Utilidad del MELD y el sodio pretrasplante en el pronóstico del trasplante hepático a corto plazo

María Carlota Londoño Hurtado

UTILIDAD DEL MELD Y EL SODIO PRETRASPLANTE EN EL PRONÓSTICO DEL TRASPLANTE HEPÁTICO A CORTO PLAZO.

Memoria de Tesis Doctoral

María Carlota Londoño Hurtado

UTILIDAD DEL MELD Y EL SODIO PRETRASPLANTE EN EL PRONÓSTICO DEL TRASPLANTE HEPÁTICO A CORTO PLAZO.

Memoria de tesis doctoral para optar al título de Doctor en Medicina

Barcelona 2011

UNIVERSIDAD DE BARCELONA

Facultad de Medicina

Departamento de Medicina

DIRECTOR: Prof. Pere Ginès Gibert

Jefe del Servicio de Hepatologia

Institut de Malalties Digestives i Metaboliques

Hospital Clínic Barcelona. IDIBAPS. CIBERehd

Profesor Departamento de Medicina

Universidad de Barcelona

AUTOR: María Carlota Londoño Hurtado

Servicio de Hepatología

Institut de Malalties Digestives i Metaboliques

Hospital Clínic Barcelona. CIBERehd

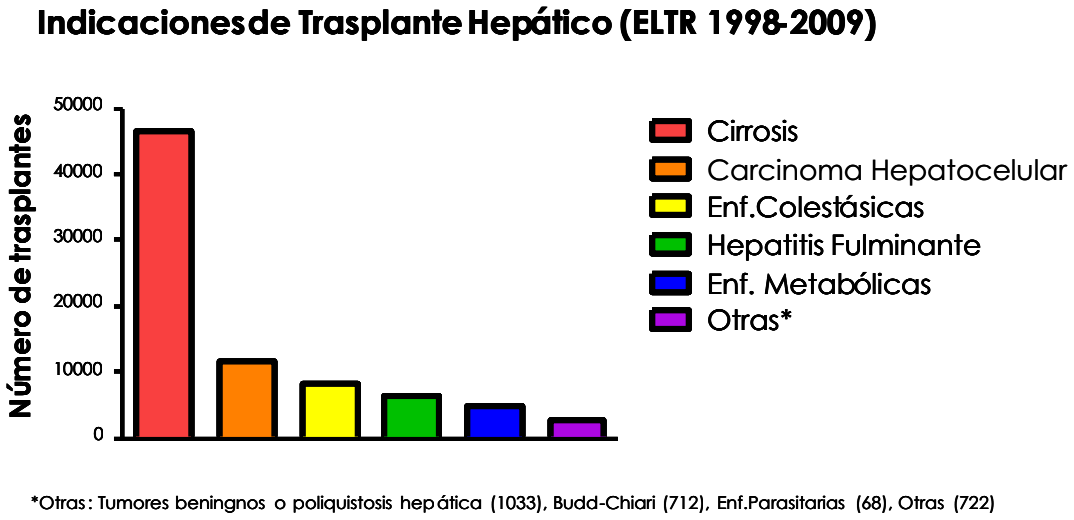
ÍNDICE

1. INTRODUCCIÓN

1.1. Trasplante hepático

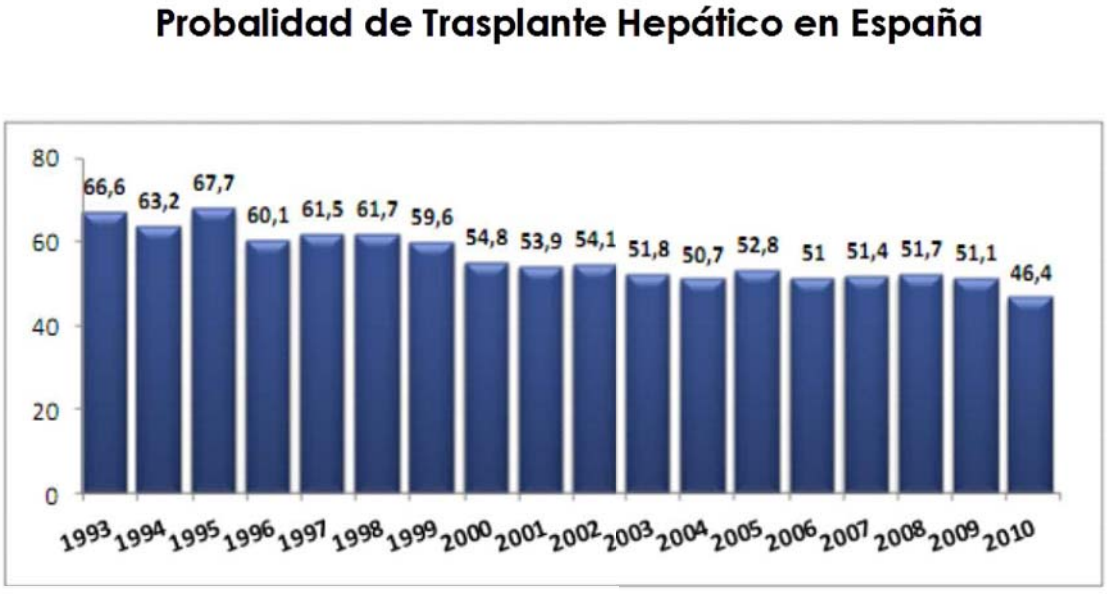
El trasplante hepático se considera el tratamiento de elección de la cirrosis hepática descompensada, el carcinoma hepatocelular, la hepatitis fulminante y algunas enfermedades metabólicas [1]. La supervivencia de los pacientes con trasplante hepático ha mejorado significativamente en la última década. Los avances en la técnica quirúrgica, el desarrollo de nuevas terapias inmunosupresoras y un mejor cuidado postoperatorio han contribuido a este aumento, con una probabilidad de supervivencia a 1, 5 y 10 años del 86%, 73% y 63%, respectivamente [2].

La indicación de un trasplante hepático debe basarse en 2 criterios: primero, el paciente debe tener una enfermedad hepática aguda o crónica irreversible o no tratable con otras terapias, y segundo, la esperanza de vida con el trasplante debe ser superior a la misma en ausencia del trasplante. Las enfermedades que indican un trasplante hepático son múltiples y en la siguiente figura se resumen las principales indicaciones según los datos del Registro Europeo de Trasplante Hepático (European Liver Transplant Registry, ELTR) durante los años 1998 a 2009 [2].



*Otras: Tumores beningnos o poliquistosis hepática (1033), Budd-Chiari (712), Enf.Parasitarias (68), Otras (722)

Según datos de la Organización Mundial de la Salud, la cirrosis hepática la octava causa de muerte en adultos de 15 a 59 años, siendo responsable de más de 300.000 defunciones [3]. Sin embargo, solo una minoría (aproximadamente una quinta parte) de ellos es remitida para valoración de trasplante hepático y un número aún menor tiene acceso a la lista de espera [4]. A pesar de las restricciones en el acceso a la lista de espera, la probabilidad de recibir un trasplante hepático, no solo en España, sino en todo el mundo sigue disminuyendo. Ello se debe a que existe una enorme desproporción entre el número de órganos disponibles y el elevado número de enfermos que necesitan un trasplante hepático. En el siguiente gráfico se puede observa como ha disminuido la probabilidad de recibir un trasplante hepático en España desde 1993 hasta el 2010 entre los paciente que se encuentran en pacientes en lista de espera en España [5].



Pacientes en lista de espera que se trasplantaron entre 1993-2010.

Esta disminución en la probabilidad de recibir un trasplante hepático hace necesario utilizar un sistema de asignación de órganos que permita otorgar el hígado a la persona que más se beneficie. El sistema ideal debe cumplir las siguientes características: 1) ser capaz de cuantificar la supervivencia a corto y medio plazo para priorizar de manera correcta los pacientes en lista de espera, 2) clasificar los pacientes de acuerdo al estadio de la enfermedad para determinar si es muy pronto, apropiado o demasiado tarde para indicar un trasplante hepático, 3) predecir el pronóstico del paciente sin importar la enfermedad de base, 4) fácil, y 5) carente de elementos subjetivos que puedan se influenciados por el juicio del clínico. Actualmente no existe una herramienta que cumpla todas estas condiciones, pero el sistema MELD es el que más se acerca [6].

1.2. MELD

El MELD (Model for End-Stage Liver Disease) se desarrolló inicialmente como una herramienta para evaluar el riesgo de muerte después de la colocación de una derivación intra-hepática porto-sistémica [7]. Este puntaje incluye variables relacionadas con la función hepática y renal (9.6[$\log_e$ creatinina en md/dL] + 3.8[$\log_e$ bilirrubina en mg/dL] + 11.2[$\log_e$ INR] + 0,643), y oscila entre 6 y 40. Tras este primer estudio, los creadores del MELD validaron los datos en una gran cohorte de pacientes y encontraron que el MELD tenía una alta precisión para estratificar los pacientes según el riesgo de muerte a 3 meses. Esta alta precisión se observó tanto en pacientes hospitalizados como en

pacientes ambulatorios con un área bajo la curva ROC (AUC) de 0,87 (IC 95% 0,82-0,92) y de 0,80 (IC 95% 0,69-0,9) [8,9]. Desde entonces el MELD es el método utilizado en la mayoría de los centros de trasplante hepático en el mundo para la asignación de órganos a pacientes en lista de espera para trasplante hepático.

El MELD tiene muchas de las características necesarias para ser considerado un buen modelo pronóstico: incorpora solo variables simples y objetivas que pueden ser determinadas en todos los laboratorios, es independiente de la etiología de la enfermedad hepática y tiene una alto valor predictivo para establecer la gravedad de la enfermedad de una forma continua [6].

A continuación se discutirá la utilidad del MELD para valorar el pronóstico de los pacientes con cirrosis hepática en lista de espera para trasplante hepático y en el periodo post-trasplante.

1.2.1. El MELD y el pronóstico en lista de espera para trasplante hepático

Dados los buenos resultados del MELD para predecir el pronóstico a corto plazo en pacientes con cirrosis hepática, en Febrero de 2002 la UNOS (United Network for Organ Sharing) decidió implementar el sistema MELD como herramienta para asignar los órganos para trasplante hepático. Desde entonces se han realizados diversos estudios que corroboran la utilidad del MELD en la valoración del pronóstico de los candidatos a trasplante. El primer estudio fue realizado por Wiesner et al en 2003, en el cual se demostró que el MELD era útil para predecir la mortalidad de los pacientes a los 3 meses su

inclusión en lista de espera. En este estudio, la mortalidad en pacientes con MELD inferior a 9 fue del 1,9%, mientras que la mortalidad en pacientes con MELD superior a 40 fue del 71,3%. El AUC del MELD en la valoración del pronóstico a 3 meses fue 0,83 (IC 95% 0,81 - 0,84) [10].

Tras la implementación del MELD como sistema de asignación de órganos, se produjo una disminución en el número de pacientes retirados de la lista de espera por progresión de su enfermedad, una disminución del tiempo medio de estancia en lista de espera y una reducción del 15 % en la mortalidad en lista [11-13]. Los resultados de estos estudios han llevado a la mayoría de los centros de trasplante en todo el mundo a adoptar el MELD como herramienta fundamental para gestionar la lista de espera para trasplante hepático.

1.2.2. El MELD y el pronóstico post-trasplante hepático.

En teoría, el modelo ideal de asignación de órganos debe favorecer, no solo a los pacientes con mayor probabilidad de morir antes del trasplante, sino también a aquellos que tengan una mayor probabilidad de vivir tras el trasplante hepático. Con los resultados de los estudios mencionados previamente parece muy claro que el MELD es un buen factor predictivo de supervivencia en lista de espera, sin embargo su utilidad para predecir la supervivencia post-trasplante es controvertida. Mientras que algunos estudios encuentran una disminución en la supervivencia en los pacientes con MELD más elevado, otros estudios no encuentran ninguna correlación [14].

En la siguiente tabla se muestran los estudios más relevantes en este sentido:

Estudio	Pacientes (n)	AUC	MELD y mortalidad post-trasplante
Kim (2001)[15]	1185	0.62	Mortalidad a 3 meses post-trasplante: MELD <10 del 5% y > 40 del 26%.
Wiesner (2001)[9]	1585	<0.70	No asociación.
Lally (2001)	376		No asociación.
Brown (2002)[16]	42		No asociación.
Onaca (2003)[17]	669		Menor supervivencia en pacientes con MELD >25 comparado con MELD <15 a 3, 6, 12, 18 y 24 meses post-trasplante.
Saab (2003)[18]	404		Mortalidad a un año: MELD <24 del 88% y MELD >24 del 65%(p <0,001).
Desai (2004) [19]	2565	0.54 (3 meses)	MELD >24 menor supervivencia a 1 año.
Jacob (2004) [20]	3838	0.58	MELD > 36
Bazarah (2004)[21]	228	0.67	El MELD no fue un factor predictivo independiente de mortalidad a 3 meses.
Habib (2004)	1472		MELD > 26 menor supervivencia a corto y largo plazo (10 años).
Yoo y Thuluvath (2005)[22]	3227		MELD mayor de 30 fue un factor predictivo independiente de mortalidad a 1 año (HR 2.9; p<0,001).
Kanwal (2005)[23]	4245		Factor predictivo independiente de mortalidad(HR 1.033; p< 0,0001)
Nagler (2005)[24]	121	0.61	No asociación.

HR: Hazard Ratio

1.2.3. Debilidades del sistema MELD.

A pesar de los numerosos estudios que demuestran la utilidad del MELD en la valoración del pronóstico de los pacientes con cirrosis hepática antes y después del trasplante hepático, el MELD es un sistema que está lejos de ser perfecto y a continuación se discuten sus debilidades.

1.2.3.1. Debilidades intrínsecas.

A pesar de que variables incluidas en el MELD (creatinina sérica, bilirrubina sérica e INR) fueron seleccionadas con base en un modelo estadístico robusto, la determinación de cada una de ellas en el laboratorio y su interpretación tienen algunas limitaciones.

Es bien sabido que la creatinina sérica está influenciada por la masa muscular, la dieta y el sexo del paciente [25]. Por otro lado los pacientes con cirrosis avanzada presentan una importante pérdida de masa muscular debida a la baja ingesta alimentaria, la disminución en la síntesis proteica y el hipermetabolismo. Todo ello hace que los valores séricos de creatinina sean más bajos en los pacientes con cirrosis hepática que en la población general y por lo tanto en este subgrupo de pacientes una creatinina normal no excluye una alteración significativa de la función renal [26]. Además en pacientes con ascitis que reciben tratamiento diurético o están en régimen de paracentesis evacuadoras, con frecuencia, la creatinina presenta fluctuaciones que producen cambios en el MELD que en realidad no reflejan un cambio significativo en el riesgo de muerte [25, 26]. Por otro lado, el tipo de técnica que se emplee en cada laboratorio para determinar la creatinina puede afectar el resultado ya que se sabe que la bilirrubina puede interferir con la determinación de la creatinina cuando se emplea el método colorimétrico, lo que puede subestimar el MELD en pacientes ictéricos [27]. Finalmente, los límites en la creatinina establecidos por la UNOS para el cálculo del MELD (entre 1 mg/dL y 4 mg/dL) pueden constituir un problema

importante ya que, por ejemplo, al seleccionar 1 mg/dL como limite inferior (para evitar valores negativos en la transformación logarítmica) se asume que todos los pacientes con creatinina inferior a 1 mg/dL tienen la misma mortalidad, lo cual no es cierto porque todos los cambios en la creatinina reflejan un cambio en la tasa de filtración glomerular [28]. Por otro lado, el corte en 4 mg/dL (para evitar un MELD muy alto en pacientes con enfermedad renal parenquimatosa) ha sido cuestionado ya que no hay datos que lo justifiquen y por el contrario puede subestimar la severidad de la enfermedad en pacientes no urémicos o en diálisis [29].

En relación a la bilirrubina sérica, se sabe que sus valores pueden fluctuar según el laboratorio en el cual se analice la muestra, un problema que es difícil de resolver [30]. Además, es importante recordar que las enfermedades colestásicas tienen una menor mortalidad en lista que las no colestásicas y por lo tanto en ellos el MELD puede sobre-estimar la gravedad de la enfermedad hepática [6].

Finalmente, aunque el INR (International Normalized Ratio) es un buen indicador del grado de disfunción hepática, este parámetro fue desarrollado para el control de los pacientes tratados con anticoagulantes orales y todavía no se han realizado estudios para validarlo en pacientes cirróticos [31]. Otra limitación del INR es la enorme variabilidad según el laboratorio en el que se realice su determinación lo cual produce diferencias clínicamente significativas en el MELD (de hasta 3 a 5 puntos) [32].

1.2.3.2. Patologías en las que el MELD no valora el riesgo de progresión de la enfermedad hepática.

El ejemplo típico de esta situación es el carcinoma hepatocelular que con frecuencia se desarrolla en pacientes con una función hepática preservada y por lo tanto un con MELD bajo. Éste es un problema frecuente ya que se sabe que aproximadamente un 10-20% de los pacientes cirróticos en lista de espera tienen un carcinoma hepatocelular. El riesgo de estos pacientes consiste en que el tumor progrese más allá de los criterios establecidos para indicar un trasplante hepático. En Cataluña, los pacientes con carcinoma hepatocelular que presenten un nódulo único entre 3 y 5 cm o más de 2 nódulos menores de 3 cm, o aquellos pacientes con riesgo de progresión (alfa-fetoproteina >200 ng/mL, fallo al tratamiento neoadyuvante o criterios de mal pronóstico en la pieza quirúrgica en pacientes sometidos a resección quirúrgica) reciben un MELD de 19, ingresan a una lista única de pacientes priorizados y por cada 3 meses de permanencia en la lista reciben 1 punto adicional [33]. Otras situaciones similares incluyen el síndrome hepatopulmonar, la hipertensión portopulmonar, la polineuropatía amoliodótica familiar, la poliquistosis hepatorenal, la fibrosis quística, entre otras. En estas circunstancias se realizan ajustes al MELD adjudicando puntos adicionales que varían según el centro [6]. En Cataluña, los pacientes con estas patologías también reciben un trato similar a los pacientes con carcinoma hepatocelular [33].

1.2.3.3. Complicaciones de la cirrosis no valoradas por el MELD.

Las complicaciones de la cirrosis que están derivadas de la hipertensión portal implican un pobre pronóstico y tienen un riesgo elevado de muerte. Sin embargo, las variables incluidas en la fórmula del MELD no siempre están influenciadas por estas situaciones y por lo tanto la severidad de la enfermedad puede estar subestimada en estos pacientes. En este sentido, Huo et al evaluó la asociación entre el MELD, las complicaciones derivadas de la hipertensión portal (encefalopatía, ascitis, hemorragia por varices esofágicas y peritonitis bacteriana espontánea), y su impacto en la supervivencia de una cohorte de pacientes cirróticos. Los autores encontraron que la presencia de estas complicaciones es un factor pronóstico de mortalidad y que cada episodio de descompensación aumenta el riesgo de muerte [34].

Además de las complicaciones de la hipertensión portal, con frecuencia, los pacientes con cirrosis hepática presentan una desnutrición importante debida a la baja ingesta alimentaria, la baja síntesis proteica y el hipermetabolismo. Alberino et al realizó un estudio para evaluar el impacto de la desnutrición en la supervivencia a 2 años en un grupo de 212 pacientes con cirrosis hepática. Los autores encontraron que los pacientes con desnutrición moderada o grave (definida como un grosor del pliegue cutáneo bicipital y un perímetro abdominal debajo del percentil 10 o 5, respectivamente) presentaban una menor supervivencia con los pacientes con parámetros nutricionales normales. En este estudio la disminución de la

masa muscular y de la grasa corporal fueron factores predictivos independientes de supervivencia a 2 años [35].

Otra de las complicaciones de la cirrosis que no esta valorada directamente por el MELD es la hiponatremia, la cual se discutirá detalladamente a continuación.

1. 3. HIPONATREMIA

1.3.1 Definición y prevalencia

Los pacientes con cirrosis pueden desarrollar 2 tipos de hiponatremia [36]: 1) Hiponatremia hipovolémica (*vera*), secundaria a pérdidas de líquido extracelular por la orina (generalmente relacionada con el tratamiento diurético) o por el tracto digestivo. Esta situación se caracteriza por la presencia de un sodio plasmático bajo, una disminución del volumen extracelular, ausencia de edemas y ascitis, deshidratación y en algunas ocasiones insuficiencia renal pre-renal. En esta situación el sodio sérico generalmente mejora tras corregir la causa, retirar el tratamiento diurético, y remplazar la pérdida de volumen con la administración de suero fisiológico. 2) Hiponatremia hipervólemica o dilucional, debida a una disminución en la excreción de agua libre que conlleva a una retención de agua desproporcionada a la retención de sodio. Este es el tipo de hiponatremia más frecuente en los pacientes cirróticos y se caracteriza por un aumento absoluto del volumen plasmático (pero que es bajo con respecto a la

marcada vasodilatación arterial), aumento del líquido extracelular, ascitis y edemas [37].

La hiponatremia en la cirrosis se define como una concentración de sodio sérico inferior a 130 mEq/L [36]. Sin embargo, este punto de corte es arbitrario y muchos pacientes cirróticos con ascitis y concentración de sodio sérico entre 130 y 135 mEq/L también tienen una alteración en la excreción de agua libre y pueden desarrollar hiponatremia (sodio menor a 130mEq/L) durante la evolución de su enfermedad. La prevalencia de hiponatremia se estima en 21,6% [38], pero puede ser más alta en pacientes hospitalizados y en aquellos con síndrome hepatorrenal [39] [40] .

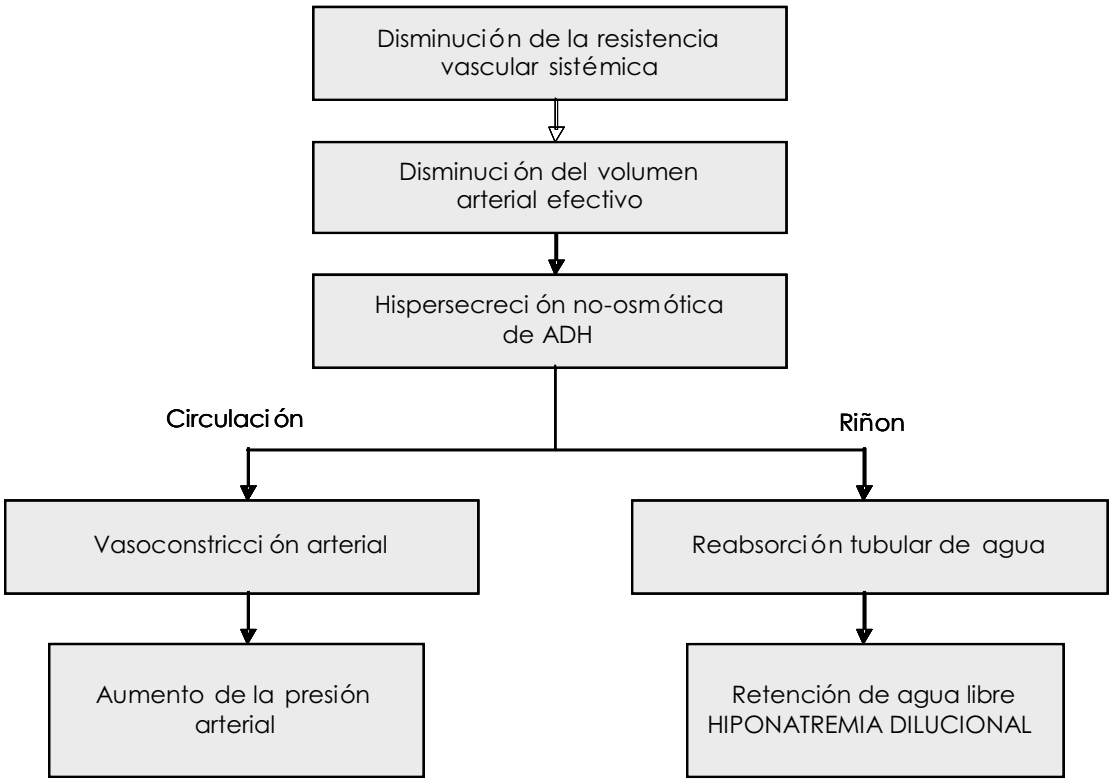
1.3.2. Patogénesis

Los pacientes cirróticos con ascitis tienen una alteración en la capacidad de excretar agua libre. En algunos pacientes esta alteración es moderada y sólo puede ser detectada por la medición del volumen urinario después de una sobrecarga hídrica. Estos pacientes son capaces de eliminar el agua normalmente y mantener una concentración de sodio sérico dentro de la normalidad pero pueden desarrollar hiponatremia tras una ingesta hídrica abundante [36]. En otros pacientes la severidad de este trastorno es tal, que retienen la mayoría del agua ingerida ocasionando hiponatremia e hipo-osmolaridad.

El principal factor responsable de la hiponatremia es el aumento de la producción de hormona anti-diurética (ADH) por la hipófisis debido a una

hipersecreción no osmótica secundaria a la disfunción circulatoria presente en la cirrosis avanzada [41]. El aumento en la liberación de ADH produce un aumento en la permeabilidad al agua del túbulo distal y el túbulo colector, lo cual facilita la reabsorción pasiva de agua de la luz del túbulo al intersticio. El efecto hidro-osmótico de la ADH se inicia a través de su interacción con los receptores V2 de la membrana basocelular del túbulo colector. Ello activa la enzima adenilciclasa, aumenta la formación de AMP cíclico y activa la formación de aquaporina- 2 (canales de agua) en la membrana luminal responsables de la retención de agua libre y la consiguiente hiponatremia dilucional [42].

En el siguiente gráfico se esquematiza la patogénesis de la hiponatremia dilucional en la cirrosis:



1.3.3 Adaptación cerebral a la hiponatremia

Dado que la concentración de sodio sérico es el principal determinante de la osmolaridad del líquido extracelular, cambios en el sodio se asocian con cambios paralelos en la osmolaridad. Así, cuando la concentración de sodio disminuye por debajo de la normalidad, el agua entra a las células (para mantener una balance osmótico) provocando edema celular [43]. El aumento en el volumen de las células afecta predominantemente al cerebro que como mecanismo de defensa inicia una salida de solutos intracelulares para disminuir la osmolaridad intracelular e igualarla a la del plasma limitando la entrada de agua a las células. Los mecanismos son complejos y en ellos participa el movimiento de agua a través de aquaporinas, principalmente aquaporina-4 [44]. En las primeras 24 horas hay una pérdida rápida de electrolitos, principalmente potasio y posteriormente hay una pérdida de compuestos orgánicos de bajo peso molecular conocidos como osmolitos orgánicos (mio-inositol, glutamina, colina y taurina) que regula de forma efectiva el volumen cerebral en el contexto de hiponatremia. La efectividad de este mecanismo depende de la severidad de la hiponatremia y su velocidad de instauración (más eficiente en la hiponatremia crónica). Existe evidencia de que estos mecanismos de adaptación ocurren en la cirrosis [45, 46]. Por el contrario, cuando la concentración de sodio regresa a la normalidad, existe una entrada de electrolitos y osmolitos en las células cerebrales. Dado que la re-entrada de los osmolitos orgánicos en las células cerebrales es lenta (sobretodo en casos de hiponatremia crónica), la

corrección rápida de la hiponatremia puede desencadenar daño cerebral debido a la falta de adaptación del cerebro a la normalización de la osmolaridad extracelular. Este fenómeno se conoce con síndrome de desmielinización osmótica (anteriormente denominada mielinolisis cerebral pontina) [43].

1.3.4. Consecuencias clínicas de la hiponatremia.

En pacientes sin enfermedad hepática, la hiponatremia se asocia con una amplia variedad de manifestaciones neurológicas relacionadas con la existencia de edema cerebral, como cefalea, desorientación, confusión déficits neurológicos focales, convulsiones, y en algunos casos muerte por herniación cerebral [43]. La severidad de las manifestaciones neurológicas se correlaciona con la velocidad de instauración de la hiponatremia. Aunque no existen estudios que evalúen las manifestaciones neurológicas de los pacientes cirróticos con hiponatremia dilucional, la experiencia indica que en estos pacientes las manifestaciones neurológicas son poco comunes. Ello se debe, probablemente, a una instauración lenta de la hiponatremia que permite una adecuada adaptación cerebral a la hipo-osmolaridad extracelular. Por otro lado existen datos en la literatura que correlacionan la aparición de encefalopatía hepática con cierto grado de edema cerebral producido el acumulo de glutamina (secundario al metabolismo del amonio) en los astrocitos [47]. En este contexto, la hiponatremia puede ocasionar una mayor salida de osmolitos contra-reguladores aumentando aún más el

edema cerebral y contribuyendo al desarrollo de la encefalopatía hepática [48].

Además de la encefalopatía hepática se ha reportado la asociación de la hiponatremia con otras complicaciones de la cirrosis aunque la información es limitada. La hiponatremia es un hallazgo frecuente en pacientes cirróticos con infecciones bacterianas [49] y es un factor de riesgo para el desarrollo de síndrome hepatorrenal [50].

1.3.5 Tratamiento de la hiponatremia en la cirrosis

Se considera que la hiponatremia se debe tratar cuando las concentración de sodio sérico es inferior a 130 mEq/L [51], sin embargo no hay evidencia sobre qué tratamiento utilizar según el nivel de sodio.

La hiponatremia hipovolémica o *vera* se debe tratar con la administración de sodio a la vez que se implementen medidas para identificar la causa de la misma. En la hiponatremia hipervolémica, la restricción hídrica (1-1,5 litros/día) es el tratamiento estándar pero su eficacia es limitada. En algunos estudios prospectivos aleatorizados comparando vaptanes (fármacos que bloquean los receptores V2 de la vasopresina en los túbulos colectores, impidiendo la reabsorción de agua a este nivel [52]) con placebo en el que ambos grupos fueron tratados con restricción hídrica, se evidenció que la eficacia de esta estrategia en mejorar los niveles de sodio en 5 mEq/L en el grupo placebo (tratado sólo con restricción hídrica) fue del 0-26% [53] [54]. Esta falta de eficacia se debe seguramente, a que en la práctica clínica es

complicado hacer una restricción hídrica inferior a 1 litro/día. La solución salina hipertónica se ha utilizado, pero su eficacia es limitada y no se recomienda porque se asocia con un mayor aumento del volumen extracelular, la ascitis y los edemas.

Finalmente, la utilización de vaptanes podría tener un papel en el tratamiento de la hiponatremia dilucional. Los resultados de la mayoría de los estudios realizados con estos fármacos demuestran que su administración por un período corto de tiempo produce un aumento del volumen urinario, la excreción de agua libre en solutos y la concentración sérica de sodio en un 45 a 82% de los pacientes [55,56].

1.3.6 Utilidad del sodio en la valoración del riesgo de muerte de los pacientes con cirrosis.

Ya en 1956, Sheila Sherlock observó que en pacientes con enfermedad hepática la presencia de un sodio sérico menor de 130 mEq/L determina un pronóstico grave y un sodio menor de 125 mEq/Lun pronóstico ominoso[57]. Desde entonces un gran número de investigaciones demostraron la importancia del sodio como factor pronóstico en la cirrosis [39, 50, 58-60]. Sin embargo, su utilidad en la valoración del riesgo de muerte se había subestimado.

En estudios realizados hace más de 20 años, se había demostrado que los parámetros de hemodinámica sistémica y de función renal eran mejores factores pronósticos de supervivencia en pacientes cirróticos con ascitis que

los parámetros de función hepática [50]. Entre estos parámetros se encuentran la tasa de filtración glomerular, la excreción urinaria de sodio, la actividad de renina plasmática, la excreción renal de agua libre después de una test de sobrecarga hídrica, la hiponatremia y la presión arterial media [59].

A raíz de estos datos, en los últimos años se han publicado varios estudios evaluando el papel de la hiponatremia como factor pronóstico en los pacientes en lista de espera para trasplante hepático. Heuman et al, estudió los factores predictivos de mortalidad en lista de espera para trasplante hepático a los 6 meses en 507 pacientes cirróticos. Los autores identificaron el MELD, la persistencia de ascitis y la hiponatremia (definida como sodio sérico menor de 135 mEq/L) como factores predictivos independientes de mortalidad en lista de espera. En pacientes con MELD inferior a 21, solo la persistencia de la ascitis y la hiponatremia fueron factores predictivos independientes de mortalidad (40% a los 180 días), resultados que fueron confirmados en una cohorte de validación[61]. Ruf et al, encontró una prevalencia de hiponatremia de 63% en los pacientes que fallecieron en los primeros 3 meses de inclusión en lista de espera, comparado con 13% en los pacientes que sobrevivieron. Tras realizar un análisis de regresión logística, se encontró que la presencia de hiponatremia se asoció con un aumento en el riesgo de muerte en pacientes con cirrosis descompensada (OR 11.92, área bajo la curva ROC 0,75). Este aumento en la mortalidad se permaneció a través de las diferentes categorías del MELD (MELD <10: 0%, MELD 10-14: 0% vs. 5%, MELD 15-19: 3,5% vs. 17%, MELD 20-24: 0% vs. 36%, MELD 25-29: 25% vs.

66%, MELD >30: 50 vs. 100%). A pesar de la alta eficacia del MELD para predecir la mortalidad en lista de espera en este estudio (AUC 0,849), cuando se incorporó el sodio sérico a la fórmula del MELD su rendimiento diagnóstico aumentó de forma significativa (AUC 0,908)[62]. Finalmente, Biggins et al realizó un estudio retrospectivo evaluando todos los pacientes incluidos en lista de espera para trasplante hepático. Los autores encontraron un aumento en el riesgo de muerte en pacientes con un sodio sérico menor de 126 mEq/L, tanto al momento del entrar en lista o como durante el tiempo de estancia en la lista (hazard ratio [HR] de 7,8 y 6,3, respectivamente). Asimismo, el área bajo la curva ROC para predecir la mortalidad a los 3 meses fue de 0,883 para el MELD y de 0,897 al añadir el sodio al MELD. Similares resultados fueron obtenidos a los 6 meses, 0,871 y 0,905, respectivamente [63].

2. JUSTIFICACIÓN Y OBJETIVOS

La presente tesis doctoral va encaminada a investigar el papel del MELD y el y el sodio sérico pre-trasplante en el pronóstico de los pacientes con cirrosis hepática en lista de espera y tras un trasplante hepático.

Como se ha mencionado previamente, diversos estudios han demostrado que tras la implementación del MELD para asignar los órganos para trasplante hepático, la mortalidad en lista de espera ha disminuido de forma significativa [11, 64]. Sin embargo, existen diversas situaciones clínicas en las que el riesgo de muerte no viene dado por la función hepática y por lo tanto el MELD no tiene capacidad pronóstica. Entre ellas se encuentran la presencia de hepatocarcinoma, ascitis refractaria, hiponatremia dilucional, peritonitis bacteriana espontánea, encefalopatía hepática, síndrome hepato-pulmonar e hipertensión porto-pulmonar.

Por otra parte, desde mediados del siglo pasado se sabe que un valor de sodio sérico inferior a 130 mEq/L es un factor predictivo negativo de supervivencia en pacientes con cirrosis hepática [50,65]. Es por ello que ha habido un creciente interés en evaluar la incorporación del nivel de sodio sérico al MELD, llegando incluso a desarrollar diferentes fórmulas para calcular el MELD-Na [9]. La adición del sodio al MELD parece sobretodo mejorar la precisión del MELD en sus rangos bajos [10].

A pesar de ello quedan algunos hechos por dilucidar en relación a la utilidad del sodio sérico y el MELD como factores pronósticos en los pacientes en lista de espera para trasplante hepático, entre los cuales se encuentran: 1) determinar si el MELD es igualmente efectivo para evaluar el pronóstico en

lista de espera a corto (3 meses) y largo plazo (12 meses), 2) valorar la precisión del sodio sérico y el MELD en la predicción del pronóstico en las diferentes sub-poblaciones de pacientes con cirrosis y 3) confirmar en una población diferente de pacientes en lista de espera si la adición del sodio al MELD mejora su capacidad pronóstica.

Por otro lado, existen estudios que demuestran que el MELD no solo es útil para determinar el pronóstico de los pacientes cirróticos en lista de espera, sino también en estimar la probabilidad de supervivencia tras el trasplante hepático[66, 67]. Sin embargo no hay estudios que evalúen el papel del sodio sérico en la estimación del pronóstico post-trasplante hepático.

Los estudios realizados dentro del margen de esta tesis doctoral se han diseñado para resolver las cuestiones pendientes en relación a la utilidad del MELD y la concentración de sodio sérico en la determinación del pronóstico de los pacientes con cirrosis hepática tanto en lista de espera como tras el trasplante hepático con los siguientes objetivos específicos:

3.1 Estudio 1:

- Determinar si el MELD es igualmente efectivo para establecer el pronóstico de los pacientes con cirrosis hepática en lista de espera para trasplante hepático, tanto a corto (3 meses) como a largo (12 meses) plazo.
- Establecer si el valor pronóstico de la concentración sérica de sodio es igual en diferentes sub-poblaciones de pacientes con cirrosis hepática.

- Evaluar si la concentración sérica de sodio puede aumentar la precisión del MELD.

3.2 Estudio 2:

- Investigar si la presencia de hiponatremia en pacientes con cirrosis hepática antes del trasplante hepático puede afectar la mortalidad post-trasplante.

- Determinar si la presencia de hiponatremia antes del trasplante hepático se asocia con un aumento en la aparición de complicaciones post-trasplante.

3. RESULTADOS

ESTUDIO 1

MELD score and serum sodium in the prediction of survival of patients with cirrhosis awaiting liver transplantation

Londoño MC, Cárdenas A, Guevara M, Quintó L, de Las Heras D, Navasa M, Rimola A, Garcia-Valdecasas JC, Arroyo V, Ginès P.

LIVER DISEASE

MELD score and serum sodium in the prediction of survival of patients with cirrhosis awaiting liver transplantation

Maria-Carlota Londoño, Andrés Cárdenas, Mónica Guevara, Llorenç Quintó, Dara de las Heras, Miguel Navasa, Antoni Rimola, Juan-Carlos Garcia-Valdecasas, Vicente Arroyo, Pere Ginès

Gut 2007;**56**:1283–1290. doi: 10.1136/gut.2006.102764

See end of article for authors' affiliations

Correspondence to: Pere Ginès, MD, Liver Unit, Hospital Clínic de Barcelona, C/Villarroel 170, 08036, Barcelona, Spain; pgines@clinic.ub.es

Revised 5 April 2007
Accepted 10 April 2007
Published Online First 23 April 2007

Background/Aims: Serum sodium predicts prognosis in cirrhosis and may improve the prognostic accuracy of the model for end-stage liver disease (MELD) score, but the available information is limited. The aim of the present study was to assess the prognostic value of serum sodium in the prediction of survival at 3 and 12 months after listing in patients with cirrhosis awaiting liver transplantation, and to compare its predictive value with that of the MELD score.

Patients and methods: 308 consecutive patients with cirrhosis listed for transplantation during a 5-year period were included in the study. The end-point was survival at 3 and 12 months before transplantation. Variables obtained at the time of listing were analysed for prognostic value using multivariable analysis. Accuracy of prognostic variables was analysed by receiver operating characteristic (ROC) curves.

Results: The MELD score and serum sodium concentration were the only independent predictors of survival at 3 and 12 months after listing. Low serum sodium was associated with an increased risk of death in all subpopulations of patients with cirrhosis categorised according to the major complication developed before listing. The area under the ROC curves for serum sodium and MELD score was not significantly different both at 3 months (0.83 vs 0.79, respectively) and at 12 months (0.70 vs 0.77, respectively). The addition of serum sodium did not significantly improve the accuracy of the MELD score in the prediction of survival at 3 and 12 months.

Conclusion: In patients with cirrhosis awaiting liver transplantation, serum sodium and MELD were found to be independent predictors of survival. Larger studies are needed to determine whether the addition of serum sodium to MELD can improve its prognostic accuracy.

The model for end-stage liver disease (MELD) score is the method most widely used for organ allocation in liver transplantation.[1–3] This model, which includes variables related to both liver and renal function, was implemented in the USA in 2002 and is currently being used in many countries to classify patients with cirrhosis awaiting transplantation according to the severity of their liver disease. Nevertheless, several studies, as well as clinical observation, indicate that some subsets of patients with cirrhosis may have high mortality despite low MELD scores.[4–7] Therefore, there is need for improvement of the MELD score. In this regard, several recent studies have shown that serum sodium concentration is a good marker of prognosis in patients awaiting transplantation.[8–10] According to the results of these studies, the use of serum sodium in the assessment of severity of cirrhosis has been recommended. However, there are several issues on the possible use of serum sodium as a predictor of prognosis that require more information, specifically: (1) whether the value of serum sodium is equally effective in the assessment of short-term prognosis (3 months) compared with mid-term prognosis (12 months); (2) whether serum sodium is equally accurate in predicting prognosis in different subpopulations of patients with cirrhosis; and (3) whether serum sodium improves the accuracy of the MELD score. The purpose of this study was to investigate these issues.

PATIENTS AND METHODS

Study population

This is a single-centre retrospective cohort study of all adult patients with cirrhosis listed for liver transplantation at the Hospital Clínic of Barcelona during the period between January 2000 and March 2005. During this period, a total of 560 patients were listed for transplantation. Two hundred and fifty-two patients were excluded from this study for the following reasons: hepatocellular carcinoma (n = 152), retransplantation (n = 48) or diseases other than cirrhosis (acute liver failure, n = 22; familial amyloidotic polyneuropathy, n = 18; or miscellaneous disorders, n = 12). Patients in whom hepatocellular carcinoma was diagnosed after listing (n = 2) and those who were found to have incidental hepatocellular carcinoma at transplantation (n = 12) were not excluded from the study. The study cohort included 308 patients with cirrhosis.

Criteria for listing patients with cirrhosis for liver transplantation throughout the study period were the existence of decompensated liver disease together with moderate-to-severe liver failure, as indicated by a Child–Pugh score ⩾7, and absence of absolute contraindications for transplantation. Patients belonging to Child–Pugh class A were only considered for transplantation if they had developed hepatic encephalopathy or had a concomitant parenchymal renal disease requiring combined liver–kidney transplantation.[11 12] At the time of listing, demographic, clinical and biochemical variables were collected and included in a specific database for patients awaiting transplantation.

Once included on the waiting list, patients were followed-up by experienced hepatologists, and complications of cirrhosis were treated according to standardised therapeutic protocols as follows. Moderate ascites was treated with low-sodium diet and diuretics (spironolactone alone or in combination with furosemide), and large ascites was treated with large-volume paracentesis plus albumin, followed by low-sodium diet and

Abbreviations: INR, international normalisation ratio; MELD, model for end-stage liver disease; ROC, receiver operating characteristic

diuretics, as described in detail elsewhere.[13 14] Ascites at the time of listing was classified as controlled or uncontrolled according to the score obtained in the Child–Pugh classification, 2 or 3, respectively.[15 16] Spontaneous bacterial peritonitis was treated with ceftriaxone plus intravenous albumin, followed by the administration of norfloxacin to prevent recurrence.[14 17] Dilutional hyponatraemia (serum sodium <130 mEq/l) was managed with fluid restriction (1–1.5 l/day), except for those patients with severe hyponatraemia (serum sodium <120 mEq/l), who were given hypertonic saline before transplantation in an attempt to increase serum sodium concentration. Hepatorenal syndrome with serum creatinine above 2 mg/dl was managed with terlipressin plus albumin.[18] Acute variceal bleeding was initially managed with either somatostatin or terlipressin associated with emergency sclerotherapy or band ligation. Prevention of recurrent bleeding was performed with the administration of β-blockers with or without variceal band ligation.[19 20] Acute hepatic encephalopathy was treated with lactulose and rectal enemas, and treatment of the precipitating cause, if any.[17]

During the study period (January 2000 to March 2005), the allocation of livers for transplantation in our centre was strictly determined by the time on the waiting list; in other words, when a liver from a cadaveric donor became available, the liver was assigned to the patient who had been on the waiting list for the longest time, matched by ABO group and body weight. Living-related liver transplantation was offered to suitable candidates. Since April 2005, the allocation of livers in our transplant programme is based on the severity of liver disease using the MELD score.

End-points and definitions

The primary end-points of the study were survival before transplantation at 3 and 12 months after inclusion on the waiting list. The MELD score at inclusion was calculated according to the formula of the United Network for Organ Sharing (UNOS) available at www.unos.org. Hyponatraemia was defined as serum sodium <130 mEq/l at the time of listing, according to the definition of the International Ascites Club.[21] Renal failure was defined as the presence of serum creatinine ⩾1.5 mg/dl at the time of listing. Hepatorenal syndrome was diagnosed using the criteria of the International Ascites Club, as reported elsewhere.[22]

Statistical analysis

Demographic, clinical and biochemical variables were analysed as possible predictors of survival in a univariate analysis, and probability curves (Kaplan–Meier) were compared with the log-rank test. Values of biochemical variables included in the statistical analysis were concurrent and obtained at the time of inclusion of patients on the waiting list. Of all clinical and biochemical variables analysed in the whole series of patients, there were only a few missing values (bilirubin in 6 patients, albumin in 6, international normalisation ratio (INR) in 5, serum creatinine in 1, and MELD score in 9). Missing values were considered as missing for the statistical analysis and were not replaced by any values. Two different survival analyses were performed: at 3 and 12 months after inclusion on the waiting list. The 3-month survival analysis included all deaths occurring between day 0 and day 90, while the 12-month survival analysis included all deaths between day 0 and day 365. Transplanted patients were considered as censored at the time of transplantation. Twenty-four patients were censored for transplantation at 3 months, and 174 patients were censored for transplantation at 12 months. Patients removed from the waiting list because of being ''too sick'' to be transplanted were considered as dead at the time of exclusion from the waiting list. Patients removed from the waiting list because of improvement of their liver function and those removed because of listing in another transplant centre were considered as censored at the time of exclusion from the waiting list. Patients still alive on the waiting list at the end of each period (3 and 12 months) were considered as censored. Predictive factors identified in the univariate analysis were included in the multivariable analysis, using Cox regression method. A stepwise forward regression method was used. Validation of the proportional hazards assumption for the final models (ie, that the relative risk of failure between subgroups in the model does not change over time) was carried out through a graphical examination of log minus log plots of the Kaplan–Meier survival curves versus the log of time, for the tertiles of the model prediction.[23 24] The final models were validated using the bootstrap method.[25 26]

The accuracy of each independent predictive factor of survival was assessed by receiver operating characteristic (ROC) curves. Comparison between ROC curves (concordance c-statistic test) was performed with the statistical package available at www.analyse-it.com, which uses the algorithm described by Hanley and McNeil.[27] Statistical analysis was performed using SPSS 10 for Windows (SPSS Inc., Chicago, IL, USA). Results are expressed as mean (SD). $p<0.05$ was considered as statistically significant. The study was approved by the Institutional Review Board of the Hospital Clínic of Barcelona.

RESULTS

Characteristics of the patients

Demographic, clinical and biochemical data of patients included in the study at the time of listing are shown in table 1. One hundred and thirty-five (44%) of the 308 patients had an abnormal serum sodium concentration (<135 mEq/l). The prevalence of low serum sodium concentration as defined by a serum sodium concentration <130, <125 and <120 mEq/l was 14, 5 and 1%, respectively.

Survival of patients on the waiting list

One-hundred and ninety (62%) out of the 308 patients included in the study underwent liver transplantation during follow-up (157 patients from deceased donors, 22 patients from living donors and 11 patients received a domino liver transplantation), 65 patients (21%) died while in the waiting list, 18 patients (6%) were removed because of listing in another transplant centre, 7 patients (2%) were excluded from the list either because they were too sick to be transplanted (4 patients) or because of marked improvement of liver function (3 patients), and 28 patients (9%) were still awaiting transplantation at the time of the analysis of the results. The median time on the waiting list was 6.4 months (range 0.1–18 months). Figure 1 shows the probability of survival on the waiting list of the whole population of included patients. The probability of survival before transplantation was 88% at 3 months and 68% at 12 months after inclusion on the waiting list.

Predictive factors of survival on the waiting list

The predictive factors of survival were analysed at two different time points: 3 and 12 months.

Three-month survival

Thirty-four (11%) of the 308 patients died within the first 3 months after inclusion on the waiting list before transplantation was performed. Table 2 shows the comparison of clinical and biochemical characteristics of patients who died and those of patients who survived the initial 3 months. Factors associated with 3-month survival in the univariate analysis

Table 1 Demographic and clinical data and liver and renal function tests at the time of listing for transplantation in the 308 patients included in the study

Age (years)	52 (9) (18–66)
Sex	
Male	207 (67%)
Female	101 (33%)
Aetiology of cirrhosis	
Hepatitis C	136 (44%)
Alcohol	80 (26%)
Hepatitis C and alcohol	25 (8%)
Hepatitis B	20 (6%)
Other*	47 (18%)
Complications of cirrhosis	
Ascites	271 (88%)
Controlled	112 (41%)
Uncontrolled	159 (59%)
Hepatic encephalopathy	145 (47%)
Variceal bleeding	91 (29%)
SBP	83 (27%)
Renal failure†	39 (13%)
Hepatorenal syndrome‡	20 (7%)
Parenchymal renal disease	19 (6%)
Bilirubin (mg/dl)§	4.3 (5) (0.2–46)
Albumin (g/l)	30 (5) (17–45)
Prothrombin time	
Ratio	54 (16) (14–100)
INR	1.5 (0.8) (1–12)
Creatinine (mg/dl)¶	1.2 (0.9) (0.3–11)
Sodium (mEq/l)	135 (5) (111–146)
MELD score	18 (5) (7–48)
Child–Pugh score	9.3 (1.8) (5–15)

INR, international normalisation ratio; MELD, model for end-stage liver disease; SBP, spontaneous bacterial peritonitis.
Data are expressed as as number (%) or mean (SD) (ranges)
*Other causes of end-stage liver disease were: cholestatic liver disease in 25 patients (8%), metabolic liver disease in 12 patients (4%), cryptogenic cirrhosis in 5 patients (2%), autoimmune liver disease in 3 patients (1%) and Budd–Chiari in 2 patients (1%).
†As defined by serum creatinine ⩾1.5 mg/dl.
‡All 20 patients had type 2 hepatorenal syndrome.
§To convert mg/dl into μmol/l multiply by 17.1.
¶To convert mg/dl into μmol/l multiply by 16.6.

were: hepatorenal syndrome, uncontrolled ascites, serum bilirubin, serum albumin, INR, serum sodium concentration and MELD score. All these variables were included in the multivariable analysis as they were considered clinically relevant. In multivariable analysis, only serum sodium and MELD score were independently associated with prognosis (table 3). When the MELD score was excluded from the multivariable analysis, factors that were independently associated with prognosis were: serum bilirubin, serum creatinine and serum sodium concentration. Figure 2 shows the individual relationship between serum sodium and MELD score and 3-month probability of survival. There was a 12% increase in the risk of death for each unit (mEq/l) decrease in serum sodium concentration between 120 and 135 mEq/l. Similarly, for each unit of increase in MELD score (between 15 and 40), the risk of death increased by 8%. The area under the ROC curves for MELD score and serum sodium were 0.79 (95% CI 0.71–0.86) and 0.83 (95% CI 0.76–0.90), respectively, the difference not being statistically significant ($p = 0.4$).

Twelve-month survival

Sixty-four (21%) of the 308 patients died within the first 12 months after inclusion on the waiting list before transplantation was performed. Table 4 shows the comparison of clinical and biochemical characteristics of patients who died and those of patients who survived within the initial 12-month period. Factors associated with 12-month survival in the univariate analysis were: hepatic encephalopathy, hepatorenal syndrome,

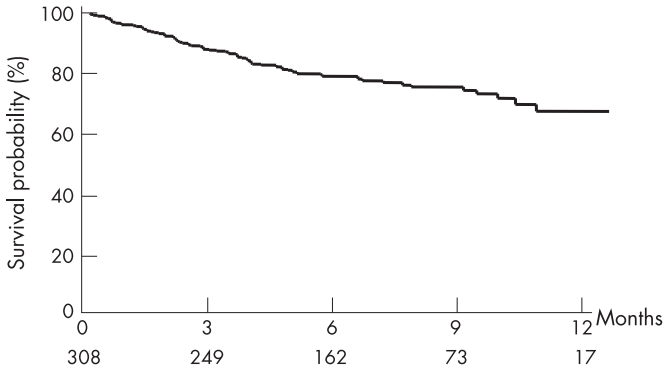


Figure 1 One-year survival before transplantation of the whole population of patients with cirrhosis included in the study. Time 0 is the time of listing. Numbers under the graph are patients at risk at each time point.

uncontrolled ascites, renal failure, serum bilirubin, INR, serum albumin, serum sodium concentration and MELD score. All these variables were included in the multivariable analysis as they were considered clinically relevant. In multivariable analysis, again serum sodium and MELD score were independently associated with prognosis (table 3). MELD score at listing in patients transplanted during the 12-month period ($n = 190$) was 15.9 (4.2) compared with 21 (5) in patients who died during the same period ($n = 64$). Corresponding values of serum sodium at listing were 136 (4) vs 132 (6) mEq/l, respectively ($p<0.05$ for both). When the MELD score was excluded from the multivariable analysis, factors that were independently associated with prognosis were: serum bilirubin, serum creatinine, INR and serum sodium concentration. Figure 3 shows the probability of survival during the first year after inclusion on the waiting list for all patients classified according to different values of serum sodium and MELD score. The area under the ROC curves for MELD score and serum sodium were 0.77 (95% CI 0.70 to 0.80) and 0.70 (95% CI 0.60 to 0.78), respectively, the difference not being statistically significant ($p = 0.14$).

To assess the possible value of serum sodium in improving the accuracy of the MELD score in the evaluation of prognosis, serum sodium concentration was incorporated in the calculation of the MELD score, using a formula described recently.[28] A MELD-Na score was then calculated for each patient and its accuracy in predicting prognosis was compared with that of the MELD score and serum sodium using ROC curves. As shown in fig 4, no significant differences were observed between the predictive value of MELD-Na at 3 and 12 months and those of the MELD score and serum sodium concentration calculated individually. The addition of the variable uncontrolled ascites to MELD-Na did not significantly improve the accuracy of MELD alone or MELD-Na in the prediction of 3- or 12-month survival (area under the ROC curve for 3-month survival: MELD 0.79, MELD-Na 0.83, MELD-Na-uncontrolled ascites 0.84; area under the ROC curve for 12-month survival: MELD 0.76; MELD-Na 0.78, MELD-Na-uncontrolled ascites 0.77). Moreover, when a separate analysis was performed in the subgroup of patients with low MELD (<21),[8] no significant differences were found between the predictive values of MELD-Na and MELD-Na-uncontrolled ascites and those of MELD score or serum sodium individually (area under the ROC curve for 3-month survival: MELD 0.74, serum sodium 0.79, MELD-Na 0.80, MELD-Na-uncontrolled ascites 0.81; area under the ROC curve for 12-month survival: MELD 0.70, serum sodium 0.62, MELD-Na 0.70, MELD-Na-uncontrolled ascites 0.60).

Table 2 Comparison of clinical and biochemical characteristics of patients who died and those of patients who survived the initial 3-month period

	Dead (n = 34)	Alive (n = 274)	p Value	Likelihood ratio
Age (years)	53 (8)	52 (9)	0.37	
Ascites	33 (97%)	238 (87%)		
Controlled	6 (18%)	106 (44%)	0.004	7.25
Uncontrolled	27 (82%)	132 (56%)		
Hepatic encephalopathy	18 (53%)	127 (46%)	0.58	0.49
GI bleeding	10 (29%)	81 (29%)	0.57	0.001
SBP	12 (35%)	71 (26%)	0.37	
Renal failure*	6 (17%)	33 (12%)	0.48	0.77
Hepatorenal syndrome†	6 (17%)	14 (5%)	0.026	5.21
Bilirubin (mg/dl)	8.5 (8.4)	3.6 (3.1)	0.000	
Albumin (g/l)	28 (5)	31 (5)	0.000	
INR	1.8 (0.5)	1.6 (0.9)	0.025	
Creatinine (mg/dl)	1 (0.3)	1.2 (1.1)	0.416	
Sodium (mEq/l)	130 (6)	136 (4)	0.000	
MELD score	21 (5)	16 (5)	0.000	

GI, gastrointestinal; INR, international normalisation ratio; MELD, model for end-stage liver disease.
*As defined by serum creatinine ⩾1.5 mg/dl.
†All patients had type 2 hepatorenal syndrome.

Serum sodium and survival in different subpopulations of patients with cirrhosis

To assess further the prognostic value of serum sodium concentration, patients were categorised according to the major complication(s) of cirrhosis they had developed before listing. The prognostic value of serum sodium was then evaluated in these subsets of patients by comparing the hazard ratio of death at 3 months in patients with and without hyponatraemia. As shown in table 5, the presence of hyponatraemia was associated with an increased risk of death in all subpopulations of patients evaluated: patients with ascites, hepatic encephalopathy, gastrointestinal bleeding, spontaneous bacterial peritonitis or renal failure. Serum sodium was an independent predictor of survival in patients with low and high MELD scores (<21 and ⩾21, respectively).

DISCUSSION

The current study reports the results of the analysis of survival and prognostic factors of a large cohort of patients with cirrhosis listed for transplantation in a single institution over a 5-year period. Several characteristics of this cohort make it unique in the assessment of prognostic factors of survival of patients with cirrhosis awaiting liver transplantation. First, it includes a relatively large number of patients treated in a single institution following standardised protocols for the management of complications of cirrhosis developing during the waiting time. Secondly, the study period was restricted to 5 years, which minimises the impact of changes in patients' management over time. Thirdly, during the period of the study, the major determinant of organ allocation was time on the waiting list. Finally, although this is a retrospective study, all variables evaluated as prognostic factors were collected prospectively in a large database at the time of inclusion of patients on the waiting list.

Table 3 Regression coefficients, odds ratios and 95% CI of odds ratios of variables with independent predictive value of survival at 3 and 12 months*

	Coefficient	OR (95% CI)
3 months		
MELD	0.102	1.1 (1.07 to 1.142)
Serum sodium	−0.095	0.90 (0.87 to 0.94)
12 months		
MELD	0.088	1.091 (1.05 to 1.138)
Serum sodium	−0.128	0.88 (0.845 to 0.916)

MELD, model for end-stage liver disease; OR, odds ratio.
*Both models were validated with the bootstrap method. In the bootstrap validations for both models, the same variables entered the bootstrap-derived models most frequently. In fact, MELD score and serum sodium concentration appeared in 94 and 100% of the analyses for 3-month survival, and in 100 and 99% of the analyses for 12-month survival, respectively. Moreover, estimated models using only MELD score and serum sodium concentration as independent predictors were observed in 76% at 3 months. At 12 months, the mentioned model was estimated in 38% of the bootstrapped samples, and in only 1% of the models these two predictors did not appear simultaneously.

The results of the current study confirm previous data indicating that the MELD score is an independent predictor of survival in patients with cirrhosis awaiting liver transplantation.[29 30] MELD score at the time of listing was an independent predictor of survival at both 3 and 12 months after inclusion of patients on the waiting list. The fact that the allocation of organs in this cohort of patients was done by time on the waiting list reinforces the value of the MELD score as the best method currently available to allocate organs when a system based on the severity of the liver disease is to be used. Comparison of ROC curves assessing the relationship between MELD score and 3- and 12-month survival probability indicates that the MELD score has a similar prognostic accuracy in the assessment of 3-month survival compared with 12-month survival (c-statistic 0.79 and 0.77, respectively). Moreover, a close look at the relationship between MELD score and 3-month survival probability indicates that a major change in survival probability occurs in values of MELD ranging from 15 to 40 (fig 2). In this range, an increase in one point in the MELD score represents an 8% decrease in 3-month survival probability. Another interesting finding of the current study was that patients with a MELD score lower than 15 have a very high probability of survival at both 3 and 12 months after listing (96 and 87%, respectively). This survival probability is similar to that reported in most transplant centres after transplantation of patients with cirrhosis.[31 32] Patients with low MELD scores are commonly listed for transplantation in transplant programmes using allocation systems based on time on the waiting list, as was the case in the current study. However, the current data showing very low waiting list mortality in this patient population cast doubts about the convenience of listing patients with low MELD scores in transplant programmes in which the allocation system is based on the severity of liver disease. An interesting and somewhat surprising finding of the current study was that hepatorenal syndrome, although significantly associated with prognosis in

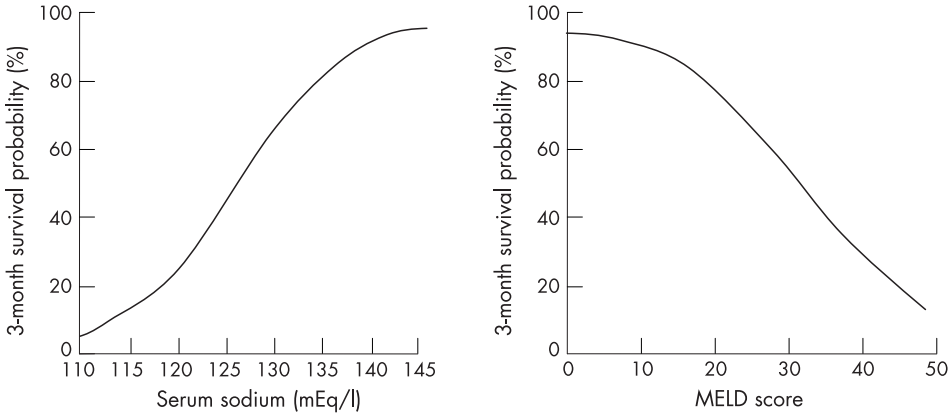


Figure 2 Relationship between serum sodium (left) and model for end-stage liver disease (MELD) score (right) and estimated 3-month probability of survival in all patients included.

the univariate analysis, was not an independent predictive factor of survival in the multivariable analysis. Although we do not have a complete explanation for this finding, it may be due, at least in part, to the fact that most patients with hepatorenal syndrome were treated with terlipressin and albumin before transplantation,[18] which could have resulted in an improvement of survival of these patients.

The results of the current study are in keeping with several recent studies in patients with cirrhosis awaiting liver transplantation as well as with previous studies in patients with cirrhosis and ascites indicating that serum sodium concentration is a very good marker of survival, at both 3 and 12 months after inclusion of patients on the waiting list.[8–10] Serum sodium concentration has also recently been shown to be a good marker of outcome after transplantation.[33] Comparison of ROC curves assessing the relationship between serum sodium concentration and 3- and 12-month survival probability indicates that serum sodium concentration has better prognostic accuracy in the assessment of 3-month survival than 12-month survival (c-statistic 0.83 and 0.70, respectively). On the other hand, a close look at the relationship between serum sodium concentration and 3-month survival probability indicates that a major change in survival probability occurs in values of serum sodium ranging from 120 to 135 (fig 2). In this range, a reduction in 1 mEq/l in serum sodium concentration is associated with a 12% decrease in 3-month survival probability. Another relevant clinical finding of this study was that patients without hyponatraemia but with a serum sodium concentration lower than normal values (ie, patients with serum sodium between 130 and 135 mEq/l) have a 12-month probability of survival significantly greater than that of patients with hyponatraemia (serum sodium >130 mEq/l) but lower than that of patients with normal serum sodium concentration (fig 3).

The reason why the MELD score is a good marker of prognosis in patients with cirrhosis who are candidates for liver transplantation is probably related to the fact that MELD combines two parameters, bilirubin and INR, that are sensitive markers of liver function, together with serum creatinine, a marker of renal function.[2] The severity of both liver and renal dysfunction has been shown to correlate with prognosis in patients with cirrhosis.[34 35] In contrast, the explanation for why serum sodium concentration is a good marker of prognosis in patients with cirrhosis is uncertain and has not been specifically investigated. It might be that serum sodium concentration reflects the severity of liver failure, because patients with hyponatraemia commonly have a more advanced liver disease compared with that of patients without hyponatraemia.[33 36] However, the results of this study as well as those from several previous studies[8–10] indicate that the prognostic value of hyponatraemia is independent of that of the MELD score, which appears to dissociate the predictive value of serum sodium from that of liver and renal failure. Alternatively, it is possible that serum sodium concentration predicts prognosis

Table 4 Comparison of clinical and biochemical characteristics of patients included in the study divided according to whether they were dead or alive at 12 months

	Dead (n = 64)	Alive (n = 244)	p Value	Likelihood ratio
Age (years)	52 (10)	52 (9)	0.9	
Ascites	60 (94%)	211 (87%)		
Controlled	14 (23%)	98 (46%)	0.001	9.3
Uncontrolled	46 (77%)	113 (54%)		
Hepatic encephalopathy	38 (59%)	107 (44%)	0.02	4.7
GI bleeding	20 (21%)	71 (29%)	0.42	0.1
SBP	19 (30%)	64 (26%)	0.348	0.28
Renal failure*	13 (20%)	26 (11%)	0.04	3.8
Hepatorenal syndrome†	9 (15%)	11 (5%)	0.01	6.38
Bilirubin (mg/dl)	6.7 (7.1)	3.7 (3.5)	0.002	
Albumin (g/l)	28 (5)	31 (5)	0.000	
INR	2 (1)	1.6 (0.8)	0.03	
Creatinine (mg/dl)	1.2 (1.1)	1.2 (1.0)	0.453	
Sodium (mEq/l)	132 (6)	136 (4)	0.000	
MELD score	21 (6)	16 (5)	0.000	

GI, gastrointestinal; INR, international normalisation ratio; MELD, model for end-stage liver disease; SBP, spontaneous bacterial peritonitis.
*As defined by serum creatinine ⩾1.5 mg/dl.
†All patients had type 2 hepatorenal syndrome.

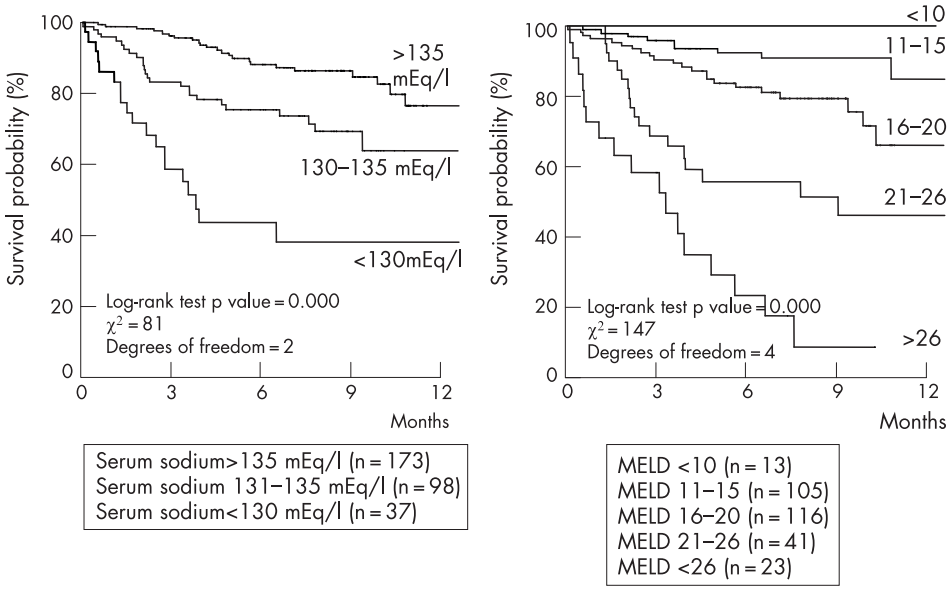


Figure 3 One year-survival before transplantation of the whole population of patients with cirrhosis according to different values of serum sodium (left) and model for end-stage liver disease (MELD) score (right).

because it reflects the severity of circulatory failure associated with advanced cirrhosis, as hyponatraemia is due to a non-osmotic hypersecretion of vasopressin, which in turn is dependent on the degree of impairment in circulatory function.[21 22 37] Finally, hyponatraemia has been reported as a predisposing factor for the development of hepatic encephalopathy,[38–40] although evidence supporting such a relationship is still limited.

Considering the results of previous studies as well as those of the current study, the question arises as to whether serum sodium concentration should be used to improve the prognostic accuracy of the MELD score in view of its simplicity and high predictive value. To assess the possible value of serum sodium in improving the accuracy of the MELD score in the evaluation of prognosis, serum sodium concentration was incorporated in the calculation of the MELD score, using a formula described recently.[28] A MELD-Na score was then calculated for each patient and its accuracy in predicting prognosis was compared with that of the MELD score and serum sodium using ROC curves. As shown in fig 4, no significant differences were observed between the predictive value of MELD-Na at 3 and 12 months and those of MELD score and serum sodium concentration calculated individually. Discrepancies between the results of the current study and those of previous studies[10 28] may be related to differences in the patient population, methods used to incorporate sodium in the MELD formula or the method used for organ allocation. On the other hand, it is important to point out that the sample size of the current study was not high enough to rule out completely a better predictive value of MELD-Na compared with MELD or serum sodium alone. In fact, the estimated power of the study was low, 11% at 3 months and 30% at 12 months. An estimated power >80% would have required the inclusion of 1268 patients which is difficult to achieve in single-centre studies, unless the study period is markedly prolonged, an approach that does not seem appropriate because it will increase the heterogeneity of the patient population. Therefore, multicentre studies with very large sample sizes would be required to test the superiority of MELD-Na with respect to MELD alone in the assessment of prognosis of patients with cirrhosis awaiting liver transplantation.

While awaiting the results of these studies, it is important to ponder the appropriateness of including serum sodium as a new variable in a score for organ allocation in liver transplantation. A

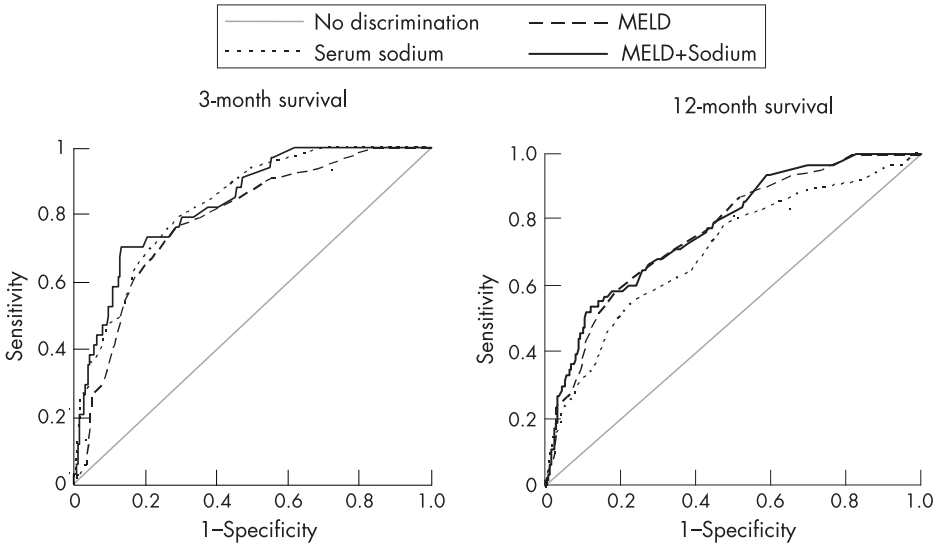


Figure 4 Receiver operating characteristic (ROC) curves of the model for end-stage liver disease (MELD) score (c-statistic (SEM) 0.79 (0.04) at 3 months and 0.77 (0.03) at 12 months), serum sodium concentration (c-statistic (SEM) 0.82 (0.03) and 0.70 (0.04), at 3 and 12 months, respectively) and MELD plus serum sodium concentration (c-statistic (SEM) 0.83 (0.03) and 0.77 (0.03), at 3 and 12 months, respectively), and survival probability at 3 (left) and 12 months (right). MELD plus serum sodium concentration was calculated as described in Hosmer and Lemeshow.[23] p = not significant for all comparisons.

Table 5 Mortality risk expressed by hazard ratio in patients included in the study with or without hyponatraemia categorised according to the presence of major complications of cirrhosis

	Hyponatraemia*	No hyponatraemia
Ascites	n = 37 5.9 (2.9 to 11.7)	n = 234 1.0 (reference)
Hepatic encephalopathy	n = 20 7.8 (3.1 to 19.8)	n = 125 1.0 (reference)
Variceal bleeding	n = 9 11.5 (3.3 to 40)	n = 82 1.0 (reference)
Spontaneous bacterial peritonitis	n = 15 13.6 (4.0 to 45)	n = 68 1.0 (reference)
Renal failure	n = 11 16.5 (1.9 to 142)	n = 28 1.0 (reference)

Data are relative risk (95% CI)
*Hyponatraemia was defined as serum sodium <130 mEq/l.

new variable should ideally meet the following criteria: good correlation with survival; easy measurement; wide availability; and stability. While serum sodium meets the first three criteria, it does not meet the fourth. In fact, serum sodium levels may have important fluctuations after simple therapeutic manoeuvres, which do not necessarily reflect changes in the severity of the disease. For example, administration of diuretics is commonly associated with marked changes in serum sodium concentration, which are of 4 mEq/l on average and can be as high as 10–15 mEq/l, and are often reversible after diuretic withdrawal.[42] Moreover, serum sodium may decrease markedly after administration of oral or intravenous hypotonic fluids due to the impaired capacity to eliminate solute-free water commonly present in patients with advanced cirrhosis.[43] Finally, the serum sodium concentration increases markedly after the administration of drugs that antagonise selectively the V2 receptors of the antidiuretic hormone. Phase 2 studies have shown that these drugs increase serum sodium concentration and improve the management of ascites in patients with cirrhosis and hyponatraemia, and may be available soon for use in clinical practice.[44–46] If the beneficial effects of these drugs are confirmed in phase 3 studies, which are currently underway, the addition of serum sodium as a variable in a new score to be used for organ allocation may be an obstacle for the use of these drugs in patients awaiting liver transplantation.

In conclusion, the results of the current study indicate that the MELD score and serum sodium concentration are the only independent predictive factors of 3- and 12-month survival in patients with cirrhosis awaiting liver transplantation. Serum sodium concentration is equally accurate in the assessment of prognosis in different subpopulations of patients with cirrhosis categorised according to the major complication developed before listing in our patient population. The addition of serum sodium to the MELD score does not appear to improve significantly the prognostic accuracy of the MELD score alone. Nevertheless, additional studies in large patient populations should be performed to address this issue further.

ACKNOWLEDGEMENTS

The authors thank Dr Juan Gonzalez-Abraldes for his help in the evaluation of data.

Authors' affiliations

Maria-Carlota Londoño, Andrés Cárdenas, Mónica Guevara, Dara de las Heras, Miguel Navasa, Antoni Rimola, Vicente Arroyo, Pere Ginès, Liver Unit, Hospital Clínic, Universitat de Barcelona, Institut de Investigacions Biomèdiques August Pi-Sunyer (IDIBAPS), CIBER de Enfermedades Hepáticas y Digestivas (CIBEREHD) and Centro de Investigaciones Biomédicas Esther Koplowitz (CIBEK), Barcelona, Spain
Juan-Carlos Garcia-Valdecasas, Department of Surgery, Hospital Clínic, Universitat de Barcelona, Institut de Investigacions Biomèdiques August Pi-Sunyer (IDIBAPS), CIBER de Enfermedades Hepáticas y Digestivas (CIBEREHD) and Centro de Investigaciones Biomédicas Esther Koplowitz (CIBEK), Barcelona, Spain
Llorenç Quintó, Department of Biostatistics, Hospital Clínic, Universitat de Barcelona, Institut de Investigacions Biomèdiques August Pi-Sunyer (IDIBAPS), CIBER de Enfermedades Hepáticas y Digestivas (CIBEREHD) and Centro de Investigaciones Biomédicas Esther Koplowitz (CIBEK), Barcelona, Spain

This study was supported by grants from Fondo de Investigación Sanitaria (FIS 05/0246) and Ministerio de Educación y Ciencia (SAF 2005-01917). Mónica Guevara was supported by a grant from Fondo de Investigación Sanitaria (FIS01/3045). Maria–Carloto Londoño has received financial support from the Fundacion Banco Bilbao Vizcaya Argentaria.

Competing interests: None.

REFERENCES

1 **Kamath PS**, Wiesner RH, Malinchoc M, *et al*. A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001;**33**:464–70.
2 **Wiesner RH**, McDiarmid SV, Kamath PS, *et al*. MELD and PELD: application on survival models to liver allocation. *Liver Transpl* 2001;**7**:567–80.
3 **Freeman RB Jr**, Wiesner RH, Harper A, *et al*. UNOS/OPTN Liver Disease Severity Score, UNOS/OPTN Liver and Intestine, and UNOS/OPTN Pediatric Transplantation Committees. The new liver allocation system: moving toward evidence-based transplantation policy, *Liver Transpl* 2002;**8**:851–8.
4 **Everson GT**. MELD: the answer or just more questions? *Gastroenterology* 2003;**124**:251–4.
5 **Freeman RB**. MELD: the holy grail of organ allocation? *J Hepatol* 2004;**42**:16–20.
6 **Cholongitas E**, Senzolo M, Triantos C, *et al*. MELD is not enough—enough of MELD? *J Hepatol* 2005;**42**:475–7.
7 **Durand F**, Valla D. Assessment of the prognosis of cirrhosis: Child–Pugh versus MELD. *J Hepatol* 2005;**42**:S100–7.
8 **Heuman DM**, Abou-Assi SG, Habib A, *et al*. Persistent ascites and low serum sodium identify patients with cirrhosis and low MELD scores who are at high risk for early death. *Hepatology* 2004;**40**:802–10.
9 **Biggins SW**, Rodriguez HJ, Bacchetti P, *et al*. Serum sodium predicts mortality in patients listed for liver transplantation. *Hepatology* 2005;**41**:32–9.
10 **Ruf AE**, Kremers WK, Chavez LL, *et al*. Addition of serum sodium into the MELD score predicts waiting list mortality better than MELD alone. *Liver Transpl* 2005;**11**:336–43.
11 **Bustamante J**, Rimola A, Ventura PJ, *et al*. Prognostic significance of hepatic encephalopathy in patients with cirrhosis. *J Hepatol* 1999;**30**:890–5.
12 **Davis CL**. Impact of pretransplant renal failure: when is listing for kidney–liver indicated? *Liver Transpl* 2005;**11**:S35–44.
13 **Moore KP**, Wong F, Gines P, *et al*. The management of ascites in cirrhosis: report on the consensus conference of the International Ascites Club. *Hepatology* 2003;**38**:258–66.
14 **Ginès P**, Cárdenas A, Arroyo V, *et al*. Management of cirrhosis and ascites. *N Engl J Med* 2004;**350**:1646–54.
15 **Pugh RN**, Murray-Lyon IM, Dawson JL, *et al*. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973;**60**:646–9.
16 **Cholongitas E**, Senzolo M, Pathc D, *et al*. Review article: scoring systems for assessing prognosis in critically ill adult cirrhotics. *Aliment Pharmacol Ther* 2006;**24**:453–64.
17 **Cárdenas A**, Ginès P. Management of complications of cirrhosis in patients awaiting liver transplantation. *J Hepatol* 2005;**42**(Suppl 1):S124–33.
18 **Ginès P**, Guevara M, Arroyo V, *et al*. Hepatorenal syndrome. *Lancet* 2003;**362**:1819–27.
19 **Bosch J**, Abraldes JG, Groszmann R. Current management of portal hypertension. *J Hepatol* 2003;**38**:S54–68.
20 **de Franchis R**. Evolving consensus in portal hypertension. Report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol* 2005;**43**:167–76.
21 **Ginès P**, Berl T, Bernardi M, *et al*. Hyponatremia in cirrhosis: from pathogenesis to treatment. *Hepatology* 1998;**28**:851–64.
22 **Arroyo V**, Ginès P, Gerbes AL, *et al*. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. International Ascites Club. *Hepatology* 1996;**23**:164–76.
23 **Hosmer DW**, Lemeshow S. *Applied logistic regression*. New York: Wiley, 1989.
24 **Collett D**. *Modelling binary data*. London: Chapman & Hall, 1991.
25 **Balckstone EH**. Breaking down barriers: helpful breakthrough statistical methods you need to understand better. *J Thorac Cardiovasc Surg* 2001;**122**:430–9.
26 **StataCorp**. Stata Statistical Softwware: Release 9. College Station, TX: StataCorp P, 2005.
27 **Hanley JA**, McNeil BJ. The meaning and use of area under a receiver operating characteristic (ROC) curve. *Radiology* 1982;**143**:29–36.
28 **Biggins SW**, Kim WR, Terrault NA, *et al*. Evidence-based incorporation of serum sodium concentration into MELD. *Gastroenterology* 2006;**130**:1652–60.
29 **Wiesner R**, Edwards E, Freeman R, *et al*. United Network for Organ Sharing Liver Disease Severity Score Committee. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology* 2003;**124**:91–6.

30 **Botta F**, Giannini E, Romagnoli P, *et al*. MELD scoring system is useful for predicting prognosis in patients with liver cirrhosis and is correlated with residual liver function: a European study. *Gut* 2003;**52**:134–9.
31 **Kim WR**, Therneau TM, Benson JT, *et al*. Deaths on the liver transplant waiting list: an analysis of competing risks. *Hepatology* 2006;**43**:345–51.
32 **Roberts MS**, Angus DC, Bryce CL, *et al*. Survival after liver transplantation in the United States: a disease-specific analysis of the UNOS database. *Liver Transpl* 2004;**10**:886–97.
33 **Londoño MC**, Guevara M, Rimola A, *et al*. Hyponatremia impairs early posttransplantation outcome in patients with cirrhosis undergoing liver transplantation. *Gastroenterology* 2006;**130**:1135–43.
34 **Llach J**, Ginès P, Arroyo V, *et al*. Prognostic value of arterial pressure, endogenous vasoactive systems, and renal function in cirrhotic patients admitted to the hospital for the treatment of ascites. *Gastroenterology* 1988;**94**:482–7.
35 **Fernández- Esparrach G**, Sánchez-Fueyo A, Ginès P, *et al*. A prognostic model for predicting survival in cirrhosis with ascites. *J Hepatol* 2001;**34**:46–52.
36 **Borroni G**, Maggi A, Sangiovanni A, *et al*. Clinical relevance of hyponatraemia for the hospital outcome of cirrhotic patients. *Dig Liver Dis* 2000;**32**:605–10.
37 **Ishikawa S**, Schrier RW. Pathogenesis of hyponatremia: the role of arginine vasopressin. In: Ginès P, Arroyo V, Rodés J, Schrier RW, eds. *Ascites and renal dysfunction in liver disease*. Oxford: Blackwell Publishing, 2005, 305–14.
38 **Baccaro ME**, Guevara M, Torre A, *et al*. Hyponatremia predispones to hepatic encephalopathy in patients with cirrosis. Results of prospective study with time-dependent analysis [abstract]. *Hepatology*. 2006;44: 233 A).
39 **Cordoba J**, Gottstein J, Blei AT. Chronic hyponatremia exacerbates ammonia-induced brain edema in rats after portacaval anastomosis. *J Hepatol* 1998;**29**:589–94.
40 **Haussinger D**, Kircheis G, Fischer R, *et al*. Hepatic encephalopathy in chronic liver disease: a clinical manifestation of astrocyte swelling and low-grade cerebral edema? *J Hepatol* 2000;**32**:1035–8.
41 **Jalan R**, Elton RA, Redhead DN, *et al*. Analysis of prognostic variables in the prediction of mortality, shunt failure, variceal rebleeding and encephalopathy following the transjugular intrahepatic portosystemic stent-shunt for variceal haemorrhage. *J Hepatol* 1995;**23**:123–8.
42 **Ginès P**, Arroyo V, Quintero E, *et al*. Comparison of paracentesis and diuretics in the treatment of cirrhotics with tense ascites. Results of a randomized study. *Gastroenterology* 1987;**93**:234–41.
43 **Arroyo V**, Rodés J, Gutierrez-Lizarriaga MA, *et al*. Prognostic value of spontaneuous hyponatremia in cirrhosis with ascites. *Am J Dig Dis* 1976;**21**:249–56.
44 **Ginès P**, Wong F, Milutinovic S, *et al*. Effects of satavaptan (SR121463B), a selective vasopressin V2 receptor antagonist, on serum sodium concentration and ascities in patients with cirrhosis and hyponatremia. *J Hepatol* 2006;**44**:S270.
45 **Wong F**, Ginès P, Watson H, *et al*. Effects of a selective vasopressin V 2 receptor antagonist, Satavaptan (SR121463B), on recurrence of ascites after large volume paracentesis [abstract]. *Hepatology*. 2006;44: 256 A).
46 **Schrier RW**, Gross P, Gheorghiade M, *et al*. Tolvaptan, a selective oral vasopressin V_2-receptor antagonist, for hyponatremia. *N Engl J Med* 2006;**355**:2099–112.

ESTUDIO 2

Hyponatremia impairs early posttransplantation outcome in patients with cirrhosis undergoing liver transplantation

Londoño MC, Guevara M, Rimola A, Navasa M, Taurà P, Mas A, García-Valdecasas JC, Arroyo V, Ginès P.

Hyponatremia Impairs Early Posttransplantation Outcome in Patients With Cirrhosis Undergoing Liver Transplantation

MARIA–CARLOTA LONDOÑO,*,† MÓNICA GUEVARA,*,† ANTONI RIMOLA,*,† MIQUEL NAVASA,*,† PILAR TAURÀ,†,§ ANTONI MAS,*,† JUAN-CARLOS GARCÍA–VALDECASAS,†,‖ VICENTE ARROYO,*,† and PERE GINÈS*,†

*Liver Unit, Hospital Clínic, Universitat de Barcelona, Barcelona; †Institut d'Investigacions Biomèdiques August Pi-Sunyer (IDIBAPS), Barcelona; §Department of Anesthesiology, Hospital Clínic, Universitat de Barcelona, Barcelona; and ‖Department of Surgery, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain

Background & Aims: **Hyponatremia is associated with reduced survival in patients with cirrhosis awaiting liver transplantation. However, it is not known whether hyponatremia also represents a risk factor of poor outcome after transplantation. We aimed to assess the effects of hyponatremia at the time of transplantation on posttransplantation outcome in patients with cirrhosis.** ***Methods:*** **Two-hundred forty-one consecutive patients with cirrhosis submitted to liver transplantation during a 4-year period (January 2000–December 2003) were included in the study. The main end point was survival at 3 months after transplantation. Secondary end points were complications within the first month after transplantation.** ***Results:*** **Patients with hyponatremia (serum sodium lower than 130 mEq/L) had a greater incidence of neurologic disorders, renal failure, and infectious complications than patients without hyponatremia (odds ratio; 4.6, 3.4 and 2.7, respectively) within the first month after transplantation. By contrast, hyponatremia was not associated with an increased incidence of severe intra-abdominal bleeding, acute rejection, or vascular and biliary complications. Hyponatremia was an independent predictive factor of early posttransplantation survival. Three-month survival of patients with hyponatremia was 84% compared with 95% of patients without hyponatremia ($P < .05$). Survival was similar after 3 months.** ***Conclusions:*** **In patients with cirrhosis, the presence of hyponatremia is associated with a high rate of neurologic disorders, infectious complications, and renal failure during the first month after transplantation and reduced 3-month survival. In cirrhosis, hyponatremia should be considered not only a risk factor of death before transplantation but also a risk factor of impaired early posttransplantation outcome.**

Hyponatremia is a common feature of patients with advanced cirrhosis.[1] The development of hyponatremia is related to an impairment of the renal capacity to excrete solute-free water, which causes retention of water in an amount disproportionate to that of sodium retained. This results in a decrease in serum sodium levels despite the existence of increased renal sodium reabsorption and high total body sodium content.[1,2] For this reason, this condition is usually referred to as dilutional hyponatremia. Several mechanisms are known to participate in the impairment of solute-free water excretion in cirrhosis and the subsequent development of hyponatremia, including a reduced delivery of filtrate to the distal nephron, impaired renal prostaglandin synthesis, and hypersecretion of arginine vasopressin (the antidiuretic hormone). Among them, the increased plasma levels of arginine vasopressin, which are secondary to a nonosmotic hypersecretion of the hormone from the neurohypophysis, appear to be the most important.[1,2]

It has been known for years that the impairment in solute-free water excretion and hyponatremia are important prognostic markers in the general population of patients with cirrhosis.[3–6] In addition, several recent studies in patients with cirrhosis awaiting liver transplantation have extended these observations by showing that patients with hyponatremia are at high risk of early death before transplantation and that the prognostic value of low serum sodium concentration is independent of the severity of cirrhosis, as assessed by model for end-stage liver disease (MELD) score.[7–9] Nevertheless, despite this growing interest in the relationship between hyponatremia and liver transplantation, to our knowledge there is no information as to whether the presence of hyponatremia before transplantation may influence posttransplantation outcome. Therefore, the current study was designed to investigate whether pretransplantation hyponatremia may affect morbidity and/or mortality after transplantation.

Abbreviations used in this paper: CPM, central pontine myelinolysis; HRS, hepatorenal syndrome.

0016-5085/06/$32.00
doi:10.1053/j.gastro.2006.02.017

Materials and Methods

Study Population

The current investigation is a single-center retrospective cohort study of 241 consecutive adult patients with cirrhosis submitted to liver transplantation at the Hospital Clínic of Barcelona during a 4-year period (January 2000–December 2003). Seventy other patients undergoing transplantation also at our center during this period of time were excluded from the study because of retransplantation (n = 24), liver diseases other than cirrhosis (acute liver failure [n = 19], familial amyloidotic polyneuropathy [n = 13], polycystic liver disease [n = 4], and hemangioendothelioma and idiopathic portal hypertension [1 patient each]), and combined liver-kidney transplantation (n = 8).

Management of Patients Before Transplantation

Complications of cirrhosis before transplantation were managed according to preestablished protocols as follows. Moderate ascites was treated with low-sodium diet and diuretics, and large ascites was treated with paracentesis plus albumin, followed by low-sodium diet and diuretics, as described in detail elsewhere.[10] Hyponatremia was managed with fluid restriction (1000 mL/day), except for those patients with severe hyponatremia (serum sodium <120 mEq/L) (n = 3), who were treated with hypertonic saline. The administration of hypertonic saline is not a standard therapy for dilutional hyponatremia in cirrhosis because its effects on sodium concentration are inconsistent and is associated with rapid accumulation of ascites and edema.[11,12] Nevertheless, in the absence of effective alternative therapies, this treatment was used in patients with severe hyponatremia in an attempt to improve serum concentration before transplantation and reduce the risk of central pontine myelinolysis (CPM) related to rapid increases in serum sodium after transplantation.[13] Of the 3 patients with severe hyponatremia treated with hypertonic saline, serum sodium concentration did not change significantly in 2 (from 116 and 115 mEq/L before treatment to 118 and 114 mEq/L after treatment, respectively) and increased markedly in 1 (from 112 mEq/L to 131 mEq/L). All of these 3 patients were alive 1 year after transplantation.

Hepatorenal syndrome (HRS) in patients awaiting liver transplantation was treated according to following criteria: patients with type 1 HRS and those with type 2 HRS with serum creatinine greater than 2 mg/dL (174 μmol/L) received terlipressin and albumin.[14] Patients with HRS type 2 with serum creatinine equal to or lower than 2 mg/dL (174 μmol/L) were not treated with terlipressin and albumin because the information on the efficacy of treatment in this group of patients was very limited at the time of the study.[14] Of the 241 patients included in the study, 14 patients had HRS before transplantation, and 2 of them met criteria for treatment. One patient had type 1 HRS and underwent transplantation after 3 days of therapy while renal function was improving (serum creatinine decreased from 6.7 mg/dL to 3.6 mg/dL), whereas the other patient had type 2 HRS and recovered from HRS with serum creatinine decreasing from 2.1 mg/dL to 1.0 mg/dL. Spontaneous bacterial peritonitis was treated with ceftriaxone plus intravenous albumin followed by norfloxacin to prevent recurrence, and the other complications of cirrhosis were managed with conventional therapy.[10,15]

Management of Patients During and After Transplantation

According to the transplantation protocol in our center, all patients were seen by an experienced hepatologist immediately before transplantation. Preoperative routine workout included a complete medical history, with particular emphasis on the possible events occurring the preceding days, physical examination; electrocardiogram; chest x-ray; and blood samples measuring liver and renal function tests, serum electrolytes, blood cell count, urine sediment, and coagulation parameters. Biochemical parameters measured immediately before transplantation were those used to evaluate the effect of liver and renal function on patient's outcome after transplantation. In patients with ascites, a diagnostic paracentesis was performed for cell count and culture. Patients were then transferred to the surgical room in which liver transplantation was performed. In all patients, transplantation was performed using the piggyback technique.[16] After surgery, patients were transferred to the intensive care unit for continued care. Standard liver and renal function tests were measured twice a day during the first 2 days and daily thereafter, unless otherwise indicated. Stable patients were transferred to a standard ward in which blood samples were routinely obtained at least twice a week to measure blood cell count, liver and renal function tests, serum electrolytes, and coagulation parameters. After discharge from the hospital, patients were followed in the outpatient clinic every month during the first 3 months and every 2–3 months during the first year, or more frequently if clinically indicated.

Standard immunosuppression in our center consisted of the administration of prednisone and tacrolimus. Prednisone was given at decreasing doses from 200 mg/day the first day to 20 mg/day at day 6 after transplantation. This dose was maintained until 1 month after transplantation. If there were no signs of rejection, prednisone was tapered progressively and stopped within 6–12 months after transplantation. Tacrolimus was started the first day after transplantation at a dose of 0.1 mg/kg/day and then adjusted to maintain blood levels between 8 and 15 ng/mL within the first 3 months. The dose of tacrolimus was then adjusted to achieve target blood levels of 7–12 ng/mL during months 4 to 12 and 5 to 10 ng/mL thereafter. Patients with diabetes mellitus before transplantation were treated with cyclosporine instead of tacrolimus, at an initial dose of 10 mg/kg per day to achieve trough blood levels between 150 and 300 ng/mL during the first 3 months, 100–200 ng/mL from months 4 to 12, and 50–150 ng/mL thereafter. In patients with serum creatinine levels equal to or greater than 1.5 mg/dL before transplantation or immediately after transplantation, the initiation of tacrolimus or cyclospor-

ine administration was delayed until a reduction in serum creatinine concentration was observed. In the meantime, patients were treated with prednisone, at identical doses as described previously, and mycophenolate mofetil at a dose of 1 g/12 hours. In patients developing renal failure after transplantation, the doses of tacrolimus or cyclosporine were reduced or the drugs temporarily withdrawn. In patients in whom these drugs were withdrawn, mycophenolate mofetil was given until renal function recovered.

End Points and Definitions

The primary end point of this study was survival at 3 months after transplantation. Secondary end points were the development of complications, including early severe intra-abdominal bleeding and renal failure, neurologic disorders, infectious complications, acute rejection, and biliary and vascular complications during the first month after transplantation.

Severe intra-abdominal bleeding was defined as the presence of abdominal hemorrhage requiring reintervention for bleeding control within the first 48 hours after surgery, elimination of intra-abdominal hematomas, and/or removal of gauzes used for packing during the surgical procedure. Renal failure was defined as an increase in serum creatinine concentration of greater than 50% of the immediate pretransplantation value to a final value greater than 2 mg/dL (174 μmol/L). Neurologic disorders were defined as the development of signs or symptoms of abnormal neurologic function and were classified as severe, which included coma, seizures, and/or CPM, and nonsevere (all other abnormalities of neurologic function).[17] Infectious complications were defined by the presence of systemic or local signs of infection together with positive cultures and/or compatible radiologic findings requiring intravenous administration of antimicrobial agents. Acute rejection was diagnosed on the basis of Banff criteria.[18] Biliary complications were defined as the presence of biliary strictures or bile leaks diagnosed by imaging techniques. Vascular complications were defined as the development of thrombosis or stenosis of hepatic artery or portal vein diagnosed by doppler ultrasound and angiography. Patients receiving a liver from a living donor (n = 35) were excluded from the analysis of biliary and vascular complications because this population has an increased risk of surgical complications compared with patients receiving a liver from a cadaveric donor.[19] Finally, hyponatremia was defined as serum sodium concentration lower than 130 mEq/L according to the definition of the International Ascites Club.[1]

Statistical Analysis

Clinical and analytical variables were analyzed as possible predictors of survival in a univariate analysis, and survival curves (Kaplan–Meier method) were compared with the log-rank test. A multivariate analysis of survival was performed using a Cox regression method. Comparisons of variables between groups of patients were made using the nonparametric Mann–Whitney test for continuous data and the χ^2 test or Fisher test for categorical data. Statistical analysis was performed using the SPSS 10 for Windows (SPSS Inc., Chicago, IL). Results are expressed as mean ± SD. $P < .05$ was considered statistically significant.

Table 1. Demographic and Clinical Data and Liver and Renal Function Tests at Time of Transplantation in the 241 Patients Included in Study

Age (*y*)	55 ± 9 (24–69)
Sex	
Male	152 (63%)
Female	89 (37%)
Etiology of cirrhosis, No. patients	
Hepatitis C	135 (56%)
Alcohol	46 (19%)
Other[a]	60 (25%)
Ascites	162 (67%)
Hepatic encephalopathy, No. patients	
Past history	82 (34%)
At transplantation	15 (6%)
Renal failure,[b] No. patients	19 (8%)
Serum bilirubin (*mg/dL*)	2.8 ± 3.5 (0.3–30)
Prothrombin time	
Ratio (%)	65 (26–100)
INR[c]	1.5 ± 0.3 (1–3.3)
Albumin (*g/L*)	32 ± 6 (18–47)
Serum creatinine (*mg/dL*)	1.0 ± 0.3 (0.4–3.6)
Serum sodium (*mEq/L*)	136 ± 5 (114–146)
MELD score	17 ± 6 (6–40)
Child-Pugh score	8 ± 2 (5–13)

NOTE. Values are mean ± SD (ranges).

[a]Hepatitis B (18 patients; 7%), hepatitis C and alcohol (13 patients; 5%), chronic cholestatic liver diseases (11 patients; 5%), and other (18 patients; 7%).

[b]As defined by serum creatinine greater than 1.5 mg/dL (133 μmol/L). Causes of renal failure were hepatorenal syndrome in 14 (type I in 1 and type II in 13) and chronic, nonfunctional renal diseases in 5 patients.

[c]International normalized ratio was calculated according to the following formula: (prothrombin time of patient/control prothrombin time)^{ISI}, ISI being the International Sensitivity Index for thromboplastins.

Results

Characteristics of the Patients

The study population includes 241 consecutive adult patients with cirrhosis undergoing liver transplantation during a 4-year period, from January 2000 to December 2003. Two hundred six out of the 241 patients included in the study (85%) received a liver from a cadaveric donor, whereas the remaining 35 patients (15%) received a graft from a living donor. Demographic, clinical, and biochemical data of patients included in the study at time of transplantation are shown in Table 1.

Prevalence of Hyponatremia at Transplantation

Nineteen of the 241 patients (8%) had hyponatremia at the time of transplantation. Patients with hyponatremia at transplantation had been hyponatremic for a mean period of 106 days (range, 12–237days). Table 2 shows the comparison of demographic and clinical data and liver and renal function tests in patients with and without hyponatremia at transplantation. Patients with hyponatremia had greater frequency of ascites and encephalopathy, more marked impairment of liver function tests, and higher MELD and Child–Pugh scores, compared with values in patients without hyponatremia. The frequency of HRS was similar in patients with and without hyponatremia (5% and 6%, respectively; P = ns).

Complications After Transplantation

One hundred twenty-seven of the 241 patients (53%) developed at least 1 major complication during the 30-day postoperative period. Overall, the most common complication was acute rejection in 52 patients (21%). In all patients, acute rejection resolved after the administration of steroid boluses and/or adjustment of doses of baseline immunosuppressive agents. Forty-six patients (18% of the whole series) developed infectious complications: 15 (33%) had pneumonia, 9 (20%) biliary tract infection, 7 (15%) urinary tract infection, 7 (15%) intraabominal infection, 5 (11%) catheter-related sepsis, and 3 (7%) sepsis of unknown origin. Resolution of the infection was obtained in 34 of the 46 patients (74%). In the remaining 12 patients, infection did not resolve and contributed to the death of the patients. Thirty-nine of the 241 patients (16%) developed renal failure within the 30-day postoperative period. Peak serum creatinine in these patients was 3.7 mg/dL (range, 2.1–9.1 mg/dL), and the median time to reach the peak value was 8 days. Nine of the 39 patients (23%) with renal failure required renal replacement therapy. No patient required long-term hemodyalisis. Patients who developed renal failure after transplantation did not have higher levels of immunosuppressive agents (tacrolimus or cyclosporine) throughout the 30-day postoperative period compared with those patients who did not develop renal failure. Thirty-two of the 241 (13%) patients included in the study developed neurologic disorders within the 30-day postoperative period. Median time to the development of neurologic disorders was 10 days (range, 2–29 days). Twenty-nine of the 32 patients (91%) developed altered mental status without focal motor disorders, associated with seizures in 4 patients, in the absence of significant lesions in cerebral computerized tomography (CT) or magnetic resonance imaging (MRI); 2 patients developed CPM and 1 patient cerebral hemorrhage. Serum sodium concentrations before and immediately after transplantation in the 2 patients who developed CPM were 146 mEq/L and 124 mEq/L vs 142 mEq/L and 140 mEq/L, respectively. In all patients, neurologic function recovered completely, except for the patient with cerebral hemorrhage and 1 of the 2 patients with CPM, who died 38 and 103 days after transplantation, respectively. This latter patient died from hepatic artery thrombosis when symptoms because of CPM were improving. There were no significant differences between patients who did and did not develop neurologic complications with respect to the blood levels of immunosuppressive agents (tacrolimus or cyclosporine) obtained throughout the 30-day postoperative period. Twenty-five of the 241 patients (10%) had severe intra-abdominal bleeding. The average number of packed red blood cells transfused in these 25 patients was 19, compared with only 5 in the remaining 216 patients ($P < .0001$). Resolution of the intra-abdominal bleeding was obtained in 23 patients. Persistent bleeding contributed to death in the remaining 2 patients. Finally, out of the 206 patients receiving a liver from a cadaveric donor, 7 patients (3%) developed biliary complications, and 11 patients (5%) developed vascular complications during the 30-day postoperative period.

To assess whether the presence of hyponatremia before transplantation was associated with an increased risk of complications after transplantation, patients were divided according to the presence or absence of hyponatremia at transplantation, and the rate of complications between the 2 groups was compared. As shown in Table 3, patients with hyponatremia had a greater risk of developing complications after transplantation than patients without hyponatremia, the difference being at the level of significance. When complications were analyzed individually, patients with hyponatremia had a significantly greater frequency of neurologic disorders, renal failure, and infectious complications. Severe neurologic disorders were also more frequent in patients with hyponatremia as compared with patients without hyponatremia (21% and 5%, respectively; $P = .003$). By contrast, the presence of hyponatremia was not associated with an increased risk of severe intra-abdominal bleeding, acute rejection, and biliary or vascular complications. Figure 1 shows the cumulative probability of development of neurologic disorders, infectious complications, and renal failure after transplantation in patients divided according to the presence or absence of hyponatremia at time of transplantation. Using regression analysis, which included demographic and clinical and laboratory variables obtained at the time of transplantation,

Table 2. Demographic and Clinical Data and Liver and Renal Function Tests at Time of Transplantation According to Presence or Absence of Hyponatremia

Variable	Hyponatremia (n = 19)	No hyponatremia (n = 222)	*P* value
Age (*y*)	52 ± 13 (24–65)	55 ± 9 (24–69)	ns
Sex			
Male	9 (47%)	143 (64%)	ns
Female	10 (53%)	79 (36%)	ns
Etiology of cirrhosis, No. patients			ns
Hepatitis C	11 (58%)	124 (56%)	
Alcohol	4 (21%)	42 (19%)	
Other	4 (21%)	56 (25%)	
Ascites, No. patients	19 (100%)	143 (64%)	<.01
Diuretics[a]			
Number of patients	12 (63%)	119 (54%)	ns
Furosemide (*mg/day*)	80 ± 69 (40–160)	45 ± 23 (20–160)	ns
Spironolactone (*mg/day*)	167 ± 121 (100–400)	105 ± 42 (25–300)	ns
Hepatorenal syndrome, No. patients	1 (5%)	13 (6%)	ns
Hepatic encephalopathy, No. patients			
Past history	9 (47%)	73 (33%)	ns
At transplantation	4 (21%)	11 (5%)	.01
Serum bilirubin (*mg/dL*)	7.5 ± 7.5 (0.6–30)	2.4 ± 2.6 (0.3–29)	<.01
Prothrombin time			
Ratio (*%*)	55 ± 22 (26–98)	66 ± 16 (32–100)	.02
INR	1.7 ± 0.5 (1–2.6)	1.5 ± 0.3 (1–3.3)	ns
Albumin (*g/L*)	28 ± 5 (22–41)	33 ± 6 (18–47)	<.01
Serum creatinine (*mg/dL*)	1.2 ± 0.6 (0.4–3.6)	1.0 ± 0.3 (0.4–2.7)	ns
Serum sodium (*mEq/L*)	125 ± 4 (114–129)	138 ± 3 (130–146)	<.01
MELD score	20 ± 7 (9–40)	17 ± 5 (6–30)	.04
Child-Pugh score	10 ± 2 (6–13)	8 ± 2 (5–13)	<.01

NOTE. Values are mean ± SD (ranges).
[a]Patients being treated with diuretics at the time of transplantation.

the study found hyponatremia to be an independent predictive factor of development of neurologic disorders and renal failure. HRS before transplantation was also an independent predictive factor of renal failure after transplantation. Six of the 14 patients with HRS before transplantation (43%) developed renal failure after transplantation compared with 33 of the 227 patients without HRS (19%) ($P = .04$).

Survival After Transplantation

Fourteen of the 241 patients (5%) died during the first 3 months after transplantation. Causes of death were infections in 7 patients (bacterial in 5 and fungal in 2); cardiovascular complications in 2; intra-abdominal bleeding in 2; and gastrointestinal bleeding, cerebral hemorrhage, and recurrence of hepatocellular carcinoma in 1 patient each.

The presence of hyponatremia at transplantation was associated with a reduced short-term survival after transplantation. As shown in Figure 2, patients with hyponatremia at the time of transplantation had a lower 3-month survival compared with that of patients without hyponatremia at the time of transplantation (84% vs 95%, respectively; $P < .05$). One-year survival was also lower in patients with hyponatremia compared with that

Table 3. Frequency of Major Complications of Transplantation in the 241 Patients Included in Study Divided According to Presence or Absence of Hyponatremia at Time of Transplantation

Complications	Hyponatremia, n (%) (n = 19)	No hyponatremia, n (%) (n = 222)	OR (95% CI)	*P* value
Any complication	14 (74)	113 (51)	2.7 (1–8)	.05
Neurologic disorders	7 (37)	25 (11)	4.6 (1.6–13)	.006
Renal failure	7 (37)	32 (14)	3.4 (1.3–9.4)	.02
Infectious complications	7 (37)	39 (17)	2.7 (1–7.3)	.04
Severe intraabdominal bleeding	4 (21)	21 (10)	2.5 (0.7–8.3)	.1
Vascular complications	0	11 (6)		.6
Biliary complications	1 (7)	6 (13)	1.6 (0.2–14)	.7
Acute rejection	2 (10)	50 (23)	0.4 (0.1–1.8)	.2

NOTE. Hyponatremia = serum sodium <130 mE/L. OR, odds ratio; CI, confidence interval.

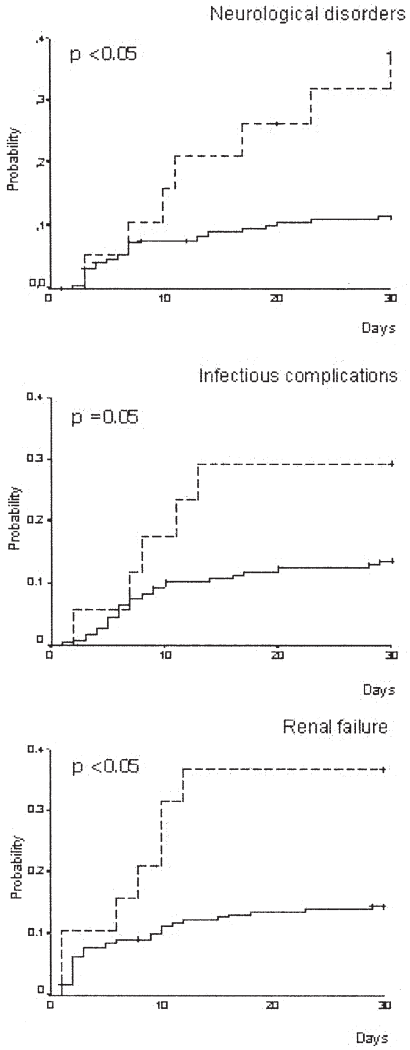


Figure 1. Probability of developing neurologic disorders, infectious complications, and renal failure in all patients included in the study divided according to the presence (*dashed line*) or absence (*solid line*) of hyponatremia at transplantation.

of patients without hyponatremia (74% vs 91%, respectively; $P = .017$). Nevertheless, when patients who died within the first 3 months after transplantation were excluded from the analysis, there were no significant differences in 1-year survival between patients with hyponatremia and patients without hyponatremia at the time of transplantation (88% vs 95%, respectively; $P = .16$).

In univariate analysis, neither the severity of liver failure, as assessed by individual liver function tests or MELD or Child–Pugh scores, serum creatinine concentration, renal failure at transplantation, nor the characteristics of the donor (cadaveric vs living related, age, liver tests, presence and degree of liver steatosis, time in intensive care unit, and ischemia time) were associated with prognosis after transplantation. The prognostic value of hyponatremia was maintained in multivariate analysis (odds ratio, 3.6).

Finally, the effect of postoperative complications on 3-month survival was also evaluated. Patients who developed renal failure after transplantation had a reduced 3-month survival compared with that of patients who did not develop renal failure (79% vs 97%, $P < .001$). Likewise, the development of infectious complications or severe intra-abdominal bleeding was also associated with a reduced 3-month survival (85% and 84%, respectively, compared with 96% and 95% in patients who did not develop these complications). By contrast, neither the development of neurologic disorders nor vascular or biliary complications were associated with a poor outcome.

Discussion

The main finding of the current study is that pretransplantation hyponatremia was associated with an impaired short-term posttransplantation outcome in a series of 241 consecutive patients with cirrhosis undergoing transplantation in a single institution over a 4-year period. Patients with hyponatremia at time of transplantation had a greater risk of major posttransplantation complications within the first month after transplantation, including neurologic disorders, renal failure, and infectious complications. The presence of hyponatremia increased the risk of developing these complications 4.6, 3.4, and 2.7 times, respectively, compared with patients undergoing transplantation without hyponatremia. More importantly, 3-month survival after transplantation was significantly lower in patients with pretransplantation hyponatremia compared with that of patients without hyponatremia (84% vs 95%, respectively; $P < .05$; Figure 2).

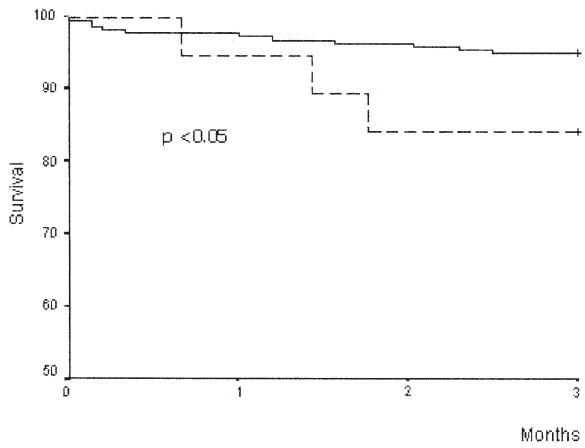


Figure 2. Three-month survival after transplantation of patients, divided according to the presence (*dashed line*) or absence (*solid line*) of hyponatremia at the time of transplantation.

It is well established that the occurrence of hyponatremia entails a poor prognosis regardless of the clinical condition causing hyponatremia. Epidemiologic studies in hospitalized patients with a variety of clinical conditions have shown an increased risk of in-hospital mortality in patients with hyponatremia as compared with nonhyponatremic controls.[20,21] Moreover, studies in patients with heart failure have shown that hyponatremia is one of the best parameters to estimate short-term mortality.[22] Finally, a number of studies in patients with cirrhosis have consistently demonstrated that hyponatremia is one of the strongest predictive factors of poor survival in several patient populations, including patients with stable ascites, patients with bacterial infections, patients treated with transjugular intrahepatic portosystemic shunts, and patients listed for transplantation.[5–9,23,24] Whether the prognostic value of hyponatremia in these different conditions is due to the fact that it is a precise marker of the disease stage or to negative direct effects of low serum sodium levels on the function of several organs (ie, central nervous system, circulatory system) or both is not known.

The results of the current study extend these previous observations and show that hyponatremia is associated with a reduced survival early (3-month) after transplantation. However, if patients with hyponatremia pretransplantation survive 3 months, then the outcome is similar to that of patients without hyponatremia pretransplantation. The lower early posttransplantation survival observed in patients with hyponatremia compared with that of patients without hyponatremia in our transplantation population was probably related, at least in part, to the fact that hyponatremia increased the risk of development of major complications early after transplantation, such as renal failure, infectious complications, and neurologic disorders, which are known to have a negative impact on survival of transplantation patients.[25–27] The possible mechanism(s) by which hyponatremia may increase the risk of these latter complications in patients with cirrhosis undergoing liver transplantation was not investigated in the current study but deserves a comment.

It is well established that the presence of hyponatremia identifies a group of patients with cirrhosis with a particularly severe impairment in circulatory function.[1,2] Clinical and experimental studies have shown convincingly that hyponatremia in cirrhosis is secondary to a marked impairment of the arterial circulation, which is characterized by a reduction in effective arterial blood volume related to an intense arterial vasodilatation of the splanchnic circulation. This reduction in effective arterial blood volume leads to a marked stimulation of the renin-angiotensin-aldosterone system and sympathetic nervous system and nonosmotic hypersecretion of arginine vasopressin.[1,2] One of the main consequences of the increased vasopressin levels is an impairment of solute-free water excretion and the subsequent development of hyponatremia. Therefore, considering that changes in arterial pressure occur frequently in patients undergoing liver transplantation, both during or after the surgical procedure, the existence of a severely impaired circulatory function before transplantation may enhance the risk of renal failure after transplantation. This situation of increased risk of renal failure in patients undergoing transplantation with hyponatremia is reminiscent of what occurs in patients with cirrhosis not submitted to transplantation in whom the presence of hyponatremia is one of the main risk factors of the development of hepatorenal syndrome.[28]

Several previous studies have suggested that the presence of hyponatremia before liver transplantation is a risk factor of neurologic complications after transplantation, although a study specifically comparing hyponatremic with nonhyponatremic patients has, to our knowledge, not been reported.[13,29] The most severe neurologic disorder described in hyponatremic patients is CPM, which has been reported to occur in 1%–2% of liver transplant recipients and is thought to be mainly related to a rapid and marked increase in serum sodium concentration after transplantation.[13,29,30] The results of the current study indicate that patients with hyponatremia at transplantation have a 4.6 times higher risk of developing neurologic complications compared with patients without hyponatremia. Patients who developed neurologic complications did not differ from those who did not develop neurologic complications with respect to changes in serum sodium concentration before and immediately after transplantation (5.4 $\pm$ 6.8 mEq/L vs 2.7 $\pm$ 3.8 mEq/L, respectively; $P = .12$). Changes in serum sodium concentration before transplantation and at 48 hours after transplantation between the 2 groups were also not significantly different. These data suggest that neurologic complications in this setting are probably related to hyponatremia and its effects on the central nervous system rather than to changes in serum sodium concentration occurring after transplantation. The incidence of CPM in patients with hyponatremia included in the current study (2 out of 19, 10%) is lower than that reported in a previous study (3 out of 12 patients, 25%).[29]

A number of studies have shown that renal failure before transplantation is an important risk factor of poor

survival after liver transplantation.[25,31,32] In the current series, neither serum creatinine levels nor the existence of renal failure before transplantation was associated with poor survival after transplantation. Most published studies demonstrating the prognostic value of pretransplantation renal failure on postransplantation outcome included patients undergoing transplantation in the 1980s or 1990s,[25,31,32] whereas the current study includes patients undergoing transplantation from 2000 to 2003. Therefore, it is possible that recent improvement in the management of transplantation patients accounts for the lack of effect of renal failure pretransplantation on survival postransplantation. These may include an improvement in general postransplantation care, the routine use of the surgical piggyback technique,[16] the modifications of immunosuppressive regimes, and treatment of HRS before transplantation.[14,33]

In conclusion, the results of the current study indicate that, in patients with cirrhosis, the presence of hyponatremia at the time of transplantation is associated with a high rate of neurologic disorders, infectious complications, and renal failure during the first month after transplantation and an impaired 3-month survival compared with patients without hyponatremia. Whether the prognostic value of hyponatremia is related directly to a possible deleterious effect of hyponatremia and the associated hypoosmolality and/or indirectly to a more advanced liver disease is not known and deserves investigation. The observation in patients awaiting transplantation,[7–9] as well as the results of the current study, that the predictive value of hyponatremia is independent of liver function, as assessed by MELD score, does not support the concept that the poor outcome of hyponatremic patients is related to the coexistence of a more severe liver disease. Whatever the reason, the results of the current study indicate that hyponatremia in cirrhosis should be considered not only a risk factor of death before transplantation but also a risk factor of impaired early posttransplantion outcome.

References

1. Ginès P, Berl T, Bernardi M, Bichet DG, Hamon G, Jimenez W, Liard JF, Martin PY, Schrier RW. Hyponatremia in cirrhosis: from pathogenesis to treatment. Hepatology 1998;28:851–864.
2. Ishikawa S, Schrier RW. Pathogenesis of hyponatremia: the role of arginine vasopressin. In: Ginès P, Arroyo V, Rodés J, Schrier RW, eds. Ascites and renal dysfunction in liver disease. Oxford, UK: Blackwell Publishing, 2005:305.
3. Hecker R, Sherlock S. Electrolyte and circulatory changes in terminal liver failure. Lancet 1956;271:1121–1125.
4. Arroyo V, Rodes J, Gutierrez-Lizarraga MA, Revert L. Prognostic value of spontaneous hyponatremia in cirrhosis with ascites. Am J Dig Dis 1976;21:249–256.
5. Llach J, Ginès P, Arroyo V, Rimola A, Tito L, Badalamenti S, Jimenez W, Gaya J, Rivera F, Rodés J. Prognostic value of arterial pressure, endogenous vasoactive systems, and renal function in cirrhotic patients admitted to the hospital for the treatment of ascites. Gastroenterology 1988;94:482–487.
6. Fernandez-Esparrach G, Sanchez-Fueyo A, Gines P, Uriz J, Quinto L, Ventura PJ, Cardenas A, Guevara M, Sort P, Jimenez W, Bataller R, Arroyo V, Rodés J. A prognostic model for predicting survival in cirrhosis with ascites. J Hepatol 2001;34:46–52.
7. Heuman DM, Abou-Assi SG, Habib A, Williams LM, Stravitz RT, Sanyal AJ, Fisher RA, Mihas AA. Persistent ascites and low serum sodium identify patients with cirrhosis and low MELD scores who are at high risk for early death. Hepatology 2004;40:802–810.
8. Biggins SW, Rodriguez HJ, Bacchetti P, Bass NM, Roberts JP, Terrault NA. Serum sodium predicts mortality in patients listed for liver transplantation. Hepatology 2005;41:32–39.
9. Ruf AE, Kremers WK, Chavez LL, Descalzi VI, Podesta LG, Villamil FG. Addition of serum sodium into the MELD score predicts waiting list mortality better than MELD alone. Liver Transpl 2005; 11:336–343.
10. Ginès P, Cardenas A, Arroyo V, Rodés J. Management of cirrhosis and ascites. N Engl J Med 2004;350:1646–1654.
11. Moore KP, Wong F, Ginès P, Bernardi M, Ochs A, Salerno F, Angeli P, Porayko M, Moreau R, Garcia-Tsao G, Jimenez W, Planas R, Arroyo V. The management of ascites in cirrhosis: report on the consensus conference of the International Ascites Club. Hepatology 2003;38:258–266.
12. Ginès P, Arroyo V, Rodés J. Ascites, hepatorenal syndrome and spontaneous bacterial peritonitis. In: McDonald J, Burroughs A, Feagan BG, eds. Evidence based-gastroenterology and hepatology. Oxford, UK: Blackwell Publishing, 2005:487.
13. Wszolek ZK, McComb RD, Pfeiffer RF, Steg RE, Wood RP, Shaw BW Jr, Markin RS. Pontine and extrapontine myelinolysis following liver transplantation. Relationship to serum sodium. Transplantation 1989;48:1006–1012.
14. Ginès P, Guevara M, Arroyo V, Rodés J. Hepatorenal syndrome. Lancet 2003;362:1819–1827.
15. Cardenas A, Ginès P. Management of complications of cirrhosis in patients awaiting liver transplantation. J Hepatol 2005; 42(Suppl 1):S124–S133.
16. Gonzalez FX, Garcia-Valdecasas JC, Grande L, Pacheco JL, Cugat E, Fuster J, Lacy AM, Taura P, Lopez-Boado MA, Rimola A, Visa J. Vena cava vascular reconstruction during orthotopic liver transplantation: a comparative study. Liver Transpl Surg 1998;4:133–140.
17. Bronster DJ, Emre S, Boccagni P, Sheiner PA, Schwartz ME, Miller CM. Central nervous system complications in liver transplant recipients—incidence, timing, and long-term follow-up. Clin Transplant 2000;14:1–7.
18. Ormonde DG, de Boer WB, Kierath A, Bell R, Shilkin KB, House AK, Jeffrey GP, Reed WD. Banff schema for grading liver allograft rejection: utility in clinical practice. Liver Transpl Surg 1999;5: 261–268.
19. Olthoff KM, Merion RM, Ghobrial RM, Abecassis MM, Fair JH, Fisher RA, Freise CE, Kam I, Pruett TL, Everhart JE, Hulbert-Shearon TE, Gillespie BW, Emond JC; A2ALL Study Group. Outcomes of 385 adult-to-adult living donor liver transplant recipients. A report from the A2ALL consortion. Ann Surg 2005;242: 314–325.
20. Anderson RJ. Hospital-associated hyponatremia. Kidney Int 1986;29:1237–1247.
21. Baran D, Hutchinson TA. The outcome of hyponatremia in a general hospital population. Clin Nephrol 1984;22:72–76.
22. Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV. Predicting mortality among patients hospitalised for heart failure. Derivation and validation of a clinical model. JAMA 2003;290: 2581–2587.
23. Follo A, Llovet JM, Navasa M, Planas R, Forns X, Francitorra A, Rimola A, Gassull MA, Arroyo V, Rodes J. Renal impairment after spontaneous bacterial peritonitis in cirrhosis: incidence, clinical

course, predictive factors and prognosis. Hepatology 1994;20: 1495–1501.
24. Jalan R, Elton RA, Redhead DN, Finlayson NDC, Hayes PC. Analysis of prognostic variables in the prediction of mortality, shunt failure, variceal rebleeding and encephalopathy following the transjugular intrahepatic portosystemic stent-shunt for variceal hemorrhage. J Hepatol 1995;23:123–128.
25. Nair S, Verma S, Thuluvath PJ. Pretransplant renal function predicts survival in patients undergoing orthotopic liver transplantation. Hepatology 2002;35:1179–1185.
26. Lewis MB, Howdle PD. Neurologic complications of liver transplantation in adults. Neurology 2003;61:1174–1178.
27. Paya CV, Hermans PE, Washington JA II, Smith TF, Anhalt JP, Wiesner RH, Krom RA. Incidence, distribution, and outcome of episodes of infection in 100 orthotopic liver transplantations. Mayo Clin Proc 1989;64:555–564.
28. Ginès A, Escorsell A, Ginès P, Saló J, Jiménez W, Inglada L, Navasa M, Clària J, Rimola A, Arroyo V, Rodés J. Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. Gastroenterology 1993;105:229–236.
29. Abbasoglu O, Goldstein RM, Vodapally MS, Jennings LW, Levy MF, Husberg BS, Klintmalm GB. Liver transplantation in hyponatremic patients with emphasis on central pontine myelinolysis. Clin Transplant 1998;12:263–269.
30. Pujol A, Graus F, Rimola A, Beltran J, Garcia-Valdecasas JC, Navasa M, Grande L, Galofre J, Visa J, Rodés J. Predictive factors of in-hospital CNS complications following liver transplantation. Neurology 1994;44:1226–1230.
31. Rimola A, Gavaler JS, Schade RR, El-Lakany S, Starzl TE, Van Thiel DH. Effects of renal impairment on liver transplantation. Gastroenterology 1987;93:148–156.
32. Ghobrial RM, Steadman R, Gornbein J, Lassman C, Holt CD, Chen P, Farmer DG, Yersiz H, Danino N, Collisson E, Baquarizo A, Han SS, Saab S, Goldstein LI, Donovan JA, Esrason K, Busuttil RW. A 10-year experience of liver transplantation for hepatitis C: analysis of factors determining outcome in over 500 patients. Ann Surg 2001;234:384–393.
33. Restuccia T, Ortega R, Guevara M, Ginès P, Alessandria C, Ozdogan O, Navasa M, Rimola A, Garcia-Valdecasas JC, Arroyo V, Rodes J. Effects of treatment of hepatorenal syndrome before transplantation on posttransplantation outcome. A case-control study. J Hepatol 2004;40:140–146.

Received October 21, 2005. Accepted December 21, 2005.

Address requests for reprints to: Pere Ginès, MD, Liver Unit, Hospital Clínic de Barcelona, C/ Villarroel 170, 08036, Barcelona, Spain. e-mail: pgines@clinic.ub.es; fax: (34) 93 4515522.

Supported by grants from the Fondo de Investigación Sanitaria (FIS 05/0246), Ministerio de Educación y Ciencia (SAF 2005-01917), and Instituto de Salud Carlos III (CO3/2 and CO3/3) and a research grant from Fundación Carolina (to M-C.L).

4. DISCUSIÓN

ESTUDIO 1: "MELD score and serum sodium in the prediction of survival of patients with cirrhosis awaiting liver transplantation".

En este estudio se confirmaron resultados preliminares [9,10] demostrando la utilidad del MELD como factor predictivo independiente de supervivencia a corto y medio plazo en pacientes en lista de espera para trasplante hepático. Sin embargo, existen algunos datos de este estudio que merecen ser comentados en detalle.

En primer lugar, a diferencia de los estudios previos, una de las características más especiales de nuestra cohorte de pacientes es que la asignación de órganos para trasplante hepático se realizaba por tiempo de inclusión en la lista de espera, es decir, el paciente con mayor tiempo en la lista recibía el órgano sin importar la gravedad del enfermo. Ello da más valor a los resultados de este estudio indicando que el MELD, a pesar de sus debilidades, es un buen sistema para la asignación de órganos para trasplante hepático. En este estudio, el mayor cambio en la probabilidad de supervivencia se produjo en rangos de MELD entre 15 y 40, donde por cada de punto de aumento en el MELD, la supervivencia en lista de espera disminuía un 8%. Además en pacientes con MELD inferior a 15, la mortalidad en lista era extremadamente baja sugiriendo que probablemente estos pacientes no se beneficien de ser incluidos en lista de espera. Ello confirma los resultados de otros estudios que indican que el beneficio en la supervivencia a corto plazo de un trasplante hepático es mayor en pacientes con valores altos de MELD. De hecho, en un estudio realizado por

Merion et al, se encontró la mortalidad en pacientes con MELD inferior a 15 era superior si recibían un trasplante hepático (HR 3,6 para MELD entre 6 y 11, y HR 2,5 para MELD entre 12 y 14)[68].

Por otra parte, en este estudio se confirman los hallazgos de otras publicaciones demostrando la utilidad del sodio para establecer el pronóstico de los pacientes cirróticos en lista de espera para trasplante hepático [61-63]. La importancia del sodio como factor pronóstico se ha confirmado en estudios posteriores que evalúan diferentes métodos para incorporar el sodio a la fórmula del MELD. En este sentido, Biggins et al realizaron un estudio en el que tras diferentes análisis estadísticos se desarrolló el siguiente modelo: MELD+1,59 (135-Na). En esta cohorte de pacientes una puntuación de MELD-Na de 20, 30 y 40 se asoció con un riesgo de muerte a los 6 meses de 6%, 16% y 37%, respectivamente[69]. Posteriormente, el mismo grupo realizó un estudio para validar los resultados de los estudios previos y refinar el puntaje MELD-Na. En esta gran cohorte de pacientes (n=6769), nuevamente el MELD y el sodio fueron factores predictivos independiente de mortalidad en lista de espera con un HR de 1,21 por cada punto de incremento en el MELD y 1,05 por cada unidad de disminución del sodio entre 125 y 140 mEq/L. Además se evidenció que el efecto del sodio era mayor en los pacientes con MELD bajo, desarrollando un nuevo modelo para calcular el MELD-Na: MELD-Na-[0,025xMELDx(140-Na)]+140. Estos datos fueron validados en una cohorte independiente de pacientes en la cual se observó que la capacidad predictiva del MELD-Na era significativamente mayor que

la del MELD (AUC 0,883 vs. 0,868, p<0,001). En nuestro estudio la adición del sodio sérico al MELD no mejoró la capacidad predictiva del MELD probablemente por el reducido número de pacientes incluidos. Con los datos mencionados anteriormente se plantea la utilidad del MELD-Na para la asignación de órganos para trasplante hepático, ya que podría ayudar a disminuir la mortalidad en lista de espera[70].

ESTUDIO 2: "Hyponatremia impairs early posttransplantation outcome in patients with cirrhosis undergoing liver transplantation".

Este fue el primer estudio en demostrar que la presencia de hiponatremia en el periodo pre-trasplante se asociaba con una disminución de la supervivencia post-trasplante a corto plazo. Asimismo, en este estudio se encontró que los pacientes con hiponatremia también presentaban un aumento en el riesgo de desarrollar complicaciones neurológicas, infecciones e insuficiencia renal durante el primer mes post-trasplante hepático. Desde entonces se han publicado otros estudios en diferentes poblaciones que confirman estos resultados. Dawwas et al, evaluó la supervivencia a 3 años de una cohorte de 5152 pacientes trasplantados en Reino Unido e Irlanda en un periodo de 11 años. Los autores encontraron que los pacientes con sodio sérico menor de 130 mEq/L presentaban un aumento en la mortalidad a los 3 meses post-trasplante (HR 1,55; IC95% 1,18-2,04), lo que confirma los resultados de la presente tesis. Este aumento en la mortalidad fue independiente del MELD, la presencia de otras

complicaciones de la cirrosis y la necesidad de soporte renal y/o ventilación mecánica [71]. Hackworth et al, realizaron un estudio retrospectivo en 213 pacientes receptores de trasplante hepático. No hubo diferencias en la supervivencia post-trasplante entre los pacientes con sodio sérico pre-trasplante mayor o menor de 130mE/L, sin embargo, los pacientes con hiponatremia en el momento del trasplante o aquellos que habían tenido hiponatremia en algún momento durante el tiempo en lista de espera presentaron un aumento en el tiempo de estancia hospitalaria, delirio post-trasplante insuficiencia renal aguda, rechazo celular agudo e infecciones durante los primeros 180 días post-trasplante [72]. De forma similar, Yun et al, estudió 2175 pacientes receptores de trasplante hepático, encontrando que los pacientes con hiponatremia presentaban un aumento en el número de complicaciones post-trasplante, mayor estancia hospitalaria y en la unidad de cuidados intensivos. En este estudio la incidencia de síndrome de desmielinización osmótica fue muy baja (0,5%) pero se correlacionó con la presencia de hiponatremia. Sin embargo, los autores no encontraron un impacto de la hiponatremia en la supervivencia post-trasplante hepático[73]. Otro estudio realizado por Fukuhara et al en receptores de trasplante hepático de donante vivo, evidenció que el MELD y el sodio sérico pre-trasplante fueron factores predictivos independientes de mortalidad post-trasplante. En este estudio los pacientes con hiponatremia presentaron un aumento significativo en la aparición de sepsis, insuficiencia renal y encefalopatía post-trasplante[74].

A pesar del creciente interés en este tema, ninguno de los estudios mencionados previamente ha investigado el mecanismo por el cual la presencia de hiponatremia pre-trasplante se asocia a un aumento en la morbi-mortalidad post-trasplante hepático, lo cual hace necesario especular sobre los posibles mecanismos con base a datos de otras poblaciones de pacientes. En primer lugar, se sabe que la hiponatremia es un factor de mal pronóstico en pacientes hospitalizados [75, 76], y de hecho el sodio sérico es un componente del Acute Physiology and Chronic Health Evaluation (APACHE), una puntuación utilizada para estimar el pronóstico en pacientes críticamente enfermos ingresados en unidad de cuidados intensivos [77].

Por otro lado, la presencia de hiponatremia en pacientes con cirrosis es el reflejo de una marcada disfunción circulatoria que produce una disminución en el volumen arterial efectivo y por lo tanto una activación del sistema renina-angiotensina-aldosterona y el sistema simpático, y un aumento en la secreción no osmótica de ADH [36]. Diversos estudios han demostrado que la hiponatremia en la cirrosis puede precipitar la aparición de sepsis [38,78], hemorragia digestiva [79] y síndrome hepatorenal [50]. Esta marcada disfunción circulatoria junto con los cambios hemodinámicas producidos durante la intervención quirúrgica del trasplante hepático y el periodo peri-operatorio inmediato, podría favorecer la aparición de insuficiencia renal post-trasplante afectando de forma significativa el pronóstico del paciente.

En segundo lugar, la asociación entre la aparición de complicaciones neurológicas, en particular síndrome de desmielinización osmótica, e

hiponatremia es bien conocida. Estudios realizados en autopsias han demostrado que aproximadamente 10% de receptores de trasplante hepático presentan síndrome de desmielinización osmótica [80], constituyendo el tercer grupo con mayor incidencia de esta entidad después los pacientes alcohólicos y aquellos con hiponatremia crónica[81]. La etiología del síndrome de desmielinización osmótica en el trasplante hepático es desconocida pero se cree que se debe a cambios osmolares en el periodo peri-operatorio en pacientes con factores de riesgo como la presencia de hiponatremia crónica, desnutrición, debilidad y tratamiento inmunosupresor [82].

Finalmente, uno de los hallazgos llamativos del estudio es que a diferencia de estudios anteriores [83], no se encontró una asociación entre la presencia de insuficiencia renal pre-trasplante y el pronóstico post-trasplante. Ello probablemente se deba a un mejor cuidado post-trasplante, la utilización rutinaria de la técnica de "piggy-back"[84], mayor uso de fármacos inmunosupresores no neurotóxicos, minimización de la dosis de inhibidores de calcineurina, y tratamiento del sindrome hepatorenal pre-trasplante[85].

En conjunto, con toda la información disponible en la literatura y los nuevos medicamentos para el tratamiento de la hiponatremia [56] cabe la necesidad de diseñar estudios clínico prospectivos que evalúen si el tratamiento de la hiponatremia en lista de espera puede disminuir la morbi-mortalidad post-trasplante.

5. CONCLUSIONES

Las conclusiones finales de los estudios que componen esta Tesis Doctoral son:

1. En pacientes con cirrosis la presencia de hiponatremia se asocia con mayor número de complicaciones neurológicas, infecciones e insuficiencia renal durante el primer mes tras el trasplante hepático.
2. La presencia de hiponatremia pre-trasplante hepático se asocia con una menor supervivencia a los 3 meses post-trasplante hepático.
3. El MELD y el sodio son predictores independiente de supervivencia en lista de espera para trasplante hepático a 3 y 12 meses de la inclusión.
4. El sodio sérico es útil para valorar el pronóstico del paciente en diferentes sub-poblaciones de pacientes con cirrosis hepática, incluyendo ascitis, encefalopatía hepática, hemorragia digestiva por varices esofágicas, peritonitis bacteriana espontánea y la insuficiencia renal.
5. La adición del sodio sérico al MELD no mejoró su capacidad en la predicción de la supervivencia en lista de espera.

6. BIBLIOGRAFÍA

1. Adam R, Hoti E. Liver transplantation: the current situation. Semin Liver Dis 2009;29:3-18.

2. European Liver Transplant Registry. Data analysis booklet. Available at: http://www.eltr.org, 2010.

3. Salud Mundial, 2003. Available at: http://www.oms.org.

4. Lucey MR, Merion RM, Henley KS, Campbell DA, Jr., Turcotte JG, Nostrant TT, Blow FC, Beresford TP. Selection for and outcome of liver transplantation in alcoholic liver disease. Gastroenterology 1992;102:1736-41.

5. Memoria de actividad. ONT 2010. Available at: http://ont.org.

6. Bernardi M, Gitto S, Biselli M. The MELD score in patients awaiting liver transplant: strengths and weaknesses. J Hepatol;54:1297-306.

7. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology 2000;31:864-71.

8. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, Kim WR. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464-70.

9. Wiesner RH, McDiarmid SV, Kamath PS, Edwards EB, Malinchoc M, Kremers WK, Krom RA, Kim WR. MELD and PELD: application of survival models to liver allocation. Liver Transpl 2001;7:567-80.

10. Wiesner R, Edwards E, Freeman R, Harper A, Kim R, Kamath P, Kremers W, Lake J, Howard T, Merion RM, Wolfe RA, Krom R. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology 2003;124:91-6.

11. Freeman RB, Wiesner RH, Edwards E, Harper A, Merion R, Wolfe R. Results of the first year of the new liver allocation plan. Liver Transpl 2004;10:7-15.

12. Wiesner R, Lake JR, Freeman RB, Gish RG. Model for end-stage liver disease (MELD) exception guidelines. Liver Transpl 2006;12:S85-7.

13. Berg CL, Steffick DE, Edwards EB, Heimbach JK, Magee JC, Washburn WK, Mazariegos GV. Liver and intestine transplantation in the United States 1998-2007. Am J Transplant 2009;9:907-31.

14. Cholongitas E, Marelli L, Shusang V, Senzolo M, Rolles K, Patch D, Burroughs AK. A systematic review of the performance of the model for end-stage liver disease (MELD) in the setting of liver transplantation. Liver Transpl 2006;12:1049-61.

15. Kim W WR, Kamath P. Prediction of liver transplant outcome using MELD scale. Transplantation 2001;71:284.

16. Brown RS, Jr., Kumar KS, Russo MW, Kinkhabwala M, Rudow DL, Harren P, Lobritto S, Emond JC. Model for end-stage liver disease and Child-Turcotte-Pugh score as predictors of pretransplantation disease severity, posttransplantation outcome, and resource utilization in United Network for Organ Sharing status 2A patients. Liver Transpl 2002;8:278-84.

17. Onaca NN, Levy MF, Sanchez EQ, Chinnakotla S, Fasola CG, Thomas MJ, Weinstein JS, Murray NG, Goldstein RM, Klintmalm GB. A correlation between the pretransplantation MELD score and mortality in the first two years after liver transplantation. Liver Transpl 2003;9:117-23.

18. Saab S, Wang V, Ibrahim AB, Durazo F, Han S, Farmer DG, Yersiz H, Morrisey M, Goldstein LI, Ghobrial RM, Busuttil RW. MELD score predicts 1-year patient survival post-orthotopic liver transplantation. Liver Transpl 2003;9:473-6.

19. Desai NM, Mange KC, Crawford MD, Abt PL, Frank AM, Markmann JW, Velidedeoglu E, Chapman WC, Markmann JF. Predicting outcome after liver transplantation: utility of the model for end-stage liver disease and a newly derived discrimination function. Transplantation 2004;77:99-106.

20. Jacob M, Copley LP, Lewsey JD, Gimson A, Toogood GJ, Rela M, van der Meulen JH. Pretransplant MELD score and post liver transplantation survival in the UK and Ireland. Liver Transpl 2004;10:903-7.

21. Bazarah SM, Peltekian KM, McAlister VC, Bitter-Suermann H, MacDonald AS. Utility of MELD and Child-Turcotte-Pugh scores and the Canadian waitlisting algorithm in predicting short-term survival after liver transplant. Clin Invest Med 2004;27:162-7.

22. Yoo HY, Thuluvath PJ. Short-term postliver transplant survival after the introduction of MELD scores for organ allocation in the United States. Liver Int 2005;25:536-41.

23. Kanwal F, Dulai GS, Spiegel BM, Yee HF, Gralnek IM. A comparison of liver transplantation outcomes in the pre- vs. post-MELD eras. Aliment Pharmacol Ther 2005;21:169-77.

24. Nagler E, Van Vlierberghe H, Colle I, Troisi R, de Hemptinne B. Impact of MELD on short-term and long-term outcome following liver transplantation: a European perspective. Eur J Gastroenterol Hepatol 2005;17:849-56.

25. Sherman DS, Fish DN, Teitelbaum I. Assessing renal function in cirrhotic patients: problems and pitfalls. Am J Kidney Dis 2003;41:269-78.

26. Francoz C, Prie D, Abdelrazek W, Moreau R, Mandot A, Belghiti J, Valla D, Durand F. Inaccuracies of creatinine and creatinine-based equations in candidates for liver transplantation with low creatinine: impact on the model for end-stage liver disease score. Liver Transpl;16:1169-77.

27. Dorwart WV. Bilirubin interference in kinetic creatinine determination. Clin Chem 1979;25:196-7.

28. Sharma P, Schaubel DE, Sima CS, Merion RM, Lok AS. Re-weighting the model for end-stage liver disease score components. Gastroenterology 2008;135:1575-81.

29. Huo TI, Hsu CY, Lin HC, Lee PC, Lee JY, Lee FY, Hou MC, Lee SD. Selecting an optimal cutoff value for creatinine in the model for end-stage liver disease equation. Clin Transplant;24:157-63.

30. Xiol X, Gines P, Castells L, Twose J, Ribalta A, Fuentes-Arderiu X, Rodriguez S, Castellote J, Navasa M, Deulofeu R. Clinically relevant differences in the model for end-stage liver disease and model for end-stage liver disease-sodium scores determined at three university-based laboratories of the same area. Liver Transpl 2009;15:300-5.

31. Tripodi A, Chantarangkul V, Primignani M, Fabris F, Dell'Era A, Sei C, Mannucci PM. The international normalized ratio calibrated for cirrhosis (INR(liver)) normalizes prothrombin time results for model for end-stage liver disease calculation. Hepatology 2007;46:520-7.

32. Trotter JF, Olson J, Lefkowitz J, Smith AD, Arjal R, Kenison J. Changes in international normalized ratio (INR) and model for endstage liver disease (MELD) based on selection of clinical laboratory. Am J Transplant 2007;7:1624-8.

33. Colmenero J RA, Navasa M. Evaluación y selección de candidatos a trasplante hepático. Available at: http://www.intra.csc.es/.

34. Huo TI, Lin HC, Lee FY, Hou MC, Lee PC, Wu JC, Chang FY, Lee SD. Occurrence of cirrhosis-related complications is a time-dependent prognostic predictor independent of baseline model for end-stage liver disease score. Liver Int 2006;26:55-61.

35. Alberino F, Gatta A, Amodio P, Merkel C, Di Pascoli L, Boffo G, Caregaro L. Nutrition and survival in patients with liver cirrhosis. Nutrition 2001;17:445-50.

36. Gines P, Berl T, Bernardi M, Bichet DG, Hamon G, Jimenez W, Liard JF, Martin PY, Schrier RW. Hyponatremia in cirrhosis: from pathogenesis to treatment. Hepatology 1998;28:851-64.

37. Ginès P CA, Schrier, R. W. Liver diseases and the Kidney. In: Schrier RW, ed. Diseases of the kidney and the urinary tract. Volume 3. 8 ed. Philadelphia: Lippincott Williams & Wilkins, 2006:2179-2205.

38. Angeli P, Wong F, Watson H, Gines P. Hyponatremia in cirrhosis: Results of a patient population survey. Hepatology 2006;44:1535-42.

39. Arroyo V, Rodes J, Gutierrez-Lizarraga MA, Revert L. Prognostic value of spontaneous hyponatremia in cirrhosis with ascites. Am J Dig Dis 1976;21:249-56.

40. Gines P, Uriz J, Calahorra B, Garcia-Tsao G, Kamath PS, Del Arbol LR, Planas R, Bosch J, Arroyo V, Rodes J. Transjugular intrahepatic portosystemic shunting versus paracentesis plus albumin for refractory ascites in cirrhosis. Gastroenterology 2002;123:1839-47.

41. Gines P, Guevara M. Hyponatremia in cirrhosis: pathogenesis, clinical significance, and management. Hepatology 2008;48:1002-10.

42. Guevara M, Gines P. [Hyponatremia in liver cirrhosis: pathogenesis and treatment]. Endocrinol Nutr;57 Suppl 2:15-21.

43. Adrogue HJ, Madias NE. Hyponatremia. N Engl J Med 2000;342:1581-9.

44. Jung JS, Bhat RV, Preston GM, Guggino WB, Baraban JM, Agre P. Molecular characterization of an aquaporin cDNA from brain: candidate osmoreceptor and regulator of water balance. Proc Natl Acad Sci U S A 1994;91:13052-6.

45. Cordoba J, Gottstein J, Blei AT. Glutamine, myo-inositol, and organic brain osmolytes after portocaval anastomosis in the rat: implications for ammonia-induced brain edema. Hepatology 1996;24:919-23.

46. Restuccia T, Gomez-Anson B, Guevara M, Alessandria C, Torre A, Alayrach ME, Terra C, Martin M, Castellvi M, Rami L, Sainz A, Gines P, Arroyo V. Effects of dilutional hyponatremia on brain organic osmolytes and water content in patients with cirrhosis. Hepatology 2004;39:1613-22.

47. Haussinger D. Low grade cerebral edema and the pathogenesis of hepatic encephalopathy in cirrhosis. Hepatology 2006;43:1187-90.

48. Guevara M, Baccaro ME, Torre A, Gomez-Anson B, Rios J, Torres F, Rami L, Monte-Rubio GC, Martin-Llahi M, Arroyo V, Gines P. Hyponatremia is a risk factor of hepatic encephalopathy in patients with cirrhosis: a prospective study with time-dependent analysis. Am J Gastroenterol 2009;104:1382-9.

49. Follo A, Llovet JM, Navasa M, Planas R, Forns X, Francitorra A, Rimola A, Gassull MA, Arroyo V, Rodes J. Renal impairment after spontaneous bacterial peritonitis in cirrhosis: incidence, clinical course, predictive factors and prognosis. Hepatology 1994;20:1495-501.

50. Gines A, Escorsell A, Gines P, Salo J, Jimenez W, Inglada L, Navasa M, Claria J, Rimola A, Arroyo V, et al. Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. Gastroenterology 1993;105:229-36.

51. Verbalis JG, Goldsmith SR, Greenberg A, Schrier RW, Sterns RH. Hyponatremia treatment guidelines 2007: expert panel recommendations. Am J Med 2007;120:S1-21.

52. Quittnat F, Gross P. Vaptans and the treatment of water-retaining disorders. Semin Nephrol 2006;26:234-43.

53. Gerbes AL, Gulberg V, Gines P, Decaux G, Gross P, Gandjini H, Djian J. Therapy of hyponatremia in cirrhosis with a vasopressin receptor antagonist: a randomized double-blind multicenter trial. Gastroenterology 2003;124:933-9.

54. Gines P, Wong F, Watson H, Milutinovic S, del Arbol LR, Olteanu D. Effects of satavaptan, a selective vasopressin V(2) receptor antagonist, on ascites and serum sodium in cirrhosis with hyponatremia: a randomized trial. Hepatology 2008;48:204-13.

55. Cassagnol M, Shogbon AO, Saad M. The Therapeutic Use of Vaptans for the Treatment of Dilutional Hyponatremia. J Pharm Pract 2011. [Epub ahead of print].

56. Cárdenas A GP, Marotta P, Czerwiec G, Oyuang J, Guevara M, Afdhal N. The safety and efficacy of tolvaptan, an oral vasopressin antagonist in the treatment of hyponatremia in cirrhosis. J Hepatol;In press 2011.

57. Hecker R, Sherlock S. Electrolyte and circulatory changes in terminal liver failure. Lancet 1956;271:1121-5.

58. Fernandez-Esparrach G, Sanchez-Fueyo A, Gines P, Uriz J, Quinto L, Ventura PJ, Cardenas A, Guevara M, Sort P, Jimenez W, Bataller R, Arroyo V, Rodes J. A prognostic model for predicting survival in cirrhosis with ascites. J Hepatol 2001;34:46-52.

59. Llach J, Gines P, Arroyo V, Rimola A, Tito L, Badalamenti S, Jimenez W, Gaya J, Rivera F, Rodes J. Prognostic value of arterial pressure, endogenous vasoactive systems, and renal function in cirrhotic patients admitted to the hospital for the treatment of ascites. Gastroenterology 1988;94:482-7.

60. Shear L, Hall PW, 3rd, Gabuzda GJ. Renal Failure in Patients with Cirrhosis of the Liver. Ii. Factors Influencing Maximal Urinary Flow Rate. Am J Med 1965;39:199-209.

61. Heuman DM, Abou-Assi SG, Habib A, Williams LM, Stravitz RT, Sanyal AJ, Fisher RA, Mihas AA. Persistent ascites and low serum sodium identify patients with cirrhosis and low MELD scores who are at high risk for early death. Hepatology 2004;40:802-10.

62. Ruf AE, Kremers WK, Chavez LL, Descalzi VI, Podesta LG, Villamil FG. Addition of serum sodium into the MELD score predicts waiting list mortality better than MELD alone. Liver Transpl 2005;11:336-43.

63. Biggins SW, Rodriguez HJ, Bacchetti P, Bass NM, Roberts JP, Terrault NA. Serum sodium predicts mortality in patients listed for liver transplantation. Hepatology 2005;41:32-9.

64. de la Mata M, Cuende N, Huet J, Bernardos A, Ferron JA, Santoyo J, Pascasio JM, Rodrigo J, Solorzano G, Martin-Vivaldi R, Alonso M. Model for end-stage liver disease score-based allocation of donors for liver transplantation: a spanish multicenter experience. Transplantation 2006;82:1429-35.

65. Arroyo V, Colmenero J. Ascites and hepatorenal syndrome in cirrhosis: pathophysiological basis of therapy and current management. J Hepatol 2003;38 Suppl 1:S69-89.

66. Briceno J, Sanchez-Hidalgo JM, Naranjo A, Ciria R, Pozo JC, Luque A, de la Mata M, Rufian S, Lopez-Cillero P. Model for end-stage liver disease can predict very early outcome after liver transplantation. Transplant Proc 2008;40:2952-4.

67. Kamath PS, Kim WR. The model for end-stage liver disease (MELD). Hepatology 2007;45:797-805.

68. Merion RM, Schaubel DE, Dykstra DM, Freeman RB, Port FK, Wolfe RA. The survival benefit of liver transplantation. Am J Transplant 2005;5:307-13.

69. Biggins SW, Kim WR, Terrault NA, Saab S, Balan V, Schiano T, Benson J, Therneau T, Kremers W, Wiesner R, Kamath P, Klintmalm G. Evidence-based incorporation of serum sodium concentration into MELD. Gastroenterology 2006;130:1652-60.

70. Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, Edwards E, Therneau TM. Hyponatremia and mortality among patients on the liver-transplant waiting list. N Engl J Med 2008;359:1018-26.

71. Dawwas MF, Lewsey JD, Neuberger JM, Gimson AE. The impact of serum sodium concentration on mortality after liver transplantation: a cohort multicenter study. Liver Transpl 2007;13:1115-24.

72. Hackworth WA, Heuman DM, Sanyal AJ, Fisher RA, Sterling RK, Luketic VA, Shiffman ML, Maluf DG, Cotterell AH, Posner MP, Stravitz RT. Effect of hyponatraemia on outcomes following orthotopic liver transplantation. Liver Int 2009;29:1071-7.

73. Yun BC, Kim WR, Benson JT, Biggins SW, Therneau TM, Kremers WK, Rosen CB, Klintmalm GB. Impact of pretransplant hyponatremia on outcome following liver transplantation. Hepatology 2009;49:1610-5.

74. Fukuhara T, Ikegami T, Morita K, Umeda K, Ueda S, Nagata S, Sugimachi K, Gion T, Yoshizumi T, Soejima Y, Taketomi A, Maehara Y. Impact of preoperative serum sodium concentration in living donor liver transplantation. J Gastroenterol Hepatol;25:978-84.

75. Anderson RJ. Hospital-associated hyponatremia. Kidney Int 1986;29:1237-47.

76. Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. JAMA 2003;290:2581-7.

77. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818-29.

78. Borroni G, Maggi A, Sangiovanni A, Cazzaniga M, Salerno F. Clinical relevance of hyponatraemia for the hospital outcome of cirrhotic patients. Dig Liver Dis 2000;32:605-10.

79. Porcel A, Diaz F, Rendon P, Macias M, Martin-Herrera L, Giron-Gonzalez JA. Dilutional hyponatremia in patients with cirrhosis and ascites. Arch Intern Med 2002;162:323-8.

80. Boon AP, Carey MP, Adams DH, Buckels J, McMaster P. Central pontine myelinolysis in liver transplantation. J Clin Pathol 1991;44:909-14.

81. Lampl C, Yazdi K. Central pontine myelinolysis. Eur Neurol 2002;47:3-10.

82. Abbasoglu O, Goldstein RM, Vodapally MS, Jennings LW, Levy MF, Husberg BS, Klintmalm GB. Liver transplantation in hyponatremic patients with emphasis on central pontine myelinolysis. Clin Transplant 1998;12:263-9.

83. Rimola A, Gavaler JS, Schade RR, el-Lankany S, Starzl TE, Van Thiel DH. Effects of renal impairment on liver transplantation. Gastroenterology 1987;93:148-56.

84. Gonzalez FX, Garcia-Valdecasas JC, Grande L, Pacheco JL, Cugat E, Fuster J, Lacy AM, Taura P, Lopez-Boado MA, Rimola A, Visa J. Vena cava vascular reconstruction during orthotopic liver transplantation: a comparative study. Liver Transpl Surg 1998;4:133-40.

85. Restuccia T, Ortega R, Guevara M, Gines P, Alessandria C, Ozdogan O, Navasa M, Rimola A, Garcia-Valdecasas JC, Arroyo V, Rodes J. Effects of treatment of hepatorenal syndrome before transplantation on posttransplantation outcome. A case-control study. J Hepatol 2004;40:140-6.