Universitat Autònoma de Barcelona

Paper de l'elastografia hepàtica i esplènica en el diagnòstic, seguiment i tractament de la malaltia hepàtica crònica avançada compensada

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TESI DOCTORAL

Paper de l'elastografia hepàtica i esplènica en el diagnòstic, seguiment i tractament de la malaltia hepàtica crònica avançada compensada

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A la meva família.

LLISTAT D'ABREVIACIONS

CHC	Carcinoma hepatocel·lular (hepatocarcinoma)
ET	Elastografia de transició
MHCAc	Malaltia hepàtica crònica avançada compensada
GPVH	Gradient de pressió venosa hepàtica
HPCS	Hipertensió portal clínicament significativa
MELD	Model for end-stage liver disease
HR	Hazard ratio
IC	Interval de confiança

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RESUM

En la malaltia hepàtica crònica es produeixen canvis en l'estructura del parènquima hepàtic que comporten l'aparició de fibrosi i, al llarg del temps, el desenvolupament d'una cirrosi hepàtica. Les principals complicacions de la cirrosi hepàtica són l'aparició d'hipertensió portal, la insuficiència hepàtica i l'augment de risc de presentar un carcinoma hepatocel·lular (CHC) o hepatocarcinoma. El tractament de la causa que ha generat la malaltia hepàtica pot canviar l'evolució natural millorant el pronòstic, sobretot si aquest es realitza en fases precoces.

L'àmplia utilització de tècniques de diagnòstic no invasiu i, sobretot, de l'elastografia de transició (ET), ens ha permès diagnosticar a pacients amb malaltia hepàtica crònica avançada en fases més precoces. Aquests pacients, tot i no haver-se descompensat mai, tenen un risc augmentat de presentar hipertensió portal i CHC pel que serà important conèixer quins d'ells desenvoluparan complicacions al llarg del seguiment i, en el cas dels pacients que hagin rebut tractament de la causa subjacent, identificar quins tindran més probabilitats de millorar el pronòstic. La present tesi pretén estudiar diferents utilitats de l'ET durant el seguiment de pacients amb malaltia hepàtica crònica avançada compensada (MHCAc). Així doncs, els objectius de la tesi van ser avaluar la capacitat de l'ET per predir complicacions (varices d'alt risc, descompensacions o CHC) en pacients amb MHCAc i donar regles senzilles que permetin la identificació de grups de risc. Per a tal finalitat, es van dur a terme tres estudis independents on es va estudiar, respectivament, la utilitat d'uns nous criteris basats en l'elastografia hepàtica i la xifra de plaquetes que permetia identificar una població amb baix risc de presentar varices de risc, estudiar els canvis dinàmics que es produeixen en l'elastografia hepàtica i esplènica en els pacients tractats amb antivirals orals per l'hepatitis C i, finalment, es va estudiar la incidència de complicacions després d'un tractament eficaç amb antivirals orals per posteriorment dissenyar una eina simple per predir el risc de presentar CHC. Amb aquests estudis es va poder concloure que: 1) l'ET en combinació amb paràmetres analítics és útil per predir el risc de complicacions en la malaltia hepàtica crònica, 2) uns nous criteris (ET <25 kPa i xifra de plaquetes >110x10^9/L) permeten identificar una població amb baixa probabilitat de presentar varices de risc fet que permet estalviar un elevat número d'endoscòpies, 3) durant el tractament amb antivirals orals es produeix un ràpid descens de l'elastografia

hepàtica i esplènica com a conseqüència de la milloria de la inflamació, 4) la incidència de complicacions posterior al tractament amb antivirals orals és baixa essent el CHC la més freqüent i, per últim, 5) un senzill nomograma basat en ET i nivells d'albúmina permet determinar el risc de CHC durant el seguiment de pacients amb MHCAc tractats amb antivirals orals.

SUMMARY

Regardless the underlying cause, in chronic liver disease there is a wound-healing process that produces fibrosis and, after a variable period of time, cirrhosis. The main complications of liver cirrhosis are portal hypertension, liver failure and hepatocellular carcinoma (HCC). Treating the underlying cause of liver disease can change the natural history improving prognosis especially in early stages.

The extended use of non-invasive diagnostic methods, especially transient elastography (TE), have helped us to diagnose patients at early phase of advanced chronic liver disease. This patient population is of particular interest because, although they have never decompensated, they have an increased risk of portal hypertension and HCC, thus, it will be important to stratify the risk of presenting complications during follow up and, in patients who have treated the underlying cause of liver disease, to know which patients will have a better prognosis. The current thesis aims to study different uses of TE during follow up of patients with compensated advanced chronic liver disease (cACLD). The main objectives were to evaluate the capacity of TE for predicting liver-related events (varices needing treatment, decompensation or HCC) in cACLD patients and to provide simple rules to identify different risk groups of developing these complications. Three different studies were performed: in the first study, we evaluated the validity of new criteria based on TE and platelet count to identify a low risk group of having varices needing treatment; in the second study, we evaluated the dynamic changes of liver and spleen stiffness in patients treated with oral antivirals for chronic hepatitis C and, in the third study, we evaluated the incidence of liver-related events after a successful treatment with oral antivirals and we designed a simple tool to predict the risk of HCC. The conclusions of this thesis were: 1) TE combined with other laboratory parameters is useful

to predict the risk of liver-related events in cACLD patients, 2) the new criteria (TE <25 kPa and platelet count >110x10^9/L) can identify a low risk group of having varices needing treatment and save a high number of unneeded endoscopies, 3) during oral antiviral therapy, there is a rapid decrease in liver and spleen stiffness due to improvement in inflammation, 4) the incidence of liver-related events after achieving sustained virological response with oral antivirals in cACLD patients is very low, being HCC the most frequent event and, finally, 5) a simple nomogram based on TE and albumin levels at follow-up can help to determine the risk of presenting HCC during follow-up in hepatitis C cACLD patients treated with oral antivirals.

1. Introducció

1. INTRODUCCIÓ

1.1 Evolució natural de la malaltia hepàtica crònica

Les agressions cròniques al fetge, com els virus o l'alcohol, ocasionen un dany tissular que provoca l'acumulació de teixit fibrós al fetge. Quan la fibrosi progressa, es produeixen canvis en l'arquitectura hepàtica, essent el resultat final la cirrosi hepàtica que és l'estadi final de la malaltia hepàtica crònica. Els canvis fibròtics que es produeixen en la cirrosi hepàtica poden provocar un deteriorament de la funció i hemodinàmica hepàtiques, augmentant el risc de desenvolupar complicacions[1]. Aquest procés de fibrosi sol ser progressiu però també s'ha demostrat que pot romandre estable o inclús revertir al cap del temps si s'elimina la noxa, fins i tot en la fase de cirrosi[2].

La cirrosi hepàtica es caracteritza per una fase asimptomàtica o compensada amb un pronòstic relativament llarg, essent la supervivència mediana d'uns 12 anys. Si la malaltia progressa, apareix la fase simptomàtica o cirrosi descompensada en la qual la pressió portal augmenta i la funció hepàtica empitjora pel que apareixen complicacions com l'ascites, l'hemorràgia per varices, l'encefalopatia hepàtica o la icterícia. La cirrosi descompensada té un mal pronòstic, essent la supervivència mediana inferior als 2 anys. La incidència de progressió de la fase compensada a la fase descompensada és del voltant del 5-7% anual[1].

Degut a què el pronòstic és molt diferent depenent de les fases de la cirrosi, serà important poder estratificar el risc de presentar complicacions en la fase compensada per tal d'aplicar mesures preventives o poder seleccionar pacients per a futurs estudis[3].

1.2 Diagnòstic de la cirrosi i les seves complicacions

Clàssicament es defineix la cirrosi hepàtica com la presència de nòduls de regeneració envoltats de teixit fibrós. Per tant, el diagnòstic de cirrosi hepàtica és histològic. La biòpsia hepàtica és el mètode *gold standard* per estudiar la fibrosi hepàtica i identificar la cirrosi. La biòpsia hepàtica es realitza, principalment, a través de dues vies, la percutània i la via transjugular, essent totes dues tècniques invasives fet que pot provocar complicacions, tot i que la incidència d'aquestes és baixa[4]. Les principals limitacions de la biòpsia hepàtica són, en primer lloc, que és una tècnica cruenta fent que no sigui útil per estudiar l'evolució de la malaltia hepàtica i, en segon lloc, els errors de la mostra, fet que qüestiona la

reproductibilitat de la tècnica, ja que la superfície estudiada és petita (representa 1/50.000 parts del parènquima hepàtic) i perquè la distribució de la fibrosi no és homogènia a tot el parènquima[4,5].

Una de les conseqüències de la cirrosi hepàtica és el desenvolupament d'hipertensió portal que facilita la formació de varices esofàgiques i/o gàstriques que poden sagnar o d'altres complicacions com l'aparició d'ascites o l'encefalopatia hepàtica[1]. La hipertensió portal s'estudia mitjançant la mesura del gradient de pressió venosa hepàtica (GPVH) que es realitza per via transjugular cateteritzant una vena suprahepàtica. El càlcul es realitza mesurant la diferència entre la pressió enclavada de la vena hepàtica i la pressió lliure de la vena hepàtica[6]. Valors de GPVH >5 mmHg són diagnòstics d'hipertensió portal. S'ha demostrat que els valors de GPVH es correlacionen directament amb el risc d'aparició de complicacions. Les complicacions derivades de la hipertensió portal, així com el desenvolupament de les varices esofàgiques, apareixen quan el GPVH augmenta per sobre de 10 mmHg, pel que el GPVH ≥10 mmHg es defineix com a hipertensió portal clínicament significativa (HPCS)[7–10]. Quan el GPVH augmenta per sobre de 12 mmHg (hipertensió portal severa) apareixen les descompensacions clíniques en forma d'hemorràgia digestiva, ascites, encefalopatia hepàtica i/o insuficiència renal[10,11].

	Cirrosi compensada		Cirrosi descompensada	
GPVH (mmHg)	**>5**	**≥10**	**>12**	**>16**
Manifestació clínica	No varices No ascites	Varices No ascites	Ascites Hemorràgia per varices Encefalopatia hepàtica	Ascites refractària Infecció bacteriana Síndrome hepatorrenal Hemorràgia recidivant
Mortalitat (% a l'any)	1%	3%	10% hemorràgia sola 20% ascites sola 30% ascites + hemorràgia	>60% global

Taula 1. Estadi de la cirrosi segons el gradient de pressió venosa hepàtica (GPVH) i les seves complicacions. Modificat de Albillos i Garcia-Tsao[12].

Una altra manera indirecta de detectar la presència d'hipertensió portal és mitjançant l'esofagoduodenoscòpia per detectar la presència de varices. És important detectar la presència de varices ja que segons la mida d'aquestes, la presència de signes vermells o la funció hepàtica estarà indicada la profilaxi primària amb beta-bloquejants, fet que pot canviar el pronòstic de la malaltia[13].

Per tant, la mesura del GPVH i l'endoscòpia són considerats els mètodes *gold standard* per l'estudi de la hipertensió portal en la cirrosi hepàtica. Però, de nou, aquestes tècniques són invasives i, en el cas del GPVH, no es pot realitzar en tots els centres. És per això que s'ha intentat buscar mètodes de diagnòstic no invasiu que ens permetin diagnosticar de manera acurada la cirrosi hepàtica i la presència d'hipertensió portal.

1.3 L'elastografia hepàtica

En els últims anys s'han introduït noves tècniques basades en ultrasons que permeten el diagnòstic no invasiu del grau de fibrosi discriminant de manera acurada la presència de fibrosi avançada o cirrosi i diferenciant-la de la no fibrosi o fibrosi lleu, permetent disminuir el nombre de biòpsies realitzades. La tècnica més validada i més àmpliament utilitzada és l'elastografia de transició (ET) (Fibroscan®, Echosens, París).

L'ET mesura la velocitat de propagació d'una ona elàstica de baixa freqüència (50 Hz) a través del fetge. La velocitat està directament relacionada amb la rigidesa hepàtica: així quan més rígid sigui el fetge, major serà la velocitat de propagació de l'ona elàstica indicant així, de manera indirecta, la presència de major fibrosi[14]. S'ha demostrat que l'ET té un millor rendiment diagnòstic per la cirrosi que per la fibrosi significativa, essent el punt de tall òptim per detectar cirrosi >13 kPa amb una àrea sota la corba >90%. No obstant, el punt de tall òptim per a cada etiologia ha demostrat ser variable[15–18].

L'ET ha canviat la manera com diagnostiquem la malaltia hepàtica crònica. Degut a què es tracta d'una tècnica no invasiva, de fàcil utilització i amb una alta reproductibilitat ha permès que sigui utilitzada en grans poblacions de pacients (programes de cribratge) i inclús en pacients amb malaltia hepàtica crònica en els quals altres mètodes (analítica i ecografia) no fan sospitar que el pacient tingui una malaltia avançada. D'aquesta manera

permet diagnosticar pacients en fases precoces de la malaltia hepàtica crònica avançada, quan encara no han desenvolupat complicacions[19].

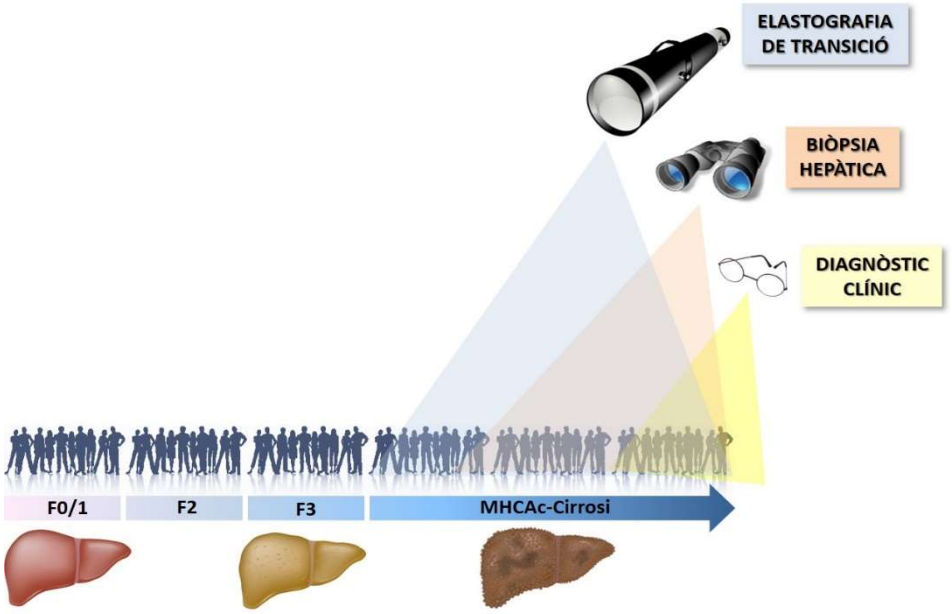

Figura 1. Impacte de l'elastografia de transició en el diagnòstic precoç de la malaltia hepàtica crònica avançada compensada (MHCAc)/cirrosi en comparació amb la biòpsia hepàtica i el diagnòstic clínic. Modificat de Augustin, et al[19].

1.4 Definició de malaltia hepàtica crònica avançada compensada

Degut a l'ampli ús de l'ET en pràctica clínica ha canviat la manera de diagnosticar la malaltia hepàtica crònica. L'ET permet el diagnòstic de la cirrosi en fases molt precoces on inclús és difícil distingir si el pacient té una fibrosi severa o una cirrosi sense una biòpsia hepàtica[19]. Hem de tenir en compte que la progressió de la fibrosi hepàtica té un curs continuat i sovint és difícil la distinció entre fibrosi severa i cirrosi. També és important tenir en compte que la hipertensió portal pot aparèixer en estadis precirròtics i que, en alguns casos, el cribratge del carcinoma hepatocel·lular (CHC) pot estar indicat en estadis precirròtics[19–22].

Per tot això, recentment, el consens de Baveno VI, format per un grup ampli d'experts en hipertensió portal, ha introduït un nou concepte per definir millor aquests pacients que es diagnostiquen en fases inicials de fibrosi severa/cirrosi mitjançant l'ET[23]. Així doncs, defineix la malaltia hepàtica crònica avançada compensada (MHCAc) en aquells pacients

amb fibrosi severa o cirrosi compensada amb o sense signes d'hipertensió portal diagnosticats mitjançant ET segons els següents criteris:

- Valors d'ET >15 kilopascals (kPa) són altament suggestius de MHCAc.
- Valors d'ET <10 kPa en absència d'altres signes clínics descarta la MHCAc.
- Valors d'ET entre 10 i 15 kPa (zona gris) són suggestius de MHCAc però es necessiten altres proves (biòpsia hepàtica, GPVH >5 mmHg o endoscòpia que demostri la presència de varices) per confirmar-ho.

Aquests dos punts de tall es van elegir per maximitzar la sensibilitat per descartar i l'especificitat per confirmar la presència de fibrosi severa o cirrosi en les diferents etiologies[24,25]. Un metanàlisi amb dades individuals de pacients ha demostrat que el punt de tall >15 kPa té una sensibilitat del 97% per detectar MHCAc i el punt de tall <10 kPa té una alta especificitat (87%) per descartar la MHCAc[26].

El més important a tenir en compte és que si diagnostiquem aquests pacients de manera precoç poden entrar en programes de cribratge (varices, hepatocarcinoma) fet que pot canviar la història natural. Estudis recents han demostrat que la prevalença d'hipertensió portal en els pacients amb MHCAc està al voltant del 80-90% i la prevalença d'HPCS està al voltant del 50-60%[27,28]. Dit d'una altra manera, prop d'un 50% no tenen HPCS i per tant, s'incrementarà el número d'endoscòpies innecessàries en el cas de cribratge de varices. Per tant, serà important identificar quins d'aquests pacients són els que tenen més risc de progressar o de presentar complicacions.

1.5 Utilitat de l'elastografia més enllà de la fibrosi

Durant els últims anys, molts estudis han intentat buscar altres utilitats de l'ET o bé sola o en combinació amb altres paràmetres. Essent les més estudiades detectar la presència d'HPCS i varices i per predir el risc de descompensació.

1.5.1 Diagnòstic no invasiu d'hipertensió portal clínicament significativa

La HPCS és un dels factors pronòstics més importants en els pacients amb MHCAc. Com hem vist, el mètode *gold standard* per diagnosticar-la és mitjançant la mesura del GPVH però és una tècnica invasiva i sovint no disponible en la majoria de centres.

L'ET ha demostrat ser útil per predir la presència d'HPCS sobretot en pacients amb malaltia hepàtica d'etiologia viral com així ho han demostrat diferents estudis i metanàlisis[29–31]. S'han proposat diferents punts de tall a l'hora de definir la presència d'HPCS segons els resultats de diferents estudis. Finalment, Baveno VI proposa que en pacients amb malaltia hepàtica crònica d'etiologia viral l'ET, sola o en combinació amb la xifra de plaquetes i la mida de la melsa, és suficient per detectar la presència d'HPCS, essent el punt de tall ≥20-25 kPa[23]. Els pacients amb valors d'ET ≥20-25 kPa tenen una probabilitat d'HPCS del 85-95%[27]. No obstant, hem de tenir en compte que aquests punts de tall no s'han estudiat en altres etiologies.

Una menció especial mereix l'elastografia esplènica. Aquesta també s'ha estudiat com a un possible marcador indirecte de la presència d'hipertensió portal demostrant una bona precisió a l'hora de detectar HPCS amb punts de talls >47.6-52.8 kPa[32,33]. No obstant, hem de tenir en compte que la realització d'elastografies esplèniques és més dificultosa, doncs precisa de la localització mitjançant ecografia prèvia, a part de què sovint els valors d'elastografia esplènica sovint superen el valor màxim de 75 kPa que permet la màquina de Fibroscan®.

1.5.2 Detecció de varices gastroesofàgiques

Fins a la publicació de les guies de Baveno VI el 2015, es recomanava el cribratge universal de varices en tots aquells pacients que es diagnosticaven de cirrosi per tal d'iniciar tractament profilàctic en els casos indicats. No obstant, com s'ha esmentat, la introducció de l'ET en pràctica clínica ha permès diagnosticar una població de pacients amb malaltia hepàtica crònica avançada en fase precoç, fet que, si bé és cert que aquests pacients poden tenir HPCS, la prevalença és menor i per tant, en molts d'ells, l'endoscòpia és innecessària.

L'ET per sí sola no és útil per predir la presència de varices, no obstant, quan es combina amb altres marcadors com la xifra de plaquetes, sí que ha demostrat tenir una bona precisió per descartar la presència de varices d'alt risc (que necessitaran tractament profilàctic). Diversos estudis han proposat diferents regles tenint en compte diferents punts de tall d'elasticitat hepàtica i de xifra de plaquetes[34–36]. Finalment, a Baveno VI, en base als estudis publicats, es va establir que els pacients amb ET <20 kPa i plaquetes >150x10^9/L

es podien estalviar l'endoscòpia de cribratge ja que el risc de varices d'alt risc era baix (<5%)[23,27]. Posteriorment a la publicació de les guies, múltiples estudis han volgut demostrar la seva validesa, confirmant que amb els criteris de Baveno VI es poden estalviar entre un 10-30% d'endoscòpies amb un risc baix de no detectar varices d'alt risc[37,38]. No obstant, al voltant d'un 30-40% d'endoscòpies continuen essent innecessàries tot i aplicant aquests criteris[39].

1.5.3 Pronòstic de la malaltia hepàtica crònica

Fa anys, un estudi retrospectiu va correlacionar el pronòstic de la malaltia hepàtica amb els valors de l'elastografia hepàtica[40]. Posteriorment, diversos estudis han estudiat la capacitat de l'ET per predir descompensacions. S'ha vist que els pacients amb ET >21.1 kPa tenen un major risc de desenvolupar complicacions[41].

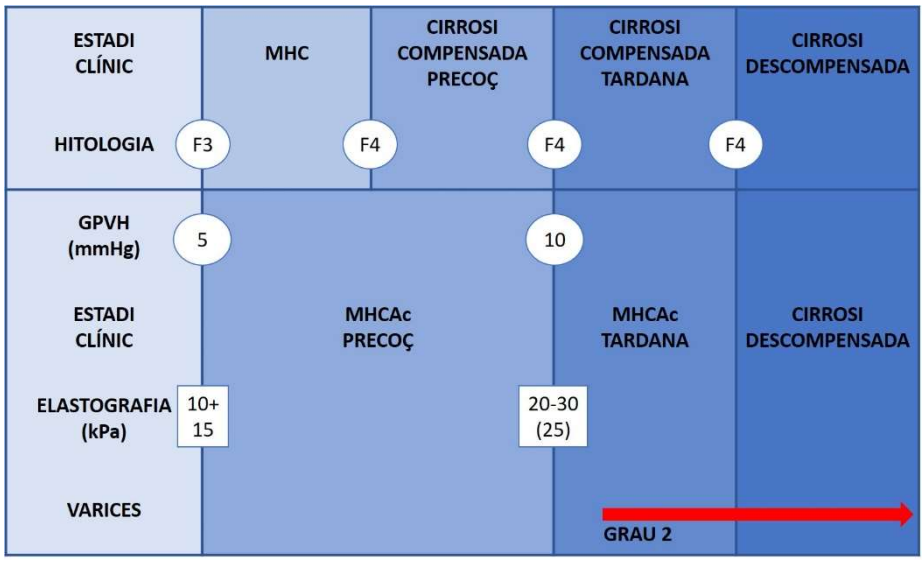

Figura 2. Definició dels diferents estadis de la malaltia hepàtica crònica avançada. Modificat de Pons, Augustin i Genescà (2017)[42]. GPVH: Gradient de pressió venosa hepàtica; MHC: Malaltia hepàtica crònica; MHCAc: Malaltia hepàtica crònica avançada compensada.

Un valor addicional de l'ET és que es pot repetir diverses vegades durant el seguiment dels pacients amb malaltia hepàtica, pel que s'ha proposat que els canvis dinàmics poden ser útils també per predir l'aparició de complicacions. Així els increments de valors de l'ET han demostrat una associació amb l'aparició de complicacions en pacients amb colangitis biliar primària, colangitis esclerosant primària i pacients amb hepatitis crònica per virus C així com també s'ha vist que hi ha relació amb l'empitjorament de la funció hepàtica en pacients amb MHCAc [43–47]. No obstant, aquests estudis no han sigut validats externament

ni tampoc es coneix el temps per repetir l'ET i la magnitud del canvi per considerar-la significativa.

1.6 Impacte del tractament de la malaltia hepàtica: el cas de l'hepatitis C

El tractament específic de l'agent causal de la malaltia hepàtica (virus, alcohol, etc.) pot canviar el curs de la història natural de la malaltia, millorant el pronòstic a llarg termini, sobretot si el tractament es fa en fases precoces de la malaltia hepàtica.

Nombrosos estudis han investigat l'efecte del tractament de l'hepatitis C en l'evolució natural de la malaltia hepàtica. Els primers tractaments basats en interferó i posteriorment interferó pegilat van demostrar ser eficaços en aconseguir la negativització del virus de manera prolongada (resposta viral sostinguda). No obstant, les taxes de resposta viral sostinguda aconseguides amb aquests tractaments era baixa, sobretot, en el cas de pacients amb fibrosi severa o cirrosi i, a més, provocaven un alt nombre d'efectes indesitjables[48,49]. Per contra, la recent introducció dels antivirals orals pel tractament de l'hepatitis C ha fet que es puguin tractar pacients amb malaltia hepàtica crònica avançada, inclús en fases descompensades, aconseguint altes taxes de resposta viral sostinguda amb molt pocs efectes secundaris[50].

1.6.1 Efecte en la regressió de la fibrosi

Molts estudis han demostrat que un cop aconseguida la resposta viral sostinguda amb tractaments basats amb interferó es produeix una milloria de la fibrosi hepàtica[51]. Aquesta milloria de la fibrosi també es pot observar en pacients amb cirrosi hepàtica, tot i que es necessita temps per demostrar aquesta regressió[52,53]. Pel que fa als antivirals orals, degut a la seva recent introducció en pràctica clínica, hi ha pocs estudis que hagin estudiat els efectes en relació a la fibrosi. Tot i així, estudis amb biòpsies aparellades han demostrat que tant la inflamació a curt termini com la fibrosi milloren[54,55]. No obstant, es desconeix la magnitud dels efectes dels antivirals orals en la regressió de la fibrosi a llarg termini.

Estudis previs basats en pacients tractats amb interferó han demostrat que l'elastografia hepàtica disminueix durant el tractament i, en els pacients que mantenen la resposta viral sostinguda, l'elastografia continua disminuint sobretot durant els primers 6 mesos, per després estabilitzar-se o disminuir molt lentament[56,57]. La magnitud del canvi, respecte del

basal, al cap de 6-12 mesos d'haver finalitzat el tractament és de -2,6 kPa (interval de confiança (IC) 95%: -1,9 a -3,4 kPa)[58].

S'ha vist que en pacients que han aconseguit la resposta viral sostinguda l'elastografia perd precisió a l'hora de determinar la presència de cirrosi, com així ho demostrà l'estudi de D'Ambrossio et al., on una cinquena part dels pacients amb ET <12 kPa tenien signes de cirrosi a la biòpsia després de 5 anys d'haver aconseguit la resposta viral sostinguda[59]. Per tant, calen estudis que valorin la precisió diagnòstica de l'elastografia per determinar el grau de fibrosi en pacients tractats.

1.6.2 Efecte en la hipertensió portal

S'ha demostrat que la resposta viral sostinguda disminueix el GPVH, tant en pacients que s'han tractat amb règims amb interferó com, recentment, amb antivirals orals[60–62]. En els pacients tractats amb antivirals orals s'ha vist que en la gran majoria de pacients amb HPCS, al cap de sis mesos d'haver finalitzat el tractament, aquesta persisteix, si bé molts d'ells presenten un descens del GPVH ≥10% respecte a l'inici del tractament[61,62]. Els pacients amb menys probabilitats de millorar el GPVH seran aquells amb albúmina baixa i amb pitjor funció hepàtica[61,63].

Finalment, recentment s'ha vist que hi ha una relació entre el GPVH després d'aconseguir la resposta viral sostinguda i el risc de presentar descompensacions[63]. Així doncs, aquells pacients que no tenen HPCS al seguiment o aquells amb HPCS que han presentat un descens del GPVH ≥10% respecte del valor basal són els que tindran menys risc de presentar descompensacions durant el seguiment.

1.6.3 Efecte en la incidència d'hepatocarcinoma

El tractament amb interferó va demostrar en molts estudis realitzats tant a països asiàtics com en països d'occident que disminueix la incidència d'hepatocarcinoma un cop aconseguida la resposta viral sostinguda. Quan es va iniciar el tractament amb antivirals orals hi va haver certa controvèrsia sobre si aquests augmentaven o no el risc d'hepatocarcinoma sobretot en aquells pacients que ja havien presentat un hepatocarcinoma previ[64,65]. No obstant, hem de tenir en compte que, a diferència dels tractats amb interferó, un gran nombre de pacients amb edat avançada i fases avançades de

la cirrosi s'han tractat amb antivirals orals i han aconseguit una resposta viral sostinguda. Així doncs, els últims metanàlisis realitzats no han objectivat un augment del risc de presentar hepatocarcinoma un cop s'han ajustat els factors com l'edat del pacient o l'estadi de la malaltia[66–69].

2. Justificació de la tesi

2. JUSTIFICACIÓ DE LA TESI

La malaltia hepàtica crònica avançada s'associa a una important morbi-mortalitat degut a què els pacients presenten un major risc de desenvolupar complicacions relacionades amb la hipertensió portal, a un deteriorament de la funció hepàtica i a un increment del risc de presentar hepatocarcinoma.

L'elastografia de transició permet el diagnòstic en fases inicials de la malaltia hepàtica crònica avançada, quan els pacients estan encara asimptomàtics. Tot i que aquests pacients tenen risc de presentar HPCS, la prevalença d'aquesta és molt menor en comparació en poblacions amb cirròtics que ja presenten signes clínics evidents i això fa que també el risc de presentar varices d'alt risc sigui menor. Les guies de Baveno VI han establert que els pacients amb malaltia hepàtica crònica amb valors d'elastografia <20 kPa i xifra de plaquetes >150x10^9/L presenten un baix risc de presentar varices d'alt risc, pel que es poden estalviar l'endoscòpia de cribratge. Aquests criteris permeten estalviar entre un 10-30% d'endoscòpies però encara es practicarien un alt nombre d'endoscòpies innecessàries. El primer estudi que conforma aquesta tesi pretén avaluar la utilitat d'uns nous criteris basats en l'elastografia que permetin estalviar un alt nombre d'endoscòpies, sense augmentar el risc de perdre varices d'alt risc no diagnosticades, i avaluar la utilitat d'aquests nous criteris en les diferents etiologies de malaltia hepàtica crònica.

El tractament amb antivirals orals pel virus de l'hepatitis C ha demostrat ser eficaç degut a l'alta taxa de respostes virals sostingudes, pràcticament sense efectes secundaris, inclús en pacients amb malaltia hepàtica crònica avançada. Degut a la seva recent introducció en pràctica clínica, no es coneixen els seus efectes a curt i mitjà termini pel que fa al pronòstic en pacients amb MHCAc. El segon estudi de la present tesi pretén estudiar els canvis dinàmics pel que fa a l'elastografia hepàtica i esplènica durant el tractament antiviral oral en aquest grup de població per tal de determinar quines implicacions té en el futur seguiment d'aquests pacients. El tercer i últim estudi, estudia la incidència de complicacions en els pacients amb MHCAc per hepatitis C un cop han aconseguit una resposta viral sostinguda i quins predictors s'associen al risc de presentar aquestes complicacions.

3. Objectius

3. OBJECTIUS

3.1 Objectiu principal

- Avaluar la capacitat de l'elastografia de transició en predir complicacions (varices, descompensacions o hepatocarcinoma) en pacients amb MHCAc, combinada amb altres exploracions complementàries.

3.2 Objectius secundaris

- Avaluar la utilitat d'uns nous criteris per descartar la presència de varices d'alt risc, basats en l'elastografia, en les diferents etiologies de la malaltia hepàtica crònica.

- Avaluar els canvis precoços en l'elasticitat hepàtica i esplènica en pacients amb MHCAc tractats amb antivirals orals pel virus de l'hepatitis C.

- Descriure la incidència de complicacions en pacients amb MHCAc per virus de l'hepatitis C que han aconseguit la resposta viral sostinguda després del tractament amb antivirals orals.

- Dissenyar un model pronòstic senzill d'utilitzar en pràctica clínica per a predir el risc de complicacions en pacients amb MHCAc tractats amb antivirals orals per l'hepatitis C.

4. Metodologia

4. METODOLOGIA

4.1 Estudi 1: Nous criteris no invasius pel cribratge de varices en pacients amb malaltia hepàtica crònica avançada compensada

4.1.1 Introducció

En el moment de la realització del primer estudi d'aquesta tesi, la validesa dels criteris de Baveno VI (elastografia <20 kPa i plaquetes >150x10^9/L) havia estat demostrada en diferents estudis[70–72], però encara fins a un 40% de les endoscòpies realitzades eren innecessàries degut a la baixa prevalença de varices d'alt risc en pacients amb MHCAc (<10%). Posteriorment, s'havien proposat diversos mètodes per millorar el número d'endoscòpies estalviades: l'estudi Anticipate[27] proposà un model continu de predicció del risc; d'altres afegir el Model For End-Stage Liver Disease (MELD) de 6 punts[73] i d'altres, canviar els diferents punts de tall de plaquetes i valors d'ET, però cap d'aquests mètodes havien estat validats en altres cohorts ni tampoc en les diferents etiologies de la malaltia hepàtica crònica.

4.1.2 Hipòtesis

És possible millorar els criteris de Baveno VI utilitzats en el cribratge de varices en pacients amb MHCAc, utilitzant la xifra de plaquetes i valors d'ET, essent també vàlids en la majoria d'etiologies.

4.1.3 Objectius

- Buscar uns nous criteris que permetin augmentar el número d'endoscòpies estalviades mantenint un risc baix de varices d'alt risc no diagnosticades (<5%).
- Analitzar la validesa dels nous criteris en les etiologies més freqüents de malaltia hepàtica crònica.
- Validar els altres criteris proposats en diferents estudis[27,34–36,73,74].

4.1.4 Pacients i mètodes

Vam dissenyar un estudi retrospectiu i multicèntric utilitzant 3 cohorts diferents amb pacients amb MHCAc, definida segons Baveno VI amb un valor d'ET ≥10 kPa, que tenien

dades d'endoscòpia i elastografia hepàtica amb un màxim de 12 mesos entre ambdues proves.

Les cohorts utilitzades i la seva finalitat van ser: 1) la cohort Anticipate formada per pacients de diferents etiologies procedents de centres europeus i del Canadà, que es va utilitzar per validar els criteris de Baveno VI i per explorar els millors criteris per aconseguir l'objectiu principal de l'estudi; 2) la cohort Londres que incloïa pacients de diferents etiologies de dos hospitals de Londres i 3) la cohort Vall d'Hebron formada per 117 pacients amb infecció crònica per hepatitis C que no s'havien tractat prèviament. Aquestes dues últimes van servir com a cohorts de validació. Finalment es van validar els nous criteris, anomenats Expanded-Baveno VI, en les diferents etiologies.

Per aquest estudi, es van definir les varices d'alt risc com aquelles varices grau I amb signes vermells, les varices grau II i les varices grau III, totes elles amb indicació de tractament profilàctic. El risc acceptable de varices d'alt risc no diagnosticades mitjançant els criteris de diagnòstic no invasiu fou <5%.

4.2 Estudi 2: Evolució de l'elastografia hepàtica i esplènica en pacients amb malaltia hepàtica crònica avançada compensada tractats amb antivirals orals

4.2.1 Introducció

El tractament amb antivirals orals pel virus de l'hepatitis C va ser introduït el 2015 a Espanya. Aquests tractaments van demostrar ser molt efectius al demostrar un alt percentatge de respostes virals sostingudes, pràcticament sense efectes secundaris. Això va permetre que pacients amb malaltia hepàtica crònica avançada poguessin ser tractats de manera efectiva. Tot i que estudis previs en pacients tractats amb interferon havien demostrat que la resposta viral sostinguda s'acompanyava d'una milloria de la fibrosi i del GPVH, es desconeixien els efectes a curt termini amb el tractament amb antivirals orals. En aquest estudi, s'estudià els canvis de l'elastografia hepàtica i esplènica durant i després del tractament amb antivirals orals, com a marcadors indirectes d'inflamació/fibrosi i d'hipertensió portal, respectivament.

4.2.2 Hipòtesis

L'elastografia hepàtica i esplènica seran útils per valorar els canvis precoços pel que fa a la inflamació que es produeix durant el tractament amb antivirals orals.

4.2.3 Objectius

- Avaluar els canvis d'elastografia hepàtica i esplènica que es produeixen en pacients amb MHCAc tractats amb antivirals orals per tal de conèixer els factors que determinen aquests canvis i les seves implicacions en el seguiment dels pacients tractats del virus de l'hepatitis C.

4.2.4 Pacients i mètodes

En aquest estudi prospectiu i unicèntric vam incloure tots els pacients amb MHCAc per hepatitis C, definida pels criteris de Baveno VI amb un valor d'ET ≥10 kPa, que iniciaven tractament amb els nous antivirals orals a partir de gener de 2015.

En tots els pacients se'ls practicà una elastografia hepàtica i esplènica i una analítica a nivell basal, a les 4 setmanes, al final del tractament i a les 24 i 48 setmanes després d'haver finalitzat el tractament. També se'ls practicà una ecografia cada 6 mesos segons pràctica clínica habitual.

Per a realitzar l'elastografia esplènica utilitzàrem el Fibroscan 502 Touch®, prèvia localització de la melsa mitjançant un petit ecògraf portàtil (Vscan®, General Electric Healthcare, Wisconsin), aplicant els mateixos criteris de qualitat de la prova que s'han establert per l'elastografia hepàtica.

Per calcular la mostra, vam tenir en compte que la milloria de l'elastografia (definida com un descens del 10% des de l'inici fins al final del tractament) succeiria en el 60% dels pacients amb una amplitud de l'interval de confiança del 30% (45-75%). La mida de la mostra requerida fou de 41 pacients.

4.3 Estudi 3: Predicció de complicacions mitjançant mètodes no invasius en pacients amb malaltia hepàtica crònica avançada compensada tractats amb antivirals orals

4.3.1 Introducció

Els antivirals orals pel virus de l'hepatitis C han demostrat ser eficaços en diferents estadis de la malaltia hepàtica (des de pacients amb fibrosi lleu fins a pacients amb cirrosi descompensada). Molts dels pacients, un cop aconseguida la curació, podran esser donats d'alta del seguiment. Per tant, és important conèixer quins pacients són els que tenen risc de desenvolupar complicacions un cop han aconseguit la resposta viral sostinguda i quins no. La població de pacients amb MHCAc són els que generen més dubte en quan al pronòstic un cop tractats, ja que molts d'ells estaran en fases molt inicials de la malaltia hepàtica crònica avançada amb més possibilitats de millorar després del tractament.

4.3.2 Hipòtesis

El pronòstic dels pacients amb MHCAc que aconsegueixin una resposta viral sostinguda millorarà i això es reflectirà amb una milloria de l'elastografia hepàtica i una disminució de les complicacions.

4.3.3 Objectius

- Descriure la incidència de complicacions relacionades amb la malaltia hepàtica en pacients amb MHCAc per hepatitis C que han aconseguit una resposta viral sostinguda amb antivirals orals.
- Identificar paràmetres basats en tècniques no invasives (elastografia i analítica) que permetin predir aquestes complicacions.
- Dissenyar un model senzill que permeti predir el risc de presentar complicacions durant el seguiment dels pacients tractats.

4.3.4 Pacients i mètodes

Vam dissenyar un estudi prospectiu, amb dos centres participants, que incloïa pacients amb MHCAc per hepatitis C que havien sigut tractats amb els nous antivirals i en els quals s'havia confirmat la resposta viral sostinguda 12 setmanes després de finalitzar el tractament. Es van excloure tots aquells pacients dels quals no disposàvem d'una

elastografia abans d'iniciar el tractament, aquells que havien presentat prèviament un hepatocarcinoma o que l'havien desenvolupat abans de confirmar la resposta viral sostinguda, els pacients trasplantats i els pacients amb coinfecció per virus de l'hepatitis B o de la immunodeficiència humana.

Es van obtenir dades a nivell basal d'elastografia (fins a 6 mesos abans d'iniciar el tractament), dades analítiques i d'ecografia. Un cop es confirmà la resposta viral sostinguda es practicaren analítiques i ecografies abdominals cada 6 mesos i una elastografia hepàtica als 12 mesos de finalitzar el tractament.

Durant el seguiment es registraren l'aparició de complicacions relacionades amb la malaltia hepàtica (aparició d'ascites, hemorràgia per varices, síndrome hepato-renal, encefalopatia hepàtica o hepatocarcinoma). També es va registrar la mortalitat. Els pacients es van seguir fins a l'aparició de la primera complicació, la mort o el 31 de desembre de 2018. Les complicacions relacionades amb la hipertensió portal foren analitzades separadament del CHC degut a la seva diferent patogènia.

Per tal d'identificar predictors de complicacions es realitzà un anàlisi univariat i, posteriorment, un anàlisi multivariat mitjançant un model de Cox. Amb l'ajuda del model multivariat es construí un nomograma per predir el risc d'aparició d'hepatocarcinoma durant el seguiment.

5. Resultats

5. RESULTATS

5.1 Estudi 1

En total a l'estudi es van incloure 925 pacients: 499 de la cohort Anticipate, 309 de la cohort de Londres i 117 pacients de la cohort de Vall d'Hebron. La prevalença de varices fou de 34,8% amb un 9,9% de varices d'alt risc. En la cohort Anticipate la prevalença de varices d'alt risc fou del 14%, en la de Londres del 4,5% i en la de Vall d'Hebron del 7,7%.

Quan vam avaluar els criteris de Baveno VI (elastografia <20 kPa i plaquetes >150x10^9/L) en la cohort Anticipate, dels 499 pacients, 68 pacients (14%) complien els criteris per no fer l'endoscòpia i d'aquests 2 pacients (3%) tenien varices d'alt risc. Per tant, vam veure que aquests criteris eren vàlids però el nombre d'endoscòpies estalviades era baix.

Al explorar nous punts de tall per augmentar el número d'endoscòpies estalviades, alguns d'ells proposats en estudis previs[35,36,74,75], vam veure que el millor criteri era el d'elastografia <25 kPa i plaquetes >110x10^9/L. Amb aquests nous criteris (Expanded-Baveno VI) es permetien estalviar un 32% d'endoscòpies amb un risc de no diagnosticar varices d'alt risc de l'1,9% (Taula 2). Quan vam explorar aquests criteris en la resta de la cohort, el número d'endoscòpies estalviades era del 40% (367/925) amb un risc de no diagnosticar varices d'alt risc de l'1,6% (6/367). Si afegíem el criteri de MELD=6, proposat per Jangouk et al[73], en els pacients que no complien els criteris Expanded-Baveno VI aconseguíem, finalment, estalviar un 45,8% d'endoscòpies amb un risc baix de perdre varices de risc (1,7%).

	Endoscòpies estalviades N=499	Varices de risc no diagnosticades
Plaquetes >150 + elastografia <20 kPa[23]	68 (14%)	2/68 (3%)
Plaquetes >150 + elastografia <25 kPa[35]	88 (17,5%)	3/88 (3,4%)
Plaquetes >150 + elastografia <30 kPa[74]	116 (23%)	6/116 (5%)
Plaquetes >125 + elastografia <25 kPa[74]	126 (25%)	3/126 (2,4%)
Plaquetes >120 + elastografia <25 kPa[75]	139 (28%)	3/139 (2,2%)
Plaquetes >110 + elastografia <25 kPa	**158 (32%)**	**3/158 (1,9%)**
Plaquetes >100 + elastografia <25 kPa[36]	182 (36,5%)	9/182 (5%)

Taula 2. Regles per augmentar el número d'endoscòpies estalviades. En negreta el criteris expandits (Expanded- Baveno VI).

Els criteris Expanded-Baveno VI van demostrar ser vàlids en les diferents etiologies.

Etiologia	Endoscòpies estalviades	Varices de risc no diagnosticades
Hepatitis C, n=584	236/584 (40%)	3/236 (1,2%)
Alcohol, n=127	49/127 (38,5%)	0/49 (0%)
EHNA, n=90	44/90 (49%)	1/44 (2,2%)
Hepatitis B, n=61	21/61 (34,4%)	1/21 (4,7%)
CBP/CEP, n=20	12/20 (60%)	1/12 (8,3%)
Hepatitis C + Alcohol, n=19	5/19 (26%)	0/5 (0%)

Taula 3. Validació dels criteris Expanded-Baveno VI (elastografia <25 kPa + plaquetes >110x10^9/L. EHNA: Esteatohepatitis no alcohòlica; CBP: Colangitis biliar primària; CEP: Colangitis esclerosant primària.

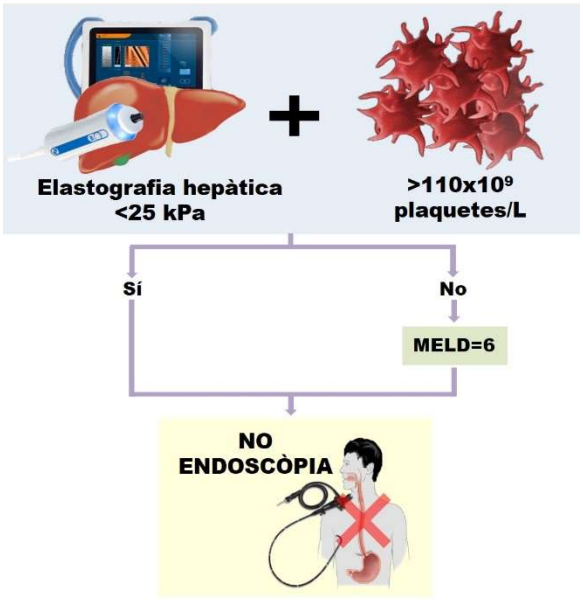

Figura 3. Algoritme proposat segons els criteris Expanded-Baveno VI.

5.2 Estudi 2

En aquest estudi vam incloure 41 pacients, la majoria d'ells genotip 1 (87,8%).

Característiques	Pacients N=41
Homes, *n (%)*	20 (48,8)
Edat, *anys*	68 (59-75)
IMC, *Kg/m²*	26,6 (24,9-29,4)
Genotip, *n (%)* 1-4 3	 39 (95,1) 2 (4,9)
No tractament previ, *n (%)*	18 (43,9)
Mida melsa, *cm*	12.9 (11,5-13,7)
Varices N=31, *n (%)* No/I/II-III	 15 (48,4)/14 (45,2)/2 (6,5)
RNA hepatitis C, *Log₁₀ IU/mL*	6,3 (6,0-6,6)
Elastografia hepàtica, *kPa*	20,8 (16,3-29,5)
Elastografia esplènica, *kPa*	45,7 (26,6-65,2)
Plaquetes, x*10⁹/L*	106,5 (82-142,5)
ALT, *IU/L*	78 (55-135)
Bilirubina, *mg/dL*	0,89 (0,68-1,11)
Albúmina, *g/dL*	3,84 (3,64-4,12)

Taula 4. Característiques basals dels pacients. Variables contínues expressades en mediana (P25-P75). IMC: Índex de massa corporal; ALT: Alanina-aminotransferasa.

Durant el tractament vam observar una ràpida milloria de la majoria de paràmetres bioquímics (plaquetes, transaminases i de l'albúmina). No obstant, durant el tractament vam observar una disminució de l'hemoglobina i un augment de la bilirubina, degut a l'hemòlisi provocada per la ribavirina, que milloraren un cop finalitzat el tractament.

	Basal	Setmana 4	Final de tractament	Setmana 24-post	Valor P
Hemoglobina (g/dL)	14,4 (12,9-15,7)	12,1 (11,4-13,2)	11,8 (11-13,0)	14 (13-15,6)	<0,001
Plaquetes (x10^9/L)	106,5 (82-142,5)	139,5 (107,5-166,5)	135,5 (106,5-171,5)	122 (104-161)	<0,001
Bilirubina (mg/dL)	0,89 (0,68-1,11)	1,41 (1,05-2,5)	1,16 (0,91-1,8)	0,73 (0,57-0,86)	<0,001
ALT (UI/L)	78 (55-135)	18 (15-21)	16 (15-20)	18 (16-23)	<0,001
AST (UI/L)	92 (66-129)	26 (23-32)	27 (23-30)	26 (23-32)	<0,001
GGT (UI/L)	92 (61-131)	38 (31-50)	28 (22-37)	35 (24-52)	<0,001
Albúmina (g/dL)	3,84 (3,64-4,12)	4,04 (3,65-4,20)	4 (3,60-4,28)	4,20 (3,90-4,50)	<0,001

Taula 5. Evolució dels paràmetres de laboratori durant el tractament i posterior a aquest (setmana 24-post). Valors expressats en mediana (P25-P75). ALT: Alanina-aminotransferasa; AST: Aspartat-aminotransferasa; GGT: Gamma-glutamil-transferasa.

Durant el tractament, l'elastografia hepàtica presentà una ràpida milloria durant les primeres 4 setmanes de tractament essent la mediana a l'inici de 20,8 kPa i al final de la quarta setmana de 17,5 kPa (P=0,002). No es van detectar diferències significatives entre la setmana 4 de tractament i el final de tractament essent l'elastografia hepàtica de 17,5 kPa i 18,3 kPa, respectivament (P=0,444). Un cop finalitzat el tractament, l'elastografia hepàtica continuà millorant tot i que aquesta milloria no fou estadísticament significativa (P=0,148). Al final de les 48 setmanes d'haver finalitzat el tractament la mediana d'elastografia hepàtica fou de 14,3 kPa.

Pel que fa a l'elastografia esplènica, també s'objectivà una baixada significativa durant les primeres 4 setmanes respecte a l'elastografia basal, essent la mediana d'elastografia esplènica inicial de 45,7 kPa i a les 4 setmanes de 33,8 kPa (P=0,047), sense observar-se canvis significatius fins al final del tractament. Un cop finalitzat el tractament, l'elastografia esplènica es va mantenir sense canvis essent la mediana de 31,2 kPa al final del seguiment.

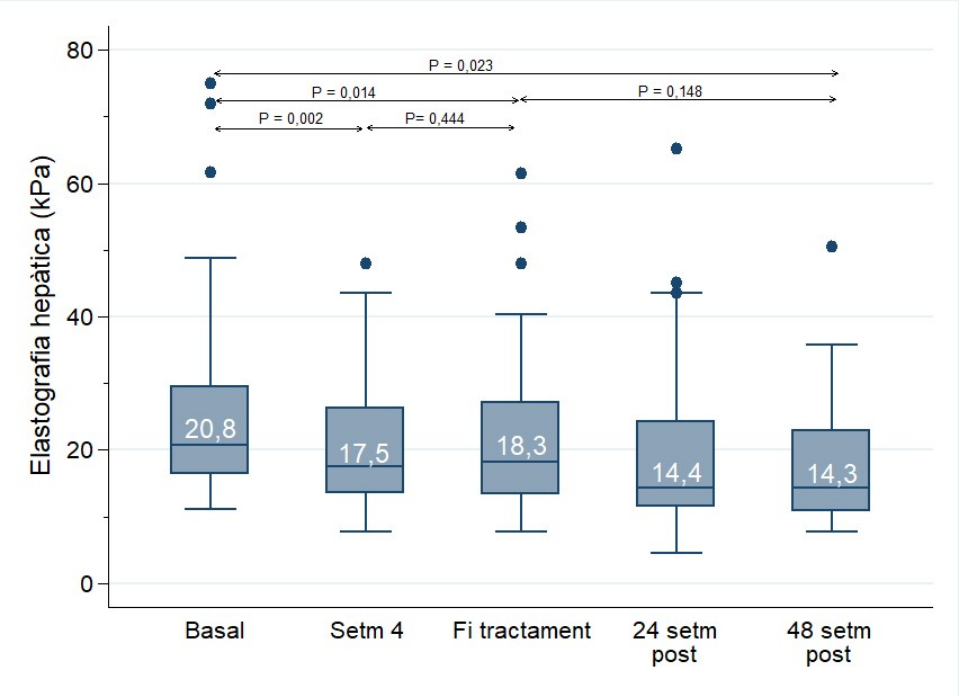

Figura 4. Evolució de l'elastografia hepàtica durant i després del tractament.

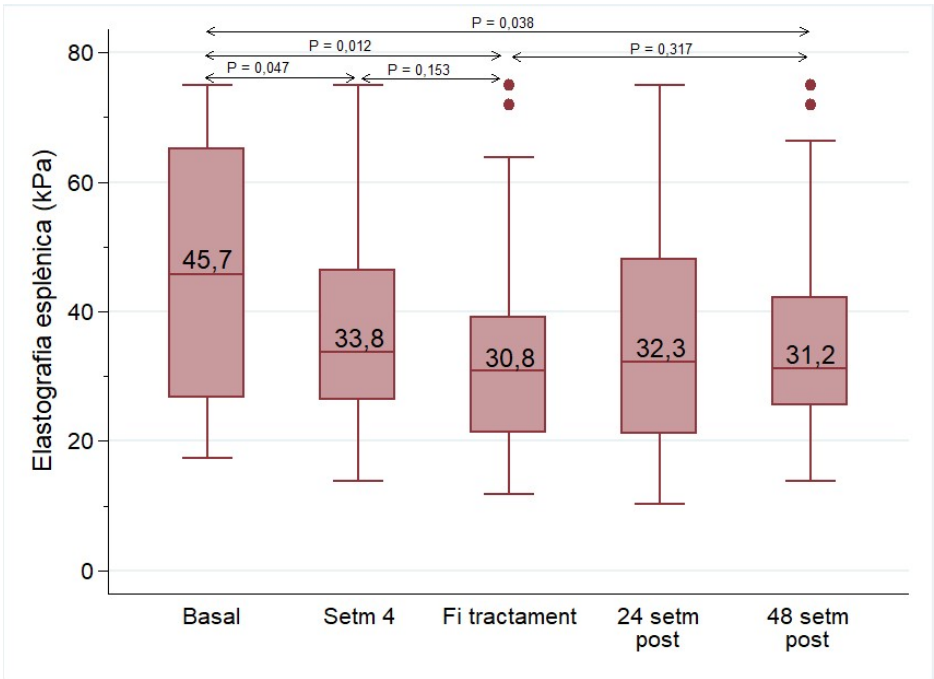

Figura 5. Evolució de l'elastografia esplènica durant i després del tractament.

Un 57,5% dels pacients van presentar una milloria ≥10% de l'elastografia hepàtica. Aquests pacients tenien valors d'elastografia esplènica més baixos, una xifra de plaquetes més alta i nivells més baixos de bilirubina a les 24 setmanes posteriors a finalitzar el tractament, comparat amb aquells pacients en els quals no els millorà l'elastografia.

Els pacients els quals van presentar una milloria de l'elastografia esplènica ≥10% (56,3%) presentaren un major augment de plaquetes durant el seguiment, comparat amb aquells pacient en els quals l'elastografia esplènica no els millorà.

5.3 Estudi 3

Un total de 1563 pacients entre els dos centres van iniciar tractament amb antivirals orals de l'1 de gener de 2015 al 31 de març de 2016, moment en què finalitzà la inclusió. D'aquests, es confirmà la resposta viral sostinguda en 1518 pacients (97,1%), incloent-se finalment 572 pacients.

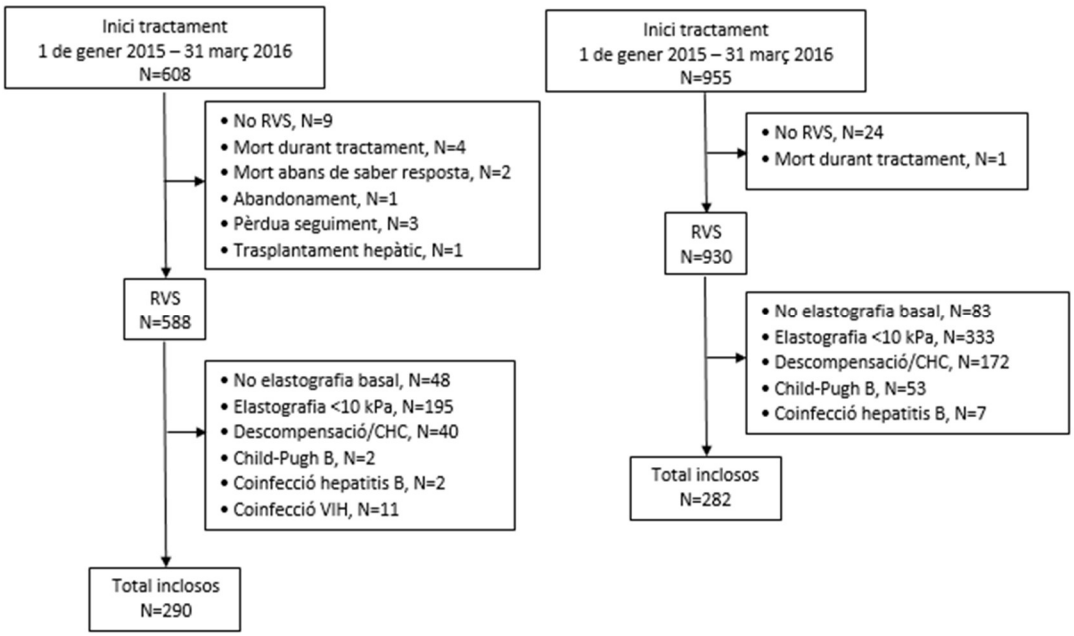

Figura 6. Diagrama de flux dels pacients inclosos a l'estudi. A l'esquerra, pacients de l'hospital Vall d'Hebron i a l'esquerra pacients de l'hospital Clínic. RVS: Resposta viral sostinguda; CHC: Carcinoma hepatocel·lular.

Característiques	Cohort total N=572	Hospital Vall d'Hebron N=290	Hospital Clínic N=282	Valor P
Edat, *anys*	65,2 (55,1-72,3)	65,3 (54,4-73,1)	65,1 (55,8-71,8)	0,895
Índex massa corporal, *kg/m²*	26,1 (24,0-28,7)	26,8 (24,2-29,2)	25,6 (23,7-28,4)	0,105
Homes, *n (%)*	282 (49,3)	144 (49,7)	138 (48,9)	0,864
Diabetis, *n (%)*	125 (21,9)	61 (21)	64 (22,7)	0,632
Hipertensió arterial, *n (%)*	262 (45,8)	135 (46,6)	127 (45)	0,717
Genotip virus C, n (%) 1 2 3 4	 490 (85,8) 10 (1,8) 39 (6,8) 32 (5,6)	 243 (83,8) 5 (1,7) 20 (6,9) 22 (7,6)	 247 (87,9) 5 (1,8) 19 (6,8) 10 (3,6)	0,216
Duració tractament, *n (%)* 12 setmanes 24 setmanes	 447 (78,1) 125 (21,9)	 223 (76,9) 67 (23,1)	 224 (79,4) 58 (20,6)	0,967
Varices*, *n (%)* No Grau I Grau II Grau III	 168 (57,7) 89 (30,6) 8 (2,8) 26 (8,9)	 83 (72,8) 23 (20,2) 7 (6,1) 1 (0,9)	 85 (48) 66 (37,3) 1 (0,6) 25 (14,1)	<0,001
Plaquetes, *x10⁹/L*	129,5 (95,5-176)	142,5 (107-194)	118 (86-152)	<0,001
INR	1,07 (1-1,15)	1,02 (0,96-1,08)	1,12 (1,07-1,19)	<0,001
Bilirubina, *mg/dL*	0,8 (0,6-1,1)	0,8 (0,6-1,0)	0,9 (0,7-1,2)	<0,001
ALT, *IU/L*	86 (58-131)	77 (50-119)	96 (66-143)	0,001
Albúmina, *g/dL*	4,2 (3,9-4,4)	4,1 (3,8-4,3)	4,2 (4-4,4)	<0,001
FIB-4	4,5 (2,6-6,7)	3,7 (2,2-6,0)	5,2 (3,3-7,6)	0,002
Child Pugh, *n (%)* 5 6	 521 (91,1) 51 (8,9)	 261 (90) 29 (10)	 260 (92,2) 22 (7,8)	0,447
Elastografia basal, *kPa*	17,3 (13,5-23,9)	16,2 (12-21,5)	17,6 (14,3-26,3)	0,004
Elastografia ≥20 kPa, *n (%)*	212 (37,1)	90 (31)	122 (43,3)	0,002

Taula 6. Característiques basals dels pacients inclosos a l'estudi 3. Variables contínues expressades en mediana (P25-P75). ALT: Alanina-aminotransferasa. * Endoscòpia basal realitzada en 114 pacients de Vall d'Hebron i 177 de l'Hospital Clínic.

L'elastografia hepàtica millorà durant el seguiment, essent la mediana d'elastografia basal de 17,3 kPa i de 11,1 kPa al final del seguiment (P<0,001). La milloria de l'elastografia, definida com a un descens de ≥20% respecte al valor basal, s'observà en 391 pacients (70%), essent de <10 kPa en quasi un 40% dels pacients de la cohort.

La mediana de seguiment fou de 2,9 anys (rang 0,3-3,8 anys) i durant aquest temps 32 pacients (5,6%) presentaren complicacions relacionades amb la malaltia hepàtica, essent la

complicació més freqüent l'hepatocarcinoma que s'observà en 25 pacients (4,4%) amb una incidència de 1,5/100 pacients-any. Cinc complicacions eren relacionades amb la hipertensió portal (2 hemorràgies per varices i 3 pacients amb ascites). La incidència d'aquestes descompensacions fou de 0,31/100 pacients-any. Finalment, dos pacients van desenvolupar un colangiocarcinoma durant el seguiment (incidència 0,1/100 pacients-any).

Els pacients que es van descompensar per complicacions relacionades amb la hipertensió portal, tots ells tenien una elastografia basal de >20 kPa i només en un d'ells l'elastografia millorà durant el seguiment. La majoria dels pacients tenien plaquetes $<100x10^9$/L i únicament el pacient que presentà la milloria de l'elastografia tenia plaquetes de $160x10^9$/L a nivell basal.

La taula 7 mostra els predictors que s'associaren al risc de presentar hepatocarcinoma durant el seguiment. En l'anàlisi univariat, els factors que s'associaren van ser l'edat, els nivells d'albúmina tant a nivell basal com durant el seguiment a l'any i tenir una elastografia <10 kPa durant el primer any de seguiment. En l'anàlisi multivariat, l'única variable a nivell basal que s'associà amb el risc de presentar hepatocarcinoma fou l'albúmina (Hazard ratio (HR) 0,29; Interval de confiança (IC) 95%: 0,11-0,76; P=0,012). Durant el seguiment, s'associaren al risc de presentar hepatocarcinoma els nivells d'albúmina (HR 0,08; IC 95%: 0,02-0,25; P<0,001) i tenir l'elastografia <10 kPa al final del seguiment (HR 0,33; IC 95%: 0,11-0,96; P=0,042).

Característiques	No CHC N=547	CHC N=25	Valor P	Anàlisi multivariat HR (95% IC; Valor P)
A nivell basal				
Edat, *anys*	65,1 (54,8-72,1)	70,5 (64,2-74,5)	**0,011**	1,04 (1-1,1; P=0,064)
Índex massa corporal, *kg/m²*	26,1 (24-28,7)	26,3 (23,8-29,3)	0,438	---
Homes, *n (%)*	269 (49,2)	13 (52)	0,783	---
Hipertensió arterial, *n (%)*	249 (45,5)	13 (52)	0,526	---
Diabetis, *n (%)*	117 (21,4)	8 (32)	0,210	---
Plaquetes, *x10⁹/L*	129 (96-176)	131 (90-206)	0,305	---
Plaquetes <150x10⁹/L, *n (%)*	347 (63,4)	15 (60)	0,728	---
Bilirubina, *mg/dL*	0,8 (0,6-1,1)	0,9 (0,7-1,2)	0,388	---
ALT, *IU/L*	87 (58-131)	80 (56-119)	0,202	---
Albúmina, *g/dL*	4,2 (3,9-4,4)	3,9 (3,6-4,2)	**0,003**	**0,29 (0,11-0,76; P=0,012)**
FIB4	4,5 (2,6-6,7)	4,5 (2,8-8)	0,745	---
Elastografia basal, *kPa*	17,1 (13,4-23,9)	20,8 (15,1-26,3)	0,245	---
Elastografia basal <20 kPa, *n (%)*	348 (63,6)	12 (48)	0,114	---
A l'any de seguiment				
Índex massa corporal, *kg/m²*	27 (24,6-29,7)	26,4 (25-28)	0,655	---
Plaquetes, *x10⁹/L*	161 (121-215)	126 (110-215)	0,470	---
Bilirubina, *mg/dL*	0,7 (0,5-0,9)	0,7 (0,6-0,8)	0,908	---
Albúmina, *g/dL*	4,4 (4,2-4,6)	4,1 (3,8-4,4)	**<0,001**	**0,08 (0,02-0,25; P <0,001)**
Elastografia al seguiment, *kPa*	10,9 (8-16,5)	17,4 (10,2-21,1)	0,089	---
Delta Elastografia, *%*	-35,3 (-49- -17,3)	-26,5 (-51,7-5,1)	0,355	---
Milloria d'elastografia, *n (%)*	378 (71,2)	13 (56,5)	0,131	---
Elastografia seguiment <10 kPa, *n (%)*	216 (40,7)	4 (17,4)	**0,025**	**0,33 (0,11-0,96; P=0,042)**

Taula 7. Factors associats amb el risc de presentar hepatocarcinoma (CHC). Variables contínues expressades en mediana (P25-P75).

Per tal de construir un model simple per predir el risc de desenvolupar hepatocarcinoma vam categoritzar les variables observades en l'anàlisi multivariable de la manera següent:

- Albúmina basal: <4 g/dL / ≥4 g/dL (punt de tall: mitjana)
- Elastografia a l'any: <10 kPa / 10-20 kPa / ≥20 kPa.
- Albúmina a l'any: <4,4 g/dL / ≥4,4 g/dL (punt de tall: mitjana)

Així doncs, el risc de presentar hepatocarcinoma si l'albúmina basal era <4 g/dL era més alt que en els pacients amb albúmina ≥4 g/dL (HR 3,27; IC 95%: 1,45-7,36; P=0,0004); si l'albúmina a l'any de seguiment era de <4,4 g/dL el risc comparat amb els que la tenien ≥4,4 g/dL fou de HR 2,36 (IC 95%: 1,02-5,47; P=0,046); i, finalment, segons el nivell de l'elastografia a l'any, els pacients amb elastografia entre 10-20 kPa tenien un major risc de

presentar hepatocarcinoma que els pacients amb elastografia <10 kPa, tot i que la diferència no era estadísticament significativa (HR 2,48; 95% IC: 0,79-7,8; P=0,120), mentre que el risc fou de HR 4,53 (IC 95%: 1,36-15,08; P=0,014) en els pacients amb elastografia ≥20 kPa comparat amb els pacients amb elastografia <10 kPa.

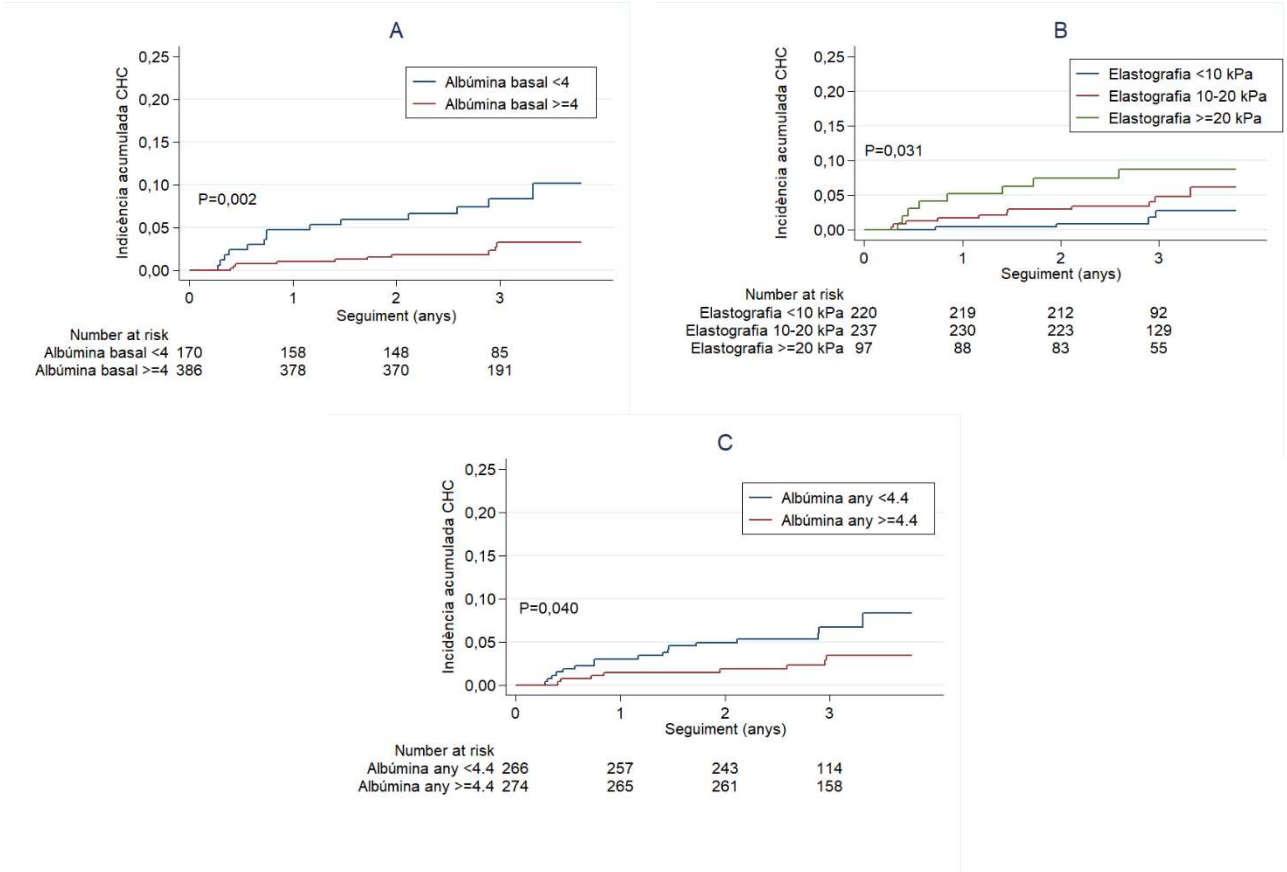

Figura 7. Incidència acumulada d'hepatocarcinoma (CHC) segons diferents subgrups: A) albúmina basal; B) elastografia a l'any; c) albúmina a l'any.

Combinant les variables albúmina i elastografia a l'any de seguiment per tal de combinar variables recollides al mateix moment, vam poder identificar, també, diferents grups de risc de presentar hepatocarcinoma, aconseguint identificar dos grups de risc: baix risc (elastografia a l'any <10 kPa o elastografia entre 10-20 kPa i albúmina a l'any ≥4,4 g/dL) i alt risc (elastografia ≥20 kPa o elastografia entre 10-20 kPa i albúmina a l'any <4,4 g/dL) (Taula 8). Finalment, amb els dos predictors vam construir un nomograma per predir la probabilitat de presentar hepatocarcinoma (Figura 8).

Categoria	Número de CHC	Pacients-any	Incidència/100 pacients-any
Albúmina al seguiment:			
≥4,4 g/dL	8	825	1,0
<4,4 g/dL	17	750	2,3
Elastografia al seguiment:			
LSM <10 kPa	4	593	0,7
LSM 10-20 kPa	11	645	1,7
LSM ≥20 kPa	8	250	3,2
Combinació elastografia-albúmina			
Elastografia <10 kPa			
+ ≥4,4 g/dL	3	351	0,9
+ <4,4 g/dL	1	271	0,4
Elastografia 10-20 kPa			
+ ≥4,4 g/dL	2	368	0,5
+ <4,4 g/dL	9	318	2,8
Elastografia ≥20 kPa			
+ ≥4,4 g/dL	2	106	1,9
+ <4,4 g/dL	6	161	3,7

Taula 8. Incidència d'hepatocarcinoma (CHC) segons diferents subgrups.

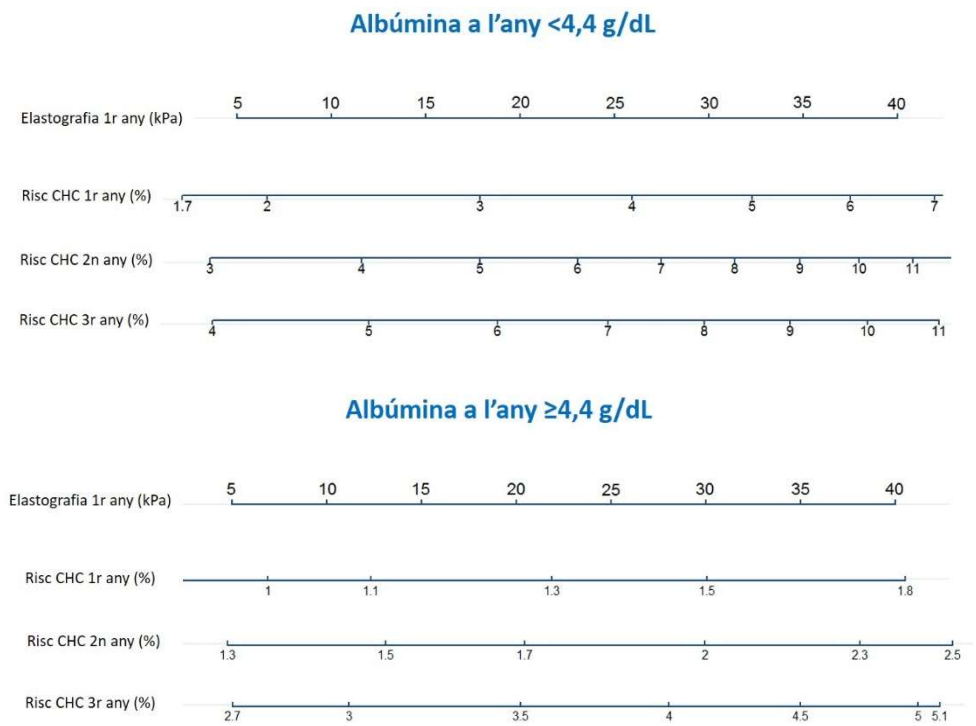

Figura 8. Nomograma per predir el risc de hepatocarcinoma (CHC) segons els nivells d'albúmina i valors d'elastografia a l'any de seguiment.

6. Discussió

6. DISCUSSIÓ

En el present treball s'estudia la utilitat de l'elastografia hepàtica amb diferents finalitats en el seguiment dels pacients amb MHCAc. El primer estudi demostra la utilitat d'uns nous criteris per detectar de manera no invasiva una població amb un baix risc (<5%) de tenir varices d'alt risc en les principals etiologies. El segon i tercer estudis, molt relacionats entre ells, valoren els canvis dinàmics de l'elastografia durant el tractament amb antivirals orals per l'hepatitis C i durant el seguiment posterior i com aquests canvis poden ser útils per predir el pronòstic dels pacients tractats.

6.1 Detecció d'una població amb baix risc de varices que precisen profilaxi

El consens de Baveno VI aportà grans canvis ja que va introduir alguns conceptes nous en relació amb l'increment de l'ús de tècniques no invasives, sobretot l'ET. Un cop publicats els criteris de Baveno VI pel cribratge de varices es va veure que, tot i que eren vàlids, eren massa conservadors ja que la quantitat d'endoscòpies estalviades era molt baixa en algunes sèries. Els resultats del primer estudi d'aquesta tesi van demostrar que aquests criteris es podien canviar per uns altres de menys conservadors, augmentant el nombre d'endoscòpies estalviades a quasi un 50% amb un risc baix de perdre varices d'alt risc (<2%).

Aquests nous criteris es van validar en el primer estudi, aplicant-los a una població de més de 900 pacients amb MHCAc de diferents etiologies amb una prevalença de varices d'alt risc del 9,9%. Posteriorment a la publicació de l'article, múltiples estudis han demostrat la validesa dels criteris Expanded-Baveno VI i també un metanàlisi ha suggerit la seva utilitat[38,76–82]. Així doncs, en una població mixta de pacients, predominantment amb hepatitis C no tractada, i una prevalença de varices d'alt risc del 12,1% amb els criteris de Baveno VI estalviaríem un 21,2% d'endoscòpies, en canvi amb els criteris expandits un 41,6% sense superar en cap dels dos casos el risc acceptat de varices d'alt risc no diagnosticades (<5%) (Taula 9).

Estudi	N	Varices d'alt risc	Etiologia	Criteris Baveno VI ET <20 + Plaq >150		N	Expanded-Baveno VI ET <25 + Plaq >110	
				FGS estalviades	VAR perdudes		FGS estalviades	VAR perdudes
Estudi 1	925	92 (10%)	Mixta (59% VHC)	198 (21,4%)	3 (1,5%)	925	367 (40%)	6 (1,6%)
Bae, et al,[82]	282	55 (19,5%)	Mixta (59% VHB)	78 (27,7%)	3 (3,8%)	282	146 (51,8%)	10 (6,8%)
Calvaruso, et al,[78]	1381	130 (9,4%)	100% VHC	216 (15,6%)	5 (2,3%)	1381	497 (36%)	13 (2,6%)
Colecchia, et al,[77]	498	100 (20,1%)	Mixta (85% VHC)	102 (20,5%)	1 (1%)	498	202 (40,6%)	8 (4%)
Colecchia, et al,; Dajti, et al[76,77]	115	15 (13%)	Mixta (41% VHC)	19 (16,5%)	0	115	34 (29,6%)	2 (6%)
Moctezuma, et al,[80]	227	28 (12,3%)	65% CBP, 35% CEP	82 (36,1%)	0	227	122 (53,7%)	6 (4,9%)
Petta, et al, (M)[81]	338	45 (13,3%)	100% EHNA	113 (33,4%)	5 (4,4%)	338	183 (54,1%)	8 (4,4%)
Petta, et al, (XL)[81]	---	14 (10,1%)	100% ENHA	---	---	138	64 (46,4%)	1 (1,6%)
Tosetti, et al,[79]	442	31 (7%)	Mixta (69% VHC)	86 (19,5%)	0	442	193 (43,7%)	0
TOTAL	**4208**	**510 (12,1%)**	**Mixta (64% VHC)**	**894 (21,2%)**	**17 (1,9%)**	**4346**	**1808 (41,6%)**	**54 (3%)**

Taula 9. Validació externa dels criteris de Baveno VI i dels Expanded-Baveno VI. ET: Elastografia de transició; Plaq: Plaquetes; N: Número de pacients; FGS: Endoscòpia; VAR: Varices d'alt risc; VHC: Hepatitis C; VHB; Hepatitis B; CBP: Colangitis biliar primària; CEP: Colangitis esclerosant primària; EHNA: Esteatohepatitis no alcohòlica.

Una altra informació rellevant de l'estudi 1 és que els criteris són vàlids en la majoria d'etiologies. En els estudis previs a la publicació dels criteris de Baveno VI, les regles que s'havien proposat per identificar pacients amb varices eren basats en poblacions majoritàriament amb hepatitis crònica per virus C. En l'estudi, tot i que la majoria de pacients continuaven essent virus C, vam intentar incloure pacients d'altres etiologies principalment per alcohol i esteatohepatitis no alcohòlica. Tot i així, vam veure que en pacients amb malalties colestàsiques i probablement hepatitis B els nous criteris Expanded-Baveno VI podrien sobrepassar el risc de perdre varices d'alt risc amb un 8,3% i un 4,7%, respectivament. En els posteriors estudis de validació hem pogut observar que els criteris Expanded-Baveno VI, efectivament, en pacients amb colangitis biliar primària i hepatitis B el risc de perdre varices d'alt risc és superior al 5%. Això possiblement es pugui explicar per la major prevalença d'hipertensió portal en estadis pre-cirròtics en les dues etiologies (Taula 10).

Etiologia	N	Criteris Baveno VI ET <20 + Plaq >150		N	Expanded-Baveno VI ET <25 + Plaq >110	
		FGS estalviades	VAR perdudes		FGS estalviades	VAR perdudes
Hepatitis C	1510	267 (17,7%)	5 (1,9%)	2011	759 (37,7%)	17 (2,2%)
Hepatitis B	170	45 (26.5%)	3 (6.7%)	227	101 (44.5%)	7 (6.9%)
Viral	351	71 (20.2%)	0	351	156 (44.4%)	0
Alcohol	91	22 (24.2%)	0	206	83 (40.3%)	2 (2.4%)
EHNA	420	134 (31.9%)	5 (3.7%)	648	334 (51.5%)	11 (3.3%)
CBP	147	58 (39.5%)	0	147	86 (58.5%)	5 (5.8%)
CEP	80	24 (30%)	0	80	36 (45%)	1 (2.8%)

Taula 10. Validació externa dels criteris de Baveno VI i Expanded-Baveno VI en les diferents etiologies. ET: Elastografia de transició; Plaq: Plaquetes; N: Número de pacients; FGS: Endoscòpia; VAR: Varices d'alt risc; EHNA: Esteatohepatitis no alcohòlica; CBP: Colangitis biliar primària; CEP: Colangitis esclerosant primària.

Dues coses a tenir present en l'estudi 1 són la prevalença de varices en la població i la variabilitat dels factors utilitzats en els criteris (plaquetes i elastografia).

Pel que fa a la prevalença de varices d'alt risc (probabilitat pre-test), sabem que aquesta pot interferir en els resultats obtinguts a l'hora d'aplicar els criteris (probabilitat post-test). Un pot suggerir que la baixa prevalença de varices d'alt risc en la població estudiada en l'estudi 1 pot haver facilitat la validació dels resultats. No obstant, hem de tenir en compte que on s'obté un major benefici a l'hora d'estalviar-se endoscòpies és en poblacions amb baixa prevalença de varices (MHCAc precoç, amb valors d'elastografia entre 10-25 kPa). Per tant, no té sentit aplicar aquests criteris en poblacions Child Pugh B o amb cirrosi descompensada els quals tenen un alt risc de presentar varices.

Els pacients amb valors de plaquetes o d'elastografia pròxims als punts de tall poden augmentar el risc de no diagnosticar varices d'alt risc degut a la variabilitat de les proves[83,84]. És per això que, en aquests casos, seria recomanable repetir les proves en un curt període de temps per confirmar si els pacients segueixen tenint criteris de baix risc.

En resum, l'estudi 1 demostra que els criteris de Baveno VI podrien ser modificats pels criteris d'Expanded-Baveno VI ja que augmenten el número d'endoscòpies que ens estalviem amb un risc baix de no diagnosticar varices d'alt risc en la majoria d'etiologies.

6.2 Canvis dinàmics de l'elastografia hepàtica i esplènica amb els nous antivirals orals

Els nous antivirals orals pel tractament de l'hepatitis C són molt efectius, causant un ràpid control de la replicació viral, amb normalització de les transaminases i, per tant, de la inflamació. Aquest mecanisme d'acció és clarament diferent de les teràpies prèvies basades amb interferó on el procés de desinflamació i control de la infecció era molt més lent.

En el segon estudi, aquests efectes ràpids dels antivirals orals es veuen reflectits en una ràpida milloria de l'elastografia hepàtica i esplènica, que ocorre a les 4 setmanes o potser abans, i el més important, aquesta ràpida milloria explicaria quasi la majoria del canvi total al llarg del seguiment total de 15 mesos. És a dir, quasi un 75% del descens total de l'elastografia hepàtica, s'observà durant les 4 primeres setmanes de tractament. Això, juntament amb la milloria de transaminases, suggeriria que el principal motiu d'aquest descens de l'elastografia és com a conseqüència d'una milloria de la inflamació més que no pas una milloria de la fibrosi. Això explicaria gran part de les discrepàncies observades entre la biòpsia hepàtica i l'elastografia. Aquest fet va ser demostrat per D'Ambrossio et al.[59] qui observà que fins a un 21% dels pacients curats de l'hepatitis C amb elastografies <12 kPa al seguiment (mitjana 61 mesos) tenien signes de cirrosi a la biòpsia.

De forma similar, l'elastografia esplènica millorà a les primeres 4 setmanes sense presentar més canvis durant el seguiment, suggerint que aquest canvi no només es deu a la milloria de la congestió esplènica i la hipertensió portal sinó a una milloria de la inflamació, també esplènica, doncs la melsa es pot considerar com un gran gangli limfàtic.

En resum, el segon estudi aporta informació valuosa dels canvis dinàmics observats de l'elastografia hepàtica i esplènica durant i després del tractament amb antivirals orals. L'estudi suggereix que la majoria dels canvis són deguts a una milloria de la inflamació tant hepàtica com esplènica i que, per tant, aquest fet s'ha de tenir en compte en el futur seguiment dels pacients, doncs tot i observar grans millories de l'elastografia, els pacients

amb MHCAc s'hauran de continuar seguint fins que estudis posteriors no demostrin si es produeixen canvis en la fibrosi o en el pronòstic significatius.

6.3 Pronòstic dels pacients tractats amb antivirals orals a curt-mitjà termini

Degut a la recent introducció dels antivirals orals per al tractament de l'hepatitis C, en el moment de la realització del tercer estudi, es desconeixien els efectes a curt-mitjà termini i les seves implicacions en el pronòstic de la malaltia hepàtica. En el tercer estudi, vam poder estudiar l'aparició de complicacions relacionades amb la malaltia hepàtica en una cohort gran de pacients amb MHCAc.

El primer que vam veure és que la incidència de complicacions després d'aconseguir la resposta viral sostinguda va ser relativament baixa, essent la complicació més freqüent l'aparició d'hepatocarcinoma (representant el 78% de les complicacions observades). Estudis prèviament publicats, havien objectivat un augment de risc de presentar hepatocarcinoma segons el valor d'elastografia hepàtica basals, essent el punt de tall ≥21.3 kPa o ≥30 kPa segons l'estudi[85,86]. En canvi, en el nostre estudi l'elastografia basal no es relacionà com a factor de risc d'hepatocarcinoma, doncs 13 pacients amb hepatocarcinoma tenien elastografies ≥20 kPa i els 12 restants, <20 kPa. Una explicació d'aquestes diferències és que els estudis mencionats incloïen pacients amb Child Pugh B, probablement amb major fibrosi hepàtica i, per tant, majors valors d'elastografia, fet que podria sobreestimar l'efecte de l'elastografia a l'hora de predir el risc d'hepatocarcinoma.

En el segon estudi havíem comprovat que gran part dels canvis que es produïen en l'elastografia eren deguts a una milloria ràpida de la inflamació. I aquesta és probablement l'explicació del perquè la milloria de l'elastografia durant el seguiment (definida tant com descens de ≥20% respecte al valor basal com de ≥30%) tampoc s'associà a una disminució del risc de presentar hepatocarcinoma en l'estudi 3.

En el nostre estudi els predictors que es van associar al risc de presentar hepatocarcinoma durant el seguiment fou l'albúmina tant a nivell basal com a l'any de seguiment i l'elastografia a l'any de seguiment. Amb la combinació dels dos últims factors vam poder identificar un grup d'alt risc de presentar hepatocarcinoma format per aquells pacients amb elastografia al seguiment ≥20 kPa i aquells amb elastografia entre 10 i 20 kPa amb una

albúmina a l'any <4,4 g/dL. Per contra, el grup de baix risc estava format per pacients amb elastografia <10 kPa i pacients amb elastografia entre 10 i 20 kPa amb albúmina a l'any ≥4,4 g/dL. Aquest últim grup, tot i ser de baix risc (incidència d'hepatocarcinoma <1/100 pacients-any), no permetia descartar l'aparició de complicacions doncs, per exemple, en el cas de pacients amb elastografia <10 kPa al seguiment es van observar 4 casos d'hepatocarcinoma, fent que amb els resultats de l'estudi hem de continuar recomanant el cribratge d'hepatocarcinoma en aquells pacients que tenien una elastografia ≥10 kPa abans de ser tractats.

Finalment amb l'ajuda d'aquests dos predictors, vam poder dissenyar un nomograma que permet determinar el risc d'aparició d'hepatocarcinoma segons el valor d'elastografia al seguiment i el valor d'albúmina, essent una eina útil i fàcil d'interpretar sense necessitat de càlculs complexes.

Per últim, la incidència de complicacions relacionades amb la hipertensió portal fou molt baixa en aquesta població formada per pacients amb MHCAc, doncs únicament 5 pacients es van descompensar. La majoria d'aquests pacients tenien elastografies basals >20 kPa i no milloraren durant el seguiment suggerint que molt probablement aquests pacients tenen una malaltia més avançada i que la curació del virus de l'hepatitis C no fa desaparèixer del tot el risc de descompensar-se.

En resum, l'estudi 3 demostra que en els pacients amb MHCAc per hepatitis C que han aconseguit la resposta viral sostinguda després de ser tractats amb antivirals orals l'hepatocarcinoma és la complicació més freqüent. L'albúmina i l'elastografia al seguiment poden ajudar determinar el risc d'aparició d'hepatocarcinoma.

7. Limitacions

7. LIMITACIONS

Una limitació comuna en els tres estudis és que els resultats dels estudis únicament poden aplicar-se en aquells pacients en els quals obtenim mesures vàlides d'elastografia. Per tant, no podran aplicar-se en centres on no es disposi d'elastografia ni tampoc en aquells pacients que no obtenim resultats de l'elastografia o quan aquests no són fiables. A més, a l'hora d'obtenir els resultats d'elastografia hem de tenir en compte els factors que els poden alterar com és la ingesta severa d'alcohol, els augments de transaminases, la insuficiència cardíaca o l'obstrucció biliar.

Pel que fa al primer estudi, les limitacions també inclourien la naturalesa retrospectiva de l'estudi, el temps entre la realització de l'endoscòpia i l'elastografia i la falta d'utilització de la sonda XL. Per contra, l'alt nombre de pacients inclosos de diferents centres d'Europa i Canadà quasi confirmaria la validació externa dels resultats.

En el segon estudi, una de les limitacions fou l'escàs nombre de pacients inclosos fet que dificultà l'anàlisi multivariat per controlar possibles factors de confusió. Per altra banda, la falta de biòpsies hepàtiques o de mesures del GPVH limiten la confirmació dels resultats, tot i que, aquest fet és difícil de resoldre doncs probablement no hagués estat ètic fer una biòpsia i un GPVH a tots els pacients a les 4 setmanes.

Per últim, una de les limitacions l'estudi 3 és que els predictors utilitzats per definir els grups de risc s'obtenen després d'un any de seguiment. En aquest cas, una manera de poder-ho resoldre seria obtenir l'elastografia al final del tractament, doncs com hem pogut observar en l'estudi 2, pràcticament l'elastografia no canvia gaire des de final del tractament fins a l'any posterior. Per contra, l'estudi ha permès estudiar una gran cohort de pacients amb MHCAc de dos centres terciaris donant informació del pronòstic després del tractament, fet que no es coneixia en aquest grup específic de població.

8. Conclusions

8. CONCLUSIONS

1. L'elastografia de transició, en combinació amb paràmetres analítics, és útil per predir el risc de complicacions hepàtiques en pacients amb malaltia hepàtica crònica avançada compensada.

2. Els nous criteris Expanded-Baveno VI (elastografia <25 kPa + plaquetes >110x10^9/L) permeten estalviar un major nombre d'endoscòpies innecessàries que els criteris originals de Baveno VI, en la majoria d'etiologies sense superar el límit del 5% de risc de no diagnosticar varices d'alt risc.

3. Durant el tractament amb antivirals orals es produeix un ràpid descens de l'elastografia hepàtica i esplènica, fet que reflectiria una milloria de la inflamació hepàtica i probablement també esplènica.

4. Els pacients amb malaltia hepàtica crònica avançada compensada que s'han tractat amb antivirals orals tenen una baixa incidència de complicacions, tot i que l'hepatocarcinoma continua essent freqüent.

5. Un senzill nomograma basat en l'elastografia hepàtica i els nivells d'albúmina a l'any permet predir el risc acumulat d'hepatocarcinoma al primer, segon i tercer any en aquells pacients que s'han tractat amb antivirals orals.

9. Línies de futur

9. LÍNIES DE FUTUR

Els mètodes de diagnòstic no invasiu han permès identificar pacients amb malaltia hepàtica avançada en fases inicials però que presenten risc de desenvolupar complicacions (hipertensió portal i hepatocarcinoma). Els estudis que conformen aquesta tesi tenen com a finalitat caracteritzar millor el pronòstic dels pacients amb malaltia hepàtica crònica avançada compensada i proporcionar eines simples i fàcils d'aplicar que ens ajudin a detectar poblacions de risc.

La utilització de l'elastografia, juntament amb la xifra de plaquetes, ens permet identificar una població de baix risc de presentar varices que necessiten tractament. La identificació d'aquest subgrup de pacients serà important de cara a dissenyar nous estudis que ens permetin trobar noves estratègies diagnòstiques per identificar els pacients que desenvoluparan hipertensió portal i nous fàrmacs que siguin útils per prevenir l'aparició de complicacions.

La introducció dels nous antivirals orals pel tractament de l'hepatitis C ha permès obtenir altes taxes de resposta, fet que modifica clarament la història natural de la malaltia millorant el pronòstic a llarg termini. Molts dels pacients que aconseguiran una resposta viral sostinguda aconseguiran taxes de supervivència similars a la població general pel que serà important poder identificar predictors que ens defineixin quin grup tindrà un bon pronòstic i podrà ser donat d'alta del seguiment. Per contra, en aquells pacients amb indicadors d'alt risc de presentar complicacions serà útil estudiar la presència de biomarcadors que ens ajudin a diagnosticar de manera precoç l'aparició d'hepatocarcinoma.

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*Annexes

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Annex 1: Publicacions

Estudi 1:

Augustin S, Pons M, Maurice JB, et al. Expanding the Baveno VI criteria for the screening of varices in patients with compensated advanced chronic liver disease. Hepatology 2017;66:1980-1988.

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Expanding the Baveno VI Criteria for the Screening of Varices in Patients With Compensated Advanced Chronic Liver Disease

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Patients with compensated advanced chronic liver disease (cACLD) can safely avoid screening endoscopy with a platelet count >150 × 10^9 cells/L and a liver stiffness measurement (LSM) <20 kPa (Baveno VI criteria). However, the total number of avoided endoscopies using this rule is relatively low. We aimed at expanding the Baveno VI criteria and validating them in additional cohorts. Patients from the Anticipate cohort (499 patients with cACLD of different etiologies) were used to study the performance of different thresholds of platelets and LSM for the identification of patients at very low risk (<5%) of having varices needing treatment (VNT). The new criteria (Expanded-Baveno VI) were validated in two additional cohorts from London (309 patients) and Barcelona (117 patients). The performance of the new criteria by etiology of cACLD was also assessed. The best new expanded classification rule was platelet count >110 × 10^9 cells/L and LSM <25 kPa. This was validated in the two additional cohorts. Overall, the Expanded-Baveno VI criteria would potentially spare 367 (40%) endoscopies (21% with Baveno VI criteria) with a risk of missing VNT of 1.6% (95% confidence interval, 0.7%-3.5%) in patients within the criteria and 0.6% (95% confidence interval, 0.3%-1.4%) in the overall population of 925 patients evaluated. The Expanded-Baveno VI criteria performed well in patients with cACLD with hepatitis C virus and alcoholic and nonalcoholic steatohepatitis. *Conclusion*: The new Expanded-Baveno VI criteria spare more endoscopies than the original criteria with a minimal risk of missing VNT in most of the main etiologies of cACLD. (HEPATOLOGY 2017;66:1980-1988).

The progressive introduction of noninvasive diagnostic tools, mainly liver elastography, in the management of chronic liver disease has enabled the identification of a population of asymptomatic patients with severe fibrosis/compensated cirrhosis, which is defined by Baveno VI consensus with the term "compensated advanced chronic liver disease" (cACLD).[1] These patients are at risk of developing any of the two determinants of prognosis in cACLD/compensated cirrhosis: the presence of clinically significant portal hypertension and the presence of gastroesophageal varices.[2,3] However, in these patients with

Abbreviations: cACLD, compensated advanced chronic liver disease; CI, confidence interval; HCV, hepatitis C virus; LSM, liver stiffness measurement; MELD, Model for End-Stage Liver Disease; VNT, varices needing treatment.

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cACLD identified in their early phases, the prevalence of varices and especially varices needing treatment (VNT; defined as per current Baveno VI guidelines as medium-large varices or small with red signs) is very low.

Based on preliminary information from studies suggesting that liver stiffness measurement (LSM) by transient elastography, in combination with other noninvasive parameters, was useful for "ruling out" patients with cACLD needing screening endoscopy,[4-7] the Baveno VI recommendations indicated that patients with cACLD, an LSM <20 kPa, and a platelet count $>150 \times 10^9$ cells/L have a very low risk of VNT and consequently can safely avoid the screening endoscopy.[1] Following that recommendation, several studies have now confirmed the validity of this risk classification rule,[8-11] which allows sparing between 10% to 30% of screening endoscopies with a very low risk of missing VNT. However, due to the low prevalence of VNT in these patients with cACLD (<10%), up to 40% of unneeded endoscopies would still be performed.[10]

Possible improvements to the current classification rule have been suggested. One regards the use of noninvasive tests (including platelets and LSM) for a continuous risk prediction model to individualize the decision to perform endoscopy (Anticipate study).[12] Other studies attempt to increase the number of spared endoscopies without increasing the risk of VNT missed. Jangouk et al.[13] reported a 12% increase in spared endoscopies (with no additional VNT missed) by expanding the Baveno VI criteria to patients with Model for End-Stage Liver Disease (MELD) = 6. In addition, a stepwise strategy using platelet count $>150 \times 10^9$ cells/L and MELD = 6 without LSM, substantially increased the number of endoscopies avoided, maintaining a very low rate of missing VNT. Finally, changes in the platelet count and LSM cutoffs have also been suggested.[5-7,14]

The main aim of the present study was to find and validate a new classification rule for avoiding screening endoscopies in patients with cACLD to maximize the number of spared endoscopies while maintaining a very low risk of missing VNT (<5%). Secondary aims of our study were: 1) to analyze the performance of the new classification rule in different etiologies of cACLD and 2) to externally validate the Baveno VI/MELD = 6 and platelet/MELD = 6 criteria and the performance of the ANTICIPATE continuous model.

Patients and Methods

STUDY COHORTS

Data from three different cohorts were retrospectively reviewed and analyzed (Table 1). In the Anticipate cohort,[12] 542 patients from four centers in Europe (one in France, one in Romania, and two in Spain) and one in Canada were evaluated. Patients

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TABLE 1. Main Characteristics of the Three Cohorts of the Study

	Anticipate Cohort N = 499	London Cohort N = 309	Vall d'Hebron Cohort N = 117	Total N = 925
Age, years	58.4 ± 10.8	58.1 ± 11.2	66.3 ± 10.3	59.4 ± 11.2
Male, n (%)	251 (50.3)	208 (67.3)	54 (46)	513 (55.4)
BMI, kg/m^2	27.1 ± 4.8	-*	27.4 ± 3.9	27 ± 5
HCV patients, n (%)	296 (59.3)	168 (54.4)	117 (100)	581 (62.8)
Child-Pugh class A, n (%)	499 (100)	274 (88.7)	112 (95.7)	885 (95.7)
Platelet, $\times 10^9$ cells/L	132 ± 64	157 ± 74	134 ± 61	140 ± 68
ALT, UI/L	83 ± 60	82 ± 68	97 ± 62	84.7 ± 63
LSM, kPa	28.1 ± 15.8	23.7 ± 14.5	22.2 ± 10.7	25.9 ± 15.0
No varices, n (%)	281 (56)	238 (77)	84 (71.8)	603 (65.2)
Low-risk varices, n (%)	149 (30)	57 (18.5)	24 (20.5)	230 (24.9)
VNT, n (%)	69 (14)	14 (4.5)	9 (7.7)	92 (9.9)

Continuous data expressed as mean ± SD.
*BMI from the London cohort was not available.
Abbreviations: ALT, alanine aminotransferase; BMI, body mass index.

from the European centers were reported, in part, in previous publications; however, there are no data regarding the total number of patients evaluated before the inclusion.[5,15-17] Patients included in that study had cACLD of any etiology defined by LSM ≥10 kPa, Child-Pugh class A, and no prior liver decompensation. Patients who had paired data on noninvasive tests (blood tests and transient elastography) and endoscopy within 3 months were included. In total, 499 patients with LSM, endoscopy, and platelet count were available for the study.

The cohort from London[8] was selected from two institutions (Royal Free Hospital and St. Mary's Hospital), and a flow chart of patient inclusion has been reported. In summary, a total of 12,331 LSM performed between 2006 and 2015 were evaluated. Of them, 9,018 were excluded because of LSM <10 kPa, 548 due to inadequate LSM, 403 were repetitions, 81 had prior decompensation or splanchnic thrombosis, and 1,471 had no endoscopy within 12 months of elastography. Finally, 310 patients with cACLD were included in this cohort (Table 1). One patient from this cohort had had a prior splenectomy and therefore had an unusually high platelet count; this patient was not considered for the validation as Baveno VI criteria could not be applied.

The third cohort, from Hospital Vall d'Hebron in Barcelona, was composed of 117 patients with cACLD with hepatitis C chronic infection evaluated before the initiation of direct-acting antivirals therapy in 2015. These patients were assessed with blood tests, transient elastography, and endoscopy between 2014 and 2015, and they do not overlap with the patients from Vall d'Hebron in the Anticipate study. Inclusion criteria were also LSM ≥10 kPa, Child-Pugh class A, no prior decompensation of liver disease, and endoscopy within 12 months of elastography. During this period, a total of 608 patients with hepatitis C virus (HCV) were evaluated for treatment. Unrealiable LSM was observed in 47 patients (7.7%), and 300 patients were patients with cACLD, from which 117 had an endoscopy performed within 12 months of elastography.

None of the patients with chronic hepatitis C were on antiviral treatment (interferon-based therapy or direct antivirals agents) at the time of inclusion or had previously received it.

TRANSIENT ELASTOGRAPHY

The three cohorts used transient elastography by Fibroscan (Echosens, Paris, France) to obtain an LSM. The quality criteria used in each cohort for LSM were the criteria recommended at the time of the inclusion of the cohorts: 10 valid measurements obtained with a success rate ≥60% and the interquartile range to median ratio ≤30%. An M probe was used in all measurements. Data of the number of unreliable/no valid LSM excluded are not available from the Anticipate cohort.

DESIGN OF THE STUDY

A sequential analysis plan was designed in order to provide responses for the different aims of the study. The different steps were the following: 1) the Anticipate cohort was first used to validate the performance of the Baveno VI criteria[1]; 2) the same cohort was

TABLE 2. Expanded Baveno VI Classification Rules to Increase the Number of Spared Endoscopies Without Increasing the Risk of VNT Missed in the Anticipate Cohort

	Spared Endoscopies N = 499	VNT Missed
Platelets >150 + LSM <20 kPa (Baveno VI)[1]*	68 (14%)	2/68 (3%, 0.8%-10%)†
Platelets >150 + LSM <25 kPa[4,5]	88 (17.5%)	3/88 (3.4%, 1.1%-9.5%)
Platelets >150 + LSM <30 kPa[14]	116 (23%)	6/116 (5%, 2.3%-10.8%)
Platelets >125 + LSM <25 kPa[14]	126 (25%)	3/126 (2.4%, 0.8%-6.7%)
Platelets >120 + LSM <25 kPa[7]	139 (28%)	3/139 (2.2%, 0.7%-6%)
Platelets >110 + LSM <25 kPa (Expanded-Baveno VI)	**158 (32%)**	**3/158 (1.9%, 0.6%-5.4%)**
Platelets >100 + LSM <25 kPa[4,6]	182 (36.5%)	9/182 (5%, 2.6%-9%)

The bold line indicates the classification rule that was selected for subsequent analysis for being the one that spared more endoscopies without increasing the rate of VNT missed.
*Reference number. †95% CI.

used to explore the expansion of criteria by adding the MELD = 6 rule and the platelet/MELD = 6 rule[13]; 3) the Anticipate cohort was also used to study the expansion of Baveno criteria by using previously proposed modified LSM and platelet cutoffs[4-7,14] and selecting the best classification rule in terms of endoscopies spared while keeping the risk of missing VNT below 5%; 4) the new selected set of criteria (Expanded-Baveno VI) were then validated in the London and Vall d'Hebron cohorts; 5) the performance of the Anticipate continuous model for predicting risk of VNT was evaluated in the three cohorts by analyzing the rate of endoscopies saved with a decision risk threshold for VNT of 5%; 6) next, the MELD = 6 criteria were again added to the new Expanded-Baveno VI criteria; 7) an analysis of the performance of the new criteria by etiology was subsequently carried out; 8) the effect of the variability of platelet count and LSM in the performance of the new criteria was finally evaluated.

STATISTICAL ANALYSIS

Continuous variables were reported as mean ± SD. Qualitative variables were compared using the chi-square test. The main outcome of interest for the validation of criteria was the prevalence of VNT. VNT was defined according to Baveno VI recommendations as small varices (grade 1) with red signs in which beta-blocker therapy is indicated or large varices (grade 2 or 3) in which treatment with beta blockers or band ligation is needed to prevent first variceal bleeding.[1] The main variable used for the optimization of criteria was the percentage of endoscopies spared while keeping the risk of missed VNT below the predefined arbitrary <5% threshold. This threshold was decided by experts in the Baveno VI consensus conference who agreed that 5% was a reasonable threshold for missing VNT; it was later endorsed by the American Gastroenterological Association technical review on hepatic elastography accepting a 5% false negative rate of missing high risk varices.[4,12,18] The choice of new cut-off values for the different parameters explored was based on published reports.[4-7,14] The development of the continuous risk prediction model for VNT by using LSM and platelets and its corresponding nomogram was extensively reported in the Anticipate study.[12] In brief, a continuous prediction model for VNT was developed by logistic regression using platelet count (capped at 150×10^9 cells/L) and LSM as covariates. The model was internally validated and corrected for optimism with bootstrapping. A nomogram for individual risk estimation was built based on the corrected logistic regression model. Data were processed using SPSS. For analyses, both SPSS and R statistical platforms were used.

Results

BAVENO VI CRITERIA IN THE ANTICIPATE COHORT

In the Anticipate cohort, 68 of 499 (14%) patients evaluated were within the Baveno VI criteria for not performing endoscopy (LSM <20 kPa and platelet count $>150 \times 10^9$ cells/L) (Table 2). Among these 68 patients, 62 had no varices, 4 (6%) had low-risk varices, and 2 (3%; 95% confidence interval [CI], 0.8%-10%) presented VNT. This represents that only 2 of 499 patients (0.4%; 95% CI, 0.1%-1.4%) had VNT missed and were therefore misclassified. This result shows that Baveno VI criteria perform well in the

TABLE 3. Performance of the Expanded Baveno VI Criteria (Platelet Count >110 + LSM <25 kPa) in All Three Cohorts

Study Cohort	Spared Endoscopies	VNT Missed/ Expanded-Baveno VI*	VNT Missed/ All Patients†
Anticipate	158/499 (32%)	3/158 (1.9%) (0.6%-5.4%)‡	3/499 (0.6%) (0.1%-1.9%)
London	161/309 (52%)	3/161 (1.9%) (0.6%-5.3%)	3/309 (1%) (0.3%-2.8%)
Vall d'Hebron	48/117 (41%)	0/48 (0%) (0.7%-9.2%)	0/117 (0%) (0%-3.1%)
All cohorts	367/925 (40%)	6/367 (1.6%) (0.7%-3.5%)	6/925 (0.6%) (0.3%-1.4%)

*Risk of missing VNT in patients within the new Expanded-Baveno VI criteria.
†Risk of missing VNT in all patients of the cohort.
‡95% CI.

Anticipate cohort, but the number of spared endoscopies was low.

BAVENO VI/MELD = 6 AND PLATELET/MELD = 6 RULES

In the Anticipate cohort, 463 patients had data to calculate the MELD score. Among these patients, 63/463 (13.6%) met the Baveno VI criteria for avoiding endoscopy with only 2/63 (3.1%; 95% CI, 0.9%-11%) VNT missed. Adding the MELD = 6 criteria in those patients who did not meet the Baveno VI criteria, the number of spared endoscopies increased by 34/400 (8.5%) with no additional VNT missed. Thus, by adding the MELD = 6 criteria to the Baveno VI criteria, a total of 97/463 (21%) endoscopies could be safely avoided with a low risk of missing VNT (2/97, 2%; 95% CI, 0.5%-7%), confirming that the number of spared endoscopies could be safely increased with a gain of 7% of endoscopies.

The other classification rule proposed by Jangouk et al.[13] was platelet count $>150 \times 10^9$ cells/L or MELD = 6 (without the use of LSM). In the Anticipate cohort, 161/463 (35%) patients had a platelet count $>150 \times 10^9$ cells/L, of whom 13 patients (8%) had VNT. Twenty-three patients (5%) had a platelet count $\leq 150 \times 10^9$ cells/L and MELD = 6 with no patients having VNT. Overall, the number of spared endoscopies with these criteria was 184 (39.7%) with 13/184 (7%; 95% CI, 4%-11.7%) VNT missed, indicating that more endoscopies might be saved but an excessive number of VNT (above the predefined objective of 5%) would be undetected.

EXPANDING THE BAVENO VI CRITERIA: THE EXPANDED-BAVENO VI CRITERIA

The exploratory data and the performance of new criteria based on the expansion of Baveno VI criteria by increasing the LSM cutoff and/or decreasing platelet count in the Anticipate cohort patients are shown in Table 2. The combined use of platelet count $>110 \times 10^9$ cells/L and LSM <25 kPa maximized the number of potentially spared endoscopies while keeping the rate of VNT missed below the predefined 5% threshold. We propose the name Expanded-Baveno VI criteria for this new classification rule.

VALIDATING THE EXPANDED-BAVENO VI CRITERIA (PLATELET COUNT >110 × 10^9 CELLS/L + LSM <25 kPa)

The performance of the new criteria in all three cohorts is shown in Table 3. Overall, the risk of missing VNT is very low (<2% with a maximum of 3.5% at the upper limit of the 95% CI), and on average, 40% of endoscopies are saved. The clinical characteristics of the 6 missed patients with VNT are described in Supporting Table S1.

The risk distribution of VNT missed in the patients within the Baveno VI criteria and the additional patients detected by the new Expanded-Baveno VI criteria (in patients beyond the original Baveno VI criteria) are depicted in Table 4. Remarkably, the risk of missing VNT is the same in both subgroups, suggesting that the new patients selected by the expanded criteria are not increasing the risk of missing VNT.

PERFORMANCE OF THE ANTICIPATE CONTINUOUS MODEL

By using the continuous predictive model of the Anticipate study with a decision threshold of 5% risk for VNT in the three cohorts (Table 5), an almost identical observed risk of missing VNT was detected with the three classification methods. While the

TABLE 4. Comparison of Risk of Missing the Presence of VNT With Baveno VI and the Additional Patients Detected by the Expanded Baveno VI Criteria

Study Cohort	VNT Missed/ Baveno VI†	Additional VNT Missed/ Expanded-Baveno VI‡
Anticipate, n = 158*	2/68 (3%)	1/90 (1.1%)
London, n = 161	1/101 (1%)	2/60 (3.3%)
Vall dHebron, n = 48	0/29	0/19
All cohorts, n = 367	3/198 (1.5%) (0.5%-4.3%)§	3/169 (1.7%) (0.4%-5.5%)

*Number of patients within the Expanded-Baveno VI criteria.
†Risk of missing VNT in patients within the original Baveno VI criteria.
‡Additional risk of VNT in patients beyond original Baveno VI criteria but within the new Expanded-Baveno VI criteria.
§95% CI.

number of saved endoscopies was higher using the Anticipate continuous model than with the original Baveno VI criteria, the Expanded-Baveno VI criteria maximized the number of saved endoscopies.

ADDING THE MELD = 6 TO THE EXPANDED-BAVENO VI CRITERIA

Overall, 883 patients from the three cohorts had information to calculate the MELD score and 357 (40.4%) were within the new Expanded-Baveno VI criteria. We tested the possibility of applying the MELD = 6 criterion to identify patients at low risk among those not fulfilling the Expanded-Baveno VI criteria (n = 526). The addition of patients identified with MELD = 6 (48/526; 9%) to the 357 patients within the Expanded-Baveno VI criteria spared a total of 405 (45.8%) endoscopies, while the risk of missing VNT remained very low (1.7%; 95% CI, 0.8%-3.5%); the gain in endoscopies saved compared to the new criteria (40.4%) was 5.4% (Table 6).

PERFORMANCE OF THE EXPANDED-BAVENO VI CRITERIA BY ETIOLOGIES

A subgroup analysis by etiologies of cACLD in all patients from the three cohorts (Table 7) was performed. The main etiology was HCV, followed by alcoholic liver disease and nonalcoholic fatty liver disease. The new rule seems to perform very well in these three main etiologies. The risk of VNT ranged between 0% and 2.2%, and the number of spared endoscopies ranged between 38.5% and 49%. For other etiologies (hepatitis B, cholestatic diseases, mixed viral and alcohol), subgroup numbers were too low to reach robust conclusions.

EFFECT OF THE VARIABILITY OF THE PARAMETERS IN THE EXPANDED-BAVENO VI CRITERIA

The variability in LSM and platelet count determinations might have an impact in the proposed new criteria, mainly when dealing with values closer to the proposed cutoffs. Thus, a sensitivity analysis was

TABLE 5. Performance of the Anticipate Study Continuous Model Compared to the Baveno VI and Expanded Baveno VI Criteria

			Anticipate Model (≤5% VNT)†		Baveno VI Criteria LSM <20 + pla >150		Expanded-Baveno VI Criteria LSM <25 + pla >110	
Study Cohort	N	VNT	EGD saved	VNT missed	EGD saved	VNT missed	EGD saved	VNT missed
Anticipate	499	69 (13.8%)	111 (22%)	3/111 (2.7%)	68 (14%)	2/68 (3%)	158 (32%)	3/158 (1.9%)
London	309	14 (4.5%)	137 (44%)	1/121 (0.8%)	101 (32.5%)	1/101 (1%)	161 (52%)	3/161 (1.8%)
Vall d'Hebron	117	9 (7.7%)	44 (38%)	0/40	29 (25%)	0/29	48 (41%)	0/48
All cohorts	925	92 (10%)	292 (32%)	4/292 (1.4%) (0.5%-3.4%)‡	198* (21.5%)	3/198 (1.5%) (0.5%-4.3%)	367* (40%)	6/367 (1.6%) (0.7%-3.5%)

*$P < 0.001$ with respect to the Anticipate model.
†Anticipate study model with a decision threshold of 5% of risk for VNT.
‡95% CI.
Abbreviations: EGD, esofagogastroduodenoscopy; pla, platelet count.

TABLE 6. Number of Spared Endoscopies and VNT Missed by Applying the MELD = 6 Criterion to Those Patients Who Did Not Fulfill the Expanded Baveno VI Criteria

Study Cohort	Spared Endoscopies	VNT Missed
Anticipate	170/463 (36.7%)	3/170 (1.8%) (0.6%-5%)*
London	179/308 (58.1%)	4/179 (2.2%) (0.9%-5.6%)
Vall d'Hebron	56/112 (50%)	0/56 (0%-6.4%)
All cohorts	405/883 (45.8%)	7/405 (1.7%) (0.8%-3.5%)

*95% CI.

conducted to account for the effects of the variability of measurements near those thresholds. Evidence from the literature indicates that with experienced personnel, LSM variability can reach 20%.[19] As for platelet counts, we performed a small evaluation in 15 patients with HCV, analyzing and comparing basal counts with 6- and 12-month prior determinations. Considering the extreme values, the oscillation was between −11% and 12%.

Therefore, taking into account the worst case scenario, that is 20% increase in LSM and 10% decrease in platelet count to the Expanded-Baveno VI criteria (platelet count $>100 \times 10^9$ cells/L + LSM <30 kPa), 11 VNT would be missed in 127 additional patients (11/127, 8.6%-95%; CI, 5%-15%) not receiving endoscopy.

Discussion

In the present cooperative study, we provide evidence that the original Baveno VI criteria for the screening of varices in patients with cACLD can be safely expanded (Expanded-Baveno VI criteria), increasing the number of endoscopies that can be avoided to almost 50% while keeping the risk of missing VNT very low. In addition, we confirm the validity of the MELD = 6 criteria added to the Baveno VI or Expanded-Baveno VI criteria, although the number of additionally saved endoscopies is low. Finally, the new classification rule seems to be applicable to all main etiologies of cACLD.

The Baveno VI consensus conference introduced some important novelties regarding the management of patients with cACLD/compensated cirrhosis, partly as a consequence of the increasing acceptance of noninvasive testing in chronic liver disease, especially transient elastography. The concept of cACLD, the criteria for avoiding screening endoscopy, and the criteria for selecting patients with clinically significant portal hypertension are all based on simple analytical and LSM values.[1] The original Baveno VI criteria for the triage of patients for screening endoscopy for varices (platelet count $>150 \times 10^9$ cells/L + LSM <20 kPa), although well validated in subsequent studies,[8-11] were also perceived as conservative; the number of spared endoscopies was relatively low, and about 40% of unneeded endoscopies would be performed using those criteria.[10] With the new Expanded-Baveno VI criteria (platelet count $>110 \times 10^9$ cells/L + LSM <25 kPa), the number of spared endoscopies could be doubled (from 21% to 40%) with a minimal risk of missing VNT (<2%). It has to be acknowledged that similar classification rules (platelet count >100-120 $\times 10^9$ cells/L and LSM <25 kPa) had been reported by different authors before the Baveno VI consensus conference[5-7] and in a recent abstract.[14]

The new classification rule has been developed in the Anticipate cohort and validated in two additional cohorts from the United Kingdom and Spain, including in total over 900 patients with cACLD. The two validation cohorts presented a lower prevalence (4.5% and 7.7%, respectively) of VNT than the Anticipate

TABLE 7. Performance of the Expanded Baveno VI Criteria by Etiologies of cACLD

Etiology	Spared Endoscopies	VNT Missed/ Expanded-Baveno VI*	VNT Missed/ All Patients†
HCV, n = 584	236/584 (40%)	3/236 (1.2%) (0.4%-3.6%)‡	3/584 (0.5%) (0.2%-1.5%)
Alcohol, n = 127	49/127 (38.5%)	0/49 (0%-7.2%)	0/127 (0%-3%)
NASH, n = 90	44/90 (49%)	1/44 (2.2%) (0.4%-12%)	1/90 (1.1%) (0.2%-6%)
HBV, n = 61	21/61 (34.4%)	1/21 (4.7%) (0.8%-22%)	1/61 (1.6%) (0.3%-8.7%)
PBC/PSC, n = 20	12/20 (60%)	1/12 (8.3%) (1.5%-35%)	1/20 (5%) (0.9%-23%)
HCV/Alcohol, n = 19	5/19 (26%)	0/5	0/19

*Risk of missing VNT in patients within the new Expanded-Baveno VI criteria.
†Risk of missing VNT in all patients of the cohort.
‡95% CI.
Abbreviations: HBV, hepatitis B virus; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

cohort (13.8%). It could be argued that this would have favored the validation of the Expanded-Baveno VI criteria; however, the cACLD population that would mostly benefit from avoiding screening endoscopies is probably the patients with cACLD with LSM values between 10 kPa and 25 kPa. It is in the early cACLD population that the risk of having VNT is very low, and consequently, avoiding endoscopies is critical. Above LSM 25 kPa, the risk of having clinically significant portal hypertension is more than 90%-95%[12] and the presence of VNT rises rapidly.

With the new Expanded-Baveno VI criteria, three additional patients with VNT were missed (Table 4; Supporting Table S1). Two of these patients, both from the London cohort, presented one of the classification rule parameters very near the proposed thresholds (platelet count 115 $\times$ 10^9 cells/L and LSM 24.2 kPa). It seems evident that applying the new criteria to patients with values approaching the cutoffs may increase the risk of missing VNT. This is also evidenced, as discussed in the results, by the effect that the variability both in LSM[19] and platelet counts[20] might have in increasing this risk. Besides measuring liver stiffness with the best possible quality criteria,[21] it is advisable, in our opinion, to repeat the LSM and platelet count after a short period in patients with values close to the cutoffs to confirm that they remain in the low-risk group.

One drawback of using a single cutoff to separate patients in two groups is there is always an unwanted loss of information. We might think that the risk of having VNT in all patients within the Expanded-Baveno VI criteria is 1.6%, while it is obvious that the real risk, better described in the 95% CI, ranges from 0% to at least 3%, being higher in patients approaching the cutoffs. For this reason, although we tend to work with binary decisions even though categorical decision rules are best suited for general recommendations, the information of the predicted risk by the continuous model of our prior Anticipate study[12] provides useful and complementary information for an individual patient. Both approaches point to the same conclusions and could be used in combination in real practice, especially in patients with values of platelets and an LSM closer to the thresholds of the Expanded-Baveno VI criteria.

Another important piece of information provided by the present study is that the new classification rule performs well when analyzed in the main etiologies of cACLD (Table 7). HCV patients were clearly overrepresented in the cohort, and the Expanded-Baveno VI criteria performed very well in this population. However, it is reassuring that in our sample with around 100 patients each with cACLD due to alcoholic and nonalcoholic steatohepatitis, the performance of the new criteria was also very good. In patients with hepatitis B, although the number of patients is lower, only one VNT was missed. Finally, patients with cholestatic liver diseases constitute a special subgroup of patients who might have portal hypertension in early phases of the disease, and clearly our numbers are too low to draw conclusions.

The MELD = 6 criteria seemed a promising tool when added to the Baveno VI criteria in the initial study.[13] Even more attractive was the proposal to use platelet count plus MELD = 6, without the need of LSM. From the data of our three cohorts, it is clear that applying the MELD = 6 criteria to patients beyond the Expanded-Baveno VI criteria can be safely done with an additional gain of spared endoscopies of around 5%. By contrast, we were unable to validate the classification rule of MELD = 6 without LSM, which would lead to an unacceptable high rate of missed VNT.

Our study has limitations, many of which have been discussed.[8,12] In short, the main limitations are the retrospective nature of the data, the time frames between endoscopy and LSM acquisition (up to 12 months), and the quality control of LSM and endoscopy reporting. Another important limitation is that including LSM in the classification criteria is, in itself, a limitation because transient elastography is not available in all centers. Moreover, we have to keep in mind that LSM cannot be performed in some patients (e.g., patients who are obese, although this can partially be solved with the use of an XL probe), and some factors, such as alcohol use, aminotransferases flares, or heart congestion, can increase liver stiffness and therefore provide falsely high LSM values. In these cases, an unneeded endoscopy might be performed. Finally, because the XL probe was not used in our study, information regarding its utility for the Expanded-Baveno VI criteria cannot be provided. Hence, in real-world practice, due to all the issues regarding LSM mentioned here, the Baveno VI criteria might not be applicable to all patients.

By contrast, the main strengths of our study are the large number of patients evaluated in many centers from different countries, the sequential validation process in external cohorts, and the similar performance of the new classification rule across different etiologies of cACLD.

In summary, the present study demonstrates that the Baveno VI criteria for avoiding screening endoscopy in patients with cACLD can be safely expanded. With the new Expanded-Baveno VI criteria (platelet count $>110 \times 10^9$ cells/L + LSM <25 kPa), more endoscopies are spared (100% increase from 21% to 40%) with a minimal risk of missing VNT in most of the main etiologies of cACLD. The MELD = 6 criteria can be safely added to the Expanded-Baveno VI criteria.

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Original Research

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Abstract

Background: We aimed to investigate the early changes in liver and spleen stiffness measurement (LSM, SSM) in hepatitis C virus (HCV) patients with compensated advanced chronic liver disease (cACLD) treated with new antivirals (DAA) to elucidate factors determining the initial change in stiffness and its implications for the long-term follow up of HCV-cured patients.

Methods: A total of 41 patients with cACLD who started DAA therapy underwent LSM and SSM at baseline, week 4, end of treatment (EOT), 24 and 48 weeks of follow up using transient elastography.

Results: LSM improved rapidly during the first 4 weeks of treatment (baseline: 20.8kPa; week 4: 17.5kPa, $p = 0.002$), with no significant changes between week 4 and EOT (18.3kPa, $p = 0.444$) and between EOT and 48-week follow up (14.3kPa, $p = 0.148$). Likewise, SSM improved rapidly (baseline: 45.7kPa; week 4: 33.8kPa, $p = 0.047$), with no significant changes between week 4 and EOT (30.8kPa, $p = 0.153$) and between EOT and 48-week follow up (31.2kPa, $p = 0.317$). A higher decrease in LSM was observed in patients with baseline ALT $\geq$ twofold upper limit normal ($2 \times$ ULN) than in those with ALT $< 2 \times$ ULN (–5.7kPa *versus* –1.6kPa). Patients who presented a decrease in LSM $\geq$ 10% during treatment compared with those with LSM $<$ 10% decrease, showed lower SSM values, higher platelet counts and lower bilirubin levels at 24-week follow up. Those with decrease in SSM $\geq$ 10%, presented a higher increase in platelets than those with SSM $<$ 10% change ($p = 0.015$).

Conclusions: LSM and SSM decrease very rapidly during DAA treatment in cACLD patients suggesting that it most probably reflects a reduction in inflammation rather than in fibrosis. cACLD patients should be maintained under surveillance independently of stiffness changes, because advanced fibrosis can still be present.

Keywords: compensated advanced chronic liver disease (cACLD), direct-acting antiviral agents (DAA), hepatitis C, inflammation, liver stiffness, spleen stiffness

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Introduction

The immediate goal of hepatitis C virus (HCV) treatment is to achieve sustained virological response (SVR), but the ultimate aim of HCV eradication is trying to improve long-term outcomes (progression of fibrosis, clinical decompensation and possibly death). Several studies have demonstrated that in patients with SVR after interferon-based treatment, liver fibrosis can regress during follow up.[1,2] Moreover, in those patients who achieve SVR, a decrease in hepatic venous pressure gradient (HVPG) can

occur and, therefore, a decrease in complications associated to portal hypertension is observed.[3–5] A lower incidence of hepatocellular carcinoma[6,7] and a reduction of all-cause mortality have also been documented.[8]

Until 2014, interferon-based treatment was the standard of care for HCV therapy. This treatment was not free from complications, especially in patients with advanced fibrosis and cirrhosis, in whom low rates of SVR were observed.[9–11] However, the introduction of new direct-acting antiviral agents (DAA) in the current treatment for HCV patients have changed this paradigm, achieving high SVR rates with minimal side effects, even in patients with cirrhosis.[12] In consequence, a huge number of patients with advanced chronic liver disease are achieving SVR, highlighting the importance of monitoring fibrosis regression to identify those patients with a higher risk of developing complications during follow up. Non-invasive methods such as transient elastography (TE) may be useful for monitoring these changes. Liver stiffness has been correlated with degree of liver fibrosis, the presence of clinically significant portal hypertension and with the risk of decompensation.[13–15] On the other hand, recently, spleen stiffness has been shown to be also correlated with HVPG and the risk of decompensation.[16,17] However, it has to be taken into account that non-invasive methods to evaluate liver fibrosis have not been validated in non-viremic patients and changes in liver stiffness after a successful antiviral treatment might not accurately reflect a real change in residual fibrosis, but rather a reduction in inflammation.

The aim of our study was to investigate the early changes in liver and spleen stiffness measurement (LSM, SSM) in HCV patients with compensated advanced chronic liver disease (cACLD) treated with new oral DAA in order to elucidate the factors determining the initial changes in stiffness and their implications for the long-term follow up of HCV-cured patients.

Patients and methods

Consecutive compensated patients with baseline LSM $\geq$10 kPa who met the Baveno VI criteria for cACLD[18] and in whom treatment with oral DAA was approved were included in this prospective small-scale study. As per definition, patients with LSM $\geq$15 kPa were considered highly suggestive of having cACLD and, for patients with LSM between 10 and 15 kPa, one of the following criteria was needed to confirm cACLD: platelet count $<150 \times 10^9$/l, spleen size $\geq$13 cm, nodular liver or collateral circulation in abdominal ultrasound, HVPG >5 mmHg, upper gastrointestinal endoscopy showing gastroesophageal varices or previous liver biopsy showing bridging fibrosis or cirrhosis. Patients with previous decompensation were excluded. The recruitment period started in January 2015 (date of the beginning of widespread DAA therapy in Spain) and finished in June 2015.

We calculated the sample size, taking into account improvement in LSM [defined as a 10% decrease in LSM from baseline to end of treatment (EOT)] could be found in 60% of treated patients with a total width of confidence interval (CI) of 30% (45–75%), that is more than four times the background 10% improvement in untreated patients. Aiming at a confidence level of 95%, a normal approximation to the binomial calculation would require a total sample size of 41 patients.[19]

The study [ClinicalTrials.gov identifier NCT 02439567] was registered on 27 April 2015.

Patients received a treatment regimen adequate for their HCV genotype. Patients with genotype 1 or 4 received treatment with Sofosbuvir 400 mg daily (Sovaldi, Gilead, Cambridge, UK), Simeprevir 150 mg daily (Olysio, Janssen, Beerse, Belgium) and weight-based dose of ribavirin (RBV) (with ranging dose 800–1200 mg) for 12 weeks. For genotype 3, patients received Sofosbuvir 400 mg daily, Daclatasvir 60 mg daily (Daklinza, Bristol-Myers Squibb, Uxbridge, UK) and a weight-based dose of RBV for 24 weeks. No other genotypes were found in our sample.

All patients underwent LSM and SSM, and biochemical tests at baseline, week 4, EOT and at 24 and 48 weeks of follow up after finishing treatment. SVR was defined as undetectable HCV-RNA at 12 weeks follow up after finishing treatment. An abdominal ultrasound was performed at baseline and every 6 months, as part of standard routine surveillance for hepatocellular carcinoma.

The study was approved by the Ethics Committee of Hospital Universitari Vall d'Hebron (CEIC) (JOA-SOF-2015-01) and was conducted in accordance with the 1975 Declaration of Helsinki

and Good Clinical Practice guidelines. All patients gave written informed consent before the inclusion.

Hepatitis C virus–ribonucleic acid quantification

Serum HCV-RNA was tested at baseline, during treatment (weeks 4, 12 or 24) and 12 weeks after treatment completion. A real-time polymerase chain reaction-based test (Cobas Ampliprep/Cobas TaqMan; Roche Molecular Diagnostics, West Sussex, UK; detection limit 15 IU/ml) was used for HCV detection and quantization. HCV genotyping was performed by deep sequencing on a 454/GS-Junior (Roche, Branford, CA, USA) platform.

Liver stiffness measurement

LSMs by TE (Fibroscan® 502 Touch, Echosens, Paris, France) were performed by a single operator with experience in more than 500 procedures (MP). LSMs were performed in a fasting state according to the usual standard procedure. Only LSMs with success rate of ⩾60% (with at least 10 valid measurements) and an interquartile-range-to-median-LSM ratio of ⩽30% were selected as valid measures. Medium or extra-large probes were selected as per device indication and, for each patient, the same probe was used during all study visits.

Spleen stiffness measurement

SSMs were performed with TE using Fibroscan® 502 Touch at the same appointment, with the same probe and the same software used for LSM, with the patient in the supine position and the left arm in maximal abduction. The spleen was localized under ultrasound assistance (Vscan®, General Electric Healthcare, Milwaukee, WI, USA), and the probe was positioned where the spleen was correctly visualized. Reliable results for spleen stiffness have not been yet validated. Therefore, the same reliable criteria for the LSM were applied.

Statistical analysis

Categorical variables are expressed as numbers (percentages) and continuous variables as median (25th percentile–75th percentile). For statistical analyses and presentation of results, differences between categorical variables were assessed by Chi-square test or Fisher's exact test, when necessary. Continuous variables were compared using the Student's t test or Mann–Whitney test as appropriate. Intragroup comparisons were made using Wilcoxon's test for paired data. The general linear model technique for analysing repeated measures was used to examine changes in biochemical parameters and TE over time. p values below 0.05 were considered statistically significant and, in paired-sample comparisons, the Bonferroni correction was applied. Statistical analyses were performed using SPSS v. 19.0 software (IBM, Armonk, NY, US) and STATA 13.1 statistical software (StataCorp, College Station, TX, US).

Table 1. Baseline characteristics of the patients included.

Characteristics	Patients $n = 41$
Male sex, *n* (%)	20 (48.8)
Age, years	68 (59–75)
BMI, kg/m^2	26.6 (24.9–29.4)
Ethnicity, *n* (%)	
White	41 (100)
HCV genotype, *n* (%)	
1–4	39 (95.1)
3	2 (4.9)*
Treatment naïve, *n* (%)	18 (43.9)
Spleen size, cm	12.9 (11.5–13.7)
Varices $n = 31$, *n* (%)	
No/I/II-III	15 (48.4)/14 (45.2)/2 (6.5)
HCV RNA level, $\log_{10}$ IU/ml	6.3 (6.0–6.6)
Liver stiffness, kPa	20.8 (16.3–29.5)
Spleen stiffness, kPa	45.7 (26.6–65.2)
Platelets, 10^9/l	106.5 (82–142.5)
ALT, IU/l	78 (55–135)
ALT ⩾ 2 × ULN, *n* (%)	17 (41.5)
Bilirubin, mg/dl	0.89 (0.68–1.11)
Albumin, g/dl	3.84 (3.64–4.12)

*One patient had a mix of genotype 1 and 3. Continuous values expressed as median (25th percentile –75th percentile). BMI, body mass index; HCV, hepatitis C virus; ALT, alanine aminotransferase; 2 × ULN, twofold upper limit normal.

Results

The baseline characteristics of the 41 patients with cACLD included are described in Table 1. All

Table 2. Laboratory parameters at study time points.

	Baseline	Week 4	EOT	24-week FU*	*p* value
Haemoglobin (g/dl)	14.4 (12.9–15.7)	12.1 (11.4–13.2)	11.8 (11–13.0)	14 (13–15.6)	<0.001
Platelets (×10⁹/l)	106.5 (82–142.5)	139.5 (107.5–166.5)	135.5 (106.5–171.5)	122 (104–161)	<0.001
Bilirubin (mg/dl)	0.89 (0.68–1.11)	1.41 (1.05–2.5)	1.16 (0.91–1.8)	0.73 (0.57–0.86)	<0.001
ALT (UI/l)	78 (55–135)	18 (15–21)	16 (15–20)	18 (16–23)	<0.001
AST (UI/l)	92 (66–129)	26 (23–32)	27 (23–30)	26 (23–32)	<0.001
GGT (UI/l)	92 (61–131)	38 (31–50)	28 (22–37)	35 (24–52)	<0.001
Albumin (g/dl)	3.84 (3.64–4.12)	4.04 (3.65–4.20)	4 (3.60–4.28)	4.20 (3.90–4.50)	<0.001

*Data of 48-week follow up were equal to 24-week follow up therefore, to simplify the table, they are not shown in the table. Values expressed as median (25th percentile–75th percentile). ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; EOT, end of treatment; FU, follow up.

patients were in Child-Pugh class A. Thirty-six patients (87.8%) were infected by genotype 1, and three patients (7.3%) were infected by genotype 4. Two patients had genotype 3 (one of them with a mixed genotype 1 and 3) and both were treated with Sofosbuvir + Daclatasvir + RBV for 24 weeks. Seventeen patients (41.5%) presented with alanine aminotransferase (ALT) levels higher than twofold upper limit normal (2 × ULN) at baseline and most of them were male (12 men *versus* 5 women).

Changes in laboratory parameters

At week 4, all patients presented with undetectable HCV-RNA. SVR was observed in 40 patients (97.6%). The patient who did not achieve SVR relapsed after finishing treatment and was HCV-genotype 1b.

Biochemical parameters improved rapidly after starting treatment (Table 2), except for haemoglobin and bilirubin that were altered during treatment due to RBV, but returned to baseline after finishing treatment.

Changes in liver and spleen stiffness during treatment

Figure 1 shows changes in liver stiffness measurements (LSM) and spleen stiffness measurements (SSM) during the study period. All patients had reliable LSM. Nine patients (22%) were not included in pairwise comparisons of SSM. One of them due to a previous splenectomy and the others due to unreliable results at some study point.

For the patient who did not achieve SVR, LSM and SSM were no longer performed after finishing treatment. LSM and SSM for this patient during treatment are represented in supplementary Figure 1.

Globally, LSM during treatment improved. Median LSM values were: 20.8 kPa (16.3–29.5 kPa) at baseline, 17.5 kPa (13.5–26.3 kPa) at week 4 and 18.3 kPa (13.3–27.2 kPa) at the EOT ($p = 0.014$). LSM improved rapidly and significantly during the first 4 weeks of treatment ($p = 0.002$), with no significant changes between week 4 and EOT ($p = 0.444$). The median change from baseline to week 4 was –4.8 kPa (95% CI: –6.4 kPa to –1.0 kPa) and from baseline to EOT was –3.3 kPa (95% CI: –5.9 to –0.5 kPa) (Figure 1A).

Significant changes in SSM were observed during treatment. Median SSM was 45.7 kPa (26.6–65.2 kPa) at baseline, 33.8 kPa (26.3–46.4 kPa) at week 4 and 30.8 kPa (21.3–39.1 kPa) at the EOT ($p = 0.012$). Similarly to LSM, SSM improved rapidly and significantly during the first 4 weeks of therapy ($p = 0.047$), with no significant changes between week 4 and EOT ($p = 0.153$). The median change from baseline to week 4 was –5.7 kPa (95% CI: –11.4 kPa–0 kPa) and from baseline to EOT –6.6 kPa (95% CI: –12.8 kPa to –1.8 kPa) (Figure 1B).

Based on ALT levels, median basal LSM was 20.8 kPa in both groups (baseline ALT $\geq 2 \times$ ULN and baseline ALT $< 2 \times$ ULN), however, patients who had baseline ALT $\geq 2 \times$ ULN presented a higher decrease in LSM during treatment, median –5.7 kPa (95% CI: –9.7–0.2 kPa), than patients with baseline ALT $< 2 \times$ ULN, median –1.6 kPa (95% CI: –5.2–2.7 kPa) ($p = 0.037$) (Figure 2).

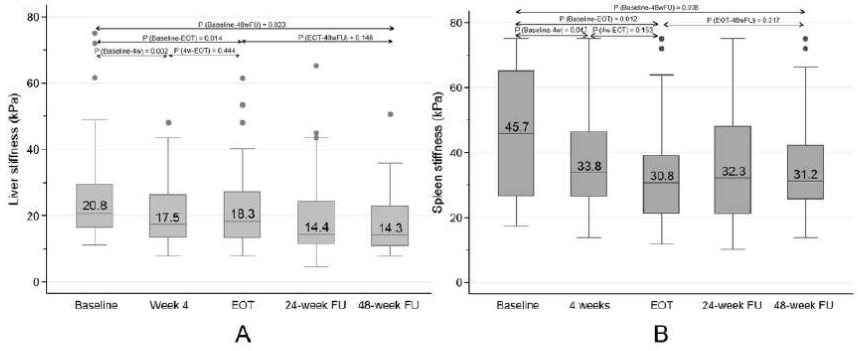

Figure 1. (A) Liver stiffness measurement at baseline, week 4, end of treatment (EOT), 24- and 48-week follow up (FU) in the 40 hepatitis C compensated advanced chronic liver disease (cACLD) patients cured with therapy. (B) Spleen stiffness measurement (SSM) at baseline, week 4, EOT, 24- and 48-week FU in the 32 hepatitis C cACLD patients with reliable values of SSM.
EOT, end of treatment; FU, follow up.

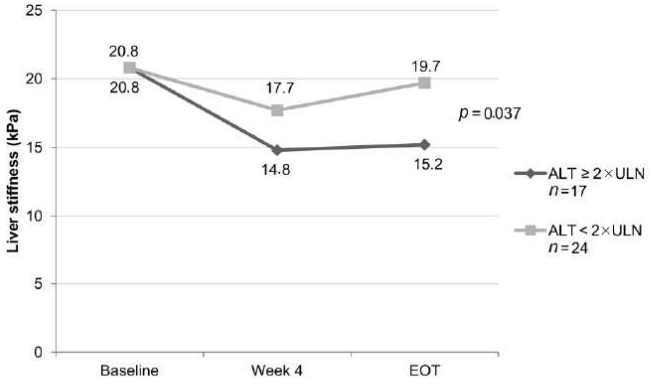

Figure 2. Median liver stiffness measurement (LSM) during treatment of hepatitis C virus compensated advanced chronic liver disease patients based on baseline (pretreatment) alanine aminotransferase (ALT) levels. Patients with baseline ALT ⩾ 2 × ULN presented a higher decrease in LSM.
cACLD, compensated advanced chronic liver disease; HCV, hepatitis C virus; ALT, alanine aminotransferase; 2 × ULN, twofold upper limit normal; EOT, end of treatment.

Changes in liver and spleen stiffness after treatment

As shown in Figure 1A, during follow up, from EOT to week 48, LSM continued improving, especially until week 24, although this improvement was not statistically significant ($p = 0.148$). Median LSM at 24 weeks of follow up (24w-FU) was 14.4 kPa (11.5–26.3 kPa) and at 48 weeks of follow up (48w-FU) was 14.3 kPa (10.8–22.9 kPa). On the other hand, SSM remained stable from EOT to 48w-FU (Figure 1B). Median SSM was 32.3 kPa (21.5–46.4 kPa) at 24w-FU and 31.2 kPa (25.5–42.2 kPa) at 48w-FU. However, both LSM and SSM decreased significantly from

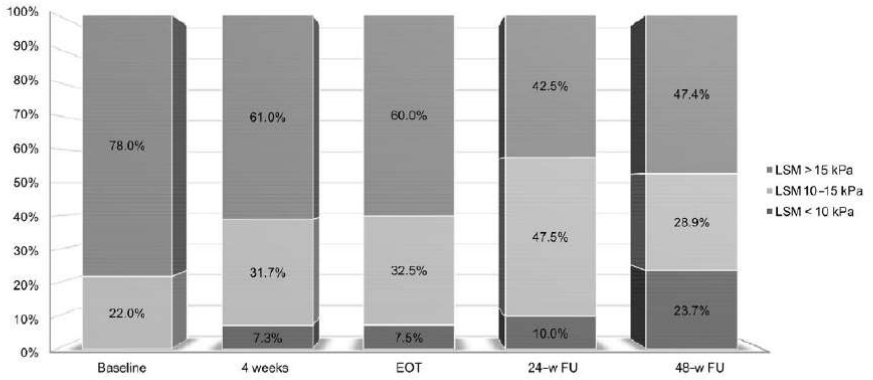

Figure 3. Proportion of treated hepatitis C virus compensated advanced chronic liver disease patients with liver stiffness measurement (LSM) < 10 kPa, 10–15 kPa and >15 kPa at each study time point.
cACLD, compensated advanced chronic liver disease; HCV, hepatitis C virus; LSM, liver stiffness measurement.

baseline to end of follow up, with a median change in LSM of −5.5 kPa (−7.4 to −2.7 kPa, $p = 0.023$) and median change in SSM of −7.1 kPa (−9.6 to −0.3 kPa, $p = 0.038$).

Figure 3 shows that the proportion of patients with LSM >15 kPa decreased progressively from the beginning of treatment until the end of follow up ($p = 0.003$), while 24% of the study population had their LSM reduced below the 10 kPa threshold.

Comparison of patient characteristics according to change in liver and spleen stiffness

Patients who presented a decrease in LSM ⩾ 10% during treatment, calculated as (EOT LSM–baseline LSM)/baseline LSM ×100, were considered to present a significant LSM improvement. Twenty-three patients (57.5%) had a significant LSM improvement. Differences between patients with or without significant LSM improvement are described in Table 3. As seen, patients with significant LSM improvement showed lower SSM values, higher platelet counts and lower bilirubin levels at 24w-FU. In addition, those patients with significant LSM improvement presented a higher decrease in SSM during treatment ($p = 0.027$) than patients without significant LSM improvement ($p = 0.870$) (Figure 4).

Platelet count was also correlated with changes in SSM. Patients with improvement in SSM ⩾ 10% (18 patients, 56.3%) from baseline to EOT, presented a higher increase in platelets, compared with those who did not present an improvement in SSM ($p = 0.015$) (Figure 5).

Liver stiffness measurement and spleen stiffness measurement changes according to surrogate markers of portal hypertension

Changes in LSM and SSM were also analysed in patients with different degrees of portal hypertension. Since HVPG measurements were not available and endoscopies were not performed in all patients, platelet count (<150 × 10^9/l or ⩾150 × 10^9/l) and LSM (<20 kPa or ⩾20 kPa) were used as surrogate markers of portal hypertension. As seen in supplementary Figure 2, patients with normal or low platelets presented similar changes in LSM, while significant LSM decrease was only observed in patients with basal LSM ⩾ 20 kPa. By contrast, significant SSM changes were only observed in patients with platelet counts < 150 × 10^9/l or LSM ⩾ 20 kPa, probably patients with higher basal portal pressure. Patients with low (normal) SSM and probably lower portal pressure remained unchanged.

Discussion

Treatment of HCV with the new DAA is extremely effective, causing a very rapid control of viral replication, normalization of transaminases and disappearance of liver inflammation. Consequently, the virological and biochemical profile of these new treatments is surely very different from the prior interferon-based therapies, in which a slower and longer process was

Table 3. Main characteristics in patients who presented a decrease in liver stiffness measurement (LSM) during treatment ⩾ 10% compared with those who presented a decrease in LSM <10%. Change in LSM is calculated as: (end-of-treatment LSM-Baseline LSM)/Baseline LSM ×100.

Characteristics	LSM ⩾ 10% (n = 23)	LSM < 10% (n = 17)	p value
Male sex, n (%)	13 (56.5)	7 (41.2)	0.491
Age, years	68 (63–75)	67 (58–73)	0.448
BMI, kg/m^2	26.0 (24.2–27.9)	27.4 (25.2–30.0)	0.251
Treatment-naïve, n (%)	10 (43.5)	8 (47.1)	0.822
Spleen size, cm	12.5 (11–13.6)	12.8 (11.9–13.5)	0.133
Baseline HCV RNA level, $\log_{10}$ IU/ml	6.5 (6.2–6.6)	6.2 (5.9–6.4)	0.085
Liver stiffness, kPa			
Baseline	20.8 (17.3–35.3)	17.5 (14.1–29.5)	0.163
24-week FU	12.8 (11.1–26.3)	14.5 (11.7–24.3)	0.487
Spleen stiffness, kPa			
Baseline	45.7 (28–65.2)	42.9 (26.5–65.1)	0.907
24-week FU	29.9 (21.5–37.4)	39.5 (20.4–59.4)	0.046
Haemoglobin, g/dl			
Baseline	14.5 (13.3–15.6)	14.2 (12.6–15.8)	0.389
EOT	11.4 (11–12.9)	11.8 (11.2–13)	0.976
Platelets, 10^9/l			
Baseline	109 (84–144)	104 (79–134)	0.571
24-week FU	133 (117–157)	105.5 (91.5–168.5)	0.054
ALT, IU/l			
Baseline	94 (53–135)	69 (55–131)	0.681
24-week FU	18.5 (16–25)	16.5 (16–22.5)	0.398
Bilirubin, mg/dl			
Baseline	0.72 (0.55–0.96)	0.93 (0.86–1.24)	0.013
24-week FU	0.59 (0.48–0.72)	0.83 (0.77–1.11)	<0.001
Albumin, g/dl			
Baseline	3.8 (3.7–4.1)	3.9 (3.5–4.1)	0.847
24-week FU	4.3 (4–4.6)	4.2 (3.9–4.5)	0.362

Continuous values expressed as median (25th percentile–75th percentile). HCV, hepatitis C virus; ALT, alanine aminotransferase; FU, follow up; BMI, body mass index; LSM, liver stiffness measurement.

probably taking place. This rapid on–off response with DAA becomes a very interesting model for investigating the dynamics of liver and spleen stiffness and learn about the contribution of the different components causing increased tissue stiffness. The results of the present study clearly indicate that liver and spleen stiffness improve very early during treatment, as early as at 4 weeks of therapy or even before, and more importantly, that this initial decrease explains for most of the final liver and spleen stiffness observed for the first 48 weeks of post-treatment follow up.

Previous studies have shown improvement in liver stiffness during long-term follow up, especially in patients who achieve SVR treated with

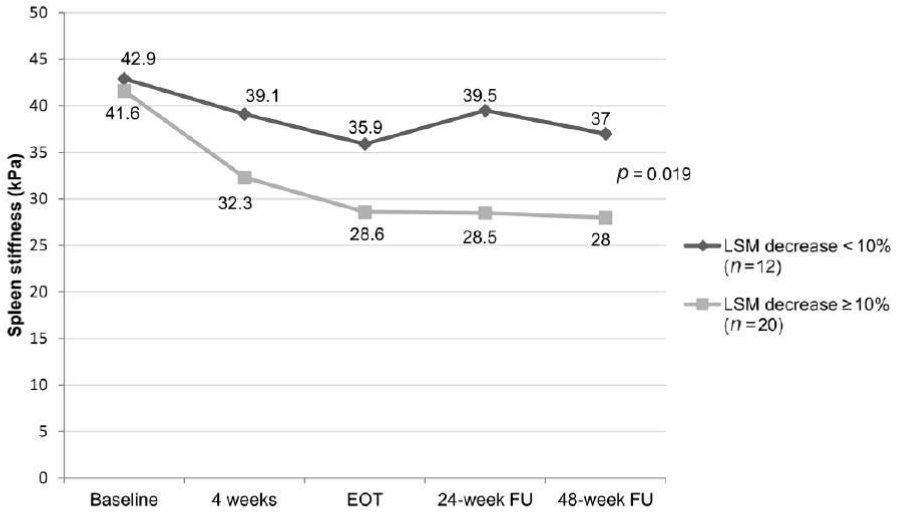

Figure 4. Spleen stiffness measurement (SSM) changes during treatment comparing hepatitis C virus compensated advanced chronic liver disease patients with a significant improvement in liver stiffness measurement (LSM) during treatment (decrease in LSM ⩾ 10% from baseline to EOT) with patients without a significant improvement (decrease in LSM < 10%). Only patients with all SSM reliable measures are represented.
cACLD, compensated advanced chronic liver disease; HCV, hepatitis C virus; FU, follow up; EOT, end of treatment; LSM, liver stiffness measurement.

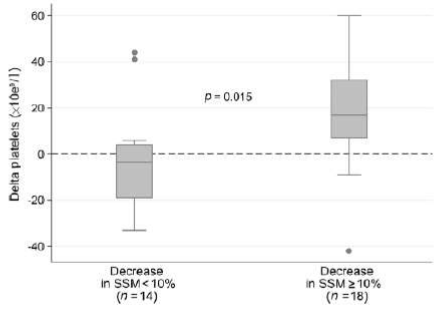

Figure 5. Change in platelets in treated hepatitis C virus compensated advanced chronic liver disease patients from baseline (pretreatment) to 24-week follow up, based on decrease in spleen stiffness measurement from baseline to EOT. Delta platelets = 24-week follow up platelet count–baseline platelet count.
cACLD, compensated advanced chronic liver disease; HCV, hepatitis C virus; SSM, spleen stiffness measurement.

interferon-based therapies. Evaluation of LSM at week 4 of treatment was rarely performed. Hézode *et al.*[20] studied patients treated with pegylated interferon-α plus RBV, and they found that patients with cirrhosis who achieved SVR presented a median decrease in LSM of 4.1 kPa at week 4 compared with a decrease of 0.7 kPa in patients with no cirrhosis. By contrast, Bernuth *et al.*[21] found that in patients with chronic HCV infection receiving sofosbuvir-based treatment, LSM increased at week 4, from a baseline LSM of 8 kPa to 12.9 kPa: one of the reasons given by the authors to explain these results is that patients did not fast prior to TE and also that the anaemia caused by combined therapy might have increased liver blood flow and liver stiffness.

One of the most remarkable findings of the present study is that the rapid liver and spleen stiffness improvement observed at 4 weeks of therapy explains most of the decrease in stiffness observed during the total 15 months of follow up. Indeed, although there was a small decline in LSM from week 4 to end of follow up (median change –1.5 kPa), approximately 75% of the decrease was observed during the first 4 weeks of therapy (median change –4.8 kPa). This observation, together with the significant correlation between

high ALT at baseline and higher decrease in LSM at 4 weeks, suggests that the main driver for the liver stiffness improvement is suppression of liver inflammation, as a consequence of viral eradication rather than a pure reduction of liver fibrosis. This conclusion bears several implications. First, that in patients with HCV cACLD, 15–20% of the observed liver stiffness is probably due to inflammation. In this regard, inflammation-adapted LSM cut-offs have been proposed, but there is a controversy about its usefulness.[22,23] Second, this explains in great part the observed discrepancies between liver histology and liver stiffness after HCV eradication. As seen in our patients, significant changes in LSM occur in 4 weeks, while it has been well documented that detectable changes in fibrosis require much more time. In our sample, 78% of our patients had baseline LSM $\geqslant$ 15 kPa and at the end of follow up, this percentage was reduced to 47%, while the percentage of patients with LSM $<$ 10 kPa and with LSM between 10–15 kPa increased progressively. However, D'Ambrosio *et al.*[24] demonstrated that 21% of patients with LSM $<$ 12 kPa after an average of 61 months from SVR still had cirrhosis in liver biopsy, indicating less accuracy of TE for diagnosing cirrhosis in nonviremic patients. Thus, in order to validate the clinical meaning of post-treatment LSM values, longer follow-up studies will be needed, taking into consideration the information regarding basal LSM, changes in LSM during follow up and post-therapy time frames.

In addition to LSM improvement, SSM also remarkably improved in a similar (and even more pronounced) pattern. All SSM improvement was seen during the first 4 weeks of therapy, with no additional change for the rest of the follow up. Again, this rapid decrease, along with the strong correlation with the decrease in liver stiffness (and liver inflammation), suggests that the main driver for this improvement is not only spleen congestion and portal hypertension decrease. Although spleen stiffness has been correlated with HVPG[16,25,26] and a reduction in HVPG during HCV treatment has been demonstrated in previous studies,[3,4,27] it seems plausible that other explanations are needed for this rapid change in spleen stiffness. In that sense, the splenomegaly classically associated to portal hypertension could be considered as a composite of congestion, enlargement and hyperplasia of splenic lymphoid tissue (white pulp), and increased angiogenesis and fibrogenesis.[28,29] In addition, increased splenic inflammation might have an additional role in HCV-infected patients, considering that spleen could be regarded as a large lymph node and HCV-infected patients consistently show hepatic perihiliar adenomegalies on liver imaging. Altogether, these findings point out to a rapid improvement in spleen inflammation or spleen remodelling due to a decrease in lymphoid tissue infiltration as the main cause for the initial spleen stiffness decrease. However, a very early decrease in portal pressure due to reduced liver inflammation could also partially contribute to decrease spleen stiffness.

Finally, as expected, all analytical parameters improved during follow up, and those not affected by RBV, improved also very early (4 weeks) during therapy. Platelet counts also followed this pattern, and again, most of the improvement observed during follow up occurred at 4 weeks of therapy. Remarkably, patients in whom a significant improvement of SSM was observed presented the greater increase in platelet counts, as compared with patients without significant SSM improvement (Fig. 5). Similar results were obtained comparing patients with or without LSM improvement. Although a correlation between changes in spleen size and increase in platelet counts after HCV therapy has been reported,[30] in our case, differences in spleen size were not observed, probably due to the short follow up. Platelet counts have been shown to increase years after SVR due to improvement in thrombopoietin production, improvement in portal hypertension and reversal of splenomegaly.[30] In our case, the rapid improvement and correlation with SSM changes suggests that platelets increase mainly due to spleen release secondary to decreased spleen sequestration.

The limitations of the present study include the small sample size and the lack of external validation. The small sample size limits the ability to control confounding factors through multivariate regression analysis. Also the lack of simultaneous liver biopsy and HVPG information is a weakness of our study with a very difficult solution, since it would be probably unethical to perform them at 4 weeks of therapy. Moreover, SSM may be technically difficult to perform in clinical practice due to the need to carry out an ultrasound prior to TE to localize the spleen, and the fact that TE is not optimized for SSM. As a consequence of that, not all patients could be evaluated for SSM and the

results might have been altered. However, we feel that this is not the case, since SSM correlated very well with LSM and platelet findings, and SSM values remained very constant after the initial decrease. Another limitation is that most of the patients (88%) were genotype 1 and all of them were White. Both genotype and ethnicity have been known to affect kinetics of liver fibrosis related to HCV.[31] Finally, the lack of a longer follow up limits the capacity to detect long-term changes in LSM and SSM that are probably related to fibrosis improvement.

In conclusion, liver and spleen stiffness decrease significantly and very rapidly during DAA treatment of HCV-infected cACLD patients and this improvement accounts for most of the stiffness improvement observed during follow up, suggesting that it most probably reflects liver and spleen improvement in inflammation and cell infiltration. These findings have important clinical implications for the follow up of cACLD HCV-cured patients, since changes in LSM after SVR cannot be interpreted just as a reduction of liver fibrosis (at least during the first year of follow up). Consequently, patients with cACLD prior to SVR cannot be discharged from follow up based on LSM improvements. Until more information from patients with longer follow up and with liver biopsy information is gathered, patients will have to remain under surveillance.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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Estudi 3:

Pons M, Rodríguez-Tajes S, Mariño Z, et al. Non-invasive prediction of liver related events in HCV compensated advanced chronic liver disease patients after oral antivirals.

En revisió

Non-invasive prediction of liver related events in HCV compensated advanced chronic liver disease patients after oral antivirals

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ABSTRACT:

Background&Aims: We aimed to describe the incidence of liver related events (LRE) in a population of hepatitis C compensated advanced chronic liver disease (cACLD) patients who achieved sustained virological response (SVR) after direct-acting antiviral (DAA) therapy and identify non-invasive parameters to predict the occurrence of LRE. **Methods:** This two-center prospective study included 572 cACLD patients who had been treated with DAA and had achieved SVR. Patients had liver stiffness measurement (LSM) ≥10 kPa at baseline and had never decompensated (Child Pugh class A). Laboratory work up and LSM was performed at baseline and at one year of follow up (FU). **Results:** The median follow-up was 2.8 years during which 32 patients (5.6%) presented LRE. The incidence rate (IR) of portal hypertension related decompensation was 0.34/100 patient-years. These patients had all baseline LSM>20 kPa and in 4 out of 5 LSM did not improve during FU. HCC occurred in 25 patients (IR 1.5/100 patient-years). Albumin levels at FU (HR 0.08, 95% CI: 0.02-0.25) and LSM <10 kPa at FU (HR 0.33, 95% CI: 0.11-0.96) were independently associated with the risk of HCC. Combining both predictors, we identified two different risk groups of HCC occurrence, being those with LSM ≥20 kPa at FU and with LSM between 10-20 kPa and albumin levels <4.4 g/dL the ones with the highest risk (IR ≥1.9/100 patient-years). Visual nomograms predicting HCC risk during time based on LSM and albumin at one year of FU were constructed. **Conclusion:** In hepatitis C cACLD patients who have achieved SVR with DAA, HCC is the most frequent LRE. Both albumin levels and LSM during FU are useful to stratify the risk of presenting HCC.

INTRODUCTION

Direct-acting antivirals (DAA) have become the new standard of care for patients with chronic hepatitis C virus (HCV) infection, demonstrating to be highly effective in achieving sustained virological response (SVR) rates regardless of HCV-genotype. Due to their safety profile and low side effects any patient in any stage of chronic liver disease (from mild fibrosis to decompensated cirrhosis) can be treated with DAA [1]. Therefore, it is important to know which patients will be prone to develop liver-related complications, such hepatocellular carcinoma (HCC) or liver decompensation, and will need a lifelong follow up and which ones will have a good prognosis so they could be safely discharged from follow up.

Several studies have demonstrated that in patients with cirrhosis who have achieved SVR after DAA therapy there is a decrease in liver-related events (LRE) due to an improvement in liver function and portal hypertension, and a decrease in the incidence of *de novo* HCC, accompanied by an overall increase in survival rates [2-7]. These studies have also demonstrated that patients with cirrhosis are at higher risk of complications

than those without cirrhosis. However, the variability in the methods for selecting and defining patients with cirrhosis in different published studies and the heterogeneity of patients included, mixing patients with compensated cirrhosis and decompensated cirrhosis, makes it hard to find predictors to identify high risk populations and validate the results.

It is also important to note that currently most of the asymptomatic patients with advanced fibrosis or cirrhosis are diagnosed by elastographic methods such transient elastography and not by liver biopsy. So, in many of these cases, the exact stage of the disease is suspected, but unconfirmed. For this reason, Baveno VI consensus defined that patients with liver stiffness measurement (LSM) ≥10 kPa and no prior decompensation were suggestive of having "compensated advanced chronic liver disease" (cACLD) [8]. This patient population is of particular interest because, although they have never decompensated, approximately 80-90% of them have portal hypertension and up to 50-60% have clinically significant portal hypertension (CSPH) [9]. It would be probably easier to identify low risk groups for LRE in this cACLD population, where some patients have an initial degree of advanced liver disease and higher odds to improve with therapy, than to identify them in mixed cirrhotic populations (Child Pugh class A-B), affected by a more advanced disease with a higher proportion of CSPH and at risk of complications, and in whom mechanisms of hepatocarcinogenesis might have been already initiated.

The aim of the present study was to describe the incidence of LRE in a population of HCV cACLD patients who achieved SVR after DAA therapy and identify non-invasive parameters (serological and elastographic) to predict the occurrence of LRE.

METHODS

This is a prospective cohort study from two tertiary hospitals (Hospital Universitari Vall d'Hebron and Hospital Clinic) from Barcelona, Spain. All adult patients (≥18 years old) who started DAA therapy for HCV infection between January 1st, 2015 and March 31st, 2016 were assessed to participate in the study. The inclusion criteria were: 1) suspected cACLD defined by LSM ≥10 kPa and no prior decompensation (ascites, variceal bleeding, hepatic encephalopathy or jaundice) according to Baveno VI definition [8]; 2) confirmed SVR 12 weeks after finishing therapy; and 3) Child Pugh class A. Patients were excluded when 1) LSM was not available before starting therapy; 2) had history of prior HCC or developed HCC before confirming SVR; 3) had prior liver transplant or 4) had concomitant coinfection with hepatitis B virus and/or human immunodeficiency virus. All consecutive patients who accepted to participate in the study were included. The study was conducted in accordance with the Declaration of Helsinki. The ethical review boards of each participating center approved the protocol. All patients gave written informed consent before the inclusion.

Study procedures

Data on demographics (age, gender, body mass index), HCV-genotype, type of DAA therapy and laboratory parameters before starting therapy such as platelet count, renal function, transaminases, INR, albumin, bilirubin, Child-Pugh and MELD scores were collected to define baseline characteristics. Data on abdominal ultrasound performed within 6 months before starting therapy was also collected. SVR was defined as undetectable HCV RNA at 12 weeks after finishing treatment using the Cobas AmpliPrep/Cobas TaqMan (Roche Molecular Diagnostics, Pleasanton, CA; lower limit of detection, 15 IU/mL). Once SVR was

confirmed, patients underwent abdominal ultrasound and laboratory work-up every 6 months, as per standard clinical practice, and LSM at 12 months after finishing treatment.

Liver stiffness measurement

LSM was performed using transient elastography (Fibroscan 502 Touch, Echosens, Paris, France) at baseline (within 6 months before starting treatment) and at one year after finishing treatment, in a fasting state, performed by a single experienced operator in each center and according to the usual standard procedure. Quality criteria used in both centers were: at least 10 valid measurements and an interquartile to median ratio ≤30%. Only valid assessments were considered for the analysis. During follow-up, improvement in LSM was defined as a decrease of ≥20% from basal LSM. This criterion was used because values above and below 15% were considered as a normal variability of the procedure (as defined per the interquartile to median ratio of 30%).

Liver related events and follow-up

During follow-up any LRE was registered. LRE were defined as occurrence of ascites, variceal bleeding, hepatorenal syndrome, hepatic encephalopathy or HCC. Follow-up started when DAA therapy was finished, however only LRE occurring after SVR was confirmed were considered. Mortality was also registered as liver-related or non-liver-related. Patients were followed until the first occurrence of LRE, death or until the end of December 2018, whichever event occurred first. Patients who were lost during follow-up, the last day known alive was registered.

Statistical analysis

For the descriptive analysis, quantitative variables were expressed as median (25th percentile – 75th percentile, interquartile range (IQR)) and qualitative variables as absolute frequency and percentage. Comparisons between groups for continuous variables were performed using Student's t test and for categorical variables using Chi-square test or Fisher's test, when appropriate. Paired data (LSM at baseline and at follow up) were analyzed using pair t test.

Due to different mechanism of occurrence and different factors that could influence its occurrence, LRE were described separately according to those related to portal hypertension (ascites, variceal bleeding, hepatorenal syndrome, hepatic encephalopathy) and HCC events. Kaplan-Meier method was used to estimate the cumulative incidence of LRE in the cohort. Comparison of the survival curves between groups was performed using the log-rank (Mantel-Cox) test. Data was censored when any of the following: LRE, death, lost or end of follow up (until 31st December, 2018), occurred first. Univariate and multivariable Cox regression analysis were performed to identify predictors of LRE. Variables found to be statistically significant in univariate analyses (defined as $p<0.1$) were included in the multivariate analysis by forward stepwise approach. Significant variables ($P<0.05$) were kept in the final Cox model to assess the hazard of LRE. The results are expressed as adjusted hazard ratio (HR) and their 95% confidence intervals (CI). Significance was considered as 2-sided p values <0.05. A nomogram was constructed to predict the risk of HCC during follow up [10]. Statistical analyses were performed using STATA 13.1 statistical software (StataCorp, College Station, TX, US).

RESULTS

Study population

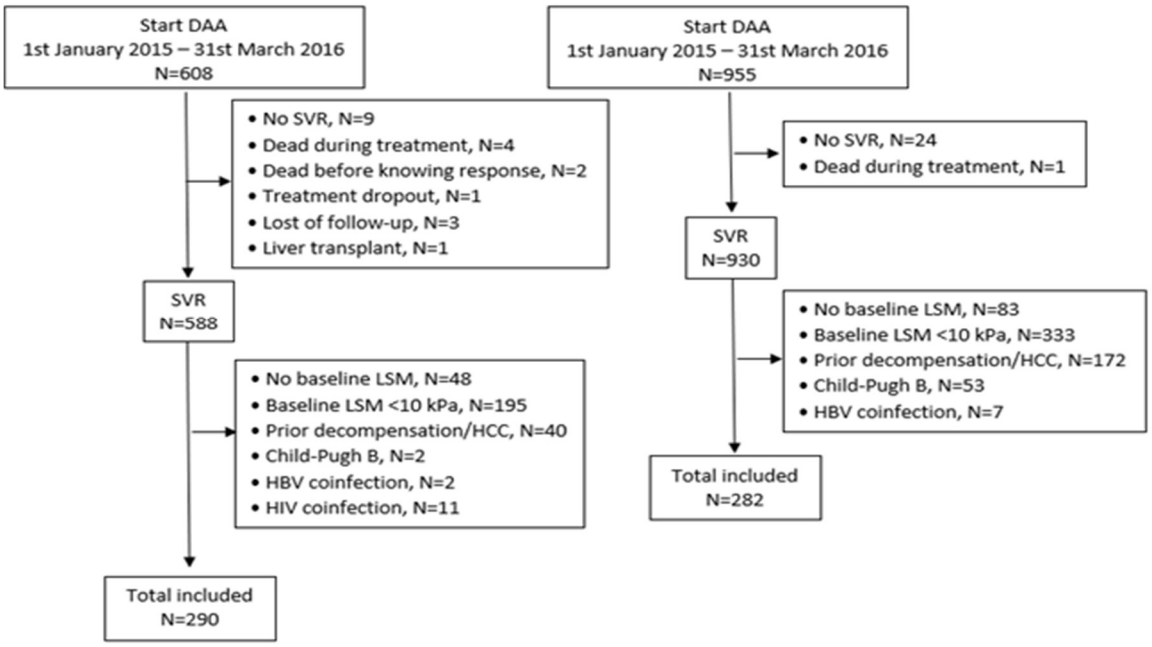


Figure 1. Study flowchart from both Hospital Vall d'Hebron (left) and Hospital Clinic (right) cohorts.

A total of 1,563 patients in both centers who started DAA therapy between January 1st, 2015 and March 31st, 2016 were evaluated for eligibility. Of them, in 1,518 patients (97.1%) SVR was confirmed and finally, a total of 572 cACLD patients were included in the study (Figure 1). The baseline characteristics of the included patients are described in table 1. The median age of the included patients was 65.2 years and 49.3% were male. Most patients had HCV genotype 1 (85.8%) and 78.1% patients were treated during 12 weeks with DAA. Some differences were detected in both cohorts. Patients from Hospital Clínic had lower platelet counts, higher bilirubin, ALT and albumin levels and higher LSM at baseline than in the Vall d'Hebron cohort.

Evolution of LSM after DAA therapy

At baseline, median LSM was 17.3 kPa (IQR 13.5-23.9 kPa). LSM was repeated in 554 patients after one year of follow-up, improving to a median of 11.1 kPa (IQR 8.1-16.8 kPa) (P<0.001), with a median decrease from baseline of 35.2%. LSM improved (defined as decrease from baseline ≥20%) in 391 patients (70.6%). Figure 2 depicts distribution of LSM at baseline and at follow up according to LSM value only in patients with both measurements; remarkably, almost 40% of the patients achieved LSM <10 kPa at follow up.

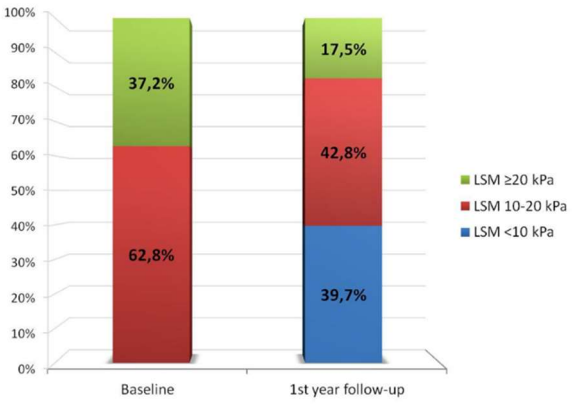


Figure 2. Proportion of patients in each category according to liver stiffness measurement (LSM) at baseline and at first year of follow up (N=554).

Characteristics	Total cohort N=572	Vall d'Hebron Hospital N=290	Hospital Clinic N=282	P value
Age, years	65.2 (55.1-72.3)	65.3 (54.4-73.1)	65.1 (55.8-71.8)	0.895
Body mass index, kg/m^2	26.1 (24.0-28.7)	26.8 (24.2-29.2)	25.6 (23.7-28.4)	0.105
Male, n (%)	282 (49.3)	144 (49.7)	138 (48.9)	0.864
Diabetes, n (%)	125 (21.9)	61 (21)	64 (22.7)	0.632
Arterial hypertension, n (%)	262 (45.8)	135 (46.6)	127 (45)	0.717
HCV genotype, n (%)				0.216
1	490 (85.8)	243 (83.8)	247 (87.9)	
2	10 (1.8)	5 (1.7)	5 (1.8)	
3	39 (6.8)	20 (6.9)	19 (6.8)	
4	32 (5.6)	22 (7.6)	10 (3.6)	
DAA therapy, n (%)				<0.001
SOF + Simeprevir	138 (24.1)	96 (33.1)	42 (15)	
SOF + Ledipasvir	226 (39.5)	140 (48.3)	86 (30.5)	
SOF + Daclatasvir	38 (6.6)	22 (7.6)	16 (5.7)	
PTV/r/O/D	130 (22.7)	21 (7.2)	109 (38.7)	
Other	40 (7)	11 (3.8)	29 (10.3)	
Ribavirin, n (%)	389 (68.1)	182 (63)	207 (73.4)	0.007
Treatment duration, n (%)				0.967
12 weeks	447 (78.1)	223 (76.9)	224 (79.4)	
24 weeks	125 (21.9)	67 (23.1)	58 (20.6)	
Varices*, n (%)				<0.001
No	168 (57.7)	83 (72.8)	85 (48)	
Grade I	89 (30.6)	23 (20.2)	66 (37.3)	
Grade II	8 (2.8)	7 (6.1)	1 (0.6)	
Grade III	26 (8.9)	1 (0.9)	25 (14.1)	
Platelet count, x10^9/L	129.5 (95.5-176)	142.5 (107-194)	118 (86-152)	<0.001
INR	1.07 (1-1.15)	1.02 (0.96-1.08)	1.12 (1.07-1.19)	<0.001
Bilirubin, mg/dL	0.8 (0.6-1.1)	0.8 (0.6-1.0)	0.9 (0.7-1.2)	<0.001
ALT, IU/L	86 (58-131)	77 (50-119)	96 (66-143)	0.001
Albumin, g/dL	4.2 (3.9-4.4)	4.1 (3.8-4.3)	4.2 (4-4.4)	<0.001
FIB-4 score	4.5 (2.6-6.7)	3.7 (2.2-6.0)	5.2 (3.3-7.6)	0.002
APRI score	1.8 (1.0-3.1)	1.5 (0.8-2.6)	2.2 (1.4-3.6)	<0.001
Child Pugh score, n (%)				0.447
5	521 (91.1)	261 (90)	260 (92.2)	
6	51 (8.9)	29 (10)	22 (7.8)	
Baseline LSM, kPa	17.3 (13.5-23.9)	16.2 (12-21.5)	17.6 (14.3-26.3)	0.004
LSM ≥20 kPa, n (%)	212 (37.1)	90 (31)	122 (43.3)	0.002

Table 1. Baseline characteristics of the patients included in the study.
*Data on previous upper gastrointestinal endoscopy was obtained from 114 patients in Vall d'Hebron Hospital and 177 in Hospital Clinic.
N: number of patients; HCV: Hepatitis C virus; DAA: Direct-antiviral agents; SOF: Sofosbuvir; PTV/r/O/D: Paritaprevir/ritonavir/Ombitasvir/Dasabuvir; ALT: Alanine-aminotransferase; LSM: Liver stiffness measurement.

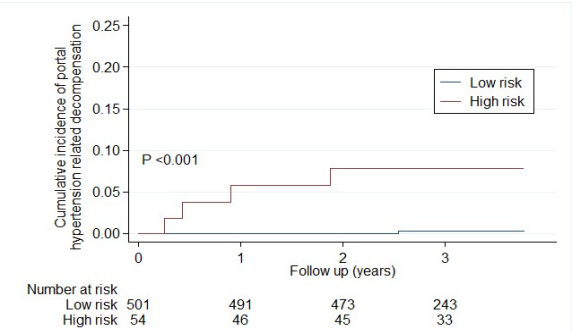
Follow up and liver related events

The median follow-up was 2.9 years (range 0.3-3.8 years) during which 17 patients (3%) were lost of follow up, 5 patients (0.9%) died from non-liver related causes and 32 patients (5.6%) presented LRE. No patients died due to liver related causes.

The most frequent LRE was HCC that occurred in 25 patients (4.4%) being the incidence rate 1.5/100 patient-years. The median time for HCC occurrence was 1 year (range 0.4-3.3 years). There were 5 patients (0.9%) who presented a portal hypertension related decompensation (2 patients suffered from variceal bleeding and 3 patients had ascites). The incidence rate for these decompensations was 0.31/100 patient-years. Two additional patients developed a cholangiocarcinoma (0.3%) during follow up (incidence rate 0.1/100 patient-years).

Factors related to portal hypertension decompensation

Due to the low incidence of events (5 patients; 0.9%), it was not possible to find predictors of occurrence of portal hypertension related events. All these 5 patients had baseline LSM >20 kPa. During follow-up, LSM only improved (decrease ≥20%) in one of the 5 patients. Four patients had baseline platelet count below 100x109/L, whereas the one whose LSM improved had baseline platelet count of 160x109/L. Characteristics of these patients are described in Supplementary table 1.



Supplementary figure 1. Kaplan-Meier showing the cumulative incidence of portal related decompensation according to patients with baseline LSM ≥20 kPa and lack of LSM improvement at follow-up (high risk) and patients who did not fulfil these characteristics (low risk).

Based on LSM, patients who had baseline LSM ≥20 kPa and lack of LSM improvement during follow up had an increased risk of developing liver decompensation (HR 39.7; 95% CI: 4.4 to 355.4) (Supplementary figure 1). Estimated incidence in this high-risk group was 2.7/100 patient-years vs 0.07/100 patient-years in the low risk group (P <0.001).

Predictors of HCC occurrence

As shown in table 2, by univariate analysis, patients who developed HCC during follow-up were older, had lower baseline and follow up albumin levels and less frequently had LSM<10 kPa at first year of follow up. Liver stiffness at follow up was higher in patients who presented HCC, but these differences were not statistically significant. By multivariate analysis, at baseline, only albumin levels (HR 0.29, 95% CI: 0.11-0.76, P=0.012) were independently associated with risk of presenting HCC during follow-up. At follow up, albumin levels (HR 0.08, 95% CI: 0.02-0.25, P <0.001) and LSM <10 kPa at follow-up (HR 0.33; 95% CI: 0.11-0.96, P=0.042) were the only predictors associated with risk of presenting HCC during follow-up.

In order to construct a simple model to predict the risk of HCC, survival curves among different subgroups based on multivariate analysis were evaluated. We categorized baseline LSM by different stablished cut-offs (<15 kPa, 15-20 kPa, ≥20 kPa) to compare risk groups [8]. Thus, patients with LSM >15 kPa were highly suggestive of having cACLD and patients

Subject	Liver related event	Baseline LSM	Follow-up LSM	Delta LSM	Baseline platelet count ($x10^9$/L)	Baseline bilirubin (mg/dL)	Baseline albumin (g/dL)	MELD score	FIB-4 score
Patient #1	Ascites	45	50.5	12.2%	99	0.6	4	7	6.7
Patient #2	Variceal bleeding	23.1	16.3	-29.4%	160	0.8	4.2	8	7.9
Patient #3	Ascites	29.1	60.4	108%	96	1	4.3	9	5.3
Patient #4	Ascites	32.8	35.2	7.3%	34	1	3.3	8	16.8
Patient #5	Variceal bleeding	20.1	26.3	30.8%	65	1.3	2.9	9	12.6

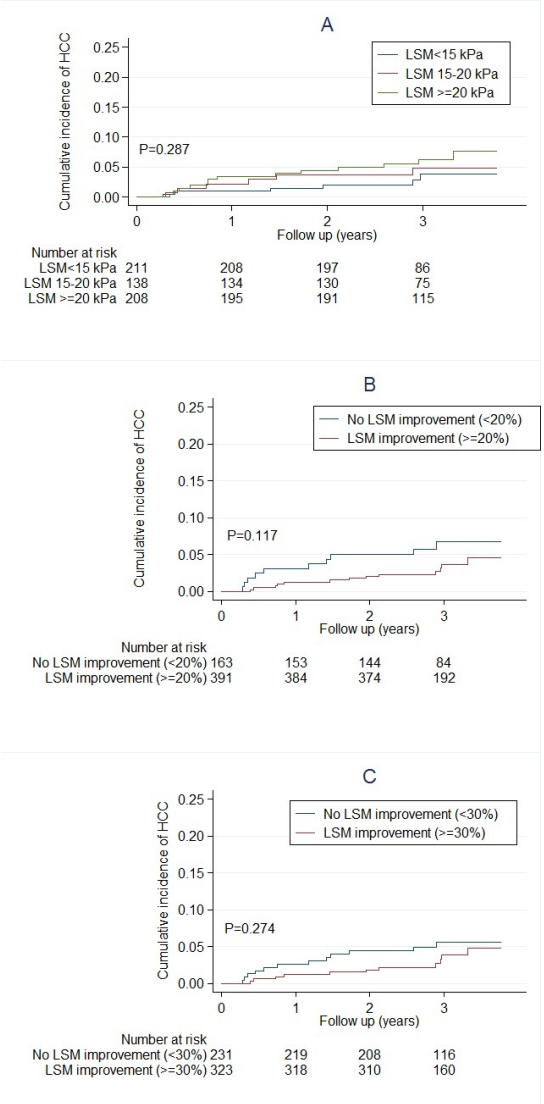
Supplementary table 1. Elastographic and laboratory parameters of patients who developed portal hypertension complications.
LSM: Liver stiffness measurement; Delta LSM: (Follow up LSM-Baseline LSM)/Baseline LSMx100; MELD: Model for end-stage liver disease.

with LSM ≥20 kPa had very high probability of having CSPH. As detected in multivariate analysis, no differences were observed in HCC occurrence according to baseline LSM (supplementary figure 2A) (P=0.287). Moreover, there were no differences in HCC occurrence in patients according to LSM improvement, neither when improvement was defined as a decrease in ≥20% (P=0.117) nor when defined as recently published (decrease in ≥30%) (P=0.274) (Supplementary figure 2B and 2C) [11].

As previously shown in table 2, HCC risk was different in patients according to baseline albumin. When selecting the cut-off of 4 g/dL based on the mean value, patients with albumin <4 g/dL at baseline had an increased risk of HCC occurrence compared to those with baseline albumin ≥4 g/dL (HR 3.27; 95% CI: 1.45-7.36; P=0.004) (Figure 3A). On the other hand, patients had different risk of developing HCC according to LSM during follow-up, observing a linear trend, that is, the higher the LSM at follow up the higher the risk of HCC (Figure 3B). Patients with LSM at follow up between 10-20 kPa had an increased, but not significant risk of HCC compared to those with LSM <10 kPa at follow up (HR 2.48; 95% CI: 0.79-7.80, P=0.120), while the HR for HCC was 4.53 (95% CI: 1.36-15.08, P=0.014) for patients with LSM ≥20 kPa at follow up compared to those with LSM <10 kPa (Figure 3B). HCC risk was also different according to albumin levels during follow up. Patients with albumin <4.4 g/dL (based on the mean value) had a high risk of developing HCC (HR 2.36; 95% CI: 1.02-5.47; P=0.046) (Figure 3C).

Characteristics	**No HCC N=547**	**HCC N=25**	**P value**	**Multivariate analysis HR (95% CI; P value)**
At baseline				
Age, years	65.1 (54.8-72.1)	70.5 (64.2-74.5)	**0.011**	1.04 (1-1.1; P=0.064)
Body mass index, kg/m^2	26.1 (24-28.7)	26.3 (23.8-29.3)	0.438	---
Male, n (%)	269 (49.2)	13 (52)	0.783	---
Arterial hypertension, n (%)	249 (45.5)	13 (52)	0.526	---
Diabetes, n (%)	117 (21.4)	8 (32)	0.210	---
Platelet count, x10^9/L	129 (96-176)	131 (90-206)	0.305	---
Platelet <150x10e9/L, n (%)	347 (63.4)	15 (60)	0.728	---
Bilirubin, mg/dL	0.8 (0.6-1.1)	0.9 (0.7-1.2)	0.388	---
ALT, IU/L	87 (58-131)	80 (56-119)	0.202	---
Albumin, g/dL	4.2 (3.9-4.4)	3.9 (3.6-4.2)	**0.003**	**0.29 (0.11-0.76; P=0.012)**
FIB4	4.5 (2.6-6.7)	4.5 (2.8-8)	0.745	---
APRI	1.8 (1.1-3.1)	1.9 (0.8-3.1)	0.452	---
MELD=6, n (%)	132 (24.1)	5 (20)	0.705	---
Baseline liver stiffness, kPa	17.1 (13.4-23.9)	20.8 (15.1-26.3)	0.245	---
Baseline LSM <20 kPa, n (%)	348 (63.6)	12 (48)	0.114	---
At follow up				
Body mass index, kg/m^2	27 (24.6-29.7)	26.4 (25-28)	0.655	---
Platelet count, x10^9/L	161 (121-215)	126 (110-215)	0.470	---
Bilirubin, mg/dL	0.7 (0.5-0.9)	0.7 (0.6-0.8)	0.908	---
Albumin, g/dL	4.4 (4.2-4.6)	4.1 (3.8-4.4)	**<0.001**	**0.08 (0.02-0.25; P <0.001)**
Follow-up Liver stiffness, kPa	10.9 (8-16.5)	17.4 (10.2-21.1)	0.089	---
Delta LSM, %	-35.3 (-49- -17.3)	-26.5 (-51.7-5.1)	0.355	---
LSM improvement*, n (%)	378 (71.2)	13 (56.5)	0.131	---
Follow-up LSM <10 kPa, n (%)	216 (40.7)	4 (17.4)	**0.025**	**0.33 (0.11-0.96; P=0.042)**

Table 2. Factors associated with risk of presenting HCC occurrence.
N: number of patients; HCC: Hepatocellular carcinoma; HR: Hazard ratio; CI: Confidence interval; MELD: Model of end stage liver disease; ALT: Alanine-aminotransferase; LSM: Liver stiffness measurement; *LSM improvement: Decrease in LSM ≥20% at follow up, compared to baseline.



Supplementary figure 2. Kaplan Meier describing the cumulative incidence of HCC occurrence according to different risk groups: A) Baseline LSM categorized; B) Improvement in LSM at follow up defined as a decrease in ≥20%; C) Improvement in LSM at follow up defined as a decrease in ≥30%. HCC: hepatocellular carcinoma; LSM: Liver stiffness measurement.

We combined both follow up albumin and LSM to identify risk groups according to predictors gathered at the same time point (1 year after finishing treatment). Table 3 shows the incidence rate of HCC according to different combinations of albumin and LSM at follow up. Incidence rates of HCC were <1/100 patient-years in patients with LSM <10 kPa at follow up and in those with LSM between 10-20 kPa and high albumin levels (≥4.4 g/dL at baseline). On the contrary patients with LSM ≥20 kPa at follow up and those with LSM 10-20 kPa and low albumin levels (<4.4 g/dL) have incidence rates of HCC ≥1.9/100 patient-years, indicating that albumin levels only impacted in HCC risk in patients with LSM between 10-20 kPa. Therefore, we identified two main risk groups, a low-risk group and a high-risk group of presenting HCC, with different estimates of HCC incidence (Figure 4). A Cox regression model was constructed using these variables (Albumin <4.4/≥4.4 and LSM at follow up <10 kPa/10-20 kPa/≥20 kPa) with a good predictive power (Harrell's C index = 0.73) (Supplementary figure 3). In figure 5, two nomograms to predict the probability of HCC occurrence during time according to albumin levels and LSM at follow up are shown.

DISCUSSION

The main findings of the present study with a cohort of HCV cACLD patients who achieved SVR after DAA therapy were, first, that the incidence of LRE was relatively low, being de novo HCC the most frequent complication and second, that using simple non-invasive predictors (albumin and LSM at follow up) we could identify two different risk groups of patients presenting HCC during follow up.

Several studies have demonstrated that in patients who have achieved SVR after DAA therapy the incidence of HCC decrease and the main predictor of its occurrence, as expected, is the presence of cirrhosis, being patients affected with a more advanced liver disease (such decompensated cirrhosis) and those with a history of HCC, the ones with the highest risk [12–21].

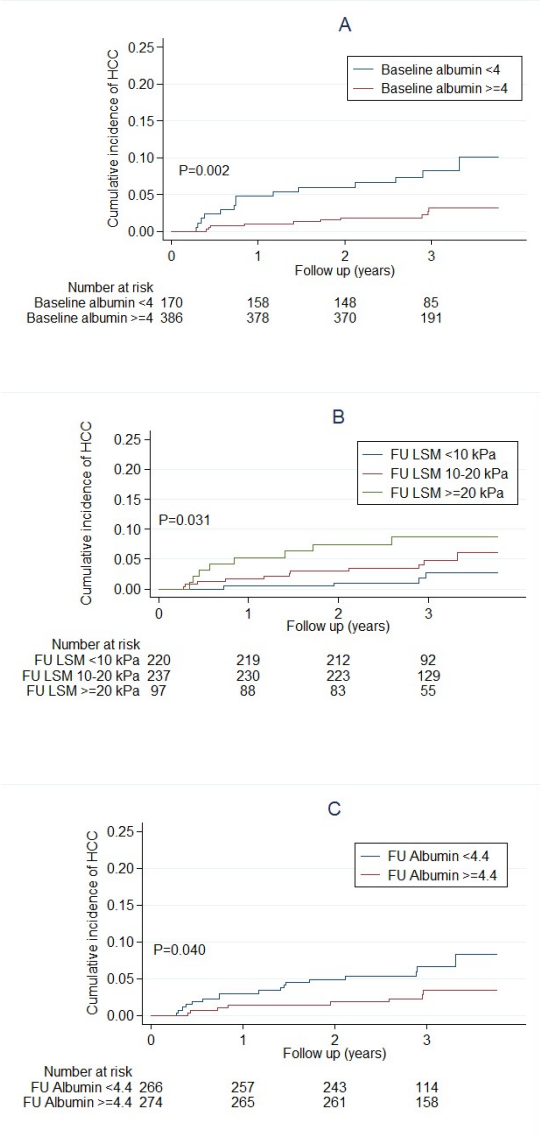


Figure 3. Cumulative incidence of HCC occurrence according to different subgroups: A) Albumin levels at baseline; B) Follow up LSM; C) Follow-up albumin levels. FU: Follow up; HCC: Hepatocellular carcinoma; LSM: Liver stiffness measurement.

HCC was the main complication observed in our study. There were 25 patients (4.4%) who developed HCC, that is 78% of all LRE observed in the cohort. The incidence rate of HCC was 1.5/100 patients-year. This incidence was similar to previous reported series which included patients with cirrhosis [16–18,22,23]. In contrast to what has been previously reported, when we stratified the risk of HCC according to LSM at baseline, we did not find differences in HCC incidence among patients with LSM ≥20 kPa and those with LSM <20 kPa. Two studies reported that patients with high baseline LSM had an increased risk of HCC [15,24]. In the study of Conti, et al., LSM ≥21.3 kPa was associated with a higher risk of presenting HCC (OR: 4.24, 95% CI: 1.50–11.97) [15]. In the same line, Degasperi, et al. found that baseline LSM was a predictor of de novo HCC being the best cut-off LSM ≥30 kPa [24]. In our cohort 212 patients had baseline LSM ≥20 kPa and of them 13 (6.1%) presented HCC, while HCC occurred in 12 patients with baseline LSM <20 kPa (3.3%), being these differences not statistically significant. One explanation of these differences between our study and previously published studies is that in both previous studies Child Pugh B patients were included. Although distribution of LSM was not described according to Child Pugh class, probably those patients with worse liver function had also higher LSM and this could overestimate the effect of baseline LSM as a predictor of HCC. In our cohort, only including patients with Child Pugh class A and no prior history of HCC, baseline LSM did not discriminate the occurrence of HCC.

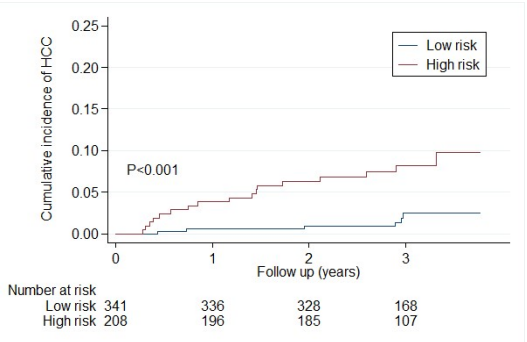


Figure 4. Cumulative incidence of HCC occurrence according to low risk group (follow up LSM <10 kPa or follow up LSM 10-20 kPa + follow up albumin ≥4.4 g/dL) or high-risk group (follow up LSM ≥20 kPa or follow up LSM 10-20 kPa + follow up albumin <4.4 g/dL).

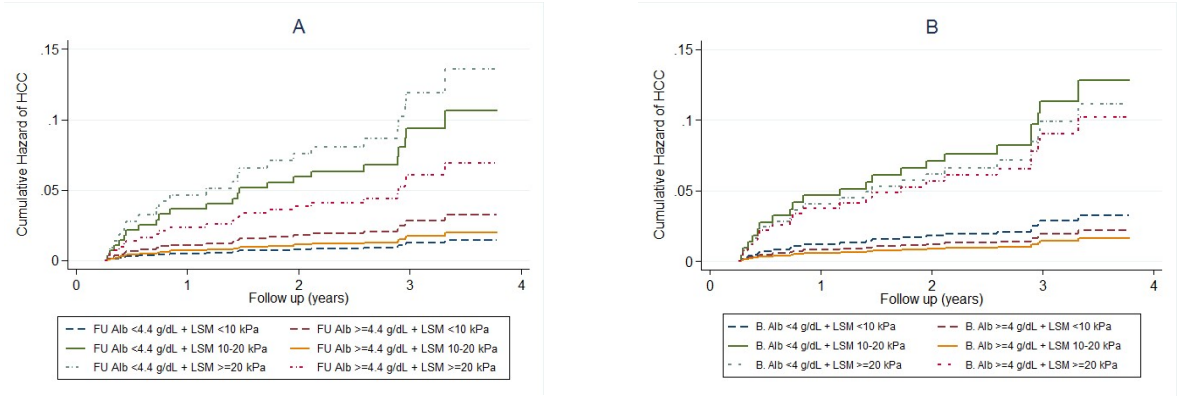
Category	Number of HCC	Patient-years	Incidence rate/100 patient-years
Albumin at follow up:			
≥4.4 g/dL	8	825	1.0
<4.4 g/dL	17	750	2.3
LSM at follow up*:			
LSM <10 kPa	4	593	0.7
LSM 10-20 kPa	11	645	1.7
LSM ≥20 kPa	8	250	3.2
Combining LSM and albumin			
LSM <10 kPa			
+ ≥4.4 g/dL	3	351	0.9
+ <4.4 g/dL	1	271	0.4
LSM 10-20 kPa			
+ ≥4.4 g/dL	2	368	0.5
+ <4.4 g/dL	9	318	2.8
LSM ≥20 kPa			
+ ≥4.4 g/dL	2	106	1.9
+ <4.4 g/dL	6	161	3.7

Table 3. Incidence rates of HCC in the cohort according to different subgroups (both albumin and LSM at follow up).
HCC: Hepatocellular carcinoma; LSM: Liver stiffness measurement (at follow up)
* In 2 patients with HCC LSM was lacking.

A retrospective study from Ravaioli, et al. including 139 patients with cirrhosis (11.5% Child Pugh B and 13.7% with previous HCC background) reported that a decrease of 30% in LSM was one of the predictors that was inversely associated with the risk of presenting HCC [11]. In our cohort, LSM improvement (defined as LSM decrease ≥20%) was not associated with the risk of HCC. LSM improved in 13 patients (52%) who developed HCC and in most of the patients who did not develop HCC (71.2%). This probably reflects that most of the early dynamic changes in LSM are related to improvement in liver inflammation and they do not accurately reflect improvement in fibrosis. It is important to note that, these high rates of LSM improvement does not translate to a decreased risk of HCC and for this reason is important to continue HCC surveillance.

The main predictors related to HCC risk in our study were albumin and follow up LSM. Although most of the patients had normal albumin levels, the risk of HCC was reduced by 58% in patients with albumin ≥4.4 g/dL at follow up. Based on both predictors (albumin and LSM at follow up), we could identify two main risk groups: patients with LSM at follow up <10 kPa or patients with LSM between 10 and 20 kPa with albumin ≥4.4 g/dL at follow up had a lower incidence of HCC (0.6/100 patients-year) compared to patients with LSM ≥20 kPa at follow up or those with LSM between 10-20 kPa but albumin <4.4 g/dL at follow up (2.9/100 patients-year). It has to be highlighted that 220 patients achieved LSM <10 kPa during follow-up and of them, 4 patients (1.8%) developed HCC. Although the risk is much lower than in patients with highest LSM at follow up, the recommendation, as in recently published guidelines, is to continue HCC surveillance after SVR in patients with pre-treatment LSM ≥10 kPa until information about longest follow up is available [25]. However, a recent study reported that surveillance for patients with advanced fibrosis (i.e. F3) who achieved SVR is not cost-effective due to the low incidence of HCC, questioning the need of continued surveillance for some specific subgroups of patients [26].

The incidence of portal hypertension-related complications was very low in this cohort, since only 5 patients (0.9%) presented liver decompensation (3 ascites and 2 variceal bleeding). This is the first prospective study with cACLD patients that reports portal hypertension complications after achieving SVR. In previous studies it has been demonstrated that SVR after DAA therapy reduces the incidence of portal hypertension-related complications [19]. However, contrary to the present study, most of the series that have evaluated the incidence of portal hypertension-related complications



Supplementary figure 3. Predictive HCC occurrence according to different subgroups in the multivariate model. A: Using follow up albumin and LSM in the multivariate model; B: Using baseline albumin and LSM at follow up in the multivariate model was also predictive of HCC occurrence. HCC: Hepatocellular carcinoma; FU Alb: Follow up albumin; LSM: Liver stiffness measurement at follow up; B. Alb: Baseline albumin.

after DAA therapy have included patients with compensated and decompensated cirrhosis and some of the predictors that had been related to decompensation, such as previous decompensation, cannot be applied in this cohort with cACLD [20,27–29]. Although we could not find predictors of decompensation due to the low incidence rates, all 5 decompensated patients had baseline LSM ≥20 kPa and in 4 out of 5 patients LSM did not improve after SVR, remaining >20 kPa. These 4 patients have also platelet count below 100x109/L. This suggests that these patients had more advanced liver disease and SVR did not reduced the risk of decompensating. Although values of LSM have not been yet validated in non-viremic patients, LSM >20 kPa after SVR seems to have high specificity in ruling in the presence of CSPH and our results support this evidence [30–32]. There was one patient, however, who developed variceal bleeding during follow up and LSM improved from 23.1 kPa to 16.3 kPa during follow up. Indeed, Lens, et al. reported that in patients with LSM <13.6 kPa at 6 months of follow up, CSPH was still present in 43% of patients [31].

Our study has some limitations. LSM were performed after one year of finishing treatment and therefore we do not have information about dynamics before and beyond that. The earliest a predictor can be determined, the more useful it is. Considering that most of the LSM decrease after SVR occurs early (at the end of therapy) [33] and that LSM values do not change much afterwards, it is plausible to assume that the same predictions about LRE presented here can be done using LSM values obtained right

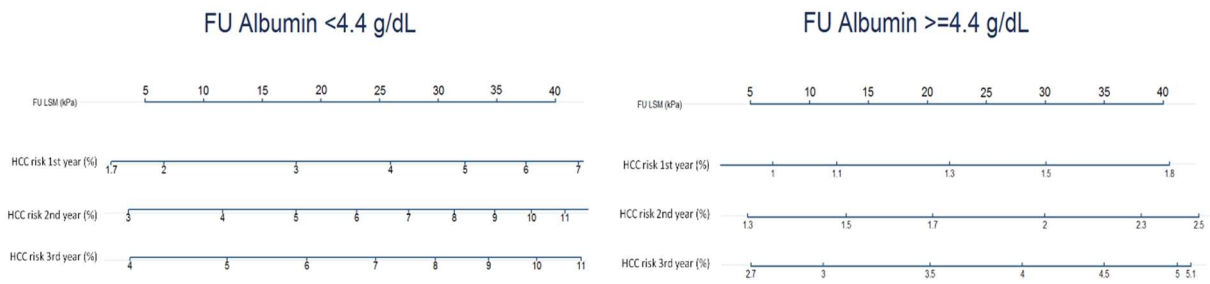


Figure 5. Nomogram to predict the risk of hepatocellular carcinoma (HCC) according to albumin and liver stiffness measurement (LSM) at follow-up (FU).

after finishing therapy. Another limitation is that the current results can only be applied to patients in which a LSM can be obtained and it is reliable. However, the strength of our study relies on being the first prospective bicentric study reporting outcomes after SVR of a large cohort of cACLD patients, Child Pugh A, with a follow up to 3.5 years, providing useful information about the prognosis and simple prediction of events in asymptomatic patients with advanced liver disease.

In conclusion, the present study demonstrates that in patients with cACLD who have achieved SVR with DAA, HCC occurrence is the most frequent liver-related complication. Both albumin levels and LSM during follow up can help to identify patients with a highest risk of presenting HCC. Although patients with LSM <10 kPa at follow up have a low risk of presenting HCC, a zero-risk subpopulation cannot be found, thus, HCC surveillance needs to be considered for all patients classified as having cACLD before therapy.

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Annex 2: Finançament i beques

Durant el període en qual s'han portat a terme els estudis de doctorat i la formació investigadora, la doctoranda ha rebut les següents ajudes:

- Contracte predoctoral PFIS, Instituto de Salud Carlos III, 2015-2018
- Contracte Río Hortega, Instituto de Salud Carlos III, 2019-present.

Els estudis que conformen la present tesi han estat finançats parcialment per:

- PI13/01289, PI14/00331, PI15/00066, PI18/00079, PI18/00961 i PI18/00947 de l'Instituto de Salud Carlos III i cofinançat per la Unió Europea (ERDF/ESF, "Investing in your future" – Una manera de hacer Europa).

- Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto de Salud Carlos III, Madrid.

Annex 3: Altres publicacions relacionades amb la tesi

Pons M, Simón-Talero M, Millán L, Ventura-Cots M, Santos B, Augustin S, Genescà J. Basal values and changes of liver stiffness predict the risk of disease progression in compensated advanced chronic liver disease. Dig Liver Dis. 2016;48:1214-9.

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Augustin S, Pons M, Genesca J. Validating the Baveno VI recommendations for screening varices. J Hepatol. 2017 Feb;66(2):459-460.

DOI: 10.1016/j.jhep.2016.09.027.

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Validating the Baveno VI recommendations for screening varices

To the Editor:

We read with great interest the recent article by Maurice *et al.* [1], in which they essentially confirm the validity of the recent Baveno VI recommendations regarding the use of transient elastography and platelet count for the screening and surveillance of gastroesophageal varices in patients with compensated advanced chronic liver disease (cACLD) [2]. Based on preliminary information from a few studies [3], the Baveno VI recommendations indicated that in patients with cACLD a liver stiffness measurement <20 kPa and a platelet count >150,000 cells/μl have a very low risk of having varices needing treatment (large varices) and consequently can avoid screening endoscopy [2]. The guidelines also advise longitudinal follow-up of these patients by annual repetition of transient elastography and platelet count, advising screening endoscopy if liver stiffness increases or platelets decrease.

The manuscript by Maurice *et al.* is the first full report after the publication of the Baveno VI Consensus report. In this study, out of 310 cACLD patients included, 102 (33%) were within the Baveno VI criteria and in this group, only two patients had large varices, representing that from the total cohort studied only 0.6% of patients with varices needing treatment would have been missed (Table 1). In addition, the authors recognized that one of these patients, who had unexpectedly high platelet levels, presented with a thalassaemia major after a prior splenectomy, and consequently the recommendations could not be applied. Another lesson to learn from this study is that common sense and careful consideration of confounding factors are the key to having an adequate applicability of clinical recommendations. Finally, another important contribution of Maurice *et al.*'s work is that the guideline recommendations seemed to perform equally well for patients with alcoholic or non-alcoholic fatty liver disease. This information, which is greatly needed, should be taken with caution due to the low number of patients of each aetiology included.

In addition to the Maurice *et al.* study, many other studies have already been reported following the publication of the Baveno VI guidelines (Table 1). Apart from the initial report by Perazzo *et al.* in this journal [4], up to seven more reports, mainly presented in the recent EASL meeting at Barcelona are now available. In summary, the Baveno VI recommendations for avoiding screening of varices in cACLD patients are clearly validated. In a total of more than 2500 patients with variable prevalence of varices, only three patients with large varices were missed after evaluating and applying the Baveno VI criteria to 1000 patients. With this strategy, around 20% of endoscopies are spared, but unfortunately, up to 40% of unneeded endoscopies would still be performed. Finally, although the Baveno VI recommendations have been a first important step, much work remains to be done. Additional classification rules or algorithms to improve them, either by changing the cut-offs of the present criteria or adding new non-invasive parameters to them, are our next challenge.

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Table 1. Summary of studies evaluating performance of Baveno VI criteria for screening endoscopy (OGD) in patients with compensated advanced chronic liver disease.

Study	N	Viral	ALD	Varices	VNT	Varices missed[#]	VNT missed[#]	OGD spared[&]	OGD unneeded[§]
Maurice *et al.* [1]	310	55%	13%	23%	5%	3.5%	0.6%	33%	48%
Perazzo *et al.* [4]	97	-	-	54%	0	6%	0	22%	29%
Tossetti *et al.* [5]	146	100%	-	45%	8%	6%	0	27%	34%
Chang *et al.*[*]	173	55%	-	31%	8%	-	1.7%	20%	-
Thabut *et al.*[*]	790	100%	-	-	-	10%	0	20%	-
Paternostro *et al.*[*]	135	47%	30%	65%	24%	3%	0	7%	30%
Silva *et al.*[*]	112	80%	7%	48%	15%	1.8%	0	11%	43%
Cales *et al.*[*]	287	26%	64%	44%	17%	2%	0	16.5%	41.5%
Ahmed *et al.*[*]	478	33%	36%	-	11%	-	0.5%	23%	-
Total	2528	-	-	41.5%	12%	4.5%	0.3%	20%	38%

N, total number of patients in the cohort; Viral, viral etiology; ALD, alcoholic liver disease; Varices, percentage of patients with any type of varices; VNT, varices needing treatment (large varices); OGD, oesophago-gastro duodenoscopy.

[*] Abstracts of the 2016 EASL meeting.

[#] Percentage of varices and VNT missed by applying the Baveno VI criteria: n varices/total n patients.

[&] Percentage of patients within the Baveno VI criteria in which OGD could be spared.

[§] Percentage of patients out of the Baveno VI criteria without varices in which OGD was unneeded.

Letters to the Editor

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Authors' contributions

SA wrote the manuscript; MP gathered the data; JG designed the work; SA, MP and JG reviewed the data and the draft.

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