona información pronóstica relevante relacionada con la supervivencia y el riesgo de descompensación. No obstante, su valor pronóstico depende de la existencia de una buena correlación entre la presión suprahepática enclavada y la presión portal. Por desgracia, los estudios que han demostrado que la presión suprahepática enclavada es capaz de estimar con precisión la presión portal no han incluido a pacientes con enfermedad hepática grasa no alcohólica, la cual se ha posicionado como la causa más frecuente de hepatopatía crónica en nuestro medio. Por otra parte, los avances continuos en las técnicas quirúrgicas y el manejo médico han dado lugar a un aumento en el número de pacientes con hipertensión portal que son derivados para una evaluación prequirúrgica. Por lo tanto, es fundamental comprender los riesgos y los beneficios de la realización de procedimientos quirúrgicos en pacientes con enfermedades crónicas del hígado. La mayoría del conocimiento actual sobre el riesgo quirúrgico en pacientes con hipertensión portal proviene de estudios realizados en pacientes con cirrosis. Sin embargo, la evidencia relacionada con el pronóstico postquirúrgico en pacientes con hipertensión portal idiopática es escasa y se limita a cirugías cada vez menos indicadas como la esplenectomía o la creación quirúrgica de una derivación portosistémica. Los trabajos incluidos en la presente tesis pretenden evaluar, por un lado, la correlación entre la presión suprahepática enclavada y la presión portal en pacientes con enfermedad hepática grasa no alcohólica, y por otro, el pronóstico postquirúrgico de los pacientes con hipertensión portal idiopática que son sometidos a una cirugía abdominal.

INTRODUCCIÓN

Definición

La hipertensión portal (HTP) es un síndrome clínico que se define como un aumento patológico de la presión en el territorio venoso portal. La relevancia de este síndrome se ve determinada por sus graves complicaciones, las cuales representan la primera causa de muerte y trasplante hepático en pacientes con enfermedades hepáticas crónicas del hígado.[1]

Recuerdo anatómico

El hígado es órgano con un doble sistema de aporte sanguíneo por lo que recibe sangre proveniente de la vena porta y la arteria hepática.[2] La sangre procedente de ambos sistemas se mezcla en los sinusoides hepáticos y es drenada por las venas suprahepáticas que, a su vez, desembocan en la vena cava inferior. En condiciones normales, el flujo sanguíneo hepático es de alrededor de 1500 mL/min o 25% del gasto cardíaco.[2] La arteria hepática aporta aproximadamente un tercio del flujo sanguíneo hepático y la mitad del oxígeno utilizable por el hígado, mientras que el resto lo suministra la vena porta. El flujo arterial hepático actúa como un amortiguador fisiológico del flujo sanguíneo hepático ya que éste se ajusta en función del flujo venoso portal.[3] De esta forma, los cambios producidos en el flujo venoso portal no condicionan oscilaciones importantes en el flujo sanguíneo hepático.[3]

Fisiopatología

El aumento patológico y sostenido de la presión hidrostática en el territorio venoso portal produce como consecuencia que el gradiente de presión entre la vena porta y la vena hepática, también conocido como gradiente de presión portosistémica (GPP), aumente por encima del rango normal que oscila entre 1 y 5 mmHg.[4] Cuando este GPP aumenta por encima de los 10 mmHg, pueden aparecer diversas complicaciones de la HTP como la hemorragia varicosa, la ascitis o la encefalopatía hepática, todas ellas responsables de una elevada morbilidad y mortalidad.[5,6] El GPP está determinado por el flujo portal y la resistencia vascular que se opone a este flujo. La relación entre estos tres factores se rige por la ley de Ohm mediante la ecuación $\Delta P = R \times Q$, en la que ΔP es el GPP, R la resistencia vascular en el territorio venoso portal y Q el flujo portal.[2] Así, en la génesis de la HTP se produce de forma inicial, un aumento en la resistencia vascular intrahepática secundaria a cambios estructurales (principalmente fibrosis) y funcionales (vasoconstricción

intrahepática), seguido de un hiperaflujo esplácnico producido por una vasodilatación venosa esplácnica.[7] Por otro lado, el aumento de la presión venosa portal promueve la formación de una red de circulación colateral que intenta descomprimir el sistema venoso portal derivando parcialmente la sangre venosa portal hacia la circulación sistémica. La formación de estas colaterales se cree secundaria a dos procesos, por un lado, la dilatación de comunicaciones preexistentes funcionalmente cerradas, y por otro, la activación de factores angiogénicos que inducen la formación de neovasos.[2,8]

Aumento de la resistencia vascular

En la HTP, el aumento en la resistencia vascular intrahepática se debe primordialmente a las alteraciones arquitecturales del parénquima hepático como el depósito de matriz extracelular (fibrosis hepática). No obstante, existe también un componente dinámico responsable del aumento del tono vascular hepático y, por tanto, del aumento de la resistencia al flujo venoso portal.[2,7] Este aumento dinámico del tono vascular hepático se debe a un aumento en la actividad de diversos agentes vasoconstrictores endógenos (endotelina, norepinefrina, angiotensina-II, vasopresina, leucotrienos, tromboxano A2) y, de forma adicional, a una respuesta vasoconstrictora aumentada a estos agentes.[7] De forma similar, estudios previos han sugerido que en el hígado cirrótico, existe una disminución de la biodisponibilidad de agentes vasodilatadores endoteliales como el óxido nítrico.[9,10]

Hiperaflujo esplácnico

En las etapas iniciales de la HTP, el aumento de la presión venosa portal, que se produce como consecuencia del aumento en la resistencia vascular hepática, produce una excesiva liberación de vasodilatadores a nivel esplácnico (óxido nítrico, prostaciclinas, endocannabinoides, glucagón, etc.) y una reducción de la sensibilidad vascular a sustancias vasoconstrictoras endógenas,[7,11] lo que explica que exista vasodilatación a pesar de la activación de los sistemas vasoconstrictores endógenos (*e.g.* sistema renina-angiotensina-aldosterona, sistema nervioso simpático) y que la vasodilatación esplácnica sea tan intensa que se acompañe de vasodilatación sistémica con hipotensión arterial. Así, a medida que la HTP empeora, se produce una importante vasodilatación esplácnica que produce una hipovolemia efectiva del lecho vascular.[7] En un intento de compensar esta situación, se estimulan los sistemas vasoconstrictores endógenos mencionados previamente produciendo una expansión de la volemia mediante la retención renal de agua y sodio.[7] La expansión de la volemia producida condiciona un aumento del retorno venoso y, por tanto, del gasto cardíaco. Así, esta situación, que combina una marcada disminución de la resistencia vascular sistémica con un aumento en el gasto cardiaco con, define la denominada, circulación hiperdinámica, la cual, contribuye a aumentar aún más el flujo sanguíneo esplácnico, perpetuando y empeorando la HTP.[12]

Etiología

La principal causa de HTP en nuestro medio es la cirrosis. Sin embargo, existen otras múltiples causas de HTP como la enfermedad vascular portosinusoidal (también conocida como hipertensión portal idiopática), la trombosis portal no cirrótica y el síndrome de Budd-Chiari, entidades que forman parte de las denominadas enfermedades vasculares hepáticas. Cualquier obstáculo u obstrucción al flujo venoso hepático en el hígado o en cualquiera de las venas que lo irrigan o drenan, podría producir un aumento de la presión venosa portal.[4] Por tanto, de acuerdo con la localización anatómica en donde se produce la resistencia al flujo, la HTP se puede clasificar en prehepática (enfermedades que afectan al eje porto-espleno-mesentérico), poshepática (enfermedades que afectan a las venas suprahepáticas o a la vena cava inferior) e intrahepática (enfermedades que afectan al parénquima hepático), la cual a su vez se puede clasificar según su origen en presinusoidal, sinusoidal y postsinusoidal (Tabla 1).

Tabla 1. Causas de la hipertensión portal.*

Prehepáticas

- Trombosis de la vena esplénica
- Trombosis portal
- Estenosis congénita de la vena porta
- Compresión extrínseca de la vena porta
- Fístula arteriovenosa
- Esplenomegalia (e.g. linfoma, enfermedad de Gaucher)

Intrahepáticas

Presinusoidal

- Hipertensión portal idiopática
- Hapatopatías colestásicas (e.g. colangitis biliar primaria, colangitis esclerosante primaria)
- Granulomatosis hepáticas (e.g. esquistosomiasis, sarcoidosis)
- Enfermedades hematológicas (e.g. linfoma, leucemia linfocítica crónica)
- Fibrosis hepática congénita
- Enfermedad poliquística del adulto
- Telangiectasia hemorrágica hereditaria (síndrome de Rendu-Osler-Weber)

Sinusoidal

- Cirrosis
- Hepatopatía por alcohol o virus hepatotrópos
- Esteatosis hepática del embarazo
- Amiloidosis
- Enfermedad hepática inducida por drogas (e.g. metotrexato, amiodarona)
- Enfermedades infiltrativas (e.g. mastositosis, enfermedad de Gaucher)

Postsinusoidal

Síndrome de obstrucción sinusoidal

Síndrome de Budd-Chiari de vaso pequeño

Hipervitaminosis A

Tumores vasculares primarios (e.g. hemangioendotelioma epitelioide, angiosarcoma)

Flebitis granulomatosas (e.g. micobacterias, sarcoidosis)

Posthepáticas

Síndrome de Budd-Chiari

Malformaciones congénitas y trombosis de la vena cava inferior

Pericarditis constrictiva

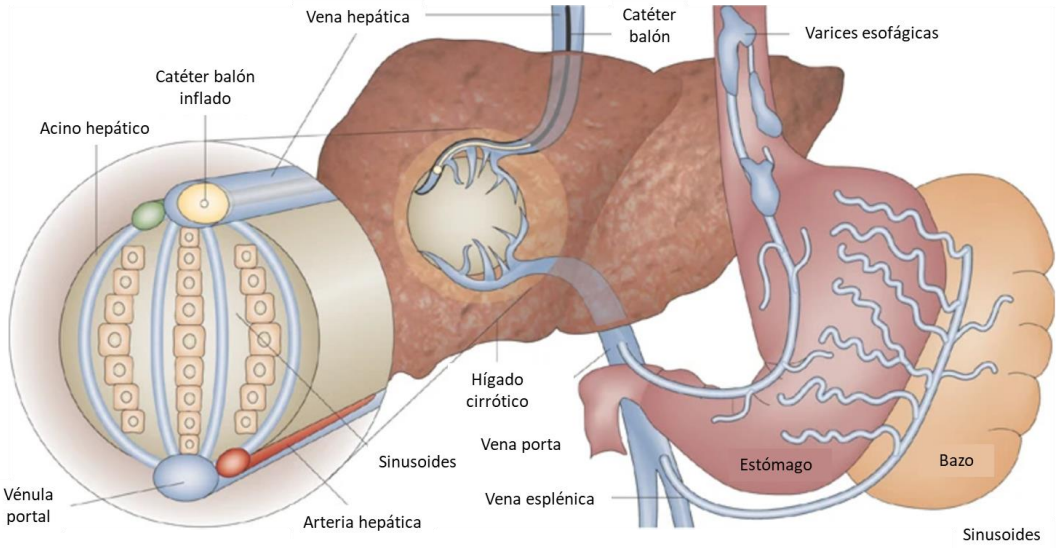
Estenosis e insuficiencia tricuspídea

**Schouten JN, García-Pagán JC, Valla DC, Janssen HL. Idiopathic noncirrhotic portal hypertension. Hepatology 2011; 54:1071.*

Diagnóstico y evaluación

La medición directa de la presión portal (PP) se realiza mediante un procedimiento invasivo que implica la punción percutánea de la vena porta. En 1956, Myers y Taylor sugirieron por primera vez que la presión suprahepática enclavada (PSE), medida tras la oclusión de una vena suprahepática, permite estimar de forma indirecta la PP.[13] A diferencia de lo que sucede con la PP, la medición de la PSE se realiza mediante el cateterismo selectivo de las venas suprahepáticas, un procedimiento mínimamente invasivo que ha demostrado ser seguro y que puede realizarse de forma ambulatoria. Para obtener la PSE es necesario ocluir la vena suprahepática con ayuda de un catéter balón o con la propia punta del catéter, lo cual permite que se forme una columna estática de sangre entre el catéter enclavado y el sinusoide, dando como resultado una lectura de la presión sinusoidal (Figura 1).[14] En el hígado sano, la existencia de una red sinusoidal de baja resistencia permite disipar la mayor parte de la presión por lo que la presión en la columna estática de sangre refleja la presión sinusoidal, que en pacientes sanos suele ser aproximadamente 1 mmHg inferior a la PP.[14] Por el contrario, cuando la afectación hepática tiene lugar en el sinusoide (*e.g.* cirrosis), la alteración en la arquitectura hepática producida por la fibrosis impide que la presión en la columna estática de sangre producida tras la oclusión de la vena suprahepática se disipe a través de las conexiones intersinusoidales por lo que ésta se equilibra con la PP.[14] Como consecuencia de lo anterior, la PSE refleja con mucha precisión la PP en pacientes con cirrosis.[15] Sin embargo, si la obstrucción al flujo venoso se produce antes del sinusoide, la presión sinusoidal permanece intacta y, por tanto, la PSE obtenida no es capaz de reflejar de forma adecuada la PP real.[16,17] Es por ello que en las enfermedades con afectación presinusoidal la PSE puede ser normal a pesar de que exista HTP.

Figura 1. Estimación de la presión portal mediante la medición de la presión suprahepática enclavada en un hígado cirrótico.*



**Bosch J, Abraldes A, Berzigotti A, García-Pagán JC. The clinical use of HVPG measurements in chronic liver disease. Nat Rev Gastroenterol Hepatol. 2009;6(10):574.*

Por otra parte, la PSE puede verse afectada por variaciones en la presión intraabdominal y puede variar en función del lugar en el que se sitúe el punto cero de referencia externo.[18] Debido a ello, se prefiere expresar su valor en forma de gradiente mediante el cálculo del gradiente de presión venosa hepática (GPVH), la diferencia entre la PSE y la presión suprahepática libre (PSL), el cual evita ambos problemas al incorporar su propio punto cero de referencia interno. Así, la medición del GPVH se ha convertido en la técnica de elección para evaluar la HTP en pacientes con cirrosis.[4] Sin embargo, la fiabilidad y reproducibilidad del GPVH depende en gran medida de la calidad y precisión con la que se realice la técnica.[14,19] Como se ha mencionado previamente, la PSE se obtiene mediante el cateterismo selectivo de las venas suprahepáticas, durante el cual, es necesario ocluir el flujo venoso hepático, ya sea, con la punta del catéter, o bien, inflando un balón localizado en su punta. Aunque ambos métodos permiten evaluar el GPVH, el uso del catéter balón ha demostrado ser el método más fiable y reproducible[20] debido a que proporciona ventajas prácticas al permitir realizar mediciones repetidas en una misma vena, y evaluar un área de parénquima hepático mayor, evitando así, que la PSE se mida en áreas de parénquima hepático con diferentes grados de afectación y, por tanto, con perfiles hemodinámicos diversos. La PSL, por su parte, debe ser medida con el catéter libre en el interior de la vena hepática a no más de 3 cm de su desembocadura hacia la vena cava inferior.[19] En este sentido, estudios previos han demostrado que el GPVH calculado con la PSL y no con la vena cava inferior, es el que predice con mayor precisión el pronóstico de los pacientes con cirrosis.[19]

De esta forma, el GPVH proporciona información pronóstica relevante relacionada con la supervivencia y el riesgo de descompensación en pacientes con cirrosis. En la cirrosis compensada, un GPVH ≥ 10 mmHg permite identificar a pacientes con un riesgo aumentado de desarrollar complicaciones de la HTP (*e.g.* hemorragia por varices, ascitis, encefalopatía hepática o hepatocarcinoma) y por ello este valor es el que se utiliza para definir la HTP clínicamente significativa.[5,6,21,22] En cambio, en pacientes con cirrosis descompensada, un GPVH ≥ 16 mmHg es capaz de identificar a pacientes con un riesgo alto de muerte o trasplante hepático durante el seguimiento.[19,23–25] Adicionalmente, el GPVH permite evaluar la respuesta a diferentes tratamientos utilizados en pacientes con HTP. Así, un descenso del GPVH ≥ 10% del valor basal o su descenso a un valor ≤ 12 mmHg, disminuye de forma significativa el riesgo de desarrollar complicaciones relacionadas con la HTP.[26,27] De forma similar, estudios longitudinales realizados en pacientes con un episodio previo de hemorragia por varices han demostrado que una disminución del GPVH ≥ 20% del valor basal o su descenso a un valor ≤ 12 mmHg se asocia de forma significativa a un menor riesgo de resangrado.[28]

Evaluación de la hipertensión portal en pacientes con enfermedad hepática grasa no alcohólica

La mayoría del conocimiento que existe sobre la HTP proviene de estudios realizados en pacientes con cirrosis por alcohol o virus hepatotropos en los que no se incluyeron a pacientes con EHGNA, enfermedad que se ha posicionado como una de las principales causas de hepatopatía en la actualidad.[29] La EHGNA abarca un espectro de enfermedades que se caracterizan por la acumulación de grasa en el interior de los hepatocitos no asociada al consumo abusivo de alcohol.[30] Por desgracia el relativamente reciente reconocimiento de esta enfermedad ha condicionado que el estudio de la HTP en estos pacientes sea aún limitado.

En los últimos años se han publicado estudios que sugieren que los mecanismos involucrados en el desarrollo de HTP en la EHGNA podrían ser, en parte, diferentes a los previamente descritos en otras etiologías de la cirrosis. Por una parte, estudios previos han demostrado que los pacientes con EHGNA pueden desarrollar HTP en etapas tempranas de la enfermedad e incluso antes del desarrollo de cirrosis.[31–33] Otro estudio, en cambio, ha sugerido que los pacientes con EHGNA pueden tener valores de GPVH más bajos en cada estadio de la fibrosis en comparación con pacientes con cirrosis por virus de la hepatitis C (VHC).[34] Finalmente, los resultados del estudio del simtuzumab,[35,36] el estudio más grande a día de hoy que evalúa el GPVH en la EHGNA, sugieren que la capacidad del GPVH para predecir el desarrollo de complicaciones de la HTP es inferior a la reportada en otras etiologías.[6] En este estudio el 14% de los pacientes con un GPVH < 10 mmHg desarrollaron complicaciones relacionadas con la HTP (hemorragia variceal, ascitis y encefalopatía hepática) durante una mediana de seguimiento de 4.7 meses,[36] mientras que en el estudio pionero de Ripoll *et al*., ninguno de los pacientes con un GPVH < 10 mmHg se descompensó durante los primeros 20 meses de seguimiento.[6] Esta evidencia en su conjunto

pone en manifiesto que el valor pronóstico del GPVH en la EHGNA es aún incierto y, por tanto, requiere de más estudio.

Impacto en el pronóstico posquirúrgico

La HTP es un factor pronóstico clave en pacientes con cirrosis que son sometidos a cirugía. En este sentido, estudios previos han demostrado que el grado de HTP, medido por el GPVH, permite identificar a aquellos pacientes con cirrosis y carcinoma hepatocelular que tienen un riesgo elevado de descompensación tras una resección hepática.[37] Por otra parte, un en estudio reciente en el que se incluyeron de forma prospectiva a 140 pacientes con cirrosis sometidos a una cirugía extrahepática electiva, se observó que la clase ASA (*American Society of Anesthesiologists*), la cirugía de alto riesgo (cirugías abdominales abiertas, cardiovasculares y torácicas) y el GPVH se asociaron de forma independiente con la muerte en el primer año después de la cirugía.[38] De hecho, los resultados de este estudio demostraron que los pacientes con un GPVH < 10 mmHg tienen un menor riesgo de morir tras la cirugía y que, por el contrario, los pacientes con un GPVH ≥ 16 mmHg, y especialmente aquellos con un GPVH ≥ 20 mmHg, tienen un riesgo aumentado de muerte después de una intervención quirúrgica electiva.[38]

Riesgo quirúrgico en pacientes con hipertensión portal idiopática

La hipertensión portal idiopática (HTPI) es una enfermedad rara que se caracteriza por la presencia de HTP en ausencia de una causa conocida como la cirrosis.[39] A pesar de su rareza, los avances recientes en su estudio han condicionado un mayor reconocimiento de esta enfermedad. Aunque la fisiopatología de la HTPI sigue siendo en gran parte desconocida, esta entidad se asocia con frecuencia a trastornos inmunológicos, hematológicos, protrombóticos, tóxicos o genéticos subyacentes.[40,41] Los estudios de laboratorio de pacientes con HTPI suelen mostrar una función hepática conservada y una disminución de hematíes, leucocitos y plaquetas secundaria a la presencia de esplenomegalia.[40,41] El pronóstico a largo plazo de los pacientes con HTPI, suele ser mejor que el de los pacientes con cirrosis.[39] Aunado a ello, las mejoras en el manejo de las complicaciones asociadas y la opción del trasplante hepático han aumentado la esperanza de vida de los pacientes con HTPI, haciendo que no sea infrecuente que estos pacientes sean considerados potenciales candidatos a tratamientos quirúrgicos y, por tanto, sean derivados para la evaluación de su riesgo quirúrgico.

La mayoría del conocimiento del riesgo quirúrgico en pacientes con HTP proviene de estudios realizados en pacientes con cirrosis, en quienes el pronóstico postoperatorio depende fundamentalmente de la severidad de la HTP, la función hepática, la presencia de comorbilidades y el tipo de cirugía.[38,42–46] A diferencia de lo que ocurre en pacientes con cirrosis, los estudios que evalúan el riesgo quirúrgico en pacientes con HTPI son escasos y se limitan a procedimientos cada vez menos indicados como la

derivación portosistémica y la esplenectomía.[47–49] Aunado a esta limitación, las conclusiones derivadas de estudios realizados en pacientes con cirrosis son difícilmente extrapolables a pacientes con HTPI debido a que estos últimos presentan una mejor función hepática.[40,41] Además, el papel del GPVH en la evaluación del riesgo quirúrgico en pacientes con HTPI se ve limitado debido a que la HTP asociada a esta enfermedad presenta un componente presinusoidal que no puede ser evaluado con precisión por el GPVH, y a que la mayoría de los pacientes con HTPI presentan comunicaciones veno-venosas intrahepáticas que impiden una medición adecuada del GPVH.[16] Todo lo anterior en su conjunto, pone en evidencia la necesidad de realizar estudios encaminados a evaluar el riesgo quirúrgico de este grupo de pacientes.

JUSTIFICACIÓN, HIPÓTESIS Y OBJETIVOS

Justificación

En los últimos años la EHGNA se ha posicionado como la causa más frecuente de hepatopatía crónica en nuestro medio,[50] y su incidencia se prevé que aumente de forma significativa a medida que crece la epidemia actual de obesidad y diabetes.[51,52] El estudio de la HTP en esta entidad parece ser, por tanto, de gran necesidad teniendo en cuenta que los avances en el conocimiento de la HTP se han producido a partir de estudios realizados en pacientes con otras causas de cirrosis. El valor pronóstico del GPVH se debe fundamentalmente a la existencia de una buena correlación entre la PSE y la PP.[15,53–56] Sin embargo, los estudios que han demostrado que la PSE es capaz de estimar con precisión la PP fueron realizados sobre todo en pacientes con cirrosis por alcohol o virus hepatotropos y ninguno incluyó a pacientes con EHGNA, por lo que la correlación entre la PSE y la PP en estos pacientes es aún desconocida.

Por otra parte, los avances continuos en las técnicas quirúrgicas y el manejo médico están dando lugar a un aumento en el número de pacientes con HTP que son derivados para una evaluación prequirúrgica. Por lo tanto, es fundamental comprender los riesgos y los beneficios de tales intervenciones en pacientes con enfermedades crónicas del hígado. El interés por la HTPI ha aumentado en los últimos años debido a un mejor conocimiento de la enfermedad y un mayor reconocimiento de esta. Los pacientes con HTPI pueden requerir cirugía abdominal para tratar condiciones no relacionadas con su enfermedad hepática o, menos frecuentemente, como tratamiento de complicaciones graves o refractarias de la HTP. Sin embargo, a diferencia de lo que ocurre en la cirrosis, la baja prevalencia de HTPI ha dificultado el desarrollo de estudios que evalúen el riesgo quirúrgico en estos pacientes. De hecho, la evidencia que existe hoy en día en pacientes con HTPI se limita a cirugías cada vez menos indicadas como la esplenectomía o la creación quirúrgica de una derivación portosistémica.[47–49] Además de ello, dado el vínculo que existe entre la HTP y el pronóstico postoperatorio, se ha propuesto la realización de técnicas de descompresión portal como la colocación de una derivación intrahepática portosistémica transyugular (TIPS, del inglés *transjugular intrahepatic porto systemic shunt*), para facilitar la cirugía abdominal y mejorar el pronóstico de los pacientes con HTP que son sometidos a cirugía.[57–62] Sin embargo, la evidencia que existe al respecto es muy limitada, especialmente en pacientes con HTPI.

Hipótesis

- La PSE podría estimar con menor precisión la PP en pacientes con cirrosis por EHGNA en comparación con pacientes con cirrosis por alcohol o VHC. Existen factores que se asocian a una peor correlación entre la PSE y la PP en pacientes con cirrosis por EHGNA.

- La realización de una cirugía abdominal implica un riesgo no despreciable de complicaciones y muerte en pacientes con HTPI. Existen factores que permiten predecir un pronóstico desfavorable en pacientes con HTPI sometidos a una cirugía abdominal.

Objetivos

Objetivos principales:

- Evaluar la precisión de la PSE para estimar la PP en pacientes con cirrosis por EHGNA y compararla con aquella observada en pacientes con cirrosis por alcohol o VHC.
- Evaluar el pronóstico postoperatorio en pacientes con HTPI sometidos a una cirugía abdominal.

Objetivos secundarios:

- En caso de que existiera una correlación subóptima entre la PSE y la PP en pacientes con cirrosis por EHGNA, conocer su causa y los factores asociados a ella.
- Conocer la frecuencia con la que la PSE infraestima o sobreestima a la PP en pacientes con cirrosis por EHGNA.
- Describir la prevalencia y el tipo de complicaciones que se producen tras una cirugía abdominal en pacientes con HTPI.
- Identificar factores de riesgo asociados a un mal pronóstico en pacientes con HTPI sometidos a cirugía abdominal.
- Evaluar el impacto de los procedimientos de descompresión portal en el pronóstico de pacientes con HTPI que requieren cirugía abdominal.

Aspectos éticos

Los pacientes incluidos en ambos estudios dieron su consentimiento firmado para que sus datos clínicos fueran utilizados en estudios de investigación futuros. Para el desarrollo de ambos estudios fue necesario obtener el consentimiento del Comité de Ética del Hospital Clínic de Barcelona y del resto de los centros participantes. Los estudios clínicos se realizaron conforme a los principios expresados en la Declaración de Helsinki.

MÉTODOS Y RESULTADOS

Estudio 1: Agreement between wedged hepatic venous pressure and portal pressure in non-alcoholic steatohepatitis-related cirrhosis.

José Ferrusquía-Acosta, Octavi Bassegoda, Laura Turco, Enric Reverter, Monica Pellone, Marcello Bianchini, Valeria Pérez-Campuzano, Enric Ripoll, Ángeles García-Criado, Isabel Graupera, Juan Carlos García-Pagán, Filippo Schepis, Marco Senzolo, Virginia Hernández-Gea.

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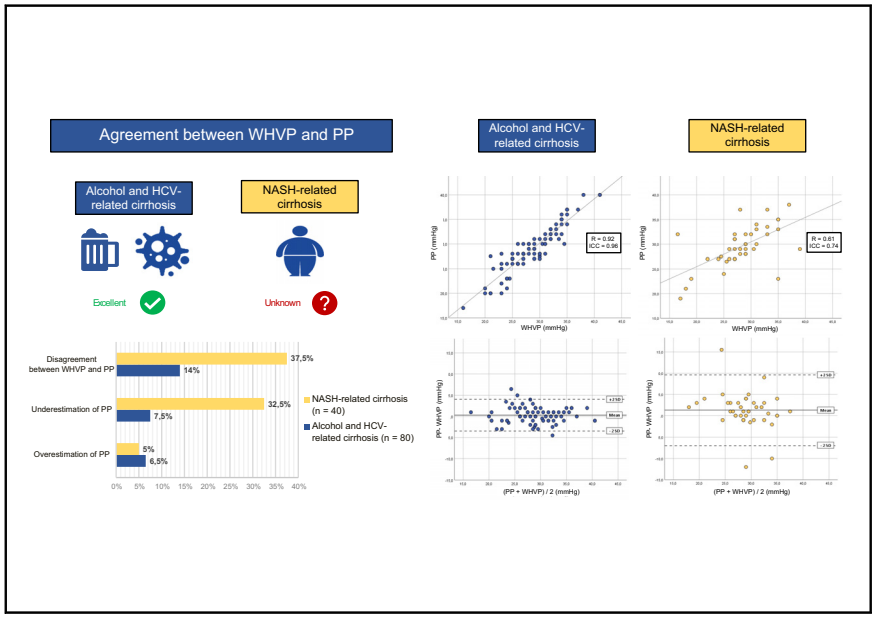
Research Article
Cirrhosis and Liver Failure

JOURNAL
OF HEPATOLOGY

Agreement between wedged hepatic venous pressure and portal pressure in non-alcoholic steatohepatitis-related cirrhosis

Graphical abstract



Highlights

- Wedge hepatic vein pressure (WHVP) accurately estimates portal pressure (PP) in patients with alcohol-related or HCV-related cirrhosis.
- Agreement between WHVP and PP in decompensated non-alcoholic steatohepatitis (NASH) cirrhosis is worse than in other aetiologies.
- WHVP tends to underestimate PP in patients with decompensated NASH cirrhosis.

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Lay summary

Portal pressure is usually assessed by measuring wedge hepatic vein pressure because of solid evidence demonstrating their excellent agreement in alcohol- and viral hepatitis-related cirrhosis. Our results show that in patients with decompensated cirrhosis caused by non-alcoholic steatohepatitis, wedge hepatic vein pressure estimates portal pressure with less accuracy than in patients with other aetiologies of cirrhosis, mainly because of portal pressure underestimation.

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Research Article
Cirrhosis and Liver Failure

JOURNAL OF HEPATOLOGY

Agreement between wedged hepatic venous pressure and portal pressure in non-alcoholic steatohepatitis-related cirrhosis

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Background & Aims: Wedge hepatic vein pressure (WHVP) accurately estimates portal pressure (PP) in alcohol- or viral hepatitis-related cirrhosis. Whether this also holds true in cirrhosis caused by non-alcoholic steatohepatitis (NASH) is unknown. We aimed to evaluate the agreement between WHVP and PP in patients with NASH cirrhosis in comparison to patients with alcohol- or HCV-related cirrhosis.

Methods: All consecutive patients with NASH cirrhosis treated with a transjugular intrahepatic portosystemic shunt (TIPS) in 3 European centres were included (NASH group; n = 40) and matched with 2 controls (1 with alcohol-related and 1 with HCV-related cirrhosis) treated with TIPS contemporaneously (control group; n = 80). Agreement was assessed by Pearson's correlation (R), intra-class correlation coefficient (ICC), and Bland-Altman method. Disagreement between WHVP and PP occurred when both pressures differed by >10% of PP value. A binary logistic regression analysis was performed to identify factors associated with this disagreement.

Results: Correlation between WHVP and PP was excellent in the control group (R 0.92; p <0.001; ICC 0.96; p <0.001) and moderate in the NASH group (R 0.61; p <0.001; ICC 0.74; p <0.001). Disagreement between WHVP and PP was more frequent in the NASH group (37.5% *vs.* 14%; p = 0.003) and was mainly because of PP underestimation. In uni- and multivariate analyses, only NASH aetiology was associated with disagreement between WHVP and PP (odds ratio 4.03; 95% CI 1.60–10.15; p = 0.003).

Conclusions: In patients with decompensated NASH cirrhosis, WHVP does not estimate PP as accurately as in patients with alcohol- or HCV-related cirrhosis, mainly because of PP underestimation. Further studies aimed to assess this agreement in patients with compensated NASH cirrhosis are needed.

Lay summary: Portal pressure is usually assessed by measuring wedge hepatic vein pressure because of solid evidence demonstrating their excellent agreement in alcohol- and viral hepatitis-related cirrhosis. Our results show that in patients with decompensated cirrhosis caused by non-alcoholic steatohepatitis, wedge hepatic vein pressure estimates portal pressure with less accuracy than in patients with other aetiologies of cirrhosis, mainly because of portal pressure underestimation.

Introduction

Portal hypertension (PH) is the strongest predictor of hepatic decompensation and death in patients with cirrhosis.[1,2] Direct measurement of portal pressure (PP) is an invasive procedure that has long been substituted by measuring the wedge hepatic vein pressure (WHVP) through the very safe and minimally invasive catheterisation of hepatic veins.[3–5] However, to avoid the impact of ascites or intra-abdominal pressure, which can falsely elevate WHVP, its measurement is usually expressed by the hepatic venous pressure gradient (HVPG)—the difference between the WHVP and the free hepatic vein pressure.[6] It is widely known that WHVP accurately estimates PP when the liver disease affects the sinusoids (sinusoidal PH), as it happens in cirrhosis.[7,8] However, this evidence comes from studies conducted in patients with cirrhosis caused by alcohol or viral hepatitis,[9–11] and none of them included patients with cirrhosis caused by non-alcoholic steatohepatitis (NASH).

Even though NASH is a modern-day disease whose natural history is poorly known, liver fibrosis degree and presence of cirrhosis have been identified as the most important risk factors for decompensation and mortality.[12–15] However, unlike other aetiologies of cirrhosis, the HVPG ability to predict hepatic decompensation has not been sufficiently evaluated in patients with NASH. In alcohol- or viral hepatitis-related cirrhosis, an

Keywords: Portal hypertension; Non-alcoholic fatty liver disease; Hepatic venous pressure gradient.
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HVPG ≥10 mmHg is associated with a higher risk of decompensation and is the threshold that defines clinically significant PH. The largest study to date evaluating HVPG in NASH cirrhosis, the simtuzumab trial,[16,17] confirmed that an HVPG ≥10 mmHg also predicts decompensation. Nevertheless, the capacity of HVPG in predicting clinical outcomes was inferior to that reported in other aetiologies.[2] Indeed, in this study, 14% of patients with an HVPG <10 mmHg developed PH-related complications (variceal haemorrhage, ascites, and hepatic encephalopathy) during a median follow-up of 4.7 months, whereas in the seminal study from Ripoll *et al.*, none of the patients with an HVPG <10 mmHg decompensated during the first 20 months of follow-up.[2] Moreover, it has been suggested that patients with NASH may have lower HVPG values for each stage of fibrosis when compared with patients with cirrhosis caused by HCV,[18] raising the concern of a possible underestimation of PP by WHVP in patients with NASH cirrhosis.

As far as we know, agreement between WHVP and PP has never been explored in patients with NASH cirrhosis. Therefore, the aim of our study was to evaluate the accuracy of WHVP for estimating PP in patients with NASH cirrhosis, and compare it with that observed in patients with alcohol- or HCV-related cirrhosis.

Patients and methods

Study cohort

We performed a multicentre cross-sectional study in 3 European centres (Hospital Clínic de Barcelona [HCB], University Hospital of Padua [UHP], and Azienda Ospedaliera-Universitaria di Modena [AOUM]) with a large experience in hepatic haemodynamic procedures and HVPG measurements. All patients with NASH cirrhosis (NASH group) who were treated with transjugular intrahepatic portosystemic shunt (TIPS) from January 2010 to December 2019 were included. Diagnosis of cirrhosis was established by unequivocal clinical, biochemical, radiological, and/or histological criteria. Diagnosis of NASH was made by histological criteria or the absence of other causes of liver disease and the presence of at least 1 cardiovascular risk factor (CVRF): hypertension, type 2 diabetes, dyslipidaemia, overweight, coronary artery disease, cerebrovascular disease, and peripheral vascular disease. Exclusion criteria were prior liver transplantation, occlusive portal vein thrombosis, hepatocellular carcinoma outside Milan criteria, presence of hepatic vein-to-vein communications that precluded from an adequate occlusion of the hepatic vein during HVPG measurement, and the occurrence of a significant event between WHVP and PP measurements. Any of the following were considered a significant event: blood product transfusion, hypovolaemic shock requiring volume restitution, local therapy for hepatocellular carcinoma, large-volume paracentesis, administration of albumin, and initiation/change in the dose of non-selective beta blockers or diuretics. Each patient in the NASH group was matched with 2 consecutive controls who were treated with TIPS contemporaneously, 1 with alcohol- and 1 with HCV-related cirrhosis (control group), adjusted by severity of liver disease (Child-Pugh score) and without any of the aforementioned exclusion criteria.

Measurement of WHVP and PP

WHVP was measured during TIPS procedure and immediately before PP measurement in 2 centres (HCB and UHP). The third centre (AOUM) measured the WHVP on a different day, but within 1 month before TIPS insertion. Only patients with stable conditions and lack of significant events between WHVP and PP measurements were included from AOUM. The external zero reference point was set at the mid-axillary line of the patient. Under local anaesthesia and ultrasound monitoring, a venous introducer was placed in the internal jugular vein by the Seldinger technique. Under fluoroscopy, a 7F balloon-tipped catheter was guided into the main right or medium hepatic vein, where free hepatic vein pressure and WHVP were measured by triplicate. In all cases, PP was measured during TIPS placement. The technique used to measure PP can be briefly summarised as follows: using a transjugular approach and under continuous ultrasonographic and radiological guidance, a transjugular liver biopsy needle was advanced into the right hepatic vein through a long sheath venous introducer. From that position, the hepatic parenchyma was punctured, reaching the portal vein and, once there, a guide wire was advanced and the needle was withdrawn, allowing a 5F catheter being advanced into the main portal trunk where PP was finally measured during at least 30 sec. Permanent tracings of WHVP and PP measurements were obtained using a multichannel recorder. The type of sedation and the use of mechanical ventilation (MV) during TIPS depended on the clinical status of the patient and the policy of the participating centre:

- In AOUM, all TIPS were performed under superficial sedation (using midazolam and fentanyl) and without MV.
- In UHP, all TIPS were performed under deep sedation (using propofol and remifentanil) and MV (using a laryngeal mask).
- In HCB, all TIPS were performed under deep sedation (using propofol and remifentanil), but the use of MV (using an orotracheal tube) was at the attending physician's discretion depending on the patient's clinical status at the time of TIPS (*e.g.* low level of consciousness, aspiration pneumonia, or persistent bleeding).

Statistical analysis

Statistical analyses were performed using SPSS 25.0 (SPSS Inc., Chicago, IL, USA). Data were expressed as frequencies (%) for categorical variables or as a median (inter-quartile range) for quantitative variables. Categorical variables were compared using either chi-square test or Fisher's exact test, where appropriate. Continuous variables were compared with either Student *t* test or Mann-Whitney *U* test, where appropriate. Agreement between WHVP and PP was assessed by Pearson's correlation (R) and the intra-class correlation coefficient (ICC) for both absolute agreement (when agreement is influenced by any difference between both pressure values) and consistency (when agreement is not influenced by systematic differences between both pressure values). ICC values can range between 0 (total lack of agreement) and 1 (perfect agreement). ICC values of <0.50 indicate poor agreement, values from 0.50 to 0.74 indicate moderate agreement, values from 0.75 to 0.90 indicate good agreement, and values of >0.90 indicate excellent agreement.[19] The agreement between WHVP and PP was also evaluated by the Bland-Altman method, which plots the difference between both pressures (Y axis) over their mean (X axis), showing the 95% limits of the agreement (mean difference ±1.96 SD). The smaller the range between these 2 limits is, the better is the agreement. This method is useful to reveal a relationship between the differences of both pressure measurements and their magnitude, and to identify any systematic bias.[20] Agreement between WHVP

and PP occurred when both pressures were identical or differed by ≤10% of PP value. Disagreement between WHVP and PP occurred when both pressures differed by >10% of PP value. Any difference between WHVP and PP ≥5 mmHg was considered a major discrepancy.[11] PP was underestimated by WHVP when the latter was lower than the former by >10% of PP value. Conversely, PP was overestimated by WHVP when the latter was higher than the former by >10% of PP value. Uni- and multivariate binary logistic regression analyses were performed to identify parameters independently associated with disagreement between WHVP and PP. Variables that presented a p value <0.10 in the univariate analysis were included in the multivariate analysis. Significance was considered as 2-sided p values <0.05.

Ethical aspects

All patients submitted to TIPS placement in all the participating centres gave their consent to use their clinical data in future studies, provided that these studies got the approval of the ethics committee of each centre. The study protocol was approved by the ethics committee of all participating centres (HCB/2019/0619, CESC 3312/AO/19, and CEP/2017/140). The study was conducted in accordance with the Declaration of Helsinki.

Results

Patient selection and baseline characteristics

From January 2010 to December 2019, a total of 61 patients with NASH cirrhosis were treated with TIPS in all participating centres. From those, 21 patients were excluded from the study (8 because of a significant event between WHVP and PP measurements, 8 because of complete portal vein thrombosis, and 5 because of the presence of hepatic vein-to-vein communications). Thus, a total of 40 patients with NASH cirrhosis were included and compared with a control group of 80 matched contemporaneous patients with cirrhosis caused by alcohol (n = 40) or HCV (n = 40).

The baseline characteristics of all patients are described in Table 1. Patients included were mainly males (74%) with a median age of 58 (51–63) yr and median Child-Pugh and model for end-stage liver disease scores of 8 (7–9) and 12 (10–15) points, respectively. Indication of TIPS was variceal bleeding in 56 (47%), refractory ascites in 57 (47%), and hepatic hydrothorax in 7 (6%) patients. Twenty patients (17%) received superficial sedation (midazolam plus fentanyl), while 100 patients (83%) were under deep sedation (propofol plus remifentanil) at the time of TIPS. Similarly, 68 (57%) patients were assisted by MV during TIPS procedure, while 52 (43%) patients were breathing spontaneously. Regarding vasoactive drugs, 19 (16%) patients were under somatostatin/terlipressin and 4 (3%) patients were under noradrenaline (mean dose 0.60 mg/h; range 0.35–0.80 mg/h)

Table 1. Baseline characteristics of patients.

	All (n = 120)	NASH group (n = 40)	Control group (n = 80)	p value*
Age (years)	58 (51–63)	60 (55–67)	56 (50–62)	0.052
Male	89 (74)	29 (73)	60 (75)	0.768
BMI (kg/m^2)	25.8 (23.7–30.0)	27.8 (24.9–30.7)	24.8 (22.9–30.0)	**0.010**
Overweight (BMI ≥25 kg/m^2)	67 (56)	30 (75)	37 (46)	**0.003**
Obesity (BMI ≥30 kg/m^2)	30 (25)	10 (25)	20 (25)	1.000
Arterial hypertension	38 (32)	21 (53)	17 (21)	**0.001**
Type 2 diabetes	52 (43)	33 (83)	19 (24)	**<0.001**
Dyslipidaemia	28 (23)	18 (45)	10 (13)	**<0.001**
Number of CVRFs	1 (1–3)	3 (2–3)	1 (0–2)	**<0.001**
Two or more CVRFs	59 (49)	37 (93)	22 (28)	**<0.001**
Charlson index	6 (4–7)	6 (5–8)	5 (4–6)	**0.001**
Previous liver decompensations and severity of liver disease				
Ascites	97 (81)	30 (75)	67 (84)	0.251
Hepatic encephalopathy	34 (28)	8 (20)	26 (33)	0.152
Variceal bleeding	61 (51)	19 (48)	42 (53)	0.606
HCC within Milan criteria	8 (8)	2 (5)	6 (8)	0.605
Child-Pugh score	8 (7–9)	8 (7–9)	8 (7–9)	0.267
MELD score	12 (10–15)	13 (10–15)	12 (10–16)	0.964
Hepatic haemodynamics and TIPS procedure				
Indication of TIPS				
Variceal bleeding	56 (47)	20 (50)	36 (45)	0.864
Ascites	57 (47)	18 (45)	39 (49)	
Hydrothorax	7 (6)	2 (5)	5 (6)	
Mechanical ventilation	68 (57)	25 (63)	43 (54)	0.362
Type of sedation				
Superficial	20 (17)	6 (15)	14 (18)	0.729
Deep	100 (83)	34 (85)	66 (83)	
Noradrenaline infusion during TIPS	4 (3)	1 (3)	3 (4)	1.000
Use of somatostatin or terlipressin	19 (16)	4 (10)	15 (19)	0.216
WHVP (mmHg)	29.0 (25.0–32.0)	28.5 (26.0–31.0)	29.0 (25.0–32.0)	0.715
PP (mmHg)	29.0 (27.0–32.0)	29.0 (27.0–32.0)	28.5 (26.0–32.0)	0.370
PP – WHVP (mmHg)	1 (–1 to 2)	1 (0–3)	0 (–1 to 2)	**0.017**

Data are expressed as median (inter-quartile range) or frequencies (%) as appropriate. Normally distributed continuous variables were compared using t test. Non-normally distributed continuous variables were compared using Mann-Whitney U test. Categorical variables were reported compared with Chi-squared test or Fisher's exact test, where appropriate. CVRFs, cardiovascular risk factors; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis; PP, portal pressure; TIPS, transjugular intrahepatic portosystemic shunt; WHVP, wedge hepatic vein pressure.
*Values in bold denote significance.

during WHVP and PP measurements. Importantly, the dose of vasoactive drugs remained unchanged between WHVP and PP measurements. As expected, patients in the NASH group had a higher Charlson comorbidity index (6 [5–8] *vs.* 5 [4–6]; $p = 0.001$) and presented more CVRFs (3 [2–3] *vs.* 1 [0–2]; $p < 0.001$), such as hypertension (53% *vs.* 21%; $p = 0.001$), type 2 diabetes (83% *vs.* 24%; $p < 0.001$), and dyslipidaemia (45% *vs.* 13%; $p < 0.001$). Similarly, patients with NASH had a higher BMI (27.8 [24.9–30.7] kg/m^2 *vs.* 24.8 [22.9–30.0] kg/m^2; $p = 0.010$). Although the proportion of patients who are overweight (BMI ≥25 kg/m^2) was higher in the NASH group (75% *vs.* 46%; $p = 0.003$), the proportion of patients with obesity (BMI ≥30 kg/m^2) was not significantly different among both groups (25% *vs.* 25%; $p = 1.000$).

Agreement between WHVP and PP

The correlation between WHVP and PP in both groups of patients is shown in Table 2 and Fig. 1. According to previously published data, the correlation between WHVP and PP was excellent in the control group (R 0.92; ICC 0.96; $p < 0.001$). Notably, this also held true after analysing the correlation in patients with alcohol- or HCV-related cirrhosis separately (R 0.93; ICC 0.97; $p < 0.001$; and R 0.91; ICC 0.95; $p < 0.001$, respectively). However, agreement was only moderate in the NASH group (R 0.61; ICC 0.74; $p < 0.001$). In both groups, ICC for absolute agreement and ICC for consistency were the same, suggesting the absence of any systematic error. Despite sample size limited subgroup analyses,[21,22] we aimed to assess the impact of factors known to modify hepatic venous pressures, such as MV, deep sedation, and treatment with vasoactive drugs.[23,24] Agreement between WHVP and PP was consistently better in the control group after excluding patients who were intubated (n = 68) or on vasoactive drugs (n = 22) during pressure measurements (Table S1). The small number of patients with NASH under superficial sedation (n = 6) prevented from analysing the agreement in this subgroup of patients. However, results remained unchanged when all patients under deep sedation (n = 100) were analysed alone (Table S1). Moreover, the type of sedation used during pressure measurements did not influence the agreement between WHVP and PP in the control group (data not shown). Similarly, results remained unchanged after excluding 20 patients in whom WHVP and PP were measured in different days (Table S1).

Bland-Altman plots were performed to assess the agreement between WHVP and PP measurements. A high individual variability was observed in the NASH group reflected by a wide 95% CI (Fig. 2). By contrast, in the control group, the small range of variation seen allows the agreement to be considered as optimal. Moreover, patients with NASH cirrhosis tended to underestimate PP as the mean of the difference between WHVP and PP moved 1.3 mmHg above the identity line (Fig. 2). Remarkably, underestimation of PP occurred irrespectively from PP magnitude.

As summarised in Table 3, disagreement between WHVP and PP (differences ≥10% of PP value) occurred in 15 (37.5%) patients with NASH cirrhosis and 11 (14%) patients with cirrhosis caused by other aetiologies ($p = 0.003$). Table S2 shows the uni- and multivariate analyses for the determination of factors associated with the disagreement between WHVP and PP. Only NASH aetiology was independently associated with this disagreement (odds ratio [OR] 4.03 [95% CI 1.60–10.15]; $p = 0.003$) (Table S2). Importantly, neither BMI nor any CVRF was associated with the disagreement between WHVP and PP. Similarly, major discrepancies between WHVP and PP (differences ≥5 mmHg) occurred in 6 (15%) patients with NASH cirrhosis and only in 2 (3%) patients with cirrhosis caused by other aetiologies ($p = 0.016$): 1 with alcohol-related cirrhosis and the other 1 with HCV-related cirrhosis.

Underestimation of PP

The disagreement between WHVP and PP was the result of underestimating PP in 13 (32.5%) patients in the NASH group and 6 (7.5%) patients in the control group. Thus, the proportion of patients in whom WHVP underestimated PP by ≥10% of PP value was greater in the NASH group than in the control group (32.5% *vs.* 7.5%; $p < 0.001$). Indeed, the median difference between WHVP and PP was higher in the NASH group than in the control group (1 [0–3] *vs.* 0 [–1 to 2] mmHg; $p = 0.017$), suggesting that in patients with NASH cirrhosis, WHVP tends to underestimate PP. Table S3 shows the uni- and multivariate analyses of factors associated with the underestimation of PP by WHVP. As shown by this analysis, only NASH aetiology was independently associated with PP underestimation (OR 5.59 [95% CI 1.91–16.33]; $p = 0.002$).

Overestimation of PP

The disagreement between WHVP and PP was the result of overestimating PP in 2 (5%) patients in the NASH group and 5 (6%) patients in the control group ($p = 1.000$): 4 with alcohol-related cirrhosis and 1 with HCV-related cirrhosis. In agreement with previous data, overestimation was associated with vascular abnormalities in the portal blood perfusion of the liver. Three patients had large portosystemic shunts, 1 patient had a large portosystemic shunt and partial vein thrombosis, and 1 patient had an extremely low portal flow velocity (5 cm/s).

Discussion

In the present study, we analysed whether the correlation between WHVP (measured by hepatic vein catheterisation) and direct PP (measured during TIPS placement) in patients with NASH cirrhosis is similar to that of patients with alcohol- or HCV-related cirrhosis. We included patients from 3 hospitals with proven expertise in liver catheterisation and rigorous pressure measurement protocols. Moreover, the WHVP measurements were performed with a balloon catheter in all cases, and patients with hepatic vein-to-vein communications that prevented an adequate occlusion of the hepatic vein were excluded.

Table 2. Correlation between WHVP and PP.

	R	95% CI	*p* value	ICC	95% CI	*p* value
NASH group (n = 40)	0.61	(0.37–0.77)	<0.001	0.74	(0.50–0.86)	<0.001
Control group (n = 80)	0.92	(0.88–0.95)	<0.001	0.96	(0.94–0.97)	<0.001
Alcohol-related cirrhosis (n = 40)	0.93	(0.88–0.97)	<0.001	0.97	(0.94–0.98)	<0.001
HCV-related cirrhosis (n = 40)	0.91	(0.84–0.95)	<0.001	0.95	(0.91–0.98)	<0.001

Correlation between WHVP and PP was assessed by Pearson's correlation (R) and the intra-class correlation coefficient (ICC). NASH, non-alcoholic steatohepatitis.

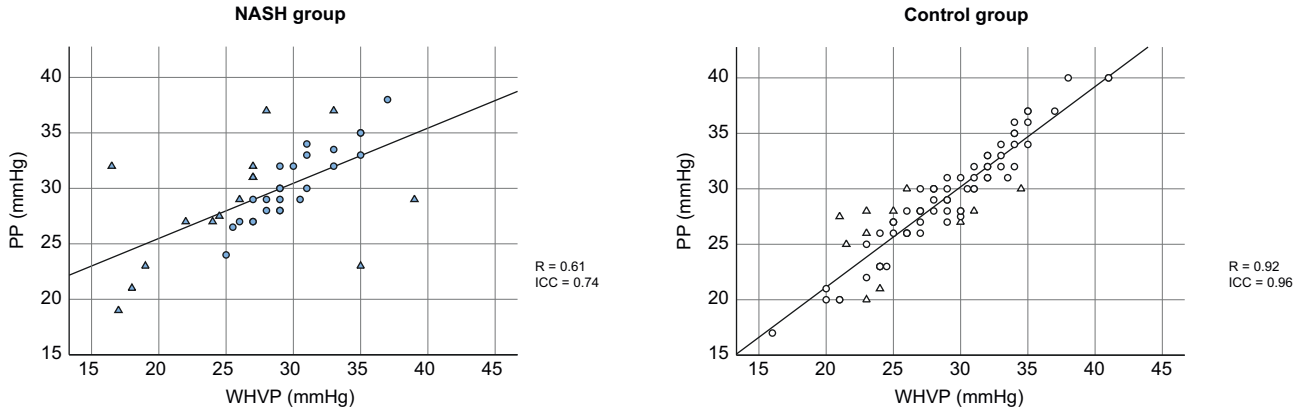

Fig. 1. Correlation between WHVP and PP in patients with NASH cirrhosis compared to that in patients with alcohol- or HCV-related cirrhosis. A greater proportion of patients with major discrepancies (≥5 mmHg) between WHVP and PP (triangle marks) can be seen in the NASH group. Values of Pearson's correlation (R) and ICC for each group are given. ICC, intra-class correlation coefficient; NASH, non-alcoholic steatohepatitis; PP, portal pressure; WHVP, wedge hepatic vein pressure.

Despite being a highly active field in research, knowledge about predictive factors of decompensation in patients with NASH is still poor. In fact, little is known about the predictive role of HVPG, which has solidly been demonstrated in other aetiologies of cirrhosis. Moreover, it has been suggested that HVPG threshold predicting decompensation may be different in NASH cirrhosis.[25] The use of HVPG relies on the excellent agreement between the direct measurement of PP and the indirect technique of measuring WHVP in patients with sinusoidal PH. However, the agreement is not that accurate in aetiologies combining sinusoidal and pre-sinusoidal damage, such as primary biliary cholangitis or non-cirrhotic PH.[26,27]

Our results indicate that the correlation between WHVP and PP in patients with NASH cirrhosis is not as good as in patients with alcohol- or HCV-related cirrhosis in whom this correlation is excellent. Our definition of disagreement included the threshold difference of 10% because HVPG reductions of this magnitude are associated with relevant clinical endpoints.[28–30] According to this definition, disagreement (differences >10% of PP value) and major discrepancies (differences ≥5 mmHg) between WHVP and PP occurred more frequently in patients with NASH cirrhosis than in patients with alcohol- or HCV-related cirrhosis. Disagreement between WHVP and PP was slightly more common in patients with lower PP values. However, this trend may be attributable to our definition of disagreement as a percentage. In fact, when analysing the data by tertiles, the proportion of patients with disagreement was not statistically different among all different subgroups (data not shown).

Our study further shows that the disagreement between WHVP and PP in the NASH group was mainly caused by PP underestimation. This may provide a physiological explanation of why, in the simtuzumab trial,[16,17] 14% of patients with cirrhosis and an HVPG <10 mmHg presented with a PH-related complication (variceal bleeding, ascites, and hepatic encephalopathy) during a median follow-up of 4.7 months, while none of the patients in the study by Ripoll *et al.* decompensated during the first 20 months of follow-up.[2] As all the patients included in our study had an HVPG ≥10 mmHg and severe complications of PH

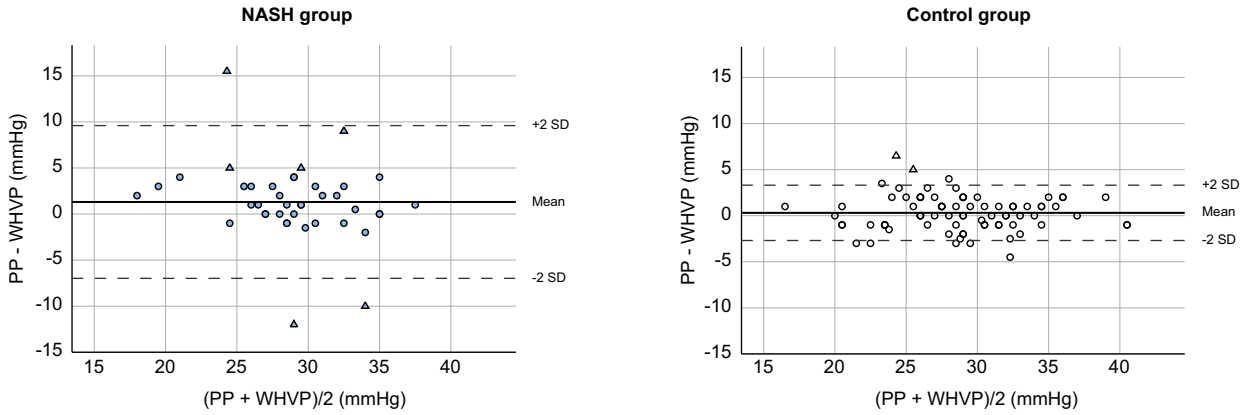

Fig. 2. Bland-Altman plot to assess the agreement between WHVP and PP in patients with NASH cirrhosis compared to that in patients with alcohol- or HCV-related cirrhosis. In the NASH group, a high variability between both pressures was observed when looking at individual values, being reflected by a wide 95% CI and a high proportion of patients (37.5%) with a difference between WHVP and PP >10% of PP value (triangle marks). In the control group, the small range of variation seen allows to consider the agreement as optimal with only 14% of patients having a difference between WHVP and PP >10% of PP value (triangle marks). NASH, non-alcoholic steatohepatitis; PP, portal pressure; WHVP, wedge hepatic vein pressure.

Table 3. Performance of WHVP in estimating PP.

	NASH group (n = 40), n (%)	Control group (n = 80), n (%)	*p* value*
Agreement between WHVP and PP	25 (62.5)	69 (86)	**0.003**
Disagreement between WHVP and PP	15 (37.5)	11 (14)	
Underestimation of PP	13 (32.5)	6 (7.5)	**<0.001**
Overestimation of PP	2 (5)	5 (6)	1.000
Major discrepancies between WHVP and PP	6 (15)	2 (3)	**0.016**

Data are expressed as frequencies (%). Categorical variables were reported compared with Chi-squared test or Fisher's exact test, where appropriate. NASH, non-alcoholic steatohepatitis; PP, portal pressure; WHVP, wedge hepatic vein pressure.
*Values in bold denote significance.

requiring TIPS, we cannot definitively confirm this hypothesis. However, all these observations suggest that HVPG thresholds predicting outcomes may be different in the NASH population and deserve to be further studied.

Underestimation of PP may be attributable to a pre-sinusoidal component of the disease. Although our data cannot shed light into the specific mechanism responsible for this observation because only a small proportion of patients with NASH cirrhosis had a liver biopsy performed within 1 yr before pressure measurements, damage in the periportal vascular area may play a pathogenic role. Indeed, periportal fibrosis is considered an early lesion necessary for bridging fibrosis development.[31] Moreover, patients with NASH have an increased risk of portal vein thrombosis, supporting the concept of a damaged portal endothelium.[32] Additionally, portal inflammation and ductular reaction at the portal tract interface comprising small biliary ductules have been described in patients with advanced NASH.[33] It may be plausible that biliary injury contributes to increased pre-sinusoidal pressure, and therefore favours PP underestimation. Whether periportal fibrosis and/or biliary injury may contribute to increase vascular tone and resistance to flow at the level of the portal venules responsible for some degree of pre-sinusoidal PH (not detected by the HVPG measurement) remains to be elucidated.

Overestimation of PP by WHVP in the setting of alcohol- or viral-related cirrhosis has been reported previously in patients with vascular abnormalities in the portal blood perfusion of the liver, including partial vein thrombosis, hepatofugal flux, or large portosystemic shunts.[4,11,34] In these situations, the sinusoidal blood flow and the hepatic sinusoidal pressures are likely to be largely dependent on the hepatic arterial perfusion. Although our sample size was too small to draw definitive conclusions, our data are in agreement with previous observations, which suggest that the presence of these vascular abnormalities shall point to the possibility of PP overestimation, regardless of the aetiology.

We recognise the limitations of our study, mainly, the small sample size and its retrospective nature. NASH cirrhosis is a modern-day disease, and although its incidence is rapidly increasing, the number of patients at very end stages of the disease is still limited. Therefore, the inclusion of 40 well-characterised patients with NASH cirrhosis treated with TIPS represents a unique cohort. We limited the study to centres with proven expertise in the performance of haemodynamic studies to guarantee reliability of pressure measurements. All centres involved have a rigorous quality control during the recording and interpretation of the haemodynamic data obtained during the procedures. Moreover, prospective data collection and careful evaluation of the pressure tracing together with the exclusion of patients with factors known to interfere with WHVP measurement (complete portal vein thrombosis and vein-to-vein communication) lower the possibility of bias.

We are aware of factors that may affect pressure measurements, such as deepness of sedation or MV, and therefore, we have performed a subgroup analysis. Although our sample size was too small to analyse subgroups precisely,[21,22] the agreement between WHVP and PP in the NASH group was worse than in the control group regardless of the type of sedation or ventilatory assistance received during pressure measurements. As vasoactive drugs are also known to modify hepatic pressures, we carefully analysed data from the 19 patients treated with terlipressin or somatostatin to guarantee that both pressure measurements were performed under equal circumstances. In the same line, 4% of the patients included were on low doses of noradrenaline because of haemodynamic instability. We decided to include them, provided that both pressure measurements were performed under the same dose of noradrenaline and the clinical situation remained completely unchanged. Indeed, the exclusion of patients under vasoactive drugs did not change our results.

Recently, it has been proposed to change the NASH terminology for metabolic-associated fatty liver disease because of the predominant impact of metabolic dysfunction to its pathogenesis.[35,36] In agreement with this definition, overweight/obesity, type 2 diabetes, and other metabolic abnormalities were frequently found in the NASH group. Aiming to discard the possibility that any of these CVRFs could have been responsible for the worse correlation between pressures, we performed a logistic regression analysis, which identified that NASH aetiology was the only factor responsible for the differences found. However, as the number of included patients with NASH was small, further studies aiming to assess the impact of these metabolic abnormalities on the agreement between WHVP and PP are needed.

Finally, as patients with NASH who were included in the study presented a decompensated liver disease, our results may only apply to this subgroup of patients. Whether the same phenomenon occurs in patients with compensated NASH cirrhosis remains an open question.

In conclusion, our results demonstrate that in patients with decompensated NASH cirrhosis, WHVP estimates PP with less accuracy than in patients with decompensated cirrhosis caused by alcohol or HCV, mainly because of PP underestimation. These results should open a new window for future studies aimed to assess the role of WHVP in estimating PP in patients with NASH at earlier stages of the disease, in whom HVPG has a meaningful prognostic value.

Abbreviations

AOUM, Azienda Ospedaliera-Universitaria di Modena; CVRF, cardiovascular risk factor; HCB, Hospital Clínic de Barcelona; HVPG, hepatic venous pressure gradient; ICC, intra-class correlation coefficient; MV, mechanical ventilation; NASH, non-alcoholic steatohepatitis; OR, odds ratio; PH, portal hypertension; PP, portal pressure; TIPS, transjugular intrahepatic portosystemic shunt; UHP, University Hospital of Padua; WHVP, wedge hepatic vein pressure.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Conceptualisation: VH-G. Data acquisition: JF-A, OB, LT, MP, MB, VC. Statistical analysis: JF-A, ERe, JCG-P, VH-G. Funding acquisition: VH-G. Methodology: JF-A, ERe, JCG-P, VH-G. Data analysis/interpretation: JF-A, ERe, IG, JCG-P, FS, MS, VH-G. Writing of original draft: JF-A, VH-G. Writing/review/editing: JF-A, ERe, IG, ERi, AG-C, JCG-P, FS, MS, VH-G. Study supervision: VH-G, JCG-P

Review/approval of final paper: all authors

Data availability statement

The research data is confidential.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2020.10.003.

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Estudio 2. Abdominal surgery in patients with idiopathic noncirrhotic portal hypertension: A multicenter retrospective study.

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Abdominal Surgery in Patients With Idiopathic Noncirrhotic Portal Hypertension: A Multicenter Retrospective Study

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In patients with idiopathic noncirrhotic portal hypertension (INCPH), data on morbidity and mortality of abdominal surgery are scarce. We retrospectively analyzed the charts of patients with INCPH undergoing abdominal surgery within the Vascular Liver Disease Interest Group network. Forty-four patients with biopsy-proven INCPH were included. Twenty-five (57%) patients had one or more extrahepatic conditions related to INCPH, and 16 (36%) had a history of ascites. Forty-five procedures were performed, including 30 that were minor and 15 major. Nine (20%) patients had one or more Dindo-Clavien grade ≥ 3 complication within 1 month after surgery. Sixteen (33%) patients had one or more portal hypertension–related complication within 3 months after surgery. Extrahepatic conditions related to INCPH (P = 0.03) and history of ascites (P = 0.02) were associated with portal hypertension–related complications within 3 months after surgery. Splenectomy was associated with development of portal vein thrombosis after surgery (P = 0.01). Four (9%) patients died within 6 months after surgery. Six-month cumulative risk of death was higher in patients with serum creatinine ≥ 100 μmol/L at surgery (33% versus 0%, P < 0.001). An unfavorable outcome (i.e., either liver or surgical complication or death) occurred in 22 (50%) patients and was associated with the presence of extrahepatic conditions related to INCPH, history of ascites, and serum creatinine ≥ 100 μmol/L: 5% of the patients with none of these features had an unfavorable outcome versus 32% and 64% when one or two or more features were present, respectively. Portal decompression procedures prior to surgery (n = 10) were not associated with postoperative outcome. *Conclusion:* Patients with INCPH are at high risk of major surgical and portal hypertension–related complications when they harbor extrahepatic conditions related to INCPH, history of ascites, or increased serum creatinine. (Hepatology 2019;70:911-924).

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Idiopathic noncirrhotic portal hypertension (INCPH) is a heterogeneous group of rare diseases causing portal hypertension and characterized by the absence of cirrhotic modification of the liver parenchyma and the patency of portal and hepatic veins. In Europe, INCPH accounts for <2% of the indications for liver biopsies.[1,2] Liver histological lesions found in patients with INCPH include obliterative portal

Abbreviations: CI, confidence interval; HR, hazard ratio; HIV, human immunodeficiency virus; HVPG, hepatic venous pressure gradient; INCPH, idiopathic noncirrhotic portal hypertension; IQR, interquartile range; PVT, portal vein thrombosis; TIPSS, transjugular intrahepatic portosystemic shunt; VALDIG, Vascular Liver Disease Interest Group.

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venopathy, hepatoportal sclerosis, nodular regenerative hyperplasia, and incomplete septal cirrhosis.[3] INCPH has been associated with various conditions including thrombophilia, hematologic malignancies, human immunodeficiency virus (HIV) infection, genetic and immunological disorders.[4,5] Patients with INCPH may develop portal hypertension–related complications but usually have preserved liver function.

Patients with chronic liver diseases may require abdominal surgery for indications related to their liver disease (e.g., splenectomy or parietal surgery) or unrelated indications. Most available data on the risk of surgery in patients with liver disease pertains to cirrhosis, where postoperative morbidity and mortality are influenced by liver dysfunction and degree of portal hypertension,[6-9] type of surgery,[10,11] and comorbidities.[9] Given the link between portal hypertension and postoperative outcome,[11] portal decompression has been proposed to facilitate abdominal surgery and improve outcome, although reported results are contrasted.[12-17]

Experience regarding abdominal surgery in patients with INCPH is mostly limited to portosystemic shunt and/or splenectomy performed in adults or children from eastern countries.[5,18-20] The present study thus aimed at evaluating the outcome of patients with INCPH undergoing abdominal surgery and at assessing the impact of preoperative portal decompression procedures.

Patients and Methods

PATIENTS

Between April 2017 and November 2017, we contacted all of the centers participating in the Vascular Liver Disease Interest Group (VALDIG) or the French network for vascular liver diseases to

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retrospectively identify all patients with INCPH having had one or more abdominal surgery. Surgeries were considered only if INCPH was known prior to the procedure or diagnosed at the time of the surgery. Patient identification was based on local databases. The study was approved by our institutional review board without need for informed consent (CCER 2017-01219) and conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

DEFINITIONS

Diagnosis of INCPH was based on the criteria proposed by VALDIG, after exclusion of cirrhosis (Supporting Table S1). Histologic diagnosis of INCPH was confirmed by pathologist experts in liver diseases. Patients with portal vein thrombosis (PVT) were included in this study if this thrombosis occurred after INCPH diagnosis. Patients with chemotherapy-induced noncirrhotic portal hypertension and/or who underwent liver resection for colorectal liver metastasis were not included because the main liver lesion in these patients is sinusoidal obstruction syndrome, i.e., a distinct entity from INCPH.[21]

Date of diagnosis of INCPH was the date of the first liver biopsy demonstrating the absence of cirrhosis while signs of portal hypertension were already present, as detailed in Supporting Table S1. According to previous reports, extrahepatic conditions associated with INCPH were classified into the following categories[22-25]: immunological disorders (autoimmune conditions, common variable immune deficiency, history of solid organ transplantation, Crohn's disease, HIV infection), recurrent abdominal infections, medication or toxins, prothrombotic state (myeloproliferative syndrome, heterozygous factor II or V Leiden, or familial history of venous thromboembolism), genetic disorders.

The following data were collected at surgery: (1) clinical features before surgery, including age, gender, American Society of Anesthesiology class,[26] age-adjusted Charlson comorbidity index (the Charlson Comorbidity index is a weighted index that takes into account the number and the seriousness of comorbid diseases by assigning points for certain illnesses[27]; the age-adjusted Charlson comorbidity index assigns an additional point for each decade of life after 50 years of age), clinical, laboratory, imaging, and endoscopic features; (2) surgical data, including indication, type of surgery, planned or emergency procedure, and laparoscopy or laparotomy. Major surgery was defined as laparotomy with operative intervention on a visceral organ.[9] History of ascites was defined as a previous ascites that was controlled with diuretics at the time of surgery or clinically detectable ascites at surgery. Portal decompression intervention before surgery included transjugular intrahepatic portosystemic shunt (TIPSS) placement or surgical portosystemic shunt. Patients in whom surgical portosystemic shunt was the indication for surgery were not included.

FOLLOW-UP

Duration of follow-up was calculated from the date of surgery. Endpoints were prespecified before data collection (Supporting Table S2). Postoperative complications were defined as any event occurring within 1 month after surgical intervention and categorized according to the Dindo-Clavien classification.[28] Portal hypertension–related complications were defined as any of the following: decompensation ascites, hepatic encephalopathy, significant portal hypertension–related bleeding,[29] acute kidney injury, or spontaneous bacterial peritonitis occurring within 3 months after surgical intervention (Supporting Table S2). Decompensation of ascites was defined as follows: (1) in patients without ascites, onset of clinically detectable ascites, confirmed by ultrasonography; (2) in patients with previous ascites not requiring paracentesis, ascites requiring two or more paracenteses within 3 months following surgery or requiring a TIPSS. Postoperative death was defined as death occurring within 6 months after surgical intervention. Finally, an unfavorable outcome was defined as either postoperative grade ≥ 3 complication according to the Dindo-Clavien classification within 1 month after surgery, portal hypertension–related complications within 3 months after surgery, or death within 6 months after surgery.

In order to evaluate the influence of portal decompression on postoperative outcome, we compared the occurrence of complications between patients who had and those who did not have a history of a portal decompression procedure, i.e., TIPSS placement or surgical portosystemic shunt, performed before abdominal surgery.

CONTROLS

We compared 6-month postoperative cumulative risk of death in patients with INCPH with that of patients with cirrhosis who had abdominal surgery, selected from a recently published cohort.[17] Two patients with cirrhosis were matched with one patient with INCPH according to the presence of ascites at surgery (either clinically detectable ascites before TIPS placement or history of ascites at the time of surgery, i.e., previous ascites controlled with diuretic therapy at surgery or clinically detectable ascites at surgery).

We also compared 3-year liver transplantation–free survival of patients with INCPH who had abdominal surgery, i.e., patients from the present cohort, with that of patients with INCPH who did not undergo abdominal surgery, prospectively included between January 2011 and June 2018 at the liver hemodynamic unit at Beaujon Hospital (Clichy, France). Diagnosis of INCPH was based on the criteria proposed by VALDIG, after exclusion of cirrhosis (Supporting Table S1). Among the 101 patients meeting these criteria, 7 were excluded because they were referred to the liver hemodynamic unit for evaluation before liver transplantation, 9 because follow-up data were not available, and 3 because they were already included in the present study.

STATISTICAL ANALYSIS

Results are presented as median (interquartile range [IQR]) or absolute number (percentage). Comparisons between quantitative variables were performed using the *t* test or Mann-Whitney test for normally and nonnormally distributed variables, respectively. The Shapiro-Wilk test was used to determine whether or not the distribution of continuous variable was normal. Comparisons between categorical variables were performed using the chi-squared or Fisher exact test, when appropriate. Univariate Cox regression analyses were performed to determine factors associated with postoperative complication grade ≥ 3 within 1 month after surgery, portal hypertension–related complications within 3 months after surgery, death within 6 months after surgery, or unfavorable outcome after surgery. Factors included in the univariate analysis were prespecified based on their previous identification as prognostic factors in patients with cirrhosis undergoing surgery and/or in patients with INCPH. These factors included age-adjusted Charlson comorbidity index,[9] extrahepatic condition associated with INCPH,[23-25] history of ascites at the time of surgery (i.e., previous ascites controlled with diuretic therapy at surgery or clinically detectable ascites at surgery),[23-25,30] varices needing treatment (i.e., medium/large esophageal and/or gastric varices, history of variceal bleeding, or history of endoscopic band ligation and/or glue),[11,30] PVT at surgery,[22] serum bilirubin at surgery,[8,9,30,31] serum creatinine at surgery,[8,9,24,30,32] major surgery,[9,10] and emergency procedures.[6-8,31] Although Model for End-Stage Liver Disease and Child-Pugh scores are known to be associated with postoperative outcome after abdominal surgery in patients with cirrhosis,[9,31,32] we deliberately chose not to insert these scores but rather serum creatinine and bilirubin because 6 patients were treated with vitamin K antagonists and serum albumin concentration was available in only 34/44 patients. We did not analyze hepatic venous pressure gradient (HVPG) because HVPG is not a good reflection of portal hypertension in patients with INCPH.[25,33]

In order to assess the influence of portal decompression on postoperative outcome, we performed additional analyses including portal decompression in the Cox regression analysis. Hazard ratios (HRs) for Cox logistic regression were provided with their 95% confidence interval (CI). Cumulative risk of death was assessed according to the Kaplan-Meier method and compared using the log-rank test. All tests were two-sided, and $P \leq 0.05$ was considered to be significant. Data handling and analysis were performed with SPSS 21.0 (SPSS Inc., Chicago, IL).

Results

PATIENT CHARACTERISTICS AT SURGERY

Between 2002 and 2017, 45 surgical interventions were performed in 44 patients from 10 centers participating in the VALDIG network or the French network for vascular liver disease (Supporting Table S4). Their characteristics at the time of surgery are presented in Table 1. INCPH was diagnosed at the time of surgery in 8 (18%) patients. In the 36 other patients, median time between INCPH diagnosis and surgery was 26 (6-50) months. Prevalence of signs of portal hypertension at INCPH diagnosis, namely ascites and

TABLE 1. Characteristics of the 44 Patients at Surgery

Characteristics	Patients With Available Data	Number (Percentage) or Median (IQR)
Clinical features		
Male gender	44	30 (68)
Age, years	44	53 (37-65)
Age-adjusted Charlson comorbidity index	44	4 (3-6)
ASA score	44	3 (2-3)
At least one extrahepatic condition associated with INCPH	44	25 (57)
Immunological disorder		18 (41)
HIV infection		5 (11)
Recurrent abdominal infection		5 (11)
Medication or toxin		5 (11)
Prothrombotic condition		2 (5)
Genetic disorder		2 (5)
At least one other cause of chronic liver disease	44	11 (25)
Excessive alcohol consumption		2 (4)
Metabolic syndrome		5 (11)
Hepatitis C virus infection		4 (9)
Diabetes mellitus	44	13 (30)
Ascites	44	
Absent		28 (64)
Controlled with diuretics		9 (14)
Clinically detected		7 (16)
History of ascites*	44	16 (36)
Hepatic encephalopathy	44	0 (0)
Previous variceal bleeding	43	18 (42)
Treatment before surgery		
Anticoagulation therapy	43	16 (36)
Antiplatelet agents	43	7 (16)
Diuretic therapy	43	15 (34)
Beta-blockers	43	18 (41)
Endoscopic data		
Gastroesophageal varices	42	
Absent		10 (24)
Small		10 (24)
Medium or large		22 (52)
Varices needing treatment†		30 (71)
Imaging data		
Portosystemic collaterals at imaging	43	25 (58)
Spleen size, cm	35	16 (14-20)
Previous splenectomy	45	3 (7)
Thrombosis of the portal venous axis	43	6 (14)
Partial occlusion		3 (7)
Complete occlusion		3 (7)
Laboratory data		
Hemoglobin, g/dL	42	11.8 (10.0-13.9)
Leukocyte count, $\times 10^9$/L	41	5.2 (3.4-10.0)
Platelet count, $\times 10^9$/L	42	87 (67-161)
INR	42	1.13 (1.02-1.47)
AST, IU/L	43	32 (25-47)
ALT, IU/L	42	26 (19-37)
ALK, IU/L	41	136 (77-251)
GGT IU/L	42	57 (23-127)
Serum bilirubin, μmol/L	43	17 (12-35)
Serum creatinine, μmol/L	44	79 (61-106)
Serum albumin, g/L	34	37 (31-41)
MELD score	39	9 (7-12)

*History of ascites at surgery was defined either as a previous history of ascites that was controlled with diuretics at the time of surgery or clinically detected ascites at surgery.
†Medium/large esophageal and/or gastric varices or history of variceal bleeding or history of endoscopic band ligation and/or glue.
Abbreviations: ALK, alkaline phosphatase; ALT, alanine aminotransferase; ASA, American Society of Anesthesiologists; AST, Aspartate aminotransferase; GGT, gamma glutamyl transpeptidase; INR, international normalized ratio; IU, international unit; MELD, Model for End-Stage Liver Disease.

gastroesophageal varices, was similar between the 8 patients in whom INCPH was diagnosed at surgery and the 36 patients with known INCPH at surgery (data not shown). At least one extrahepatic condition associated with INCPH was present in 25 (57%) patients, including 23 with either immunological disorder or HIV infection. Fourteen (32%) had two or more conditions. Age-adjusted Charlson comorbidity index was ≥ 3 in 35 (80%) patients, indicating that significant comorbidities were common. Liver function was preserved in the majority of the patients because 32 (73%) patients had serum bilirubin ≤ 34 μmol/L, 32 (73%) had an international normalized ratio < 1.5, none had hepatic encephalopathy, and only 7 (16%) had clinically detectable ascites, including 2 (5%) with tense ascites at surgery (Table 1). Eleven (25%) patients had serum creatinine ≥ 100 μmol/L before surgery. HVPG was measured in 28 (64%) patients. Median (IQR) HVPG was 9 (6-15) mm Hg.

Sixteen (36%) patients were treated with anticoagulants before surgery, including low–molecular weight heparin (n = 7), nonfractioned heparin (n = 1), fondaparinux (n = 1), rivaroxaban (n = 1), and vitamin

K antagonists (n = 6). Among these 16 patients, anticoagulation was stopped before surgical intervention in 8 patients. Thus, 8 (18%) patients were still treated with anticoagulation therapy at the date of surgery. Seven (16%) patients were treated with antiplatelet agents before surgery, including aspirin (n = 6) and clopidogrel (n = 1). Among these 7 patients, antiplatelet agents had been stopped before surgical intervention in 2 patients. Thus, 5 (11%) patients were still treated with antiplatelet agents at the date of surgery.

Type of and indications for abdominal surgery are detailed in Table 2. One patient underwent two different operations (emergency surgery for perforated gastric ulcer suture, followed by elective abdominoplasty, 2 years later). There were 15 (33%) major and 30 (67%) minor interventions (including 12 laparoscopic surgeries). Eleven interventions (24%) were emergency surgeries, whereas the 34 (76%) remaining were planned interventions. Among the 7 patients with elevated serum creatinine concentration (i.e., ≥ 100 μmol/L) and a history of ascites at surgery, 3 had major surgery and 2 others had emergency surgery (Supporting Table S5). In the perioperative period, red blood cells and platelets were transfused in 11 (24%) and 8 (18%) patients, respectively.

TABLE 2. Type and Indications for the 45 Surgical Interventions

Minor surgeries	30
Open surgeries	18
Abdominal wall	13
Hernia repair	10
Alfapump implantation	1
Abdominoplasty	1
Surgical exploration	1
Cholecystectomy	2
Retroperitoneum mass excision	1
Appendicectomy	1
Cesarean section	1
Laparoscopic surgeries	12
Abdominal wall	2
Surgical exploration	1
Peritoneal catheter placement	1
Cholecystectomy	4
Splenectomy	1
Colorectal surgery	4
Ileal resection (Crohn's disease)	2
Appendicectomy	2
Partial liver resection	1
Major surgeries	15
Urologic or kidney surgery	5
Renal transplantation	2
Nephrectomy	2
Renal carcinoma	1
Bleeding after renal biopsy	1
Cystectomy and hysterectomy for urothelial carcinoma	1
Splenectomy	5
Splenectomy alone	3
Splenectomy + caudal pancreatectomy	1
Splenectomy + portocaval shunt	1
Colic resection	2
Crohn's disease	1
Colorectal cancer	1
Gastric and pancreatic surgery	2
Gastrectomy for gastric neoplasia	1
Pancreatectomy for neuroendocrine neoplasia	1
Partial liver resection	1

POSTOPERATIVE COMPLICATIONS WITHIN 1 MONTH AFTER SURGERY

According to the Dindo-Clavien classification, 61 postoperative complications occurred in 31 (70%) patients within 1 month after surgery (Table 3). A median of 2 (1.0-3.0) complications occurred per patient. In 9 (20%) patients, postoperative complications were classified as grade ≥ 3 or more according to the Dindo-Clavien classification.

Ten (22%) patients developed postoperative bleeding, including 4 classified as grade ≥ 3 according to the Dindo-Clavien classification. Three patients required an intervention (surgical or radiological), and 2 required transfusion of red blood cells and/or platelet units (Supporting Table S6). Antiplatelet agents at surgery (3/10 [30%] versus 2/35 [6%], $P = 0.03$) as well as anticoagulation (5/10 [50%] versus 3/35 [9%], $P = 0.003$) were the only factors associated with postoperative bleeding among those tested, as indicated in Table 1. Platelet count at surgery was similar in patients with or without postoperative bleeding ($P = 0.6$).

Nineteen postoperative infections occurred in 15 (33%) patients, including only one classified as grade ≥ 3 according to the Dindo-Clavien classification. No patient developed postoperative liver failure.

None of the prespecified factors were significantly associated with the development of at least one grade ≥ 3 complication according to the Dindo-Clavien classification (Table 4).

TABLE 3. Details on 61 Surgical or Postoperative Complications That Occurred in 31 Patients Within 1 Month After Surgery

Type of complication	
Infection	19
Lung	5
Urinary tract infection	3
Skin infection	3
Intra-abdominal infection	3
Cholangitis	1
Clostridium difficile infection	1
No source identified	3
Postoperative bleeding	10
Fistula/leak	5
Abdominal leak	3
Urinary leak	2
Digestive complications	5
Vomiting	2
Ileus	3
Cardiopulmonary	8
Respiratory failure	1
Venous thrombosis	2
Pleural effusion	3
Hypotension	1
Tako-Tsubo syndrome	1
Liver	1
Moderate liver failure	1
Neurologic	1
Confusion	1
Pain*	7
Other	5
Diabetes decompensation	4
Anemia	1

*All seven reported complications were classified grade 1 according to the Dindo-Clavien classifications (i.e., any deviation from the normal postoperative course without the need for additional treatment).

PORTAL HYPERTENSION–RELATED COMPLICATIONS WITHIN 3 MONTHS AFTER SURGERY

Twenty-seven portal hypertension–related complications occurred in 16 (36%) patients within 3 months after surgery. Median time between surgery and occurrence of such complications was 6 (1-17) days. Decompensation of ascites, occurring in 12 (26%) patients, was the most frequent of such complications. In two patients, a TIPSS was placed for refractory ascites, 5.9 and 7.5 months after surgery, respectively. Hepatic encephalopathy, variceal bleeding, spontaneous bacterial peritonitis, and acute kidney injury occurred in 3 (7%), 2 (4%), 3 (7%), and 7 (16%) patients, respectively. One patient had TIPSS placement for refractory variceal bleeding 14 days after surgery. Resolution of a portal hypertension–related complication occurred in 15 out of the 16 patients, after 26 (10-59) days. One patient died 5.7 months after surgery (patient 7, Table 5). Length of hospital stay was significantly longer in patients who developed portal hypertension–related complications than in those who did not (30 [6-45] days versus 6 [3-16] days, $P = 0.002$).

Factors associated with the occurrence of at least one portal hypertension–related complication included a history of ascites and extrahepatic conditions associated with INCPH. Serum creatinine at surgery was not associated with the occurrence of at least one portal hypertension–related complication (Table 4).

PVT AFTER SURGERY

Five (11%) patients developed *de novo* PVT, 28 (range 1-45) days after surgical intervention (Supporting Table S7). Interestingly, three out of these five surgeries were splenectomies, whereas two involved other surgical interventions. PVT occurred in 3 out of the 6 patients (50%) who had splenectomy versus 2 out of the 39 (5%) who had another surgical intervention ($P = 0.01$). Overall, complete recanalization was observed in 3 of 5 patients. Two out of the 3 patients received anticoagulation, and complete recanalization was observed after 4 and 5.5 months, respectively. The third patient did not receive anticoagulation because a TIPSS was inserted; complete recanalization was observed after 8 months.

DEATH AFTER SURGERY

Thirteen (29%) patients were admitted to the intensive care unit after surgery, with a median (IQR) length of stay in the intensive care unit of 4 (2-7) days. Median (IQR) overall length of hospital stay was 10 (4-28) days. Four patients died within 6 months after surgery. Their characteristics are presented in Table 5. None of the patients underwent liver transplantation within the observation period.

Age-adjusted Charlson comorbidity index and serum creatinine level were associated with death within 6 months after surgery (Table 4). Patients with

TABLE 4. Univariate Cox Regression Analysis Evaluating Prespecified Factors Before Surgery, Associated With the Occurrence of Major Endpoints After Surgery

	HR	95% CI		*P*
At least one grade 3 or more complication within 1 month after surgery (n = 9)				
Age-adjusted comorbidity index	1.103	0.866	1.404	0.427
Extrahepatic condition associated with INCPH	1.387	0.331	5.810	0.654
History of ascites*	1.340	0.300	5.988	0.702
Varices needing treatment†	2.056	0.240	17.600	0.511
Portal vein thrombosis	2.104	0.363	12.196	0.407
Serum bilirubin	1.012	0.994	1.031	0.189
Serum creatinine	1.002	0.999	1.006	0.188
Major surgery	0.556	0.138	2.242	0.409
Emergency procedure	2.920	0.712	11.981	0.137
At least one portal hypertension related complication‡ within 3 months after surgery (n = 16)				
Age-adjusted comorbidity index	1.074	0.913	1.264	0.390
Extrahepatic condition associated with INCPH	**3.973**	**1.129**	**13.982**	**0.032**
History of ascites*	**3.144**	**1.162**	**8.504**	**0.024**
Varices needing treatment†	0.858	0.298	2.472	0.777
Portal vein thrombosis	0.750	0.170	3.304	0.704
Serum bilirubin	0.991	0.972	1.012	0.401
Serum creatinine	1.002	0.999	1.005	0.112
Major surgery	0.634	0.236	1.704	0.366
Emergency procedure	1.676	0.581	4.830	0.339
Death within 6 months after surgery (n = 4)				
Age-adjusted comorbidity index	**1.372**	**1.040**	**1.810**	**0.025**
Extrahepatic condition associated with INCPH	0.800	0.113	5.679	0.823
History of ascites*	5.292	0.550	50.919	0.149
Varices needing treatment†	1.116	0.116	10.728	0.925
Portal vein thrombosis	0.039	<0.001	6466.507	0.597
Serum bilirubin	0.797	0.622	1.022	0.074
Serum creatinine	**1.007**	**1.003**	**1.012**	**0.002**
Major surgery	0.487	0.069	3.455	0.471
Emergency procedure	0.992	0.103	9.540	0.994
Unfavorable outcome after surgery§ (n = 22)				
Age-adjusted comorbidity index	1.099	0.963	1.254	0.163
Extrahepatic condition associated with INCPH	**2.410**	**0.939**	**6.186**	**0.067**
History of ascites*	**3.892**	**1.650**	**9.180**	**0.002**
Varices needing treatment†	1.007	0.390	2.598	0.989
Portal vein thrombosis	1.425	0.479	4.237	0.524
Serum bilirubin	0.999	0.985	1.014	0.901
Serum creatinine	**1.003**	**1.000**	**1.005**	**0.056**
Major surgery	0.851	0.356	2.032	0.716
Emergency procedure	2.136	0.865	5.276	0.100

Bold indicates significant associations.
*History of ascites at surgery was defined either as a previous history of ascites that was controlled with diuretics at the time of surgery or clinically detected ascites at surgery.
†Medium/large esophageal and/or gastric varices or history of variceal bleeding or history of endoscopic band ligation and/or glue.
‡Portal hypertension–related complications were defined as any of decompensation ascites, hepatic encephalopathy, significant portal hypertension–related bleeding, acute kidney injury, or spontaneous bacterial peritonitis occurring within 3 months after surgical intervention. Decompensation of ascites was defined as follows: (1) in patients without ascites, onset of clinically detectable ascites, confirmed by ultrasonography; (2) in patients with previous ascites not requiring paracentesis, ascites requiring two or more paracenteses within 3 months following surgery or requiring a TIPSS.
§An unfavorable outcome after surgery was defined as either postoperative complication grade ≥ 3 within 1 month after surgery or portal hypertension–related complications within 3 months after surgery or death within 6 months after surgery.

TABLE 5. Characteristics of the 4 Patients Who Died Within 6 Months After Surgery

	Patient 7	Patient 8	Patient 20	Patient 41
Patient's features at surgery				
Age, years	73	65	51	66
Gender	Male	Male	Male	Male
Age-adjusted charlson comorbidity index	8	6	9	8
ASA score	3	3	3	4
Extrahepatic condition associated with INCPH	Previous renal transplantation Azathioprine	None	None	Recurrent abdominal infection *NOD2* mutation
Ascites	None	Tense	Diuretic-sensitive ascites	Tense
History of variceal bleeding	No	No	Yes	Yes
Esophageal varices	Medium size	Absence	Medium size	Medium -size
Portal vein thrombosis	No	No	No	No
Platelet count, $\times 10^9$/L	99	273	144	52
INR	1	1	0.94	1.16
Serum bilirubin, μmol/L	16	6	8	8
Serum creatinine, μmol/L	533	300	552	143
MELD	14	12	14	9
Surgery				
TIPSS performed before surgery	No	Yes	No	No
Surgical intervention	Renal retransplantation	Peritoneal catheter placement	Nephrectomy	Alfapump implantation
Indication	End-stage renal failure	Refractory ascites	Fistula after renal biopsy	Refractory ascites
Postoperative outcome				
Occurrence of portal hypertension–related complication after surgery	Yes Ascites Variceal bleeding Hepatic encephalopathy Spontaneous bacterial peritonitis	No	Yes Spontaneous bacterial peritonitis	No
Other postoperative complication	Leakage	Wound infection	Pleural infection Tako-Tsubo syndrome Acute kidney injury	None
Duration between surgery and death	5.7 months	2.2 months	4.3 months	3.8 months
Cause of death	Variceal bleeding	Cardiac arrest	Pneumonia	Septic shock

Abbreviations: ASA, American Society of Anesthesiologists; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; *NOD2*, nucleotide binding oligomerization domain containing 2.

age-adjusted Charlson comorbidity index ≥ 6 before surgery had a 6-month cumulative risk of death of 27% versus 0% for patients with an index below this threshold (P = 0.002). We have previously reported that serum creatinine level > 100 μmol/L is associated with a poor outcome after TIPSS in patients with INCPH.[25] Using this threshold here, we observed that patients with serum creatinine ≥ 100 μmol/L had a 6-month cumulative risk of death of 33% versus 0% for patients with serum creatinine below this threshold (Fig. 1).

We compared 6-month cumulative risk of death after abdominal surgery of patients with INCPH to that of patients with cirrhosis matched according to the presence of ascites at surgery. One patient with INCPH could not be matched according to the

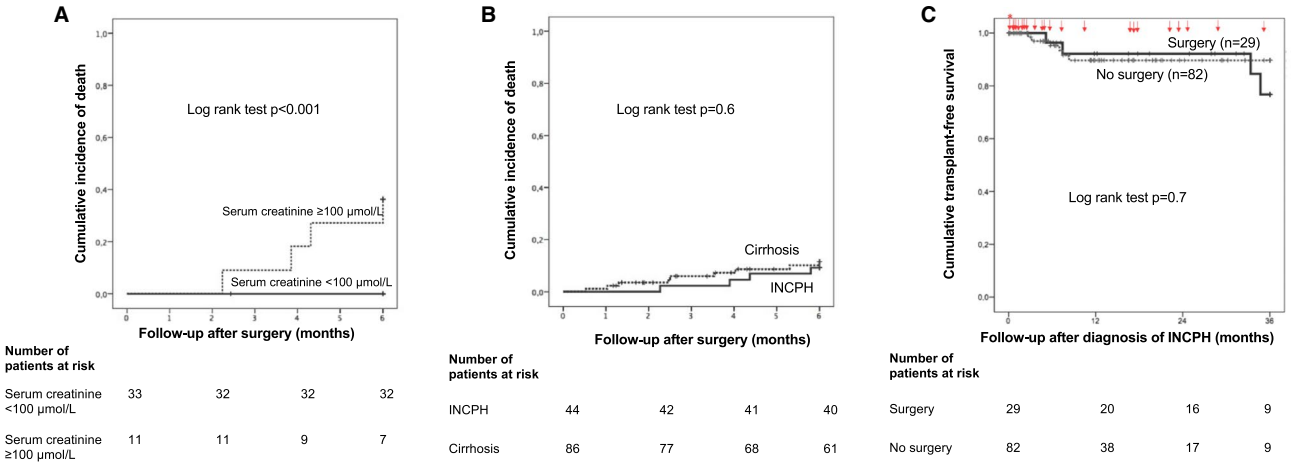

FIG. 1. (A) Cumulative incidence of death at 6 months after abdominal surgery, according to serum creatinine before surgery. (B) Cumulative incidence of death at 6 months after abdominal surgery in 44 patients with INCPH and in 86 patients with cirrhosis matched for ascites at surgery. (C) Transplant-free survival, from date of diagnosis of INCPH, in patients undergoing or not abdominal surgery during follow-up. Each red arrow indicates an abdominal surgery. For 8/29 patients, INCPH was diagnosed at surgery (red star).

presence of ascites, explaining why 43 patients with INCPH were compared to 86 patients with cirrhosis. Characteristics of the 86 patients with cirrhosis are shown in Supporting Table S3. Six-month cumulative risk of death was similar between the two groups (Fig. 1B).

In addition, in order to evaluate the impact of abdominal surgery on overall outcome of patients with INCPH, we compared 3-year liver transplantation–free survival of patients with INCPH who had abdominal surgery within 3 years after diagnosis of INCPH (29 patients from the present study) to that of patients with INCPH but without abdominal surgery (n = 82). Three-year transplant-free survival was similar between the two groups (Fig. 1C).

OVERALL POSTOPERATIVE UNFAVORABLE OUTCOME

Overall postoperative outcome was unfavorable in 22 (50%) patients. History of ascites was associated with an unfavorable outcome (Table 4). As extrahepatic conditions related with INCPH and serum creatinine levels fell short of statistical significance and as we have previously reported that these features are associated with a poor outcome after TIPSS in patients with INCPH,[25] we classified patients according to these items and to history of ascites at surgery. Five percent of the patients with neither extrahepatic condition associated with INCPH nor history of ascites at surgery nor serum creatinine ≥ 100 µmol/L had an unfavorable outcome (Fig. 2). Only one patient without these criteria had an unfavorable outcome; this patient had postoperative bleeding after cholecystectomy, requiring reintervention under local anesthesia. By contrast, 64% of the patients with two or more features had an unfavorable outcome.

INFLUENCE OF PORTAL DECOMPRESSION ON POSTOPERATIVE OUTCOME

Eleven patients had portal decompression prior to, or at the time of, surgery (Fig. 3). In 1 of these patients, portosystemic shunt was the indication for surgery, with concomitant splenectomy (Table 2 and Fig. 3). In the 10 remaining patients, median time between portal decompression and surgical intervention was 4.0 (0.3-44.6) months.

In order to assess the effect of portal decompression on the outcome after surgery, we compared the outcome of the 10 patients who had either TIPSS or portosystemic shunt before surgery to the 33 patients who did not (Supporting Table S8). Except for

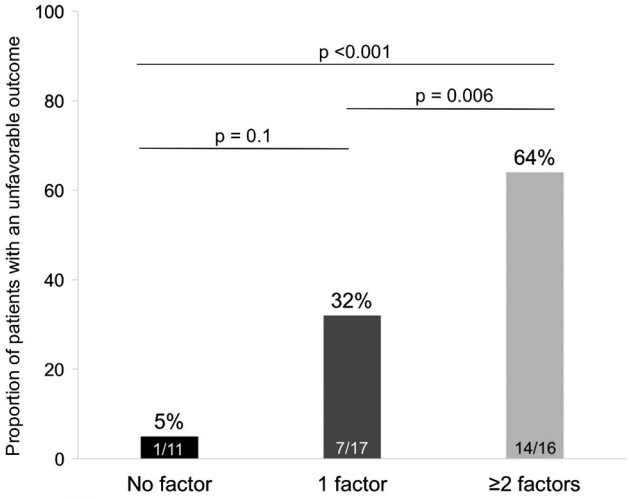

FIG. 2. Proportion of the patients having an unfavorable outcome after surgery according to the presence of extrahepatic conditions associated with INCPH serum creatinine ≥ 100 μmol/L and/or history of ascites at surgery. An unfavorable outcome was defined as any postoperative complication grade ≥ 3 within 1 month after surgery, portal hypertension–related complications within 3 months after surgery, or death within 6 months after surgery. Eleven patients had neither an extrahepatic condition associated with INCPH nor serum creatinine ≥ 100 μmol/L nor history of ascites at surgery, 17 patients had one out of the three features of an extrahepatic condition associated with INCPH, and 16 patients had at least two of the three features.

beta-blockers, baseline characteristics did not differ between the two groups. Postoperative outcomes did not differ between patients with previous TIPSS or portosystemic shunt and those without. Of patients who had a previous TIPSS or surgical portosystemic shunt, 1 had a grade ≥ 3 complication within 1 month after surgery (leakage) and 3 had at least one portal hypertension–related complication within 3 months after surgery (1 had decompensation of ascites, 1 decompensation of ascites and encephalopathy, and 1 acute kidney injury). When included in the univariate Cox regression analysis, portal decompression was not associated with either portal hypertension–related complications (HR [95% CI], 0.746 [0.212-2.618]; P = 0.647) or death within 6 months after surgery (HR [95% CI], 1.153 [0.120-11.088]; P = 0.902). Furthermore, portal decompression was not associated with an unfavorable outcome after surgery (HR [95% CI], 0.874 [0.322-2.372]; P = 0.792).

Discussion

This study, focusing on the outcome of patients with INCPH undergoing abdominal surgery, shows that 6-month mortality after surgery was 9%, affecting patients with comorbidities and/or serum creatinine level ≥ 100 μmol/L. Patients without extrahepatic conditions related to INCPH, without increased serum creatinine, and without a history of ascites at surgery had a favorable postoperative outcome. Although this study gathered the largest number of patients with INCPH undergoing abdominal surgery reported to date, interpretation of the results should take into account that number of patients included remained limited, that the study was retrospective, and that various surgical interventions were performed. Given the rarity of the disease, conducting a prospective study seems, however, not realistic.

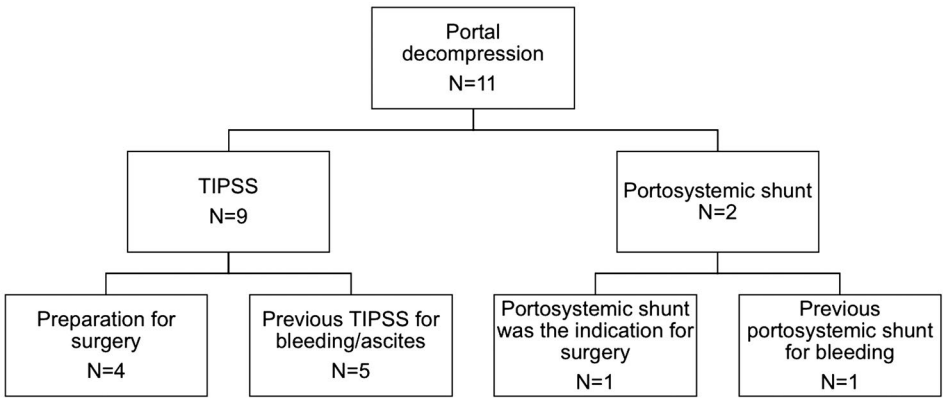

FIG. 3. Distribution of the patients according to the type and the indication for portal decompression.

The main information derived from this study is that mortality of patients with INCPH undergoing abdominal surgery is higher than that reported in the general population. We observed a 6-month mortality rate of 9% (95% CI, 1%-17%) in patients with INCPH, while in the general population, in-hospital or 1-month mortality after abdominal surgery ranges from 3% (95% CI, 0.4%-7%) to 12% (95% CI, 7%-18%).[34-36] We observed that the 6-month mortality rate of patients with INCPH did not differ from that of patients with cirrhosis, matched for ascites, who underwent abdominal surgery between 2005 and 2016.[17] It should, however, be noted that mortality of patients with cirrhosis in this cohort was lower than previously reported.[7,10,30-32] Indeed, in patients with cirrhosis, reported mortality after surgery ranges from 7% (95% CI, 2%-12%) to 30% (95% CI, 15%-44%)[7,8,30,32] at 1 month, 30% (95% CI, 24%-36%) at 3 months, and 54% (95% CI, 47%-61%) at 1 year.[31] This lower mortality observed in patients with cirrhosis may be related to a better selection of candidates for abdominal surgery and to the fact that these procedures were performed in tertiary centers. This outcome of patients with INCPH after surgery echoes the overall survival of patients with INCPH outside the surgical setting, known to be intermediate between the general population and patients with cirrhosis.[23] In the present study, comorbidities were the main drivers of postoperative mortality as death within 6 months after surgery was restricted to patients with age-adjusted Charlson comorbidity index ≥ 6 or with serum creatinine ≥ 100 μmol/L before surgery. This finding is in line with the natural history of INCPH, where half the mortality is accounted for by extrahepatic comorbidities,[22-24] as well as with the outcome after TIPSS placement where mortality is associated with serum creatinine and the presence of extrahepatic conditions associated with INCPH.[25] Interestingly, transplant-free survival after INCPH diagnosis was similar in patients who did and did not undergo abdominal surgery during follow-up, suggesting that, in selected patients managed in expert centers, surgery does not have a deleterious impact on the natural history of INCPH. We did not find any association between the type of intervention and postoperative outcomes but cannot rule out a lack of power due to the limited sample size.

The second major finding of the present study was that portal hypertension–related complications, especially ascites, were the most frequent, occurring within 3 months after surgery in 36% and 26% of the patients, respectively. Portal hypertension–related complications increased the length of hospital stay, and 3/16 (19%) required a TIPSS after surgery for refractory ascites or variceal bleeding. However, portal hypertension-related complications were transient in most patients. These results suggest that portal hypertension *per se* should not be regarded as a definite contraindication for abdominal surgery in patients with INCPH.

De novo PVT occurred in 5 (11%) patients after surgery. Interestingly, PVT following splenectomy was 10-fold more frequent than following other surgeries. Reported rates of PVT following splenectomy range between 17% (95% CI, 13%-21%) and 36% (95% CI, 17%-55%) in patients with cirrhosis[37,38] and 54% (95% CI, 46%-61%) in patients with benign hematologic disorders.[39] In the present study, the incidence of PVT was similar to that of patients without cirrhosis because PVT was observed in 50% (95% CI 9%-90%) of the patients with INCPH and splenectomy. Four cases of PVT were diagnosed within 1 month after surgery. Recanalization occurred in 60% of the patients. These findings suggest that routine ultrasound examination at 1 week, 1 month, and 3 months after surgery would allow early detection of PVT, especially after splenectomy.

Infections within 1 month after surgery were common, being observed in 34% of the patients. This figure is in the same range as estimates of postoperative infections after abdominal surgery in patients with cirrhosis and higher than in the general population (29% [95% CI, 21%-36%] and 13% [95% CI, 12%-14%], respectively; $P < 0.001$).[40] In cirrhosis, the risk of infection is likely related to altered innate and adaptive immunity and to increased bacterial translocation.[41] In patients with INCPH, susceptibility to infection may be related to portal hypertension but also to extrahepatic conditions associated with INCPH, namely immunological disorders and HIV infection. Bleeding occurred within 1 month in 10 (22%) patients and was associated with administration of anticoagulant or antiplatelet agents. This high incidence is reminiscent of the frequent bleeding episodes reported in patients with Budd-Chiari syndrome undergoing invasive procedures while receiving anticoagulation therapy.[42]

In the present study, we identified a group of patients having an unfavorable outcome, namely those with an extrahepatic condition associated with

INCPH, elevated serum creatinine, and/or significant ascites before surgery. By contrast, only 5% of the patients with neither an extrahepatic condition associated with INCPH nor elevated serum creatinine nor significant ascites before surgery had an unfavorable outcome. These simple features could be helpful in making a decision for abdominal surgery with the appropriate information provided to the patient on the risks of the intervention. Due to the retrospective and uncontrolled design of the study, we could not evaluate the survival benefit of surgery (versus no intervention), taking into account the indication of surgery, the severity of INCPH, and extrahepatic comorbidities.

In patients with cirrhosis, the experience of preemptive TIPSS placement before surgery is limited to small, retrospective studies.[12-17] A limited number of studies compared patients with cirrhosis with preserved or moderately impaired liver function who had preoperative TIPSS to patients who underwent elective surgery without preoperative TIPSS. Outcome after surgery was similar between patients who had those who did not have a preoperative TIPSS.[15,17] In the present study, portal decompression was not associated with postoperative outcome after surgery. However, the present findings are insufficient to draw any firm conclusion for or against preemptive portal decompression before surgery in patients with INCPH. Indeed, TIPSS was placed as a preparation for surgery in only 4 patients; in the 5 remaining patients, TIPSS had been previously inserted for other reasons, with sometimes a broad interval of time between TIPSS insertion and surgery. Larger dedicated studies are thus needed to address this important question.

In conclusion, in this study, we observed that patients with INCPH were at high risk of major surgical and portal hypertension–related complications when they harbored extrahepatic conditions related to INCPH and/or increased serum creatinine and/or a history of ascites. Comorbidities and higher serum creatinine were significantly associated with 6-month mortality. Further studies are needed to evaluate the impact of each type of surgery on the natural history of INCPH and the influence of TIPSS on postoperative outcome.

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Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.30628/suppinfo.

Resumen de los resultados

Estudio 1. Agreement between wedged hepatic venous pressure and portal pressure in non-alcoholic steatohepatitis-related cirrhosis.

Selección de pacientes y características basales.

- Desde enero de 2010 hasta diciembre de 2019, se incluyeron un total de 40 pacientes con cirrosis por EHGNA, los cuales se compararon con un grupo control constituido por 80 pacientes con cirrosis por alcohol (n = 40) o VHC (n = 40).
- Los pacientes incluidos fueron en su mayoría hombres (74%) con una mediana de edad de 58 (51-63) años y una mediana de puntuaciones de Child-Pugh y MELD (del inglés, *Model for End-stage Liver Disease*) de 8 (7-9) y 12 (10-15) puntos, respectivamente. Las indicaciones de TIPS fueron la hemorragia por varices (47%), la ascitis refractaria (47%) y el hidrotórax hepático (6%). El 17% de los pacientes recibió sedación superficial con midazolam y fentanilo mientras que el 83% restante recibió sedación profunda con propofol y remifentanilo. El 57% de los pacientes fueron asistidos con ventilación mecánica durante la realización del TIPS y el 43% respiraron espontáneamente. Finalmente, el 19% fueron tratados con drogas vasoactivas (somatostatina, terlipresina y/o noradrenalina) durante la medición de ambas presiones.
- Como era de esperar, los pacientes con EHGNA tuvieron un índice de comorbilidad de Charlson ajustado por edad[63] más alto [6 (5-8) vs 5 (4-6); *p=0.001*] y presentaron más factores de riesgo cardiovascular [3 (2-3) vs 1 (0-2); *p <0,001*] en concordancia con una mayor prevalencia de hipertensión arterial (53% vs 21%, *p=0.001*), diabetes tipo 2 (83% vs 24%; *p <0.001*) y dislipidemia (45% vs 13%, *p <0.001*). Igualmente, los pacientes con EHGNA tuvieron un índice de masa corporal (IMC) más alto que el grupo control [27.8 (24.9 – 30.7) vs 24.8 (22.9 – 30.0); *p=0.010*] y, aunque la proporción de pacientes con sobrepeso (IMC ≥ 25 kg / m2) fue mayor en pacientes con EHGNA (75% vs 46%, *p=0.003*), la proporción de pacientes con obesidad (IMC ≥ 30 kg/m^2) no fue significativamente diferente entre ambos grupos (25% vs 25%, *p=1.000*).

Correlación entre la PSE y la PP.

- De acuerdo con datos previamente publicados, la correlación entre la PSE y la PP fue excelente en el grupo control analizado en su conjunto (R: 0.92; CCI: 0.96; *p <0.001*) o por separado (Alcohol = R: 0.93; CCI: 0.97; *p <0.001* / VHC = R: 0.91; CCI: 0.95; *p <0.001*). Por el contrario, la correlación entre ambas presiones fue moderada en los pacientes con EHGNA (R: 0.61; CCI: 0.74; *p <0.001*).
- La concordancia entre la PSE y la PP fue consistentemente mejor en el grupo control después de excluir a los pacientes que fueron intubados (n = 68) o tratados con fármacos vasoactivos (n = 22). El tamaño muestral impidió analizar la correlación en pacientes con sedación superficial. Sin embargo, los resultados fueron similares cuando los pacientes con sedación profunda (n = 100) fueron

analizados de forma aislada. Del mismo modo, los resultados se mantuvieron sin cambios después de excluir a 20 pacientes en los que la PSE y la PP fueron medidas en días diferentes, pero siempre dentro del último mes, previo a la colocación del TIPS.

- Los gráficos de Bland-Altman mostraron una alta variabilidad individual en el grupo de pacientes con EHGNA reflejada por un amplio intervalo de confianza del 95%. Por el contrario, en el grupo control, la escasa variabilidad observada permitió que la concordancia entre ambas presiones fuera considerada como óptima.

Discrepancia entre la PSE y la PSL.

- La discrepancia entre la PSE y la PP (diferencias ≥ 10% del valor de la PP) ocurrió en el 37.5% de los pacientes con EHGNA y en 14% de los pacientes en el grupo control (*p=0.003*). La EHGNA, como causa de la cirrosis, fue el único factor que, en el análisis multivariado ajustado según la etiología y los niveles de bilirrubina sérica, se asoció de forma independiente a una discrepancia entre ambas presiones [OR: 4.03 (IC del 95%: 1.60 – 10.15); *p=0.003*].
- Las discrepancias significativas entre la PSE y la PP (diferencias ≥ 5 mmHg) ocurrieron en el 15% de los pacientes con cirrosis por EHGNA y solo en el 3% de los pacientes con cirrosis por otras etiologías (*p=0.016*).
- La discrepancia entre la PSE y la PP se produjo como resultado de una infraestimación de la PP en el 32.5% de los pacientes con EHGNA y en el 7.5% de los pacientes en el grupo control (*p <0.001*). La EHGNA, como etiología de la cirrosis, fue el único factor que, en el análisis multivariado ajustado según la etiología y los niveles de fosfatasa alcalina sérica, se asoció de forma independiente con la infraestimación de la PP [OR: 5.59 (IC del 95%: 1.91 – 16.33); *p=0.002*].
- La discrepancia entre la PSE y la PP se produjo como consecuencia de una sobreestimación de la PP en 2 (5%) pacientes con EHGNA y en 5 (6%) pacientes en el grupo control (*p=1.000*). De acuerdo con lo previamente reportado, 5 de los 7 pacientes en quienes la PSE sobreestimó a la PP presentaron anomalías vasculares en la perfusión hepática (circulación colateral de gran calibre, trombosis parcial de la vena porta y un flujo portal muy lento de 5 cm/s).

Estudio 2. Abdominal surgery in patients with idiopathic noncirrhotic portal hypertension: A multicenter retrospective study.

Selección de pacientes y características basales

- Entre 2002 y 2017 se realizaron 45 intervenciones quirúrgicas en 44 pacientes con HTPI de 10 centros. El diagnóstico de HTPI se realizó al momento de la cirugía en el 18% de los pacientes, mientras que el 82% restante la HTPI se diagnosticó antes de la cirugía (mediana del tiempo entre el diagnóstico y la cirugía de 26 [6-50] meses). La mayoría de los pacientes incluidos fueron hombres (68%) con una mediana de edad de 53 (37-65) años y una mediana de MELD al momento de la cirugía de 9 (7-12) puntos. El 57% de los pacientes presentaron al menos una condición extrahepática

asociada a la HTPI (enfermedades inmunológicas, protrombóticas o genéticas, infecciones abdominales recurrentes, medicamentos o toxinas) y el 32% de ellos tenían dos o más condiciones. El índice de comorbilidad de Charlson ajustado por edad[63] fue ≥ 3 en el 80% de los pacientes, lo que indica que la coexistencia de comorbilidades era frecuente.

- Del total de cirugías realizadas, el 33% fueron consideradas intervenciones mayores y el 67% intervenciones menores. El 27% de las cirugías se realizaron mediante laparoscopia y el 73% fueron cirugías abiertas. El 24% de las intervenciones quirúrgicas se realizaron de forma emergente, mientras que el 76% restante fueron electivas.

Complicaciones postquirúrgicas en el primer mes posterior a la cirugía

- Se produjeron 61 complicaciones postquirúrgicas en 31 (70%) pacientes en el plazo de 1 mes después de la cirugía, siendo en 9 (20%) de estos pacientes complicaciones grado ≥ 3 según la clasificación de Dindo-Clavien[64], es decir, complicaciones que requirieron de alguna intervención quirúrgica, endoscópica o radiológica. Diez (22%) pacientes desarrollaron hemorragia como complicación posquirúrgica. El tratamiento con antiagregantes plaquetarios (30% vs 6%; *p=0.030*) y anticoagulantes al momento de la cirugía (50% vs 9%; *p=0.003*) fueron los únicos factores que se asociaron al desarrollo de una hemorragia como complicación posoperatoria. Se produjeron 19 infecciones postquirúrgicas en 15 (33%) pacientes, de las cuales solo una de ellas fue clasificada como complicación grado ≥ 3 según la clasificación de Dindo-Clavien. Ninguno de los factores predefinidos (índice de comorbilidad de Charlson ajustado por edad, condiciones extrahepáticas asociadas a la HTPI, antecedente de ascitis, varices que requieren de tratamiento, trombosis portal, bilirrubina sérica, creatinina sérica, cirugía mayor y cirugía emergente) en base a su identificación previa como factores pronósticos en pacientes con cirrosis sometidos a cirugía y/o en pacientes con HTPI, se asoció de forma significativa con el desarrollo de complicaciones postquirúrgicas grado ≥ 3 según la clasificación de Dindo-Clavien.

Complicaciones relacionadas con la HTP en los primeros 3 meses posteriores a la cirugía

- Se produjeron 27 complicaciones relacionadas con la HTP en 16 (36%) pacientes durante los primeros 3 meses posteriores a la cirugía. La mediana de tiempo entre la cirugía y la aparición de tales complicaciones fue de 6 (1 a 17) días. La ascitis, que se produjo en 12 (26%) pacientes, fue la más frecuente de dichas complicaciones. La tasa de hemorragia por varices, encefalopatía hepática, peritonitis bacteriana espontánea e insuficiencia renal aguda a los 3 meses de la cirugía fue del 4%, 7%, 7% y 16%, respectivamente. Tres pacientes fueron tratados con TIPS en los primeros 3 meses tras la cirugía, dos de ellos por ascitis refractaria (a los 6 y 8 meses) y uno por hemorragia varicosa (a los 14 días). De los factores predefinidos, solo el antecedente de ascitis (HR 3.14 [1.16-8.50]; *p=0.024*) y la presencia de condiciones extrahepáticas (HR 3.97 [1.13-13.98]; *p=0.032*) se asociaron de forma significativa al desarrollo de complicaciones relacionadas con la HTP en los primeros 3 meses posteriores a la cirugía.

- Cinco (11%) pacientes desarrollaron trombosis esplácnica de nueva aparición, una mediana de 28 (rango: 1-45) días después de la intervención quirúrgica. La trombosis esplácnica se produjo en 3 de los 6 pacientes (50%) que se sometieron a una esplenectomía, mientras que solo 2 de los 39 pacientes (5%) que fueron sometidos a otro tipo de intervención quirúrgica presentaron esta complicación (*p=0.010*).

Muerte y trasplante hepático a los 6 meses de la cirugía

- Cuatro (9%) pacientes murieron dentro de los 6 primeros meses posteriores a la cirugía. Ningún paciente recibió un trasplante hepático dentro del mismo período de observación. De los factores predefinidos, solo el índice de comorbilidad de Charlson ajustado por edad (HR 1.37 [1.04-1.81]; *p=0.025*) y la creatinina sérica (HR 1.01 [1.00-1.01]; *p=0.002*) se asociaron de forma significativa con la muerte en los primeros 6 meses posteriores a la cirugía.
- Se comparó el riesgo acumulado de muerte a los 6 meses de la cirugía en pacientes con HTPI con el de pacientes con cirrosis emparejados según la presencia de ascitis, siendo este riesgo similar entre ambos grupos (*p=0.6*). Además, para evaluar el impacto de la cirugía abdominal en el pronóstico de los pacientes con HTPI, se comparó la supervivencia libre de trasplante hepático a los 3 años de los pacientes con HTPI sometidos a cirugía abdominal en los primeros 3 años posteriores a su diagnóstico (n=29) con a la de los pacientes con HTPI que no habían sido sometidos a cirugía abdominal (n=82), siendo la supervivencia libre de trasplante similar en ambos grupos (*p=0.7*).

Pronóstico postoperatorio desfavorable

- El 50% de los pacientes presentaron un pronóstico postoperatorio desfavorable, el cual se definió como el desarrollo de complicaciones quirúrgicas grado ≥ 3 (según la clasificación de Dindo-Clavien) en el primer mes, complicaciones relacionadas con la HTP en los primeros 3 meses o la muerte/trasplante hepático en los primeros 6 meses desde la cirugía.
- De los factores predefinidos, el antecedente de ascitis fue el único factor que se asoció a un pronóstico postoperatorio desfavorable (HR 3.89 [1.65-9.18]; *p=0.002*). De forma adicional, los pacientes con condiciones extrahepáticas asociadas a la HTPI (HR 2.41 [0.94-6.19]; *p=0.067*) y los pacientes con una creatinina sérica ≥ 1.13 mg/dL (HR 1.00 [1.00-1.01]; *p=0.056*) mostraron una tendencia no significativa a tener un pronóstico desfavorable.

Influencia de la derivación portosistémica en el riesgo quirúrgico

- Once (25%) pacientes fueron tratados con una derivación portosistémica antes (n=10) o en el momento de la cirugía (n=1). En los pacientes con antecedente de derivación portosistémica previa a la cirugía, la mediana del tiempo entre la derivación portosistémica y la intervención quirúrgica fue de 4 (0.3 a 44.6) meses. El pronóstico postquirúrgico de los pacientes con antecedente de TIPS previo a la cirugía fue similar al de los pacientes sin TIPS.

DISCUSIÓN

La mayoría del conocimiento actual de la HTP proviene de estudios que se realizaron en pacientes con cirrosis por alcohol o hepatitis virales. A pesar de que la prevalencia e incidencia de la EHGNA están aumentando de forma significativa, el valor pronóstico del GPVH en esta enfermedad es aún incierto.[65] Como se ha mencionado previamente, la utilidad predictiva del GPVH se basa en una excelente concordancia entre la PSE y la PP en pacientes con HTP de origen sinusoidal. Sin embargo, esta concordancia no es tan precisa en etiologías de la HTP que combinan el daño hepático sinusoidal y presinusoidal como, por ejemplo, la colangitis biliar primaria o la HTPI.[16,17]

En el presente estudio, analizamos el valor de la PSE (medida mediante el cateterismo selectivo de una vena suprahepática) para estimar la PP (medida de forma directa durante la colocación de un TIPS) en pacientes con cirrosis descompensada por EHGNA. Nuestros resultados indican que, en estos pacientes, la correlación entre la PSE y la PP no es tan buena como en aquellos pacientes con cirrosis por alcohol o VHC, en quienes la correlación es excelente. De hecho, en nuestro estudio un porcentaje alto de pacientes con EHGNA presentaron una discrepancia entre la PSE y la PP (diferencia ≥ 10% del valor de la PP) en comparación con su baja frecuencia en pacientes con cirrosis por alcohol o VHC (37.5% vs 14%; *p=0.003*). La definición de discrepancia utilizada en nuestro estudio se basó en una diferencia de presiones mayor o igual al 10% del valor de la PP porque reducciones del GPVH de esta magnitud se asocian con eventos clínicos relevantes.[26,27]

Es necesario tener en cuenta ciertos factores que pueden influir en los resultados obtenidos durante un estudio hemodinámico hepático. En este sentido, se ha demostrado que el tipo de sedación y soporte ventilatorio utilizados pueden afectar la medición de presiones.[66,67] Sin embargo, nuestros resultados sugieren que el grado de concordancia entre la PSE y la PP en pacientes con EHGNA es inferior al observado en el grupo control independientemente del tipo de sedación o soporte ventilatorio utilizados durante la colocación del TIPS. Por otro lado, aunque la somatostatina y terlipresina producen cambios hemodinámicos en la circulación esplácnica después de un episodio agudo de hemorragia por varices,[68] estos cambios no deberían afectar la concordancia entre la PSE y la PP a menos que se produzca un evento significativo (*e.g.* cambio en la dosis de los fármacos vasoactivos, administración fluidos o hemoderivados, sangrado intraabdominal debido a una complicación relacionada con el procedimiento) entre la medición de ambas presiones. Aunque en nuestro estudio el 16% de los pacientes fueron tratados con drogas vasoactivas (somatostatina, terlipresina o noradrenalina), todos ellos se mantuvieron hemodinámicamente estables durante la medición de presiones y ningún evento significativo ocurrió entre la medición de la PSE y la medición de la PP. Más aún, la exclusión de pacientes tratados con fármacos vasoactivos no modificó nuestros resultados.

Como era esperable, los pacientes con EHGNA presentaron una mayor prevalencia de algunos factores de riesgo cardiovascular como el sobrepeso, la hipertensión arterial, la dislipemia y la diabetes mellitus tipo 2. Con el objetivo de descartar la posibilidad de que alguno de estos factores pudiera ser responsable de los resultados encontrados, realizamos un análisis de regresión logística que identificó a la etiología por EHGNA como único factor responsable de las diferencias encontradas. Sin embargo, la influencia de estas alteraciones metabólicas sobre la correlación entre la PSE y la PP no se puede descartar del todo debido al limitado número de pacientes con cirrosis por EGHNA que se incluyeron en el estudio.

Otro hallazgo significativo de nuestro estudio es que una discrepancia entre la PSE y la PP en los pacientes con EHGNA se debe principalmente a que la PSE tiende a infraestimar la PP real. Este hecho, podría explicar por qué en el ensayo del simtuzumab,[35,36] el 14% de los pacientes cirróticos con un HVPG < 10 mmHg presentaron una complicación de la HTP durante una mediana de seguimiento de 4.7 meses, mientras que ninguno de los pacientes del estudio de Ripoll *et al.* se descompensó durante los primeros 20 meses de seguimiento.[6] Aunque nuestro estudio no puede confirmar estos resultados debido a que la totalidad de pacientes incluidos tenían un GPVH ≥ 10 mmHg, nuestros resultados sugieren que los valores de GPVH que predicen descompensación y muerte podrían ser diferentes en los pacientes con cirrosis por EHGNA y, por tanto, merecen estudios específicos.

La infraestimación de la PP puede deberse a la existencia de un componente presinusoidal en la enfermedad. Aunque nuestros datos no pueden arrojar luz sobre el mecanismo responsable de esta observación debido a que solo a una pequeña proporción de pacientes con EHGNA fueron biopsiados en el año previo a la colocación del TIPS, un daño en el lecho vascular periportal podría ser el causante de cierto grado de HTP presinusoidal. De hecho, la fibrosis periportal es el tipo de fibrosis predominante en la población pediátrica con EHGNA[69] y en pacientes adultos ha sido considerada una lesión temprana que se asocia a una enfermedad más grave y a un peor pronóstico.[70] Por otra parte, la reacción ductular, previamente descrita en pacientes con EHGNA,[71,72] es una lesión reactiva al daño celular producida en el interfaz del tracto portal que comprende pequeños conductos biliares con un complejo acompañante de estroma y células inflamatorias.[73] Puede ser plausible que la reacción ductular y la inflamación periportal contribuyan a aumentar la presión presinusoidal y, por tanto, favorezcan la infraestimación de la PP. La trombosis microvascular también podría desempeñar un papel en el desarrollo de HTP en pacientes con EHGNA.[74] Estudios en pacientes con cirrosis han demostrado que la anticoagulación con heparina previene la trombosis portal, disminuye el riesgo de descompensación y mejora la supervivencia presumiblemente por sus efectos sobre la microtrombosis.[75] Aunque esta hipótesis no ha sido estudiada en pacientes con cirrosis por EHGNA, existen estudios que sugieren que estos pacientes presentan un perfil protrombótico y un mayor riesgo de trombosis que los pacientes con cirrosis por otras etiologías.[76,77]

En un número inferior de pacientes, la PSE sobreestimó la PP. Estudios previos sugieren que, en pacientes con cirrosis por alcohol o VHC, la PSE puede sobreestimar a la PP cuando existen determinadas alteraciones de la perfusión hepática como una trombosis portal parcial, un flujo hepatofugal o la existencia de circulación colateral portosistémica de gran calibre.[15,53,78] En estas situaciones, es probable que la presión sinusoidal dependan en gran medida del flujo arterial hepático. Aunque nuestro tamaño muestral fue demasiado pequeño para sacar conclusiones definitivas, nuestros datos concuerdan con estas observaciones, que sugieren que la presencia de determinadas anomalías vasculares condicionadas por la arterialización del flujo portal pueden producir que la PP sea sobreestimada por la PSE, independientemente de la etiología.

Reconocemos las limitaciones de nuestro estudio, principalmente el pequeño tamaño muestral y su naturaleza retrospectiva. Sin embargo, aunque la incidencia de la EHGNA está aumentando rápidamente, el número de pacientes en las etapas finales de la enfermedad sigue siendo limitado. Por otra parte, decidimos limitar el estudio a centros con gran experiencia en la realización de estudios hemodinámicos hepáticos para garantizar la fiabilidad de las mediciones. Por todo ello, la inclusión de 40 pacientes bien caracterizados con cirrosis por EHGNA tratados con TIPS representa una cohorte única. Igualmente, la recopilación prospectiva de datos y la evaluación cuidadosa del trazado de presión junto con la exclusión de pacientes con factores que interfieren con la medición de la PSE (trombosis completa de la vena porta, presencia de comunicantes veno-venosas en el hepatograma) reducen la posibilidad de sesgo. Finalmente, dado que los pacientes incluidos en el estudio presentaban una enfermedad hepática descompensada, nuestros resultados solo pueden aplicarse a este subgrupo de pacientes.

En cuanto al riesgo quirúrgico en pacientes con HTPI que son sometidos a una cirugía abdominal, nuestros resultados indican que éstos pacientes tienen una mortalidad a los 6 meses del 9%, siendo esta especialmente acentuada en pacientes con un índice de comorbilidad de Charlson ajustado por edad ≥ 6 puntos y/o valores de creatinina sérica ≥ 1.13 mg/dL. Por otra parte, nuestros resultados sugieren que la mortalidad en los pacientes con HTPI sometidos a cirugía abdominal fue similar a la observada en pacientes con cirrosis emparejados según la presencia de ascitis al momento de la cirugía (9% y 10% respectivamente).[62] Esta similitud sugiere que en pacientes con hepatopatía crónica, el grado de HTP, la coexistencia de comorbilidades y la complejidad de la cirugía son los principales factores predictivos de mal pronóstico tras una cirugía. De hecho, en el estudio de Reverter *et al.* las variables asociadas a una mayor mortalidad fueron el GPVH, que evalúa el grado de HTP, la clase ASA que evalúa la coexistencia de comorbilidades, y la realización de una cirugía de alto riesgo. En este sentido, aunque en el presente estudio no encontramos ninguna asociación entre el tipo de cirugía abdominal realizada (*e.g.* mayor vs menor, emergente vs electiva, abierta vs laparoscópica) y el pronóstico posoperatorio, no podemos descartar que la exista debido a que nuestro tamaño muestral fue limitado. Es de destacar que la mortalidad observada en el grupo de pacientes con cirrosis fue muy similar a la reportada en estudios recientes.[38,45] Sin embargo, la mortalidad en pacientes con cirrosis sometidos a cirugía ha mejorado de

forma significativa en comparación con la reportada en estudios más antiguos en los que la mortalidad reportada era muy elevada (mortalidad al 1º mes del 20%, al 3º mes del 30% y al 1º año del 46%).[42,46] Ello, es probablemente debido a una mejor selección de los candidatos a cirugía y a los avances que se han producido en las técnicas quirúrgicas y en el tratamiento médico de los pacientes con cirrosis, diferencias que probablemente también se pueden extrapolar a los pacientes con HTPI. En el presente estudio, la mortalidad a los 6 meses de la cirugía se restringió a aquellos pacientes con un índice de comorbilidad de Charlson ajustado por edad ≥ 6 puntos y/o valores de creatinina sérica ≥ 1.13 mg/dL. Estos hallazgos van en línea con la historia natural de la HTPI, en la cual la mortalidad se asocia a la presencia de ascitis y a la coexistencia de condiciones extrahepáticas asociadas,[40,41] y con el pronóstico de los pacientes con HTPI que son sometidos a la colocación de un TIPS, en quienes la mortalidad se correlaciona con la coexistencia de condiciones extrahepáticas asociadas y valores de creatinina sérica ≥ 1.13 mg/dL.[79] Curiosamente, la supervivencia libre de trasplante después del diagnóstico de HTPI fue similar en aquellos pacientes que se sometieron a una cirugía abdominal que en los que no lo hicieron, lo que sugiere que, cuando la cirugía se realiza en centros expertos y en pacientes seleccionados, ésta no tiene un impacto deletéreo en la historia natural de la enfermedad.

El segundo hallazgo importante del presente estudio fue que hasta el 36% de los pacientes con HTPI que se sometieron a cirugía abdominal presentaron al menos una complicación relacionada con la HTP dentro de los primeros 3 meses posteriores a la cirugía, siendo la ascitis, la complicación más frecuente con una prevalencia del 26%. Aunque los pacientes que desarrollaron complicaciones de la HTP tras la cirugía tuvieron una estancia hospitalaria más larga y el 19% de ellos requirieron un TIPS tras la cirugía, estas complicaciones fueron transitorias y manejables en la mayoría de los casos, lo cual sugiere que su desarrollo no indica *per se* un mal pronóstico. Por otra parte, un 11% de los pacientes desarrollaron una trombosis portal *de novo*, siendo esta complicación 10 veces más frecuente en pacientes sometidos a una esplenectomía que en aquellos sometidos a otras cirugías. Las tasas reportadas de trombosis portal después de una esplenectomía oscilan entre el 17% y el 36% en pacientes con cirrosis[80,81] y el 54% en pacientes con trastornos hematológicos benignos.[82] En el presente estudio, la incidencia de trombosis portal tras una esplenectomía fue del 50%, siendo esta incidencia mayor que la reportada en pacientes cirróticos y similar a la de pacientes con trastornos hematológicos de base. Todo lo anterior hace eco del especial cuidado que se debe de tener al considerar esta técnica quirúrgica en pacientes con HTPI y del elevado riesgo protrombótico que tienen estos pacientes. Por otra parte, en nuestro estudio 4 de los 5 casos de trombosis portal fueron diagnosticados dentro del primer mes después de la cirugía, lo que sugiere que la realización de un control ecográfico rutinario a la 1º semana, 1º mes y 3º mes después de la cirugía permitiría la detección temprana de trombosis portal, sobre todo, después de una esplenectomía. Finalmente, en cuanto a las complicaciones posquirúrgicas no relacionadas con la HTP, aunque su desarrollo fue muy frecuente en nuestra cohorte, la mayoría de estas complicaciones fueron leves y se autolimitaron sin requerir ninguna intervención médica ni quirúrgica.

Por otra parte, en nuestro estudio el 50% de los pacientes con HTPI sometidos a cirugía presentaron un pronóstico desfavorable, definido como la ocurrencia de complicaciones posquirúrgicas grado ≥ 3 según la clasificación de Dindo-Clavien en el primer mes, complicaciones asociadas a la HTP en los primeros 3 meses o muerte o trasplante en los primeros 6 meses posteriores a la cirugía. Teniendo en cuenta que la presencia de ascitis al momento de la cirugía se asoció de forma significativa a un pronóstico desfavorable y que la coexistencia de condiciones asociadas a la HTPI y los valores de creatinina sérica ≥ 1.13 mg/dL se asociaron a un mal pronóstico en estudios previos,[40,41,79] decidimos clasificar a los pacientes según la presencia o ausencia de estas tres características clínicas. Así, observamos que solo el 5% de los pacientes que no presentaban ninguna de estas características presentaron un pronóstico desfavorable mientras que el 64% de los pacientes con dos o más de estas características presentaron un pronóstico desfavorable. De esta forma, nuestros resultados permiten clasificar el riesgo quirúrgico de los pacientes con HTPI en base a tres criterios clínicos, que pueden ayudar en la toma de decisiones y que permiten brindar al paciente información sobre los riesgos que implica la realización de una intervención quirúrgica. Cabe la pena destacar que la mayoría de los pacientes que presentaron un pronóstico desfavorable sobrevivieron y que la mayoría de las complicaciones posquirúrgicas y relacionadas con la HTP tuvieron un curso benigno y presentaron una buena respuesta al tratamiento. Lo anterior, por tanto, debe de ser también tomado en cuenta a la hora de evaluar el riesgo quirúrgico en pacientes con HTPI.

Finalmente, dado el vínculo que existe entre la HTP y el pronóstico postquirúrgico, la realización de un TIPS previo a la cirugía ha sido propuesta con la finalidad de mejorar los resultados tras la cirugía. Sin embargo, la evidencia que existe a favor o en contra de la colocación de un TIPS preventivo antes de la cirugía se limita a pequeños estudios retrospectivos con resultados contradictorios.[57–62] En nuestro estudio, la colocación de un TIPS antes de la cirugía no influyó en el pronóstico posquirúrgico. Sin embargo, nuestros resultados son insuficientes para sacar una conclusión firme a favor o en contra de la colocación prequirúrgica de un TIPS. De hecho, el TIPS fue colocado como puente a la cirugía solo en 4 pacientes, mientras que el resto se colocaron por otras razones con un intervalo de tiempo entre la colocación del TIPS y la cirugía muy variable.

Aunque el presente estudio reunió el mayor número de pacientes con HTPI sometidos a cirugía abdominal hasta la fecha, la interpretación de nuestros resultados debe tener en cuenta la naturaleza retrospectiva del estudio, la diversidad de las intervenciones quirúrgicas realizadas y que el tamaño muestral limitado. No obstante, dada la rareza de esta enfermedad, la realización de un estudio prospectivo parece difícil de llevar a cabo. Además, el estudio se limitó a la evaluación de pacientes sometidos a cirugía abdominal por lo que nuestros resultados solo se pueden aplicar a este tipo de cirugías. A pesar de estas limitaciones, nuestros resultados sugieren que la presencia de ascitis, la coexistencia de condiciones asociadas a la HTPI y los valores de creatinina sérica deben de ser tomados en cuenta en la toma de decisiones durante la evaluación del riesgo quirúrgico en pacientes con HTPI.

CONCLUSIONES

- En congruencia con estudios previos, nuestros resultados reafirman que la PSE es capaz de estimar de forma muy precisa la PP real en pacientes con cirrosis por alcohol o VHC.
- En pacientes con cirrosis descompensada por EHGNA, la PSE estima la PP con menor precisión que en pacientes con cirrosis descompensada por alcohol o VHC.
- La PSE tiende a infraestimar la PP real en pacientes con cirrosis descompensada por EHGNA, sugiriendo que existe un componente presinusoidal en la patogénesis de la HTP asociada a esta enfermedad.
- Los pacientes con HTPI sometidos a una cirugía abdominal tienen un riesgo no despreciable de presentar un pronóstico posquirúrgico desfavorable, especialmente cuando presentan antecedente de ascitis, condiciones extrahepáticas asociadas a la HTPI o niveles de creatinina sérica ≥ 1.13 mg/dL. A pesar de ello, la mayoría de las complicaciones posquirúrgicas y relacionadas con la HTP tienen un curso benigno y no suponen una considerable morbimortalidad.
- Un índice de comorbilidad de Charlson ajustado por edad ≥ 6 y niveles de creatinina sérica ≥ 1.13 mg/dL se asocian de forma significativa a una mayor mortalidad en pacientes con HTPI sometidos a cirugía abdominal.
- El desarrollo de trombosis esplácnica como complicación posquirúrgica es especialmente frecuente en pacientes con HTPI que son sometidos a una esplenectomía.

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6. **Ferrusquía-Acosta J**, Turco L, Hernández-Gea V. "Reply to: "Underestimation of portal pressures by wedge hepatic venous pressures in patients with non-alcoholic steatohepatitis related cirrhosis-Possibilities and implications". J Hepatol. 2020 [epub ahead of print].
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AYUDAS OBTENIDAS

1. Beca ***"Ampliación de Estudios en España"*** otorgada por la Asociación Española para el Estudio del Hígado (AEEH) en el año 2016.
2. Beca ***"Iniciació a la Recerca"*** otorgada por la Societat Catalana de Digestologia (SCD) en el año 2017.