Universitat Autònoma de Barcelona

EL REINGRESO HOSPITALARIO PRECOZ EN EL PACIENTE CIRR.TICO DESCOMPENSADO

BETTY PAOLA MORALES ARRIETA

UNIVERSIDAD AUTÓNOMA DE BARCELONA

Departamento de Medicina
Programa de Doctorado en Medicina

Tesis doctoral

EL REINGRESO HOSPITALARIO PRECOZ EN EL PACIENTE CIRRÓTICO DESCOMPENSADO

BETTY PAOLA MORALES ARRIETA

Director de la tesis: Dra. Helena Masnou Ridaura
Tutor de la tesis: Dr. Ramon Planas Vilà

Servicio de Aparato Digestivo
Hospital Universitario Germans Trias i Pujol
2017

***A Dios**, **a Carmen** mi madre, **a Guillermo** mi esposo y **a Valeria** mi hija, por ser los pilares importantes en mi vida*

***A Lil Martha** mi prima, que compartía junto conmigo el sueño del doctorado, pero a quien Dios la llamó para hacer cosas más importantes a su lado.*

AGRADECIMIENTOS

Esta tesis doctoral es resultado de un trabajo en equipo, del sacrificio personal y familiar, de muchas horas de dedicación y del apoyo y colaboración de diferentes personas pertenecientes o no al estudio. Por ello, quiero agradecer en primer lugar, a Dios por poner en mi camino este nuevo reto y permitirme finalizarlo acompañada de él.

A mi familia que de una u otra forma, vivieron de cerca todo el proceso de esta tesis doctoral. En especial a mi esposo Guillermo Martínez, quien me apoyó desde el minuto cero, fue mi bastón y motor en los momentos de flaqueza, fue quien probó los sabores amargos y dulces de todo el proceso y quien estuvo siempre a mi lado. A mi hija Valeria, por regalarme minutos de su tiempo, inclusive desde que estaba en el vientre, para que yo pudiera dedicárselos a la tesis. A mis padres, Carmen y Dario, por darme las herramientas para llegar hasta aquí y permitirme ser lo que soy. Sin sus enseñanzas, no hubiera podido enfrentarme a este reto. A mis hermanos, en

especial a Omar, por apoyarme y colaborarme durante el estudio de investigación.

También quiero agradecer de manera muy especial a mis directores/tutores de la tesis. A la Dra. Helena Masnou y al Dr. Ramón Planas, por confiar en mi y brindarme la oportunidad de llevar a cabo esta tesis doctoral. Muchas gracias por todo el apoyo que me dieron, por el tiempo dedicado, por su accesibilidad, su agilidad, su sabiduría, su exigencia, sus consejos y su disponibilidad en todo momento. Es un honor para mí tenerlos de directores.

Al servicio de Digestivo del Hospital Germans Trias i Pujol, especialmente a la Unidad de Hepatología conformada por la Dra. Rosa Morillas, Dra. Marga Sala, Dra. Helena Masnou, Ramón Bartolí, Dulce López y antiguo jefe, Dr. Ramon Planas. Muchas gracias por todas las enseñanzas recibidas y por permitirme enamorarme cada día más de la Hepatología. Son ejemplos a seguir.

A los coautores de los estudios que conforman esta tesis doctoral, en especial a la Dra. Irma Sala, Dr. Eduard Cabrè y Ramón Bartolí por sus conocimientos, guía y colaboración en la parte estadística de los trabajos. Así como también a Aranza y el Dr. Josep Roca, quienes también me brindaron su ayuda a pesar de no hacer parte del estudio.

Al Instituto de Investigación del Hospital Germans Trias i Pujol por la beca otorgada para realizar el proyecto de HEPACONTROL. A el personal del Hospital de Día de Hepatología por trabajar a la mano conmigo y también a los pacientes, que gracias a ellos pudimos realizar los estudios y son los que permiten que se continúe avanzando en la investigación.

ABREVIATURAS

- AASLD: American Association for the study of the Liver Disease
- AHRQ: Agency for Healthcare Research in Quality
- cACLD: Compensated advanced chronic liver disease
- CHC: Carcinoma hepatocelular
- CMS: Centers for Medicare and Medicaid Services
- CCTP: The Community-based Care Transitions Program
- EH: Encefalopatía hepática.
- EHGNA: Enfermedad hepática grasa no alcohólica
- EHNA: Esteatohepatitis no alcohólica
- EPOC: Enfermedad pulmonar obstructiva crónica
- GPVH: Gradiente de presión venosa hepática
- HPCS: Hipertensión portal clínicamente significativa

- MedPAC: Medicare Payment Advisory Commission
- OMS: Organización Mundial de la Salud
- VHB: Virus hepatitis B.
- VHC: Virus hepatitis C.

INDICE

Páginas

INDICE FIGURAS

Páginas

INDICE TABLAS

Páginas

INTRODUCCIÓN

1. INTRODUCCIÓN

La cirrosis es el estadio final de las distintas enfermedades hepáticas crónicas y se caracteriza por una alteración de la arquitectura normal del hígado con sustitución del tejido hepático sano por tejido fibroso y nódulos de regeneración. Estos cambios histológicos ocasionan hipertensión portal e insuficiencia hepática [1]. La cirrosis se caracteriza inicialmente por una fase asintomática en la que la enfermedad se encuentra compensada, seguida de una fase sintomática y rápidamente progresiva, denominada cirrosis descompensada, en la que se producen las complicaciones derivadas de la hipertensión portal y de la insuficiencia hepática [2].

A medida que la enfermedad avanza existe una mayor susceptibilidad a desarrollar estas complicaciones, lo que produce un deterioro en la calidad de salud y la esperanza de vida se ve notablemente reducida, por lo que, hoy en día, el trasplante hepático sigue siendo la única opción curativa. Además, cuando los pacientes cirróticos se descompensan

provocan una gran carga asistencial y económica.

En el año 2010, la cirrosis fue responsable de aproximadamente un millón de muertes a nivel mundial, un 33% más que en el año 1990, siendo las principales causas de la cirrosis el alcohol, la infección crónica por el virus de la hepatitis B y por el virus de la hepatitis C [3]. En Europa, según datos de la Organización Mundial de la Salud (OMS), la cirrosis representa el 1,8% de todas las causas de muerte (170.000 muertes al año), siendo Europa sudoriental y nororiental las zonas con mayor tasa de mortalidad en las últimas décadas, unas 10-20 veces más alta que en el resto de países europeos [4,5].

Por todo ello se considera que los programas preventivos, el manejo precoz de las complicaciones y las estrategias de seguimiento de los pacientes con cirrosis, son realmente necesarios para mejorar su supervivencia y calidad de vida.

1.1. Etiología de la cirrosis

Existen innumerables causas de cirrosis ya que cualquier daño hepático crónico puede desencadenar la enfermedad. **Tabla 1**

En Europa el consumo abusivo de alcohol, la infección crónica por virus de la hepatitis B y C y los síndromes metabólicos relacionados con el sobrepeso, diabetes y la obesidad son las principales causas de cirrosis y cáncer hepático primario [4] En la última década se ha descrito una prevalencia de la hepatitis crónica C en Europa del 0,13-3,26 % y del 0,5-0,7% de la hepatitis crónica B. Por otra parte, se han descrito prevalencias del 2-44% de la enfermedad hepática grasa no alcohólica (EHGNA), llegando a tasas del 42.6-69,5% en la subpoblación de diabetes mellitus tipo 2 [4].

En Estados Unidos (EEUU), las causas más frecuentes de cirrosis son la infección crónica por virus de la hepatitis C, el enolismo y la EHGNA, las cuales representaron aproximadamente el 80% de los pacientes en lista de espera de trasplante hepático entre los años 2004 y 2013 [6]. Mientras que en la región Asia-Pacífico, la infección crónica por virus el de la

hepatitis B es la principal causa de cirrosis [7].

TABLA 1. Clasificación etiológica de la cirrosis
- **Alcohol**
- **Hepatitis vírica**
- **Obstrucción biliar** • **Cirrosis biliar primaria** • **Cirrosis biliar secundaria (ej. Colangitis esclerosante primaria)**
- **Enfermedad metabólica congénita** • **Hemocromatosis** • **Enfermedad de Wilson** • **Déficit de alfa-1-antitripsina** • **Fibrosis quística** • **Galactosemia** • **Glucogenosis tipos III y IV** • **Tirosinemia** • **Intolerancia hereditaria a la fructosa** • **Telangiectasia hemorrágica hereditari**
- **Enfermedad metabólica adquirida** • **Esteatohepatitis no alcohólica**
- **Causas vasculares** • **Hígado de estasis crónico** • **Enfermedad veno-oclusiva del hígado**
- **Hepatitis autoinmune**
- **Fármacos y toxinas**
- **Sífilis**
- **Sarcoidosis**
- **Bypass yeyuno-ileal**
- **Hipervitaminosis A**
- **Idiopática o criptogénica**

Bernal V. Gastroenterología y Hepatología; Problemas comunes en la práctica clínica 2º edición. Pag:867-892 [2]

1.2. Historia natural de la cirrosis.

La cirrosis presenta una evolución lentamente progresiva, con un inicio de la fibrosis durante años e incluso décadas (15-20 años) antes de establecerse la cirrosis [8,9]. Este proceso es dinámico e incluye cambios histológicos, hemodinámicos, clínicos y biológicos [10].

La historia natural de la cirrosis dependerá de la causa y de su posible tratamiento y se caracteriza, como ya se ha mencionado previamente, por una fase compensada y otra descompensada.

1.2.1. Cirrosis compensada

En esta fase, el paciente cirrótico se encuentra asintomático, dado que la función hepática aún está conservada. La supervivencia de los pacientes con cirrosis compensada es significativamente mayor con respecto a los pacientes con cirrosis descompensada, con una mediana de supervivencia de >12 años [11].

En esta etapa, la presión portal puede ser normal o ligeramente elevada. En la IV Conferencia Internacional de Consenso de Hipertensión Portal de Baveno, se clasificó los pacientes de esta fase en dos estadios: sin varices esofágicas (estadio 1) y con varices esofágicas (estadio 2). Se han descrito distintas tasas de morbimortalidad en función del estadio en el que se encuentren los pacientes. En un estudio prospectivo en el que se evaluaron 402 pacientes con cirrosis compensada, los cuales fueron estratificados en estadio 1 y 2, se observó que a los 6 años, los pacientes con varices esofágicas (estadio 2) tenían mayor incidencia de carcinoma hepatocelular (CHC) respecto los pacientes en estadio 1 (29 frente al 9%; p <0,001), mayor incidencia de presentar cualquier complicación de la cirrosis (66 frente al 26%, p <0,001) y mayor mortalidad o necesidad de trasplante hepático (45 frente al 15%, p <0,001) [12]. Más recientemente, D'Amico y cols. evaluaron una cohorte de 494 pacientes cirróticos, en los que describieron tasas de progresión a estadios más avanzados a los 5 años de seguimiento del 34,4% en los pacientes con un estadio 1 y del 42% en los

pacientes con un estadio 2, con tasas de mortalidad a los 5 años en ambos estadios de 1,5 y 10%, respectivamente [13].

Clásicamente, los factores predictores que se han asociado a la mortalidad en los pacientes con cirrosis compensada son la edad y variables relacionadas con la presencia de hipertensión portal clínicamente significativa (HPCS) (gradiente de presión venosa portal >10 mmHg), como son la presencia de varices esofágicas, esplenomegalia, plaquetopenia, etc. [11,14].

Dado que la progresión de la fibrosis avanzada a cirrosis es un proceso continuo, a menudo la distinción clínica entre ambos grupos de pacientes se hace difícil por lo que, en la última Conferencia Internacional de Consenso en la Hipertensión Portal de Baveno VI, se propuso el término alternativo de "Enfermedad hepática crónica avanzada compensada" (cACLD, de sus siglas en inglés *compensated advanced chronic liver disease*), haciendo énfasis en que la hipertensión portal puede ocurrir antes de que se establezca un diagnóstico anatómico formal de la cirrosis. Esta entidad abarcaría pacientes con

cirrosis y aquellos con fibrosis hepática avanzada con hipertensión portal (GPVH> 5 mm Hg). Sin embargo, los dos términos: “cACLD y cirrosis compensada” son hoy en día aceptados [15]. En las últimas guías prácticas de la hemorragia digestiva por hipertensión portal de la AASLD (American Association for the study of the Liver Disease), describen que los pacientes con cirrosis compensada o cACLD pueden dividirse en dos estadíos dependiendo de la presión portal, en aquellos con hipertensión portal leve (gradiente de presión venosa hepática (GPVH) > 5 pero < 10 mm Hg) y aquellos con HPCS. Además, estos últimos los sub-clasifican en función de la ausencia o presencia de varices esofágicas [16].

1.2.2. Cirrosis descompensada:

Esta fase se caracteriza por una progresión de la enfermedad, en la que aparecen complicaciones secundarias a la hipertensión portal y/o a la insuficiencia hepática. El desarrollo de cualquiera de las complicaciones (ascitis, hemorragia digestiva por hipertensión portal o encefalopatía hepática (EH))

marca la transición de una fase compensada a una descompensada, lo que ocurre en una tasa de aproximadamente un 5-7% por año [16]. Además, el desarrollo de otras complicaciones tales como el (re) sangrado, la insuficiencia renal, la ascitis refractaria, el síndrome hepatorenal, el síndrome hepatopulmonar y la peritonitis bacteriana espontánea pueden acelerar la progresión de la enfermedad y empeorar su pronóstico [11]. Por otro lado, el desarrollo de un CHC se asocia de forma independiente con un aumento del riesgo de descompensación de la cirrosis, así como con un empeoramiento del curso de la enfermedad en cualquier etapa [17].

En la IV Conferencia Internacional de Consenso de Hipertensión Portal de Baveno, se propuso diferenciar cuatro estadios en la historia natural de la cirrosis: estadio 1 y 2 en la fase compensada (sin y con varices esofagogástricas, respectivamente, ya comentados previamente) y otros dos en la fase descompensada (estadio 3: presencia de ascitis con o sin varices esofagogástricas; estadio 4: hemorragia digestiva por

hipertensión portal, con o sin ascitis) [18]. Sin embargo, en los últimos años se ha sugerido modificar esta clasificación y diferenciar tres estadios clínicos en la fase descompensada, de manera que el estadio 3 se caracterizaría por la presencia de hemorragia digestiva por hipertensión portal, sin otra complicación acompañante, cuya tasa de mortalidad al año es de un 10%; el estadio 4 en el que existiría ascitis, ictericia o EH, con un tasa de mortalidad de 21% al año y el estadio 5 en la que coexistirían más de una complicación, indicando mayor disfunción hepática y con una tasa de mortalidad del 27% anual [19]. Basándose en esta nueva estadificación, D'Amico y cols. realizaron un nuevo estudio evaluando la tasa de progresión de la cirrosis, en el que se objetivó una disminución de la supervivencia a medida que avanzaba la enfermedad, siendo la mortalidad a los 5 años de un 20% en los pacientes en estadio 3, del 30% en estadio 4 y del 88% en el estadio 5 ($P<0,0001$) [13].

La ascitis es la complicación más frecuente de la cirrosis, seguida de la hemorragia digestiva por hipertensión portal, las

infecciones y la EH [20,21,22]. Una vez el paciente presenta descompensación de la cirrosis, puede llegar a desarrollar una complicación diferente a la inicial o inclusive cursar con combinación de ellas, lo que predispone a estos pacientes a un deterioro en su calidad de vida, una mayor tasa de morbi-mortalidad y un mayor uso de recursos sanitarios.

Así mismo, existen diversos estudios en los se demuestra que los pacientes cirróticos que han requerido ingreso hospitalario por presentar alguna complicación de su enfermedad de base, tienen un riesgo importante de reingresar, en especial los pacientes con EH [20, 23, 24, 25]. Un trabajo realizado por nuestro grupo, en el que se evaluó la historia natural de 200 pacientes con cirrosis descompensada por VHC, se describió una probabilidad global de reingreso al año del 45,1%, siendo más frecuente este riesgo en el subgrupo de paciente que presentaban EH (73.3%). Durante un seguimiento medio de 34±2 meses, la media de reingresos por paciente fue de 2,5 con una estancia media hospitalaria de 42 días por paciente [20]. Posteriormente, en un estudio en el que se incluyeron 402

pacientes con cirrosis descompensada de diferentes etiologías a los que se les hizo una mediana de seguimiento de 203 días, un 69% de los pacientes tuvieron uno o más reingresos, con una mediana de dos reingresos (límites: 0-40) y una mediana de tiempo hasta el primer reingreso de 67 días [26].

En este sentido, un estudio realizado en EEUU, mostró que los pacientes con cirrosis presentan más comorbilidades, utilizan con más frecuencia los servicios de salud (hospitalizaciones, estancias en residencias de ancianos, atención domiciliaria por enfermería y visitas médicas) y necesitan más del doble de horas de cuidado en el hogar por personal no sanitario (un miembro de la familia o persona no remunerada) por semana ($p < 0,001$), comparado con la población general [27]. Según datos de la AHRQ (de sus siglas en inglés *Agency for Healthcare Research in Quality*), en EEUU los pacientes con cirrosis tuvieron un incremento en el número de consultas al servicio de urgencias (de 411.869 en el año 2006 a 548.092 en el año 2011), incrementándose durante el mismo período de tiempo el número de altas hospitalarias por descompensación de la

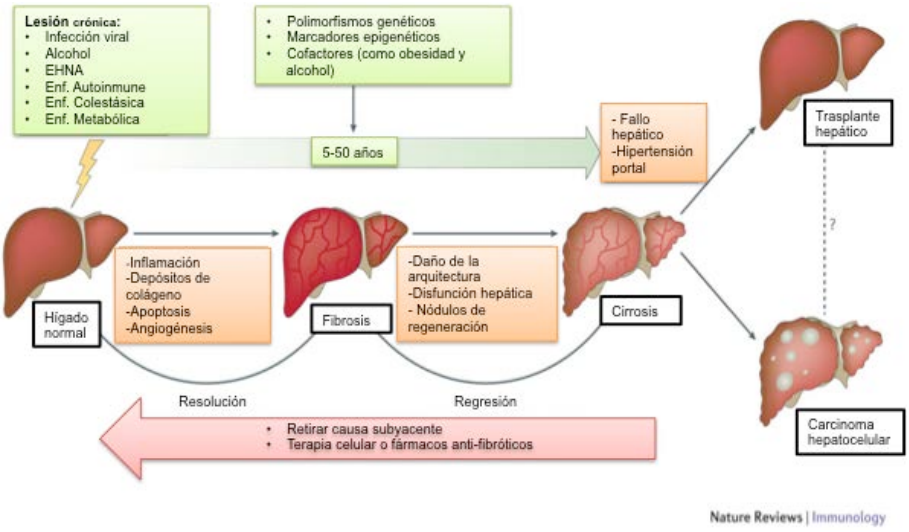
cirrosis (de 436.901 a 576.573) [28,29]. Esta mayor demanda de atención sanitaria conlleva una repercusión económica. De acuerdo al Healthcare Cost and Utilization Project, en EEUU se ha objetivado un aumento en los gastos hospitalarios asociados a las complicaciones de la cirrosis del año 1993 al 2009, en especial por la EH, dado que han aumentado el número de ingresos por esta causa, los costos directos del tratamiento, días de estancia hospitalaria, la recurrencia de nuevos episodios, etc. Por ejemplo, los gastos hospitalarios asociados a la EH aumentaron de $11.808 en 1993 a $35.875 en 2009 [30]. Por otra parte, es importante tener en cuenta los costos indirectos que se generan de la atención sanitaria de estos paciente, como son la pérdida de productividad del trabajo, los accidentes automovilísticos resultantes de pacientes con EH mínima, entre otros, que también tienen un impacto en la carga económica en la cirrosis descompensada y que hasta la fecha, no han sido examinados [30].

Recientemente, Bajaj et al. [25] realizaron el primer estudio multicéntrico evaluando el reingreso en cirróticos descompensados, en el que incluyeron pacientes de 14 centros

del North American Consortium for the Study of End-Stage Liver Disease. Se observó que más de la mitad de los pacientes (53%) reingresaron a los 3 meses tras el alta hospitalaria y este reingreso se asociaba con el estadio de la cirrosis, la diabetes y las infecciones nosocomiales.

Por lo que, tal y como se ha comentado previamente, los pacientes cirróticos presentan unas tasas altas de morbi-mortalidad y un riesgo de reingreso hospitalario, lo que conlleva una peor percepción de su estado de salud y una mayor discapacidad funcional, en comparación con la población general [27,31], en especial los pacientes con desnutrición, EH, ascitis y hemorragia variceal [32].

Fig.1. Historia natural de la cirrosis



Modificado de Pellicoro et al. Nat Rev Immunol. 2014;14(3):181-194 [33].

1.3. Reingreso precoz

Se conoce como reingreso precoz aquel ingreso no programado que se produce tras el alta del paciente en un plazo igual o menor a 30 días. Este reingreso puede estar relacionado o no con el motivo que justificó el primer ingreso y frecuentemente es usado como un indicador de calidad de la atención hospitalaria debido a que existen reingresos que podrían ser prevenibles o evitados si la atención previa hubiera sido la adecuada

[34,35,36,37,38]. Existen diversos factores que influyen en la probabilidad de reingreso precoz; factores del paciente (edad, gravedad y cronicidad de la enfermedad subyacente, presencia de comorbilidades), factores sociodemográficos (apoyo familiar o de un cuidador, nivel educativo, accesibilidad al sistema sanitario) y factores asociados al ingreso previo (calidad de los cuidados durante el ingreso o medidas tomadas al momento del alta que podrían haber prevenido el reingreso) [39].

El reingreso precoz es frecuente en diferentes enfermedades tanto médicas como quirúrgicas, genera un alto coste para el sistema sanitario y se considera potencialmente prevenible. En un estudio retrospectivo, en el que se evaluaron 11.855.702 pacientes dados de alta de un servicio médico o quirúrgico hospitalario en EEUU entre el año 2003 y 2004, un 19,6% de los pacientes fueron readmitidos de manera precoz, siendo la insuficiencia cardíaca y la neumonía las principales causas de reingreso precoz en ambos grupos. La mitad de los pacientes (50,2%) que habían reingresado antes de 30 días tras el alta del servicio médico, no habían recibido ninguna visita de control

durante ese periodo y un 70,5% de los pacientes con reingreso precoz tras el alta de cirugía, reingresaron por una condición médica. El costo estimado de reingreso fue de 17,4 mil millones de dólares, lo cual representa cerca de un 20% del presupuesto sanitario de EEUU [34]. The Medicare Payment Advisory Commission (MedPAC), agencia responsable de asesorar al congreso de los EEUU sobre temas que afectan el programa de cobertura de seguridad social a mayores de 65 años o discapacitados (programa Medicare), estimó en su informe del 2007 que el 12% de los reingresos en EEUU eran potencialmente evitables debido a que a menudo resultan de defectos prevenibles al alta tales como, las infecciones hospitalarias y otras complicaciones, de una mala planificación del seguimiento, de una comunicación inadecuada de las instrucciones al alta y de una falta de conciliación y coordinación de los medicamentos. Además, estimó que la prevención de un 10% de estos reingresos podría ahorrar hasta mil millones de dólares [40]. En este sentido, con el fin de reducir las tasas de reingreso precoz, en el año 2012 el CMS (Centers for Medicare and Medicaid Services), agencia federal

del Departamento de salud de los EEUU encargada de administrar el programa Medicare, instauró penalizaciones de carácter económico a los hospitales cuando éstos superaban el umbral de reingreso precoz establecido para el infarto agudo del miocardio, la insuficiencia cardíaca y la neumonía y posteriormente en el año 2015, se expandió para los pacientes con exacerbación aguda de la enfermedad pulmonar obstructiva crónica (EPOC), pacientes ingresados de manera programada para artroplastia total de cadera y artroplastia total de rodilla [41]

Hasta el momento actual existen pocos estudios que hayan evaluado la incidencia y los factores predictores del reingreso precoz en la cirrosis descompensada en comparación con otras enfermedades crónicas como la insuficiencia cardíaca, la diabetes y la enfermedad pulmonar obstructiva crónica [41-50]. La mayoría de estos estudios se han llevado a cabo en EEUU, donde se ha descrito una incidencia del reingreso precoz que oscila entre el 20 y el 37% [24,26, 51, 52, 53]. Por otra parte, los factores predictores de reingresos precoz que se han obtenido, varían de un estudio a otro, debido principalmente a la gran

heterogenicidad de los distintos trabajos, lo que dificulta la obtenciones de conclusiones robustas.

1.4. Estrategias para reducir el reingreso precoz

Teniendo en cuenta que el reingreso precoz en la cirrosis es una problemática frecuente, se ha asociado a peor pronóstico, genera un alto costo para el sistema sanitario y es potencialmente prevenible, se han diseñado programas estratégicos para intentar reducir el reingreso hospitalario y las consecuencias que éste genera.

Existen numerosos estudios que han evaluado diversas intervenciones para reducir el reingreso precoz en diferentes enfermedades, sobre todo en personas de edad avanzada y con insuficiencia cardíaca [54-68]. En una revisión sistemática publicada en 2011, en el que se incluyeron 43 estudios en los que se evaluaban y describían las diferentes estrategias aplicadas a pacientes con diversas condiciones médicas, clasificaron las intervenciones para reducir el reingreso antes de

los 30 días en tres grupos principales: **a) intervenciones previas al alta** que incluyeron educación al paciente, revisión de los medicamentos, plan de seguimiento al alta y programación de una cita de control antes del alta; **b) intervenciones posteriores al alta** que incluyeron llamadas telefónicas de seguimiento, acceso a líneas telefónicas directas para atención del paciente, comunicación oportuna con los cuidadores del paciente, seguimiento ambulatorio oportuno y visitas domiciliarias post-alta y **c) intervenciones "puentes" entre el hospital y el domicilio** en las que incluyeron instrucciones del alta al paciente, "transition coach" que es la intervención de una persona que interactúa y enseña el autocuidado al paciente antes y después del alta (por ejemplo una enfermera) y la continuidad del control por el por el mismo equipo médico a nivel hospitalario y ambulatorio [69].

Más recientemente, se ha publicado un meta-análisis que incluye 42 estudios aleatorios publicados desde el año 1990 hasta el 2013 que evaluaban el efecto de las distintas intervenciones sobre el reingreso precoz en pacientes adultos hospitalizados por una causa médica o quirúrgica durante más

de 24 horas y que fueron dados de alta a domicilio. Las intervenciones se dividieron en 18 estrategias o componentes diferentes que incluyen desde seguimiento telefónico, educación al paciente, visitas domiciliarias, rehabilitación, coordinación logística para la atención post-hospitalaria, telemonitoreo, educación especial por un farmacéutico para la comprensión de los medicamentos, visita de seguimiento antes del alta, entre otros. Se observó una reducción del reingreso precoz en los 42 estudios. Sin embargo, los estudios en los que las intervenciones incluyeron varios componentes, aquellas en los que se involucraron más de un individuo en el cuidado del paciente posterior al alta y aquellas en las que se proporcionó un mayor apoyo al paciente para su autocuidado fueron las que demostraron mayor eficacia, siendo 1,4, 1,3 y 1,3 veces más efectivas que el resto de intervenciones, respectivamente [70].

En los últimos años se está promoviendo la implementación de los llamados cuidados transicionales, en los que el elemento central es una visita médica de seguimiento a los 7-14 días tras el alta hospitalaria. En dicha visita se hace un reconocimiento y

una revisión de los tratamientos prescritos, se siguen algoritmos diagnósticos y se toman decisiones terapéuticas de acuerdo al estado del paciente al momento de la visita. Además, engloba otros aspectos como promover la educación del paciente referente a su enfermedad, brindar indicaciones post-alta, dar facilidades de acceso de los pacientes a los cuidados y servicios médicos, etc [71]. Para ello, desde el año 2013 en EEUU el CMS destina fondos adicionales (500 millones de dólares) a mejorar los programas de atención transicional (CCTP: The Community-based Care Transitions Program) con el objetivo de reducir la tasa del reingreso precoz en los hospitales [41,72].

Existen muy pocos estudios que evalúen estrategias específicas dirigidas a reducir el reingreso precoz en los pacientes con cirrosis descompensada [53,73,74,75,76,77]. Estos trabajos incluyen una gran variedad de intervenciones que van dirigidas tanto a la educación de los profesionales sanitarios (sesiones educativas para médicos, creación de protocolos de tratamiento al ingreso), a la educación e información del paciente (consulta

por un especialista (gastroenterólogo/hepatólogo) durante el ingreso, sugerencias de autocuidado) y al seguimiento posterior a la hospitalización. Los resultados obtenidos son dispares entre sí, desde una reducción en la tasa del reingreso precoz, así como en la mortalidad en los pacientes cirróticos descompensados a los que se les implementó la estrategia específica, hasta no encontrar diferencias o incluso presentar un aumento del riesgo del reingreso precoz en el grupo de estudio.

Esta disparidad de resultados, así como la escasez de estudios en nuestro medio que permitan conocer el alcance real del problema del reingreso precoz en la población cirrótica, no sólo en términos clínicos sino también en términos económicos, alienta y obliga a la búsqueda de nuevas estrategias encaminadas a mejorar el manejo de estos paciente a fin de conseguir una atención más eficaz, dirigida en definitiva, a mejorar la calidad de vida y optimizar los recursos económicos disponibles.

JUSTIFICACIÓN E HIPÓTESIS

2. JUSTIFICACIÓN E HIPÓTESIS

El reingreso precoz en los pacientes con cirrosis descompensada, al igual que en otras enfermedades crónicas (insuficiencia cardiaca, diabetes, EPOC), comporta una problemática con alto impacto no sólo en el aspecto clínico sino también asistencial y económico, lo que significa que involucra y afecta al paciente, familiares, equipo médico y el sistema sanitario. No obstante, a diferencia de las otras enfermedades, en la cirrosis existen pocos estudios que hayan evaluado el reingreso precoz, tanto para identificar sus causas, como de aplicación de estrategias en búsqueda de soluciones a dicho problema. Además, los estudios existentes presentan disparidad en sus resultados y la mayoría han sido evaluados en la población norteamericana cuyas comorbilidades y sistema de salud son diferentes a la de la población europea. Todo ello contribuye a que aún no exista un protocolo estandarizado a nivel general para el seguimiento post-hospitalario de estos pacientes, con el objetivo de controlar y reducir el reingreso precoz.

Este contexto, nos ha motivado a estudiar el reingreso precoz en nuestra población de pacientes con cirrosis descompensada, inicialmente valorando el estado actual del problema (incidencia de reingreso precoz, factores de riesgo, grupos de riesgo, etc) y posteriormente evaluando posibles soluciones, con la creación de un programa de mejora de la asistencia post-hospitalaria del paciente cirrótico descompensado, aplicando las nuevas estrategias transicionales. Para ello, en la presente tesis doctoral hemos realizado dos estudios en los que se desarrollan cada uno de estos aspectos.

Hipótesis:

- La población de cirróticos descompensados en nuestro medio cursan con una alta incidencia de reingreso precoz
- Los pacientes con reingreso precoz presentan mayor mortalidad en comparación con los pacientes que no reingresan o lo hacen después de los 30 días tras el alta.
- El programa de seguimiento transicional (HEPACONTROL) reduce el reingreso precoz en los pacientes con cirrosis descompensada

OBJETIVOS

3. OBJETIVOS

3.1 Objetivos principales

- Identificar los factores de riesgo del reingreso precoz en los pacientes con cirrosis descompensada.
- Implementar “HEPACONTROL”: un programa de seguimiento especializado para reducir el reingreso precoz en los pacientes cirróticos descompensados.

3.2 Objetivos secundarios

- Evaluar la incidencia del reingreso precoz en nuestra población de pacientes con cirrosis descompensada.
- Analizar el impacto del reingreso precoz en la mortalidad.
- Valorar el efecto de “HEPACONTROL” en la tasa de consultas al servicio de urgencias por descompensación de la cirrosis tras el alta hospitalaria.
- Determinar la influencia de “HEPACONTROL” en la mortalidad de los pacientes con cirrosis descompensada.
- Analizar el impacto económico al implementar el programa “HEPACONTROL”

ESTUDIO 1: "Reingreso hospitalario precoz (≤30 días) en el paciente cirrótico descompensado: Incidencia, impacto en la mortalidad y factores predictores".

4. ESTUDIO 1

)(2017) 903–909

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

Early hospital readmission in decompensated cirrhosis: Incidence, impact on mortality, and predictive factors

Betty P. Morales[a,*], Ramon Planas[a,b], Ramon Bartoli[b,c], Rosa M. Morillas[a,b], Margarita Sala[a,b], Eduard Cabré[a,b], Irma Casas[d], Helena Masnou[a]

[a] Hospital Universitari Germans Trias i Pujol, Liver Unit, Gastroenterology, Departament of Medicine, Universitat Autònoma de Barcelona, Badalona, Barcelona, Spain
[b] Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas, CIBERHED, Barcelona, Spain
[c] Fundació Germans Trias i Pujol, Gastroenterology, Badalona, Spain
[d] Hospital Universitari Germans Trias i Pujol, Preventive Medicine and Epidemiology Department, Autonomous University of Barcelona, Badalona, Barcelona, Spain

ARTICLE INFO

Article history:
Received 13 October 2016
Received in revised form 5 February 2017
Accepted 9 March 2017
Available online 18 March 2017

Keywords:
Decompensated cirrhosis
Hospital readmissions
Independent predictors
Mortality

ABSTRACT

Background & aims: The early hospital readmission of patients with decompensated cirrhosis is a current problem. A study is presented on the incidence, the impact on mortality, and the predictive factors of early hospital readmission.
Patients and methods: On the study included 112 cirrhotic patients, discharged after some decompensation between January 2013 and May 2014. Multivariate analyses were performed to identify predictors of early readmission and mortality.
Results: The early readmission rate was 29.5%. The predictive factors were male gender (OR: 2.81; 95% CI: 1.07–7.35), Model for End-Stage Liver Disease-sodium score ≥15 (OR: 3.79; 95% CI 1.48–9.64), and Charlson index ≥7 (OR: 4.34, 95% CI 1.65–11.4). This model enabled patients to be classified into low or high risk of early readmissions (13.6% vs. 52.2%). The mortality rate was significantly higher among patients with early readmission (73% vs. 35%) ($p < .0001$). After adjusting for the Model for End-Stage Liver Disease-sodium score, Charlson index, dependence in activities of daily living, educational status, and number of medications on discharge, the early readmission was independently associated with mortality.
Conclusions: Early hospital readmission is common, and is independently associated with mortality. Male gender, MELD-Na ≥15, and Charlson index ≥7 are predictors of early readmission. These results could be used to develop future strategies to reduce early readmission.

1. Introduction

Cirrhosis is the end stage of chronic liver disease, is associated with high mortality, and is the second leading cause of digestive tract disease-related death (after colorectal cancer) [1]. The World Health Organization reports that liver cirrhosis is responsible for about 170,000 deaths in Europe each year [2]. Cirrhosis is also responsible for significant morbidity and health-care costs. It leads to more than 150,000 hospital admissions, costing nearly 4 billion dollars each year in the United States [3]. When a patient is hospitalized for decompensated cirrhosis, the risk of readmission is very high, with an overall actuarial probability of readmission at 1 year of 45% [4].

Readmission within 30 days after hospital discharge (early readmission) among the Medicare population often leads to high health care costs, and also has become a measurement of quality of health care [5]. Of those discharged from an acute-care hospital in the United States between 2003 and 2004, 19.6% were readmitted within 1 month, at a cost of more than 17 billion dollars, which represents nearly 20% of the Medicare budget [6].

There are currently few studies that have assessed predictors of early readmission in decompensated cirrhosis [7–11] compared to other chronic diseases, such as heart failure and chronic obstructive pulmonary disease [12–16]. Moreover, these were conducted in the United States. Therefore, the aims of this study were to identify the incidence of early readmission (≤30 days) in patients with decompensated cirrhosis, its impact on mortality, and the predic-

* Corresponding author at: Ctra. de Canyet, s/n, 08916, Badalona, Spain. Fax: +34 934978951.
E-mail address: betty.pao82@hotmail.com (B.P. Morales).

http://dx.doi.org/10.1016/j.dld.2017.03.005
1590-8658/

tive factors that will allow us to classify the patients in risk groups of early readmission in our population.

2. Patients and methods

2.1. Patients

This retrospective, longitudinal, and observational study, was conducted in the Hepatology Unit of the University Hospital Germans Trias i Pujol (Badalona, Spain). It included cirrhotic patients discharged between January 2013 and May 2014, after being admitted due to some decompensation:

- Hepatic encephalopathy (EH), defined as a brain dysfunction caused by liver insufficiency and/or portosystemic shunting (PSS) [17]. Patients with EH grade I to grade IV according to West Haven criteria were included.
- Portal hypertensive bleeding diagnosed by emergency endoscopy on observing one of the following: (1) active bleeding from a varix; (2) white nipple or clot adherent to a varix; (3) when varices are the only lesion found, and if blood is present in the stomach or endoscopy is performed after 24 h of hemorrhage [18].
- Spontaneous bacterial peritonitis (SBP), defined as >250 polymorphonuclear cells per high-power field and/or monomicrobial culture in the ascitic fluid [19].
- Clinically evident ascites documented on physical examination: moderate (grade 2) or large ascites (grade 3), according to the classification of The International Ascites Club [19], with or without acute kidney injury (AKI), defined as a serum creatinine increase of over .3 mg/dL or by 50% from baseline [20].

The follow-up was until death, or the end of the study period in December 2014.

Exclusion criteria were the following: decompensated cirrhosis patients who died, or had voluntary discharge during the index hospitalization, and patients with HIV infection.

Data collected as regards the index hospitalization included: demographic data (gender, age, dependence in activities of daily living (ADLs), educational status, living alone), etiology of cirrhosis, history of admissions for decompensated cirrhosis in the previous year, presence of hepatocellular carcinoma, Barcelona Clinic liver cancer (BCLC) staging, Body Mass Index (BMI), Charlson index (estimated survival at 10 years, depending on the age and comorbidities of the patient), the main cause of admission, presence of infection (non-SBP infections), acute kidney injury (AKI) during the index hospitalization, length of hospital stay, discharge location (nursing facility or home) and most recent values on discharge, including Model for End-stage Liver disease-sodium (MELD-Na) score, laboratory values (platelet count, serum bilirubin, prothrombin time, serum albumin, serum sodium, and serum creatinine), and number of medications.

We evaluated readmissions for decompensated cirrhosis (HE, ascites, with or without renal failure, portal hypertensive bleeding, or SBP) or any other cause, but complicated for some decompensation of cirrhosis in our hospita,l or at other institutions during the study period, time to first readmission (<or> 30 days), and the total number of hospital readmissions at the end of follow-up. In patients with multiple admissions, only the first admission was considered as the index hospitalization, and the others were considered readmissions.

In addition, an analysis was made on the number of emergency service consultations post-discharge, and the mortality at the end of study.

When there was more than one decompensation of cirrhosis at admission, the criteria used to define the main cause of admission were the following: (1) Whenever portal hypertensive bleeding was coincident with another complication, it was considered the main cause of admission, because it frequently causes bacterial infection or hepatic encephalopathy; (2) When bleeding was not present at admission, infection (SBP) was considered the main cause of hospitalization; and (3) In patients with hepatic encephalopathy and ascites, the main cause was the former.

Data were compiled by examining the computerized medical record for each patient and by telephone follow-ups. The study protocol was in compliance with the ethical standards of the Helsinki Declaration of 1975 and was approved by the Ethics Committee of University Hospital Germans Trias i Pujol as part of a larger study of a program to improve the post-discharge support of decompensated cirrhotic patients. Informed consent was obtained from each patient.

2.2. Statistical analysis

To evaluate the predictive factors of early hospital readmission we compared the two groups (patients with and without early hospital readmission) using the Chi-square test for qualitative variables [continuous variables were categorized according to the best cut-off values using receiver operating characteristic (ROC) curve analysis]. Variables that were found to be different ($p < .05$) in the univariate analysis were used to create different nested models by logistic regression and were then compared by Likelihood ratio tests (LRTs) to select the significant variables and to determine the best model. This procedure was performed because the number of significant variables was greater than the number of events, and all of them have been associated with re-hospitalization in previous studies. The results were presented as odds-ratios with a 95% confidence interval. Model calibration was evaluated using the Hosmer–Lemeshow goodness of fit test. Model discrimination was assessed by the c-statistic using ROC curve analysis. Logistic regression was used as the time of readmission was not taken into account. The final model obtained, allowed us to classify the patients into early readmission risk groups.

A univariate and multivariate analyses were used to evaluate if the early hospital readmission is a predictive factor of mortality in a patient with decompensated cirrhosis. They were performed using the Kaplan–Meier method and compared with the log-Rank test. Those variables with a $p < .05$ were included in a multivariate Cox regression analysis, and the results were presented as a hazard ratio with a 95% confidence interval.

Statistical analysis of the data was performed using the IBM SPSS version 21 statistical software (SPSS Inc. and Microsoft Corp., Chicago, IL).

3. Results

A total of 126 patients met the inclusion criteria, but 14 of them were excluded due to one with a voluntary discharge, and 13 died during the index hospitalization. None were infected with HIV. Therefore, the study finally included a total of 112 patients with a mean follow up of 11.1 ± 7.2 months.

Clinical characteristics of the cohort are shown in Table 1. The mean age of patients was 65.2 ± 11.8 years. The cohort was predominantly male (57.1%), and had a BMI ≥ 25 kg/m^2 (56.3%). The main origins of cirrhosis were hepatitis C virus (HCV) (39.3%) and alcohol (38.4%), and the mean of MELD-Na at discharge was 14.7 ± 4.9. Ascites was the main reason for the index admission (55.4%), and the mean of length of hospital stay was 21.0 ± 15.0 days.

Sixty-four (57.2%) patients were readmitted during the follow-up period, with a readmission rate of 3.5/person-year. The median time to early readmission was 11 days (range: 8–16). Thirty-three

Table 1
Demographic, clinical and laboratory data obtained at discharge from index hospitalization.

Variables	Overall (n= 112)	30-day readmission (n=33)	No 30-day readmission (n=79)	p Value
Male sex, *n* (%)	64 (57.1)	24 (72.7)	40 (50.6)	.031
Age, *mean* ± *SD* (yr)	65.2 ± 11.8	68.3 ± 10.5	64.0 ± 12.1	.075
Lives alone, *n* (%)	16 (14.3)	3 (9.1)	13 (16.5)	.310
Dependence in activities of daily living, *n* (%)	22 (19.6)	7 (21.2)	15 (19.0)	.787
Educational status (Elementary School), *n* (%)	77 (75.5)	24 (80.0)	53 (73.6)	.494
Admissions in the year before index hospitalization, (sí), *n* (%)	29 (25.9)	13 (39.4)	16 (20.3)	.035
Etiology of liver disease, *n* (%)				
- Alcohol	43 (38.4)	13 (39.4)	30 (38.0)	.754
- HVC	44 (39.3)	11 (33.3)	33 (41.8)	
- HVB	6 (5.4)	2 (6.1)	4 (5.1)	
- NASH	5 (4.5)	1 (3.0)	4 (5.1)	
- Others	14 (12.5)	6 (18.2)	8 (10.1)	
MELD-Na score, *mean* ± *SD*	14.7 ± 4.9	16.9 ± 5.0	13.8 ± 4.6	.002
BMI (kg/m^2), *n* (%)				
- <18.5	9 (8.0)	3 (9.1)	6 (7.6)	.926
- 18.5–24.9	40 (35.7)	11 (33.3)	29 (36.7)	
- >25	63 (56.3)	19 (57.6)	44 (55.7)	
Hepatocellular carcinoma, *n* (%)	33 (29.5)	14 (42.4)	19 (24.1)	.052
BCLC staging, *n* (%)				
- BCLC 0	1 (3.0)	1 (7.1)	0 (0)	.120
- BCLC A	6 (18.2)	1 (7.1)	5 (26.3)	.480
- BCLC B	7 (21.2)	4 (28.6)	3 (15.8)	.097
- BCLC C	9 (27.3)	1 (7.1)	8 (42.1)	.208
- BCLC D	10 (30.3)	7 (50)	3 (15.8)	.003
Charlson Index, *mean* ± *SD*	6.6 ± 2.8	7.6 ± 2.3	6.2 ± 2.9	.017
Cause of index admission, *n* (%)				
- Ascites	62 (55.4)	18 (54.5)	44 (55.7)	.330
- Portal hypertensive bleed	22 (19.6)	6 (18.2)	16 (20.3)	
- Hepatic encephalopathy	15 (13.4)	7 (21.2)	8 (10.1)	
- SBP	13 (11.6)	2 (6.1)	11 (13.9)	
Acute Kidney injury during the index hospitalization, *n* (%)	53 (47.3)	19 (57.6)	34 (43.0)	.160
Staging of AKI, *n* (%)				
- Stage 1	36 (67.9)	15 (78.9)	21 (61.8)	.294
- Stage 2	8 (15.1)	1 (5.3)	7 (20.6)	
- Stage 3	9 (17.0)	3 (15.8)	6 (17.6)	
Response to treatment of AKI				
- No response	5 (9.4)	2 (10.5)	3 (8.8)	.925
- Parcial response	10 (18.9)	4 (21.1)	6 (17.6)	
- Full response	38 (71.7)	13 (68.4)	25 (73.5)	
Infection during the index hospitalization, *n* (%)	53 (47.3)	17 (51.5)	36 (45.6)	.566
Serum sodium (mmol/L), *mean* ± *SD*	136.3 ± 4.0	134.6 ± 4.0	137.0 ± 3.7	.004
Serum bilirrubin (mg/dL), *mean* ± *SD*	2.4 ± 2.9	3.4 ± 4.2	2.0 ± 1.9	.079
Prothrombin time (%), *mean* ± *SD*	68.8 ± 16.1	66.8 ± 17.8	69.7 ± 15.3	.402
Serum albumina (g/L), *mean* ± *SD*	28.7 ± 4.8	28.0 ± 5.0	29.0 ± 4.7	.356
Platelet count (x10^9/L), *mean* ± *SD*	105.2 ± 68.7	105.5 ± 87.2	105.1 ± 59.9	.974
Serum creatinine (mg/dL), *mean* ± *SD*	1.0 ± 0.8	1.0 ± 0.38	1.0 ± 0.97	.730
Lenght of stay (days), *mean* ± *SD*	21.0 ± 15.0	20.4 ± 9.9	21.2 ± 16.7	.816
Discargue location, *n* (%)				
- Home	107 (95.5)	33 (100)	74 (93.7)	.139
- Nursing facility	5 (4.5)	0 (0)	5 (6.3)	
Number of medications on discharge, *mean* ± *SD*	7.5 ± 3.3	8.3 ± 3.2	7.1 ± 3.3	.081
Number of emergency service consultations post-discharge, *mean* ± *SD*	1.7 ± 2.3	2.3 ± 1.9	1.4 ± 2.4	.073
Number of total readmission at the end of follow-up, *mean* ± *SD*	1.1 ± 1.4	1.7 ± 0.9	0.9 ± 1.6	.013
Cause of readmission, *n* (%)				
- Hepatic encephalopathy	31 (48.4)	21 (63.6)	10 (32.3)	.004
- Ascites	24 (37.5)	6 (18.2)	18 (58.1)	
- Portal hypertensive bleed	6 (9.4)	5 (15.2)	1(3.2)	
- SBP	2 (3.1)	0 (0)	2 (6.5)	
- Acute Kidney injury	1 (1.6)	1 (3.0)	0 (0)	
Mortality at the end of follow-up, *n* (%)	52 (46.4)	24 (72.7)	28 (35.4)	<.0001

MELD-Na, Model for End-Stage Liver Disease-sodium; BMI, Body Mass Index; SBP, Spontaneous Bacterial Peritonitis; BCLC, Barcelona Clinic liver cancer staging; AKI stage1 (sCr increase ≥0.3 mg/dL or ≥1.5-2 fold from baseline); AKI stage 2 (sCr increase >2-fold to 3-fold from baseline); AKI stage 3 (sCr increase >3-fold from baseline or sCr ≥4.0 mg/dL with an acute increase ≥0.3 mg/dL or initiation of renal replacement therapy.

(29.5%) patients were readmitted within 30 days, 31 (27.7%) were readmitted after 30 days, and 48 (42.9%) were not readmitted during the study period.

The main cause of early hospital readmission was hepatic encephalopathy (63.6%), for which the precipitating factors were diuretics overdose (38%), non-SBP infections (38%), constipation (14.5%), and use of benzodiazepines (9.5%). The other causes of readmission in the early readmission group were ascites (18.2%) and GI bleeding (15.2%). In patients readmitted after 30 days, ascites was the main cause of readmission (58.1%), followed by HE (32.3%) and SBP (6.5%) Table 1.

Patients with early hospital readmission had a higher number of readmissions during the follow-up period than patients with no early readmission (mean 1.7 ± .9 *vs.* .9 ± 1.6; $p = .013$). Emergency service consultations post-discharge were also higher in this group of patients (mean of 2.3 ± 1.9 *vs.* 1.4 ± 2.4), but the difference was not statistically significant ($p = .073$).

3.1. Predictors of early hospital readmission (Table 2)

The variables associated with 30-day readmission ($p < .05$) in the univariate analysis were: age ≥63 years ($p = .014$), male gender ($p = .031$), history of admissions for decompensated cirrhosis in the previous year ($p = .035$), MELD-Na ≥15 at discharge ($p = .005$), Charlson index ≥7 ($p = .002$), BCLC stage D hepatocellular carcinoma ($p = .003$), hyponatremia ≤135 mmol/L ($p = .002$), serum creatinine ≥.9 mg/dL ($p < .001$), and the number of medications at discharge ≥7 ($p = .007$). Of these, the serum sodium and creatinine were excluded from nested models because they were calculated in the MELD-Na score. The age and BCLC stage D hepatocellular carcinoma variables were also excluded because they were included in the Charlson index.

Considering that the number of variables (5) exceeds the number of outcome events (n = 33) and the variables have been associated with the early hospital readmission in patients with and without cirrhosis, we performed nested models by regression logistic and compared with Likelihood ratio tests (LRTs).

A total of five nested models were created. The initial model included the Charlson index, taking into account their statistical significance and OR, for which LRTs were 125.3. The following models were created, including the Charlson index and the other variables. The number of medications at discharge ≥7 and the history of admissions for decompensated cirrhosis in the previous year were not significant and were removed from the model Table 3.

The final model of the predictors of early hospital readmission included: male gender (OR: 2.81; 95% CI: 1.07–7.35; $p = .035$), MELD-Na score ≥15 (OR: 3.79; 95% CI 1.48–9.64; $p = .005$) and Charlson index ≥7 (OR: 4.34, 95% CI 1.65–11.4; $p = .003$) with a LRTs of 112.46, Hosmer–Lemeshow test of 0.657 and a predictive capability with a c-statistic of .76 (95% CI: .66–.86).

The final model allowed the patients to be stratified into groups of risk. Patients with high risk were readmitted within 30 days in 52.2% (24/46) of cases, while patients with low-risk only 13.6% (9/66) were readmitted early (RR: 3.82; 95% CI: 1.96–7.46; $p < .0001$) Fig. 1. The mean time to early readmission was 28.7 days in the lowest-risk group, compared with 20.7 days in the highest risk group ($p < .0001$).

3.2. Impact of early hospital readmission on mortality (Table 4)

The overall mortality at the end of follow-up was 46.4% (52/112). The mortality rate was significantly higher in patients who were readmitted within 30 days than those with no early readmission (72.7% *vs.* 35.4%) (OR: 4.85; 95% CI 1.98–11.87; $p < .0001$). Fig. 2 shows the probability of 1-year survival in the two groups of patients.

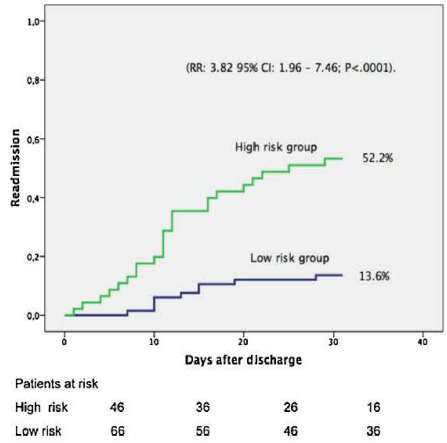


Fig. 1. Risk groups of early readmission according the final model. Low-risk group (n = 66): 13.6% of patients were readmitted within 30 days. High risk group (n = 46): 52.2% of patients were early readmitted (p < .0001).

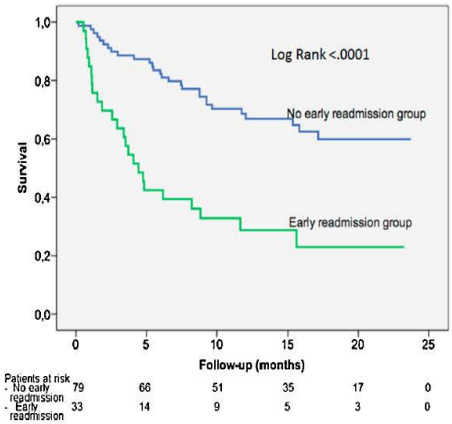


Fig. 2. Survival at the end of follow-up between patients with & without early readmission.

The most frequent causes of death were advanced stage HCC (29.2% of patients in early readmission group *vs.* 39.3% of patients with no early readmission, $p = .444$), bacterial infections no-SPB (29.2% *vs.* 21.4%, $p = .521$), and gastrointestinal bleeding (16.7% *vs.* 3.6%, $p = .110$).

The variables associated with mortality at the end of follow-up ($p < .05$) in the univariate analysis were: age ≥63 years ($p < .0001$), BCLC stage D hepatocellular carcinoma ($p < .0001$), early hospital readmission ($p < .0001$), Charlson index ≥7 ($p < .0001$), MELD-Na ≥15 at discharge ($p = .014$), dependence in activities of daily living (ADLs) ($p = .006$), elementary school education ($p = .044$), number of medications on discharge ≥7 ($p = .028$), and serum creatinine ≥.9 mg/dL ($p < .0001$).

The BCLC stage D hepatocellular carcinoma and age variables were excluded from the Cox multivariate regression analysis as they were included in the Charlson index, as well as the serum creatinine variable as it was included in the MELD-Na score.

Table 2
Predictors of early hospital readmission.

Variables	Number of variable	Univariate analysis			Final model		
		OR	CI 95%	p Value	OR	CI 95%	p Value
Charlson index ≥7	V1	3.92	(1.57–9.77)	.002	4.34	(1.65–11.4)	.003
MELD-NA score ≥15	V2	3.37	(1.41–8.04)	.005	3.79	(1.48–9.64)	.005
Number of medications on discharge ≥7	V3	3.37	(1.35–8.37)	.007	1.88	(.64–5.53)	.165
Male sex	V4	2.60	(1.07–6.29)	.031	2.81	(1.07–7.35)	.035
Admissions for decompensated cirrhosis in the previous year	V5	2.55	(1.05–6.22)	.035	2.22	(.75–6.45)	.142
BCLC stage D HCC[a]	V6	6.8	(1.6–28.3)	.003			
Serum creatinine ≥0.8 mg/dL[a]	V7	4.0	(1.55–10.3)	.003	–	–	–
Serum sodium ≤135 mmol/L[a]	V8	3.78	(1.59–8.78)	.002	–	–	–
Age ≥63 years[a]	V9	3.04	(1.22–7.57)	.014	–	–	–

OR, Odds Ratio; CI, Confidence interval. BCLC, Barcelona Clinic liver cancer staging HCC, Hepatocellular carcinoma.
Continuous variables were categorized according to the best cut-offs identified by ROC statistics.
[a] Variables excluded from nested models: the creatinine and serum sodium because they were included in the MELD-Na score and the BCLC stage D and age because they were included in the Charlson index.

Table 3
Nested models.

Variables analized	Variables in the model	Likelihood ratio tests (LRTs)	Variables excluded
V1	V1	125.39	–
V1 + V2	V1 + V2	117.21	–
V1 + V2 + V3	V1 + V2	117.21	V3
V1 + V2 + V4	V1 + V2 + V4	112.46	–
V1 + V2 + V4 + V5	V1 + V2 + V4	112.46	V5

Table 4
Impact of early hospital readmission on mortality.

Variables	Univariate analysis			Multivariate analysis		
	HR	CI 95%	p Value	HR	CI 95%	p Value
Early hospital readmission	1.56	(5.75–11.88)	<.0001	2.40	(1.25–4.61)	.009
MELD-Na score ≥15	1.34	(9.84–15.10)	.014	1.94	(1.04–3.62)	.036
Charlson index ≥7	1.21	(8.98–13.76)	<.0001	2.47	(1.14–5.32)	.021
Dependence in activities of daily living	1.87	(6.46–13.81)	.006	2.22	(1.13–4.38)	.020
Elementary School	1.07	(12.15–16.38)	.044	1.21	(.48–3.09)	.678
Number of medications on discharge ≥7	1.22	(10.53–15.36)	.028	1.02	(.47–2.20)	.954
Serum creatinine ≥0.9 mg/dL[a]	1.32	(8.81–13.98)	<.0001	–	–	–
Age ≥63 years[a]	1.17	(9.34–13.98)	<.0001	–	–	–
BCLC stage D HCC[a]	1.34	(5.93–11.19)	<.0001	–	–	–

HR, Hazard Ratio; CI: Confidence interval. HCC, Hepatocellular carcinoma.
[a] Variables excluded from the multivariate Cox regression analysis: the BCLC stage D HCC and age because they were included in the Charlson index and the serum creatinine because it was included in the MELD-Na score.

Finally, early hospital readmission was an independent predictor of mortality (HR: 2.40, 95% CI: 1.25–4.61; $p = .009$), adjusted for a Charlson index ≥7 (HR: 2.47; 95% CI: 1.14–5.32; $p = .021$), ADLs (HR: 2.27, 95% CI: 1.13–4.38; $p = .020$), MELD-Na ≥15 (HR: 1.94; 95% CI: 1.04–3.62; $p = .036$), elementary school education (HR: 1.21, 95% CI: .48–3.09; $p = .678$), and number of medications on discharge ≥7 (HR: 1.02, 95% CI: .47–2.20; $p = .954$).

4. Discussion

This study found that early hospital readmission (≤30 days) among patients with decompensated cirrhosis is common, with an incidence of 29%. The early readmission had a negative impact on the survival, since the patients readmitted within 30 days had higher mortality (73% vs. 35%), and was also an independent predictor of mortality. The independent predictors of early hospital readmission were male gender, Charlson index ≥7, and MELD-Na score ≥15 at discharge. These predictors enabled the patients to be classified into two groups, one high risk (52.2% readmitted within 30 days), and one low risk (13.6% readmitted within 30 days).

Hyponatremia is a prognostic factor in cirrhosis. It has been associated with impaired health related quality life, as well as being a risk factor for increased morbidity and mortality before and after liver transplantation, and also as an increased risk of developing hepato-renal syndrome [21]. The incorporation of serum sodium into the model for end-stage liver disease (MELD-Na score) provided a more accurate survival prediction than the MELD alone in chronic liver disease [22,23]. The MELD-Na score significantly increased the efficacy of the MELD score to predict waiting-list mortality [23], and it has been used for allocation for liver transplant candidates in the United States since January 2016 [24]. Furthermore, the MELD-Na score has also been shown to be a feasible and independent prognostic predictor for both short- and long-term outcomes in HCC patients [25], and in a recent study it was a more valuable model than Maddrey discriminant function index to predict short-term mortality in patients with alcoholic hepatitis [26]. Another predictive role of MELD-Na score was found in our study, since it was associated with increased risk of early hospital readmission due to the poor prognosis of these patients, and to the increased susceptibility of developing complications from liver disease, along with the demand for medical care.

A new aspect in our study is the role of the Charlson Comorbidity index as an independent factor of early hospital readmission in patients with decompensated cirrhosis. It had been previously described as a risk factor, but in patients discharged from medical or surgical departments [27]. It is a method of predicting mor-

tality by classifying comorbid conditions and patient age [28]. It seems reasonable to think that older people with several comorbidities have an increased susceptibility to develop adverse effects due to medication, increased polypharmacy, poor compliance with instructions at discharge, and increased demand for medical care, which may explain the high rate of early readmission. This index was also evaluated in the study by Volk et al. [7], without becoming an independent predictive factor of readmission. This difference could be explained due to the median age of their patients being lower than ours (54 vs. 66 years), which could lead to having fewer comorbidities.

In our study, as in that by Berman et al. [8] and Singal [9], being male was an independent predictor of early hospital readmission. This could be explained by predominance of male patients in the study population, the differences in the evolution of chronic liver disease between men and women [29], and psychosocial differences in the way women seek care at discharge.

In the current study, we included other variables known to be predictors of cirrhosis, such as BMI [30,31], the presence of AKI [32], and infections during hospitalization [33], although there were no significant differences between patients with and with no early hospital readmission. However, we thought it would be interesting to perform future, prospective, multicenter studies with a larger number of patients to determine their real impact on the early readmission.

The final model of independent predictors of early readmission had a c-statistic value of .76, indicating moderate predictive ability, which permitted us to create risk groups. In our study, 13.6% of low-risk patients were readmitted within 30-days, while in the high-risk group, 52.2% of patients were readmitted. In studies by Volk [7] and Singal et al. [9], risk groups were also created, with similar percentages of early hospital readmission (22% and 20% in low-risk groups, and 55% and 45% in the high risk groups, respectively). Although the risk factors for 30-day readmission found in our study are not modifiable (except MELD-Na in some cases), the identification of these allows us to identify patients at highest risk of early readmission during hospitalization. It could be useful for designing future specific surveillance and follow-up strategies at discharge for this group of patients, as a program of transitional interventions with closer specialized monitoring, in order to reduce the incidence of early hospital readmission, and improve survival and quality of life.

It is interesting to note that the main cause of admission was ascites; however the main cause for early hospital readmission was hepatic encephalopathy (not associated with portal hypertensive bleeding or SPB), which makes us suspect that the diuretic therapy, complications associated with this, and a lack of closer follow-up, with analytical and clinical evaluation of these patients, could be influencing the development of decompensation, especially hepatic encephalopathy. This is a point that should be taken into account in order to improve the management of these patients.

Limitations of this study include its retrospective nature. It was performed in a single hospital, which could limit the generalizability of our results, and, finally, the lack of validation of the final model predictors of early hospital readmission.

In conclusion, this study identified that early readmission is common in decompensated cirrhotic patients, and is associated with increased mortality. Male gender, advanced liver failure (MELD-Na), and Charlson index ≥7 are independent predictors of readmission within 30 days, which enabled patients to be classified into low and high risk with moderate accuracy. These results are potentially useful to guide future interventions aimed at reducing 30-day hospital readmission.

Conflict of interest

None declared.

Disclosure statement

Betty P. Morales receives a grant of "Germans Trias i Pujol" Health Sciences Research Institute (IGTP).

Acknowledgement

Betty P. Morales are supported by a grant of the "Germans Trias i Pujol" Health Sciences Research Institute (IGTP).

References

[1] Everhart JE, Ruhl CE. Burden of digestive diseases in the United States part I: overall and upper gastrointestinal diseases. Gastroenterology 2009;136:376–86.

[2] Blachier M, Leleu H, Peck-Radosavljevic M, et al. The burden of liver disease in Europe: a review of available epidemiological data. Journal of Hepatology 2013;58:593–608.

[3] Talwalkar JA. Prophylaxis with beta blockers as a performance measure of quality health care in cirrhosis. Gastroenterology 2006;130:1005–7.

[4] Planas R, Ballesté B, Alvarez MA, et al. Natural history of decompensated hepatitis C virus-related cirrhosis. A study of 200 patients. Journal of Hepatology 2004;40:823–30.

[5] Hansen L, Young RS, Hinami K, et al. Interventions to reduce 30-day rehospitalization: a systematic review. Annals of Internal Medicine 2011;155:520–8.

[6] Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. New England Journal of Medicine 2009;360:1418–28.

[7] Volk ML, Tocco R, Bazick J, et al. Hospital readmissions among patients with decompensated cirrhosis. The American Journal of Gastroenterology 2012;107:247–52.

[8] Berman K, Tandra S, Forssell K, et al. Incidence and predictors of 30-day readmission among patients hospitalized for advanced liver disease. Clinical Gastroenterology and Hepatology 2011;9:254–9.

[9] Singal A, Rahimi R, Clark C, et al. An automated model using electronic medical record data identifies patients with cirrhosis at high risk for readmission. Clinical Gastroenterology and Hepatology 2013;11:1335–41.

[10] Bini EJ, Weinshel EH, Generoso R, et al. Impact of gastroenterology consultation on the outcomes of patients admitted to the hospital with decompensated cirrhosis. Hepatology 2001;34:1089–95.

[11] Ganesh Swaytha, Rogal Shari S, Yadav Dhiraj, et al. Risk factors for frequent readmissions and barriers to transplantation in patients with cirrhosis'. PLoS One 2013;8:e55140.

[12] Ross JS, Mulvey GK, Stauffer B, et al. Statistical models and patient predictors of readmission for heart failure: a systematic review. Archives of Internal Medicine 2008;168:1371–86.

[13] Hernandez AF, Greiner MA, Fonarow GC, et al. Relationship between early physician follow-up and 30-day readmission among Medicare beneficiaries hospitalized for heart failure. JAMA 2010;303:1716–22.

[14] Hernandez MB, Schwartz RS, Asher C, et al. Predictors of 30-day readmission in patients hospitalized with decompensated heart failure. Clinical Cardiology 2013;36:542–7.

[15] Gudmundsson G, Gislason T, Janson C, et al. Risk factors for rehospitalisation in COPD: role of health status, anxiety and depression. European Respiratory Journal 2005;26:414.

[16] Roberts C, Lowe D, Bucknall C, et al. Clinical audit indicators of outcome following admission to hospital with acute exacerbation of chronic obstructive pulmonary disease. BMJ 2002;57:137.

[17] Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. Journal of Hepatology 2014. http://dx.doi.org/10.1016/j.jhep.2014.05.042.

[18] Garcia-Tsao G, Abraldes J, Berzigotti A, et al. Portal hypertensive bleeding in cirrhosis: risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. Hepatology 2017;65.

[19] EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrosis. Journal of Hepatology 2010;53:397–417.

[20] Angeli P, Ginès P, Wong F, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. Journal of Hepatology 2015;62:968–74.

[21] Savio J, Thuluvath PJ. Hyponatremia in cirrosis: pathophysiology and management. World Journal of Gastroenterology 2015;21:3197–205.

[22] Biggins SW, Kim WR, Terrault NA, et al. Evidence-based incorporation of serum sodium concentration into MELD. Gastroenterology 2006;130:1652–60.

[23] 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 Transplantation 2005;11:336–43.

[24] Kalra A1, Wedd JP, Biggins SW. Changing prioritization for transplantation: MELD-Na, hepatocellular carcinoma exceptions, and more. Current Opinion in Organ Transplantation 2016;21:120–6.

[25] Huo TI, Lin HC, Hsia CY, et al. The MELD-Na is an independent short- and long-term prognostic predictor for hepatocellular carcinoma: a prospective survey. Digestive and Liver Disease 2008;40:882–9.
[26] Amieva-Balmori M, Mejia-Loza S, Ramos-González R, et al. Model for end-stage liver disease-Na score or Maddrey discrimination function index, which score is best? World Journal of Hepatology 2015;7:2119–26.
[27] Walraven C, Dhalla I, Bell C, et al. Derivation and validation of an index to predict early death or unplanned readmission after discharge from hospital to the community. Canadian Medical Association Journal 2010;182:551–7.
[28] Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of Chronic Diseases 1987;40:373–83.
[29] Poynard T, Mathurin P, Lai CL, et al. A comparison of fibrosis progression in chronic liver diseases. Journal of Hepatology 2003;38:257–65.
[30] Berzigotti A, Garcia-Tsao G, Bosch J, et al. Obesity is an independent risk factor por clinical decompensation in patients with cirrhosis. Hepatology 2011;54:555–61.
[31] Berzigotti A, Abraldes JG. Impact of obesity and insulin-resistance on cirrhosis and portal hypertension. Gastroenterologia y Hepatologia 2013;36:527–33.
[32] Belcher JM, Garcia-Tsao G, Sanyal AJ, et al. Association of AKI with mortality and complications in hospitalized patients with cirrosis. Hepatology 2013;57:753–62.
[33] Borzio M, Salerno F, Piantoni L, et al. Bacterial infection in patients with advanced cirrhosis: a multicentre prospective study. Digestive and Liver Disease 2001;33:41–8.

ESTUDIO 2: “HEPACONTROL. Un programa que reduce el reingreso precoz, la mortalidad a los 60 días y el gasto sanitario en la cirrosis descompensada”.

5. ESTUDIO 2

G Model
YDLD-3515; No. of Pages 8
ARTICLE IN PRESS
Digestive and Liver Disease xxx (2017) xxx–xxx
Contents lists available at ScienceDirect
Digestive and Liver Disease
journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

HEPACONTROL. A program that reduces early readmissions, mortality at 60 days, and healthcare costs in decompensated cirrhosis

Betty P. Morales[a,b,*], Ramon Planas[a,b,c], Ramon Bartoli[c,d], Rosa M. Morillas[a,c], Margarita Sala[a,c], Irma Casas[e], Carolina Armengol[c,d], Helena Masnou[a]

[a] University Hospital Germans Trias i Pujol, Liver Unit, Gastroenterology, Barcelona, Spain
[b] Department of Medicine — Autonomous University of Barcelona, Barcelona, Spain
[c] Centre for Biomedical Research in Liver and Digestive Diseases, CIBERHED (According to its Initials in Spanish), Barcelona, Spain
[d] The Germans Trias i Pujol Foundation, Gastroenterology, Spain
[e] University Hospital Germans Trias i Pujol, Preventive Medicine and Epidemiology Department, Autonomous University of Barcelona, Barcelona, Spain

ARTICLE INFO

Article history:
Received 11 May 2017
Received in revised form 6 August 2017
Accepted 7 August 2017
Available online xxx

Keywords:
Decompensated cirrhosis
Early readmission
Intervention to decrease readmissions

ABSTRACT

Background & aims: Decompensated cirrhosis patients have an elevated incidence of early readmission, mortality and economic burden. The aims of HEPACONTROL were to reduce early readmission and to evaluate its impact on mortality and emergency department visits.
Patients and methods: Quasi-experimental study with control group which compared two cohorts of patients discharged after being admitted for cirrhosis-related complications. A prospective cohort (n = 80), who followed the HEPACONTROL program, which began with a follow-up examination seven days after discharge at the Hepatology Unit Day Hospital and a retrospective cohort of patients (n = 112), who had been given a standard follow-up. Outcome variables that were compared between both groups were early readmission rates, the number of emergency department visits post-discharge, financial costs and mortality.
Results: The rate of early readmission was lower in the group with HEPACONTROL (11.3% *vs* 29.5%; $P = .003$). Also, the mean number of visits to the emergency department post-discharge (1.10 ± 1.64 *vs* 1.71 ± 2.36; $P = .035$), mortality at 60 days (3.8% *vs* 14.3%; $P = .016$), and the cost of early readmission were all lower compared with the group with standard follow-up ($P = .029$).
Conclusions: HEPACONTROL decreases the incidence of early readmission the rate of emergency department visits and mortality at 60 days in patients with decompensated cirrhosis, and it is cost-effective.

1. Introduction

Cirrhosis is a complex condition whose sufferers are susceptible to complications associated with a marked reduction in life expectancy and high healthcare services use [1–3].

Once a cirrhotic patient is hospitalized for a complication, the incidence of readmissions for the same or another cirrhosis-related decompensation is very high [4]. In a recent study, more than half (53%) of decompensated cirrhosis patients had been readmitted by three months after discharge [5]. Various other studies have shown readmission occurring even earlier (≤30 days after discharge) in 20–37% of the patient population [6–11], with an associated cost per readmission that is reported to exceed $20,000 in the U.S. [7] and €10,000 in Europe [12]. Furthermore, early readmission has been associated with a higher risk of mortality, even after adjusting for other risk factors such as the severity of liver disease [7–9]. Male sex, MELD-Na ≥15 and Charlson index ≥7 were the factors predictive of early readmission reported in our recent study [11].

Early readmission, which is frequent in different diseases generates a high cost burden for the healthcare system and has even become an indicator of the quality of hospital care [13–15]. All these difficulties have led to the design of strategic programs that attempt to reduce hospital readmissions and the consequences they generate. Transitional care has recently been promoted where the central element is a visit within 7–14 days after discharge with a clinician, who makes decisions about medication reconciliation and treatment management [16,17].

* Corresponding author at: Ctra. de Canyet, s/n, 08916, Badalona, Spain. Fax: +34 934978951.
E-mail address: betty.pao82@hotmail.com (B.P. Morales).

http://dx.doi.org/10.1016/j.dld.2017.08.024
1590-8658/

Please cite this article in press as: Morales BP, et al. HEPACONTROL. A program that reduces early readmissions, mortality at 60 days, and healthcare costs in decompensated cirrhosis. Dig Liver Dis (2017), http://dx.doi.org/10.1016/j.dld.2017.08.024

G Model
YDLD-3515; No. of Pages 8
ARTICLE IN PRESS

Though more than 50 studies have evaluated different interventions designed to reduce early readmission related to various diseases, they have mostly involved advanced aged patients and/or patients with heart failure [18–24]. Very few studies have evaluated specific readmission reduction strategies (including transitional interventions) in decompensated cirrhosis patients [12,25–29], and these few have reported contradictory results.

To address the need for further research on follow-up strategies to avoid or reduce early readmission rates for decompensated cirrhosis patients, we designed HEPACONTROL, a program whose hallmark is close patient monitoring carried out by specialized consultation in the Hepatology Unit Day Hospital within seven days after discharge, with the option of further examinations, or diagnostic procedures and/or therapy, which can be performed in real time if necessary. The primary goal of this study was to evaluate the impact of HEPACONTROL on the early readmission of patients with decompensated cirrhosis. Its secondary goals were to assess the program's cost-effectiveness as well as its possible impact on the rate of emergency department visits post-discharge and mortality.

2. Patients and methods

2.1. Selection criteria and patients

In June 2014 the Day hospital was created in the Hepatology Unit at the Germans Trias y Pujol Hospital in Badalona, Spain, in order to provide a close follow-up to cirrhotic patients. In this context, we designed a quasi-experimental study with control group in which a prospective cohort consisting of patients discharged between June 2014 and October 2015 who had participated in the HEPACONTROL monitoring program (Group 1) was compared with a retrospective cohort consisting of patients discharged between January 2013 and May 2014 (prior to the creation of Hepatology Unit Day Hospital) who had received a standard follow-up program (Group 2). Subjects were all cirrhotic patients discharged after being initially admitted for one of the following cirrhosis-related complications: hepatic encephalopathy (HE), ascites with or without renal failure, upper gastrointestinal bleeding (UGIB) or spontaneous bacterial peritonitis (SBP).

The minimum follow-up period for both cohorts was seven months or until the death of the patient. Patients were excluded from the study if (a) they had been discharged against medical advice or died during the index hospitalization or (b) they were infected with Human Immunodeficiency Virus (HIV). Furthermore, in the prospective cohort, patients were also excluded if (c) their care was taken over by the original referring health center (d) they failed to attend the scheduled follow-up visit at the Hepatology Unit Day Hospital seven days after discharge (because they forgot, refused, died, etc.)

2.2. Group 1 (with HEPACONTROL)

All patients included in the experimental HEPACONTROL group received a close follow-up examination by a hepatology specialist at the Hepatology Unit Day Hospital within seven days after their discharge.

Clinical evaluation in the follow-up visit included recording of vital signs and body weight and a physical exam. Patients were also interviewed to determine precipitating and risk factors for possible cirrhosis-related complications and to confirm compliance with medication and diet recommendations given at discharge. Patients were asked about bowel movements at home and the color and appearance of stools, if there was a relapse or a new decompensation appeared. Additionally, we performed a laboratory test (hemogram, coagulation, serum bilirubin, albumin, sodium, potassium and serum creatinine) on all patients at seven days after discharge.

The management of patients during follow-up was performed in accordance with EASL, AASLD and Baveno guidelines. For example, treatment was re-adjusted when indicated (failure to appropriately titrate lactulose or add rifaximin for prevention of recurrent episodes of HE, adjustment of diuretics in the event of over-diuresis or ascites, adjustment of beta-blockers for prophylaxis of UGIB, administration of norfloxacin in patients requiring prophylaxis of SBP); additional diagnostic or therapeutic procedures (such as blood or urine cultures, ultrasound or X-ray studies, diagnostic or evacuating paracentesis, blood transfusions, etc.) were performed as needed; and/or the patient was readmitted if the situation so required.

Patients in Group 1 were monitored in the HEPACONTROL program until they stabilized and then referred for outpatient hepatology check-ups. They could be re-evaluated by the Hepatology Unit Day Hospital if referred by the hepatology outpatient department, or emergency department, or at the request of the patient.

All patients in this group additionally received a leaflet with information regarding warning signs to take into account, preventive measures, and/or easy instructions of what to do in case of decompensation, as well as contact details and working hours of the Hepatology Unit Day Hospital (Supplementary Material).

2.3. Group 2 (without HEPACONTROL)

In what constituted the control group, patients went through a standard follow-up program which consisted of a laboratory test (hemogram, coagulation, transaminases, serum bilirubin, albumin, sodium, potassium and serum creatinine) followed by a check-up visit by a specialist physician at the regular outpatient services within the first two months after discharge, but did not include the opportunity to perform radiological studies or even obtain further laboratory data in real time. When the patient needed such exams, they were referred to the hospital's emergency department. This group of patients did not have access to the Hepatology Unit Day Hospital, given that it did not exist at that time.

2.4. Clinical variables

The variables evaluated in both groups included sociodemographic data; clinical data: etiology of cirrhosis, Model for End-stage Liver Disease-sodium (MELD-Na) score at time of discharge, number of hospitalizations due to complications during the year prior to admission, presence of hepatocellular carcinoma (HCC), body mass index (BMI), Charlson index, reason for admission, presence of infection or acutekidney injury (AKI) during admission, days of hospital stay, number of medications; and laboratory data at time of discharge. When more than one complication was present at admission, the criteria used to select the main cause were as follows: (1) whenever portal hypertensive bleeding co-occurred with another complication, it was considered the main cause of admission because it frequently causes bacterial infection or HE; (2) when the hemorrhage was not present at the time of admission, infection (SBP) was considered to be the main cause; and (3) in patients with both HE and ascites, the first complication to appear was regarded as the main cause.

2.5. Objective variables of the study

To evaluate the impact of the HEPACONTROL program on the early readmission rate of patients with decompensated cirrhosis (our main goal), we analyzed readmissions for complications of cirrhosis in our hospital or in a different hospital during the period of the study. We also analyzed the time elapsed between discharge

Please cite this article in press as: Morales BP, et al. HEPACONTROL. A program that reduces early readmissions, mortality at 60 days, and healthcare costs in decompensated cirrhosis. Dig Liver Dis (2017), http://dx.doi.org/10.1016/j.dld.2017.08.024

G Model
YDLD-3515; No.of Pages 8
ARTICLE IN PRESS
B.P. Morales et al. / Digestive and Liver Disease xxx (2017) xxx–xxx

and readmission (either < or >30 days), and the total number of readmissions until the end of the follow-up period. For patients with multiple admissions, only the first admission was considered the index hospitalization, all others being considered readmissions.

To meet our secondary goals, we analyzed the following for both groups: (a) the number of emergency department visits after discharge; (b) mortality at 30, 60 and 90 days and at the end of the study; and (c) the economic costs of emergency department visits and early hospital readmission. This was calculated taking into account the days of hospital stay due to readmission, and number of visits at the Day Hospital or emergency department for each patient, in complance with "Diari Oficial de la Generalitat de Catalunya" (DOGL 6326 del 01/03/2013).

We collected data by reviewing digital medical records (especially in the case of Group 2, since this was a retrospective cohort), by in-person consultations in the case of patients in Group 1, and follow-up telephone calls.

2.6. Statistical analysis

The comparison between the groups was carried out using the Student-*t* test for quantitative variables, and the χ^2 test for categorical variables. The results of the quantitative variables were expressed by mean ± standard deviation (SD). A 2-tailed P value of .05 was considered statistically significant.

To evaluate the influence of the HEPACONTROL program on early readmission rates, a univariate analysis was performed where statistically significant variables were included in a stepwise logic regression multivariate model.

Early hospital readmission, in both groups, was represented by survival curves using the Kaplan–Meier method and compared by the log-Rank test.

All statistical tests were performed using IBM SPSS Statistics version 21 (SPSS Inc. and Microsoft Corp., Chicago, IL).

2.7. Ethical registration of the study

The study protocol was adjusted to the ethical norms of the Helsinki Declaration of 1975 and was approved by the Research Ethics Committee of the Germans Trias i Pujol Hospital (Ref. CEI: PI-14-069 del 19/09/2014). Informed consent was signed by each patient.

3. Results

3.1. Selection and characteristics of patients

A total of 239 patients met the inclusion criteria during the study period (n = 113 in Group 1; n = 121 in Group 2), of which 47 patients were excluded: 24 because of death during hospitalization (n = 11 in Group 1 and n = 13 in Group 2), one because of discharge against medical advice (Group 2), three because of HIV infection (Group 1), four because they failed to attend their follow-up visit at the Hepatology Unit Day Hospital after discharge (Group 1) and 15 because their care was transferred to their local referring health center (Group 1). In the end, data from a total of 192 patients (n = 80 in Group 1; n = 112 in Group 2) with an average follow-up period of 10.7 ± 6.8 months were included in our analysis.

The general characteristics of the patients are shown in Table 1. The mean age in both groups was 65 ± 11.8 years and most were male (70% in Group 1 and 57.1% in Group 2). The most frequent etiology of cirrhosis was alcohol (43.8% and 38.4%) and HCV (41.3% and 39.3%), with a mean MELD-Na score of 15.0 ± 5.0 (15.5 ± 5 in Group 1 and 14.7 ± 4.9 in Group 2). The main indication for index admission was ascites (67.5% in Group 1 and 55.4% Group 2), followed by encephalopathy and SBP (11.3% each one) in Group 1, and UGIB (19.6%) in Group 2. The differences in the general characteristics between groups were that in Group 1 there was a lower incidence of infection during hospitalization (32.5% *vs* 47.3%, respectively; *P* = .040), the Charlson index was higher (7.7 ± 2.7 *vs* 6.6 ± 2.8; *P* = .009), the mean time of thromboplastin was lower (62.9 ± 19% *vs* 68.8 ± 6.1%; *P* = .022), and the mean hospital stay of the index admission was lower (16.8 ± 13 days *vs* 21 ± 15 days; *P* = .046), compared to Group 2.

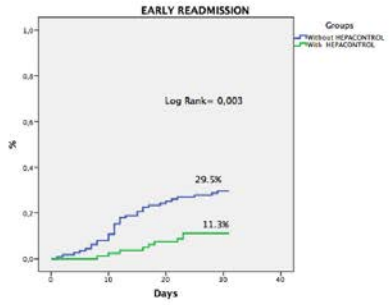


Fig. 1. Comparison of early readmission percentage between groups 1 and 2. Patients included in HEPACONTROL (Group 1) showed a significant reduction in early re-admission compared with the patients in Group 2 (11.3% *vs* 29.5% = 9/80 *vs* 33/112) (RR: .38; 95% CI:.19–.75; *P* = .003).

One hundred and one (52.6%) patients out of the total study population were readmitted during the follow-up period, with 42 (21.9%) patients readmitted within 30 days and 59 (27.7%) after 30 days. The remaining 91 (47.4%) patients were not readmitted during the study period.

3.2. Impact of the HEPACONTROL program on early readmission (≤30 days)

The total number of patients who were readmitted for a cirrhosis-related complication at least once during the period of the study was slightly higher in Group 2 (57.1%) compared with Group 1 (46.3%), without reaching statistical significance (*P* = .136). Of these, the patients in Group 1 showed a significant reduction in early readmission (≤30 days) compared with the patients of Group 2 (11.3% *vs* 29.5% = 9/80 *vs* 33/112) (RR: .38; 95% CI: .19–.75; *P* = .003) (Fig. 1). Furthermore, in Group 1 the time elapsed until early readmission was longer than in Group 2 (mean 29.38 ± 4.9 days *vs* 25.43 ± 9.2 days; *P* < .001) and hospital stays during readmission wereof shorter duration (10.4 ± 3.7 days *vs* 18.36 ± 14.4 days; *P* = .007). There was no significant difference in the percentage of readmissions after 30 days between groups (35% in Group 1 and 27.7% Group 2; *P* = .278).

The main reason for early readmission in both groups was HE (44% in Group 1 and 63.6% in Group 2; *P* = .298) and ascites was the second cause (33.3% *vs* 21.2%; *P* = .449). Other reasons for early readmission were UGIB (11.1% in Group 1 *vs* 15.2% Group 2; *P* = .759), and SBP (11.1 *vs* 0%; *P* = .053). On the other hand, ascites was the main cause of readmission >30 days after discharge in both groups (42.9% in Group 1 *vs* 58.1% Group 2; *P* = .243).

Since in Group 1 the mean hospital stay and the incidence of infection during index hospitalization were lower, a sub-analysis was done of the control group (Group 2, without HEPACONTROL), where the independent predictors of early hospital readmission in this cohort of patients were male sex, Charlson index ≥7 and MELD-

Please cite this article in press as: Morales BP, et al. HEPACONTROL. A program that reduces early readmissions, mortality at 60 days, and healthcare costs in decompensated cirrhosis. Dig Liver Dis (2017), http://dx.doi.org/10.1016/j.dld.2017.08.024

G Model
YDLD-3515; No. of Pages 8
ARTICLE IN PRESS

Table 1
Comparison between patients of Group 1 (with HEPACONTROL) and Group 2 (without HEPACONTROL).

Variables	Overall (n = 192)	Group 1 (n = 80)	Group 2 (n = 112)	P value
Male sex, *n* (%)	120 (62.5)	56 (70)	64 (57.1)	.070
Age, *mean* ± *SD* (yr)	65.3 ± 11.8	65.5 ± 11.8	65.2 ± 11.8	.896
Lives alone, *n* (%)	29 (15.1)	13 (16.3)	16 (14.3)	.708
dependence in activities of daily living, n (%)	35 (18.2)	13 (16.3)	22 (19.6)	.548
Educational status (Elementary School), *n* (%)	138 (75.8)	61 (76.3)	77 (75.5)	.905
Admissions in the year before index hospitalization, (sí), *n* (%)	.53 ± .9	29 (38.7)	29 (27.4)	.10
Etiology of liver disease, *n* (%)				
- Alcohol	78 (40.6)	35 (43,8)	43 (38.4)	.293
- HVC	77 (40.1)	33 (41.3)	44 (39.3)	
- HVB	6 (3.1)	0 (0)	6 (5.4)	
- NASH	9 (4.7)	4 (5)	5 (4.5)	
- Others	22 (11.5)	8 (10)	14 (12.5)	
MELD-Na score, *mean* ± *SD*	15.0 ± 5.0	15.5 ± 5.0	14.7 ± 4.9	.302
BMI (kg/m^2), *n* (%)				
- <18.5	10 (5.2)	1 (1.3)	9 (8)	.086
- 18.5–24.9	75 (39.1)	35 (43.8)	40 (35.7)	
- >25	107 (55.7)	44 (55)	63 (56.3)	
Hepatocellular carcinoma, *n* (%)	57 (29.7)	24 (30)	33 (29.5)	.936
Charlson Index, *mean* ± *SD*	7.13 ± 2.82	7.7 ± 2.7	6.68 ± 2.8	.008
Cause of index admission, *n* (%)				
- Ascites	116 (60.4)	54 (67.5)	62 (55.4)	.252
- Portal hypertensive bleed	30 (15.6)	8 (10)	22 (19.6)	
- HE	24 (12.5)	9 (11.3)	15 (13.4)	
- SBP	22 (11.5)	9 (11.3)	13 (11.6)	
AKI during the index hospitalization, *n* (%)	90 (46.9)	37 (46.3)	53 (47.3)	.883
Infection during the index hospitalization, *n* (%)	79 (41.1)	26 (32.5)	53 (47.3)	.040
Serum sodium (mmol/L), *mean* ± *SD*	136.0 ± 4	135.7 ± 3.9	136.3 ± 4	.318
Serum bilirrubin (mg/dL), *mean* ± *SD*	2.3 ± 2.6	2.2 ± 2.2	2.4 ± 2.9	.568
Prothrombin time (%), *mean* ± *SD*	66.4 ± 17.5	62.9 ± 19	68.8 ± 16.1	.022
Serum albumin (g/L), *mean* ± *SD*	29.3 ± 5.1	30.1 ± 5.4	28.7 ± 4.8	.057
Platelet count (x10^9/L), *mean* ± *SD*	107.1 ± 66.5	109.8 ± 63.7	105.2 ± 68.7	.635
Serum creatinine (mg/dL), *mean* ± *SD*	1 ± .79	.9 ± .7	1 ± .8	.625
Lenght of stay (days), *mean* ± *SD*	19.2 ± 14.3	16.8 ± 13.0	21.0 ± 15.0	.046
Number of medications on discharge, *mean* ± *SD*	7.5 ± 3.2	7.6 ± 3.1	7.5 ± 3.3	.750
Readmissions, n (%)				
- Readmissions ≤30 days	42 (21.9)	9 (11.3)	33 (29.5)	.003
- Readmissions >30 days	59 (30.7)	28 (35)	31 (27.7)	.278
- No readmissions	91 (47.4)	43 (53.8)	48 (42.9)	.136
Cause of readmission, *n* (%)				
- HE	25 (59.5)	4 (44.4)	21 (63.6)	.202
- Ascites	10 (23.8)	3 (33.3)	7 (21.2)	
- Portal hypertensive bleed	6 (14.3)	1 (11.1)	5 (15.2)	
- SBP	1 (2.4)	1 (11.1)	0 (0)	
Number of emergency department visits post-discharge, *mean* ± *SD*	1.4 ± 2.1	1.1 ± 1.6	1.7 ± 2.3	.035
Mortality, *n* (%)				
- 30 days	7 (3.6)	1 (1.3)	6 (5.4)	.134
- 60 days	19 (9.9)	3 (3.8)	16 (14.3)	.016
- 90 days	34 (17.7)	13 (16.3)	21 (18.8)	.655
- At the end of follow-up	93 (48.4)	41 (51.3)	52 (46.4)	.510

MELD-Na: Model for End-Stage Liver Disease sodium; BMI: body mass index; SBP: spontaneous bacterial peritonitis; HE: hepatic encephalopathy; AKI: Acute Kidney injury. NASH: Nonalcoholic steatohepatitis; HVC: virus hepatitis C; HVB: virus hepatitis B.

Na score ≥15 at discharge, whereas infections and length of stay were not. Therefore, these variables did not influence our results. In fact, the difference in the mean hospital stay at index admission between the two groups was due to the fact that once patients from the prospective cohort were stabilized, they had the possibility of being closely followed and having their treatment adjusted at the Day Hospital (e.g. adjustment of diuretics or beta-blockers). In addition, they could have laboratory tests done or continue the program of evacuating paracentesis without being hospitalized.

The differences between the patients with and without early readmission are shown in Table 2A. The variables that were statistically significant for early readmission in the univariate analysis were the presence of HCC (P = .013), MELD-Na (P = .002), Group 1/2 (with/without HEPACONTROL) (P = .003), Charlson index score (P = .042), serum albumin (P = .029), serum sodium (P = .002) and the number of medications at discharge (P = .038). From the multivariate model were excluded the serum sodium, because it is included in the MELD-Na score, and HCC, because it is included in the Charlson index.

Finally, Table 2B shows that the HEPACONTROL program proved to be a protective factor against early readmission in patients with decompensated cirrhosis (OR: .21; 95% CI: .091–.516), adjusted for MELD-Na score (OR: 1.21; 95% CI: 1.040–1.209), Charlson index (OR: 1.15; 95% CI: 1.010–1.328), serum albumin (OR: .95; 95% CI: .882–1.028), and number of medications at discharge (OR: 1.06; 95 CI%: .943–1.206)

Please cite this article in press as: Morales BP, et al. HEPACONTROL. A program that reduces early readmissions, mortality at 60 days, and healthcare costs in decompensated cirrhosis. Dig Liver Dis (2017), http://dx.doi.org/10.1016/j.dld.2017.08.024

G Model
YDLD-3515; No. of Pages 8
ARTICLE IN PRESS
B.P. Morales et al. / Digestive and Liver Disease xxx (2017) xxx–xxx 5

Table 2A
Comparison between patients with or without early hospital readmission. Bold values represent statistically significant outcomes.

Variables	Overall (n = 192)	≤30-day readmission (n = 42)	No 30-day readmission (n = 150)	P value
Group (1/2) (with/without HEPACONTROL)	**80/112**	**9/33**	**71/79**	**.003**
Male sex, *n* (%)	120 (62.5)	31 (73.8)	89 (59.3)	.087
Age, *mean ± SD* (yr)	653 ± 11.8	68.1 ± 10.3	64.6 ± 12.1	.065
Lives alone, *n* (%)	29 (15.1)	5 (11.9)	24 (16)	.512
dependence in activities of daily living, n (%)	35 (18.2)	8 (19)	27 (18)	.876
Educational status (Elementary School), *n* (%)	138 (75.8)	32 (82.1)	106 (74.1)	.306
Admissions in the year before index hospitalization, (sí), *n* (%)	.53 ± .9	.79 ± 1.2	.4 ± .8	.105
Etiology of liver disease, *n* (%)				
- Alcohol	78 (40.6)	18 (42.9)	60 (40)	.554
- HVC	77 (40.1)	14 (33.3)	63 (42)	
- HVB	6 (3.1)	2 (4.8)	4 (2.7)	
- NASH	9 (4.7)	1 (2.4)	8 (5.3)	
- Others	22 (11.5)	7 (16.7)	15 (10)	
MELD-Na score, *mean ± SD*	**15.0 ± 5.0**	**17.2 ± 4.8**	**14.4 ± 4.8**	**.001**
Hepatocellular carcinoma, *n* (%)	**57 (29.7)**	**19 (45.2)**	**38 (25.3)**	**.013**
Charlson Index, *mean ± SD*	**60 (53.6)**	**7.9 ± 2.4**	**6.9 ± 2.8**	**.042**
Esophageal varices, *n* (%)	152 (79.2)	33 (78.6)	119 (79.3)	.914
BMI (kg/m^2), *n* (%)				
- <18.5	10 (5.2)	3 (7.1)	7 (4.7)	.272
- 18.5–24.9	75 (39.1)	12 (28.6)	63 (42)	
- >25	107 (55.7)	27 (64.3)	80 (53.3)	
Cause of index admission, *n* (%)				
- Ascites	116 (60.4)	23 (54.8)	93 (62)	.267
- Portal hypertensive bleed	30 (15.6)	6 (14.3)	24 (16)	
- HE	24 (12.5)	9 (21.4)	15 (10)	
- SBP	22 (11.5)	4 (9.5)	18 (12)	
AKI during the index hospitalization, *n* (%)	90 (46.9)	23 (54.8)	67 (44.7)	.247
Infection during the index hospitalization, *n* (%)	79 (41.1)	22 (52.4)	57 (38)	.094
Serum sodium (mmol/L), *mean ± SD*	**136 ± 4**	**134.3 ± 4.1**	**136.5 ± 3.8**	**.002**
Serum bilirrubin (mg/dL), *mean ± SD*	2.3 ± 2.6	3.3 ± 4	2 ± 2	.066
Prothrombin time (%), *mean ± SD*	66.42 ± 17.5	64.5 ± 17.5	66.9 ± 17.6	.437
Serum albumin (g/L), *mean ± SD*	**29.3 ± 5.1**	**27.8 ± 5.1**	**29.7 ± 5**	**.029**
Platelet count (x10^9/L), *mean ± SD*	107.1 ± 66.5	101.9 ± 79	108.6 ± 62.8	.564
Serum creatinine (mg/dL), *mean ± SD*	1 ± .79	1 ± .3	1 ± .8	.515
Lenght of stay (days), *mean ± SD*	19.2 ± 14.3	20.1 ± 10.1	19 ± 15.3	.644
Number of medications on discharge, *mean ± SD*	**7.5 ± 3.2**	**8.5 ± 3.2**	**7.3 ± 3.2**	**.038**

MELD-Na: Model for End-Stage Liver Disease sodium; BMI: body mass index; SBP: spontaneous bacterial peritonitis; HE: hepatic encephalopathy; AKI: Acute Kidney injury. NASH: Nonalcoholic steatohepatitis; HVC: virus hepatitis C; HVB: virus hepatitis B.

Table 2B
Impact of HEPACONTROL on the early readmission rate.

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
Group (1/2) (with/without HEPACONTROL)	.30	(.13–.66)	.003	.21	(.08–.53)	.001
Meld-Na score	1.11	(1.04– 1.19)	.001	1.21	(1.04–1.20)	.003
Charlson index	1.13	(1.00– 1.28)	.042	1.15	(1.01–1.32)	.036
Number of medications on discharge	1.11	(1.00–1.23)	.038	1.06	(.94–1.20)	.308
Serum albumin	.92	(.85–.99)	.029	.95	(.88–1.02)	.211
Hepatocellular carcinoma[a]	2.42	(1.18–4.96)	.013	–	–	–
Serum sodium[a]	.87	(.80–.95)	.002	–	–	–

– HEPACONTROL program is shown to be a protective factor against early re-admission in patients with decompensated cirrhosis.
[a] Serum sodium was excluded from the multivariate model because it is included in the MELD-Na score and HCC because it is included in the Charlson index.

3.3. Emergency department visits after discharge

The mean number of emergency department visits due to cirrhosis-related complications after discharge was lower in patients in Group 1 than in Group 2 (1.10 ± 1.64 *vs* 1.71 ± 2.36; *P* = .035). In the study population (n = 192), patients who had been readmitted early made more emergency department visits compared to those who were readmitted after 30 days (mean 2.36 ± 2.02 *vs* 1.21 ± 2.07, respectively; *P* = .002).

3.4. Mortality at 30, 60, 90 days and at the end of follow-up (Fig. 2)

Mortality at 60 days of follow-up was significantly lower in patients in Group 1 than those in Group 2 (3.8% *vs* 14.3%; *P* = .016. RR: .26; 95% CI: .07–.87). However, there were no differences in mortality at 30 days (1.3% in Group 1 *vs* 5.4% in Group 2; *P* = .134), at 90 days (16.3% *vs* 18.8%; *P* = .655), or at the end of the follow-up period (51.3% *vs* 46.4%; *P* = .510).

Please cite this article in press as: Morales BP, et al. HEPACONTROL. A program that reduces early readmissions, mortality at 60 days, and healthcare costs in decompensated cirrhosis. Dig Liver Dis (2017), http://dx.doi.org/10.1016/j.dld.2017.08.024

G Model
YDLD-3515; No. of Pages 8
ARTICLE IN PRESS

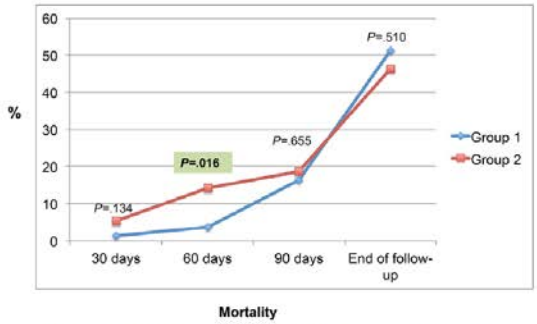


Fig. 2. Mortality at 30, 60, 90 days and at the end of follow-up between both groups.

The most frequent causes of death were advanced HCC (31.7% in Group 1 and 34.6% in Group 2; $P = .768$), bacterial infections other than SBP (22% *vs* 25%; $P = .731$) and UGIB (7.3% *vs* 9.6%; $P = .695$).

3.5. Costs (Table 3)

Overall and specific costs of the program during the period of the study are detailed in Table 3.

Patients included in the HEPACONTROL program (n = 80) had a mean of 2.2 ± 1.08 consultations at the Hepatology Unit Day Hospital after discharge, and a mean of 4.3 ± 2.65 consultations during the whole period of the study. The mean cost of monitoring patients after discharge in the HEPACONTROL program was €517.70 ± 304 per patient, which included a specialized consultation and diagnostic procedures and/or therapies. The cost of early readmission (<30 days) was lower in Group 1 (mean €6.809 ± 2.441 *vs* €11.380 ± 9.318; $P = .016$), which includes the cost of all activities performed at the Day Hospital (mean €7.277 ± 2.408 *vs* €11.380 ± 9.318.20; $P = .029$). The overall cost of emergency department visits after discharge between groups was also lower for Group 1 (mean €210.10 ± 313.70 *vs* €327.40 ± 451.70; $P = .035$).

4. Discussion

Our study demonstrates that the application of the HEPACONTROL program for improving outpatient care for decompensated cirrhosis patients has advantages over standard outpatient care, because it achieved a reduction in early readmission, mortality at 60 days, the rate of emergency department visits post-discharge and economic costs.

The model implemented in our study is based on new strategies of transitional care, where the ability to implement an early follow-up by a specialized team in hepatology and the possibility of performing diagnostic procedures or therapy in real time can allow medical services to reduce the risk of readmission in the short term. Our results confirm the positive effects of such a transitional strategy.

Several previous studies have demonstrated the protective effect on early readmission rates of a follow-up program for decompensated patients. However, the present study differed from these earlier ones in several important ways. First of all, unlike Morando et al. [12], which only included decompensated cirrhosis patients suffering from ascites, or Johnson et al. [28], which only included patients with gastrointestinal bleeding, our work included other complications such as SBP and HE. We were thus able offer the follow-up strategy described here to a greater cirrhotic population susceptible of readmission and evaluate its impact. Moreover, in Morando et al. the date of the subsequent check-up in the intervention group was set from one week to three months after discharge, depending on the degree of severity and/or grade of instability of the liver disease, while in the HEPACONTROL program evaluated here all patients were visited within seven days after discharge regardless of the severity of the cirrhosis. We felt this was essential since it has been shown that there is approximately a 20% rate of early readmission even in low-risk patients [7,9], and there are preventable readmissions not associated with disease severity that can be detected early if warning signs are recognized and treatment dosage adjusted appropriately.

The standard follow-up offered the control group also differed in our study relative to previous work. The novel program described in Morando et al. was compared to a standard model of outpatient care performed principally by a primary care physician, while in our study the standard follow-up offered to the control group was performed by a specialist physician. We were thus able to demonstrate that the reduction of early readmission rates depends not only on whether the follow-up physician is a specialist or not but also on other factors such as the resources available (radiological studies, procedures, or laboratory data in real-time) and the immediacy of patient access to them.

In another study published recently [26], which also evaluated the impact of implementing early clinical monitoring after discharge (i.e. transitional intervention), a reduction in early readmission was not substantiated. However, this last work was of a retrospective nature, and regarded any contact with the healthcare system during the first week after discharge as outpatient monitoring, without taking into account the reason for the consultation or the medical specialist who executed the follow-up (primary care physician, emergency department physician, hepatology specialist, internal medicine physician, other specialists, etc.), which could lead to possible complications of cirrhosis going unnoticed, and without taking the adequate preventative measures in time to prevent early readmission.

With regard to the benefits shown by the HEPACONTROL program, in patients who underwent it a reduction in the percentage of early readmission due to HE was detected, although this was not significantly different from the readmission rate in our control group. In attempting to explain this lack of a significant difference, it should be taken into account that a variety of factors can increase the risk of decompensation and readmission in these patients, whether related to their hepatic disease or level of liver failure, the

Please cite this article in press as: Morales BP, et al. HEPACONTROL. A program that reduces early readmissions, mortality at 60 days, and healthcare costs in decompensated cirrhosis. Dig Liver Dis (2017), http://dx.doi.org/10.1016/j.dld.2017.08.024

Table 3
Costs (€) per patient of early readmission (A) and of emergency department visits (B) after discharge between both groups during the period of the study.

A

Costs (€), *mean* ± *SD*	Group 1 (With HEPACONTROL) (n = 9/80)	Group 2 (Without HEPACONTROL) (n = 33/112)	P value
Costs of Day Hospital	517.7 ± 304	–	–
Costs of early readmission without Day Hospital	6809.7 ± 2441.9	11,380.3 ± 9318.2	.016
Global costs of early readmission	7277.7 ± 2408.9	11,380.3 ± 9318.2	.029

B

Costs (€), *mean* ± *SD*	Group 1 (With HEPACONTROL) (n = 80)	Group 2 (Without HEPACONTROL) (n = 112)	P value
Cost of an emergency department visit	191	191	–
Mean of emergency department visit after discharge	1.10 ± 1.64	1.71 ± 2.36	.035
Global cost of emergency department visits	210.1 ± 313.7	327.4 ± 451.7	.035

presence of comorbidities, lack of family support or poor adherence to treatment, so that, despite being submitted to a strict and early follow-up program, in some cases readmission is inevitable. However, we believe that it is very important to establish strategic plans directed at improving the management of this group of patients that minimize to the extent possible the risk of complications and, consequently, readmission.

With regard to mortality rates, the application of the HEPACONTROL program achieved a reduction in mortality at 60 days after discharge and a marked trend to less mortality at 30 days (probably related to the limited number of patients). Mortality at 90 days was not reduced, though we believe that this can be explained by the fact that patients with advanced cirrhosis have a high risk of presenting major complications and a worse prognosis, so it is more difficult to reduce the risk of death either in the short or long term. In our study, 29.7% of patients had HCC, moderate hepatocellular failure, and a mean age of 65 years, which could explain why there was no improvement in long-term survival despite the implementation of the HEPACONTROL program, and the impact of the program on the short-term mortality rates of those patients whose health was seriously compromised at the time of initial hospitalization was likewise limited.

Another finding of the HEPACONTROL program was the reduction in the number of post-discharge emergency department visits. This was due to the fact that the intervention model provided the possibility of visiting the Day Hospital or contacting the specialized care team in the presence of a symptom of decompensation of liver disease, thus obtaining direct and immediate attention and avoiding visits to the emergency department. Last, but not least, the HEPACONTROL program reduced the cost of care for patients with decompensated cirrhosis as a consequence of the reduction in both early readmission and emergency department visits.

The limitations of our study are the limited number of patients and the retrospective nature of the control group.

In conclusion, the HEPACONTROL transitional intervention program reduces early readmission, mortality at 60 days, post-discharge emergency department visits and the economic costs of decompensated cirrhosis patients. These results encourage the continuation of the search for and implementation of standardized transitional follow-up strategies for patients with decompensated cirrhosis, a population affected by a chronic disease for whom there are few studies regarding the management and reduction of early readmission.

Conflict of interest
None declared.

Financial support

Betty P. Morales receives a grant of "Germans Trias i Pujol" Health Sciences Research Institute (IGTP).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.dld.2017.08.024.

References

[1] D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol 2006;44(1):217–31.
[2] Zipprich A, Garcia-Tsao G, Rogowski S, Fleig WE, Seufferlein T, Dollinger MM. Prognostic indicators of survival in patients with compensated and decompensated cirrosis. Liver Int 2012;32(October (9)):1407–14.
[3] Colleen K, McIlvennan Zubin J, Eapen Larry A Allen. Hospital readmissions reduction program. Circulation 2015;131(20):1796–803.
[4] Planas R, Ballesté B, Alvarez MA, Rivera M, Montoliu S, Galeras JA, et al. Natural history of decompensated hepatitis C virus-related cirrhosis. A study of 200 patients. J Hepatol 2004;40:823–30.
[5] Bajaj J, Rajender K, Tandon P, Wong F, Kamath P, Garcia-Tsao G, et al. The 3-month readmission rate remains unacceptably high in a large North American cohort of patients with cirrhosis. Hepatology 2016;64(1):200–8.
[6] Volk M. Hospital readmissions for decompensated cirrhosis. Clin Liver Dis 2014;4(6).
[7] Volk ML, Tocco RS, Bazick J, Rakoski M, Lok A. Hospital readmissions among patients with decompensated cirrhosis. Am J Gastroenterol 2012;107:247–52.
[8] Berman K, Tandra S, Forssell K, Vuppalanchi R, Burton Jr JR, Nguyen J, et al. Incidence and predictors of 30-day readmission among patients hospitalized for advanced liver disease. Clin Gastroenterol Hepatol 2011;9:254–9.
[9] Singal A, Rahimi R, Clark C, Ma Y, Cuthbert J, Rockey D, et al. An automated model using electronic medical record data identifies patients with cirrhosis at high risk for readmission. Clin Gastroenterol Hepatol 2013;11:1335–41.
[10] Tapper E, Halbert B, Mellinger J. Rates of and reason for hospital readmissions in patients with cirrhosis: a multistate population-based cohort study. Clin Gastroenterol Hepatol 2016;14(8 (August)):1181–8.
[11] Morales B, Planas R, Bartoli R, Morillas RM, Sala M, Cabré E, et al. Early hospital readmission in decompensated cirrhosis: incidence, impact on mortality and predictive factors. Dig Liver Dis 2017;49:903–9, http://dx.doi.org/10.1016/j.dld.2017.03.005.
[12] Morando F, Maresio G, Piano S, Fasolato S, Cavallin M, Romano A, et al. How to improve care in outpatients with cirrhosis and ascites: a new model of care coordination by consultant hepatologists. J Hepatol 2013;59:257–64.
[13] Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. N Engl J Med 2009;360(14 (April)):1418–28.
[14] Dharmarajan K, Hsieh AF, Lin Z, Bueno H, Ross JS, Horwitz LI, et al. Diagnoses and timing of 30-day readmissions after hospitalization for heart failure, acute myocardial infarction, or pneumonia. JAMA 2013;309(4 (January)):355–63.
[15] Nolte E, Roland M, Guthrie S, Brereton L. Preventing emergency readmissions to hospital. A scoping review. RAND Corporation; 2012 www.rand.org.
[16] PYALeadership Briefing: Providing and Billing Medicare for Transitional Care Management. http://www.pyapc.com/resources/collateral/white-papers/TCM-whitepaper-PYA.pdf. [1 November 2014].
[17] Centers for Medicare & Medicaid Services. Physician value-based payment modifier under the Medicare physician fee schedule: final rule. https://www.cms.gov/outreach-and-education/outreach/npc/downloads/presentation-qrur-112012.pdf.
[18] Hansen LO, Young RS, Hinami K, Leung A, Williams MV. Interventions to reduce 30-day rehospitalization: a systematic review. Ann Intern Med 2011;155:520–8.
[19] Jack BW, Chetty VK, Anthony D, Greenwald JL, Sanchez GM, Johnson AE, et al. A reengineered hospital discharge program to decrease rehospitalization: a randomized trial. Ann Intern Med 2009;150(3 (February)):178–87.
[20] Feltner C, Jones CD, Cene CW, Zheng ZJ, Sueta CA, Coker-Schwimmer EJ, et al. Transitional care interventions to prevent readmissions for persons with heart

Please cite this article in press as: Morales BP, et al. HEPACONTROL. A program that reduces early readmissions, mortality at 60 days, and healthcare costs in decompensated cirrhosis. Dig Liver Dis (2017), http://dx.doi.org/10.1016/j.dld.2017.08.024

G Model
YDLD-3515; No. of Pages 8
ARTICLE IN PRESS

failure: a systematic review and meta-analysis. Ann Intern Med 2014 Jun 3;160(11):774–84.
[21] Hernandez AF, Greiner MA, Fonarow GC, Hammill BG, Heidenreich PA, Yancy CW, et al. Relationship between early physician follow-up and 30-day readmission among Medicare beneficiaries hospitalized for heart failure. JAMA 2010;303(17 (May)):1716–22.
[22] Hess CN, Shah BR, Peng SA, Thomas L, Roe MT, Peterson ED. Association of early physician follow-up and 30-day readmission after non-ST-segment-elevation myocardial infarction among older patients. Circulation 2013;128(11 (September)):1206–13.
[23] Sharma G, Kuo YF, Freeman JL, Zhang DD, Goodwin JS. Outpatient follow-up visit and 30-day emergency department visit and readmission in patients hospitalized for chronic obstructive pulmonary disease. Arch Intern Med 2010;170(18 (October)):1664–70.
[24] McAlister FA, Youngson E, Bakal JA, Kaul P, Ezekowitz J, Van WC. Impact of physician continuity on death or urgent readmission after discharge among patients with heart failure. CMAJ 2013;185(14 (October)):E681–9.
[25] Wigg AJ, McCormick R, Wundke R, Woodman R. Efficacy of a chronic disease management model for patients with chronic liver failure. Clin Gastroenterol Hepatol 2013;11:850–8.
[26] Kanwal F, Asch SM, Kramer JR, Cao Y, Asrani S, El-Serag HB. Early outpatient follow-up and 30-day outcomes in patients hospitalized with cirrhosis. Hepatology 2016;64(2):569–81.
[27] Tapper EB, Finkelstein D, Mittleman MA, Piatkowski G, Chang M, Lai M. A quality improvement initiative reduces 30-day rate of readmission for patients with cirrhosis. Clin Gastroenterol Hepatol 2016;14:753–9.
[28] Johnson E, Spier B, Leff J, Lucey MR, Said A. Optimising the care of patients with cirrhosis and gastrointestinal haemorrhage: a quality improvement study. Aliment Pharmacol Ther 2011;34:76–82.
[29] Ghaoui R, Friderici J, Desilets D, Lagu T, Visintainer P, Belo A, et al. Outcomes associated with a mandatory gastroenterology consultation to improve the quality of care of patients hospitalized with decompensated cirrhosis. J Hosp Med 2015;10(4):236–41.

DISCUSIÓN GLOBAL

6. DISCUSIÓN GLOBAL

Los estudios que conforman esta tesis doctoral confirman que el reingreso precoz (≤30 días) en los pacientes con cirrosis descompensada es frecuente, con una incidencia del 29%. El grado de insuficiencia hepatocelular avanzada (MELD-Na ≥15), el sexo masculino y el índice de Charlson ≥7 se comportan como factores predictores independientes de reingreso precoz. Además, el reingreso ≤30 días tras el alta hospitalaria, influye negativamente en la supervivencia de estos pacientes y es un factor predictor independiente de mortalidad. Al aplicar el programa transicional de seguimiento post-hospitalario HEPACONTROL se consiguió no sólo reducir el reingreso precoz sino también la mortalidad a los 60 días, la tasa de consultas al servicio de urgencias posterior al alta y el gasto económico.

Consideramos que los resultados obtenidos en esta tesis doctoral son alentadores y suponen una herramienta importante para el conocimiento del estado actual del reingreso precoz en

la población con cirrosis descompensada, dado que es una problemática frecuente y sin embargo, poco estudiada en nuestro medio, con un impacto elevado no sólo en la morbi-mortalidad, sino que también conlleva un aumento muy importante del uso de recursos sanitarios [26, 51, 52, 53].

En el primer estudio, observamos que la incidencia del reingreso precoz en nuestra población de pacientes cirróticos descompensados es similar a la descrita en los pacientes norteamericanos, la cual oscila entre en un 20-37% [24,26, 51, 52,53], lo que confirma que es una problemática global y con una tasa de incidencia considerable. De los factores predictores de reingreso precoz identificados en nuestro estudio, el grado de insuficiencia hepática y la edad, coinciden con los factores predictores de reingreso precoz descritos en el trabajo de Berman y cols. [51] y Singal y cols. [52], lo que reafirma que dichas variables juegan un papel clave y se asocian a una mayor susceptibilidad de los pacientes a desarrollar complicaciones y consecuentemente, a la mayor demanda de

recursos sanitarios. Sin embargo, a diferencia de los otros autores, en nuestro estudio el índice de Charlson también se comportó como un factor independiente del reingreso precoz en los pacientes con cirrosis descompensada. Parece razonable pensar que el hecho de presentar una mayor edad y el número de comorbilidades se asocie a un aumento en la susceptibilidad de desarrollar efectos adversos a los medicamentos, mal cumplimiento de las indicaciones al momento del alta, mayor polimedicación y demanda de los recursos sanitarios, lo que explicaría su elevada tasa de reingreso precoz. Este índice también fue evaluado en el estudio de Volk et al.[26] sin llegar a ser un factor predictor independiente del reingreso precoz, posiblemente porque la mediana de edad de sus pacientes era inferior al nuestro (54 frente a 66 años), lo que podría conllevar a presentar menos comorbilidades.

Los factores predictores de reingreso precoz identificados, nos permitió crear grupos de riesgo y clasificar a los pacientes como de alto y bajo riesgo de reingreso. El 52,2% de pacientes del

grupo de alto riesgo, reingresaron de forma precoz, comparado con el 13.6% de los pacientes del grupo de bajo riesgo. Teniendo en cuenta estos resultados, junto con el impacto clínico y económico del reingreso precoz, consideramos importante establecer una estrategia transicional de seguimiento post-hospitalaria precoz a todos los pacientes cirróticos dados de alta tras presentar una complicación, con especial énfasis en los pacientes con alto riesgo de reingreso.

Al implementar el programa HEPACONTROL conseguimos disminuir a menos de la mitad el porcentaje del reingreso precoz con respecto a los pacientes que hicieron un seguimiento estándar (113 frente al 29,5%), siendo HEPACONTROL un factor protector del reingreso ≤30 días. Estos resultados son consecuencia de la suma de tres intervenciones claves: realizar un control precoz tras el alta hospitalaria, que éste sea realizado por un equipo especializado en Hepatología y, por último, contar con la posibilidad de realizar procedimientos diagnósticos o terapéuticos en tiempo real si fuera necesario. Consideramos que para poder conseguir

un resultado óptimo no debe faltar ninguna de estas intervenciones. Así, por ejemplo, en el estudio de Kanwal y cols. [77] en el que también se evaluó una estrategia transicional basada en el control clínico precoz a los siete días después del alta hospitalaria no se consiguió una reducción del reingreso precoz. A diferencia de nuestro trabajo, los autores consideraron como control clínico cualquier contacto con el sistema sanitario sin tener en cuenta el motivo de la consulta ni el médico especialista que hizo el seguimiento (médico de urgencias, especialista en hepatología, médico de medicina interna, otros especialistas, etc). En este sentido, creemos importante el hecho que el clínico que realiza el control post-hospitalario sea un profesional habituado y entrenado en el manejo de los pacientes con cirrosis. Por otra parte, en el estudio de Morando y cols. [53] se realizó un seguimiento posterior al alta (entre los 7 días y los 3 meses, dependiendo de la gravedad de enfermedad hepática) por un equipo especializado y con la posibilidad de realizar procedimientos diagnósticos o terapéuticos en tiempo real en Hospital de Día. Sin embargo, en este trabajo el programa sólo se implementó

en los pacientes que habían ingresado por descompensación ascítica. A pesar de conseguir una reducción del reingreso precoz, consideramos que el hecho de ampliar la estrategia de seguimiento a todos los paciente cirróticos ingresados sin tener en cuenta el tipo de descompensación, permite actuar sobre la población de más riesgo de reingreso precoz ya que la ascitis, por sí sola, no representa un factor independiente de reingreso ≤ 30 días.

En nuestro primer estudio, también identificamos el reingreso precoz como un factor de riesgo independiente de mortalidad. Al aplicar el programa HEPACONTROL, conseguimos una reducción de la mortalidad a los 60 días tras el alta hospitalaria, posiblemente asociado al hecho de disminuir el reingreso precoz. Sin embargo, no hubo diferencias en la mortalidad a los 30 días, 90 días ni al final del seguimiento. Esto podría explicarse porque a pesar de hacerse un seguimiento estrecho que nos permite tomar decisiones oportunas y precisas en cuanto a diagnóstico, prevención y tratamiento de posibles descompensaciones de forma rápida, existen pacientes con

cirrosis avanzada que presentan un alto riesgo de presentar complicaciones mayores y con peor pronóstico, en los que será más difícil disminuir el riesgo de muerte, ya sea a corto o a largo plazo. Además, a pesar que el reingreso precoz es un factor de riesgo de mortalidad, son varios los factores clínicos que también influyen en la supervivencia de los pacientes cirróticos descompensados, por lo que no es suficiente el control de sólo uno de ellos.

Otra de las ventajas del programa HEPACONTROL es la atención más personalizada y continuada al paciente, así como a la familia y al entorno (cuidador, médico de familia, etc.). Se definen unas pautas de actuación ante signos de alarma de descompensación y en caso de aparición existe un contacto más cercano y directo con su equipo de atención especializada. Como consecuencia de esto y no menos importante, HEPACONTROL consiguió una reducción del número de consultas al servicio de urgencias por complicaciones asociadas a la cirrosis, lo que a su vez permitió un ahorro en el gasto sanitario, sumado también al ahorro por la reducción del

reingreso precoz. Teniendo en cuenta el contexto económico actual, así como el alto gasto sanitario que generan las enfermedades crónicas, estos resultados abren la puerta a evaluar nuevas estrategias de seguimiento post-hospitalaria que favorezcan el ahorro económico y una mayor optimización de los recursos disponibles. Por tanto concluimos que HEPACONTROL tiene un impacto clínico y económico, que se ve reflejado no sólo en el paciente, sino también en su familia, en su entorno y en el sistema sanitario.

Las limitaciones de nuestros estudios se han descrito en cada uno de los artículos.

CONCLUSIONES

7. CONCLUSIONES

1. El reingreso precoz (≤ 30 días) en la cirrosis descompensada es frecuente, con una incidencia de un 29,5%.
2. Los factores de riesgo de reingreso precoz en los pacientes cirróticos descompensados son el sexo masculino, la insuficiencia hepática avanzada (MELD-Na ≥15) y el índice de Charlson ≥7 puntos.
3. El reingreso precoz es un factor de riesgo independiente de mortalidad en los pacientes con cirrosis descompensada, a pesar de ajustarse a otras variables tales como el grado de insuficiencia hepática
4. El modelo predictivo de reingreso precoz obtenido en nuestro estudio, permite estratificar a los pacientes en grupo de bajo o alto riesgo, con una capacidad de predicción moderada.
5. El programa de intervención transicional HEPACONTROL es una estrategia de seguimiento que

disminuye significativamente la incidencia del reingreso precoz de los pacientes con cirrosis descompensada.

6. HEPACONTROL consigue reducir la tasa de consultas al servicio de urgencias tras el alta hospitalaria, lo que comporta una mejoría de la calidad de vida de estos pacientes y una reducción de la sobrecarga asistencial en el área de urgencias.
7. La implementación de HEPACONTROL disminuye la mortalidad a los 60 días tras el alta hospitalaria, en comparación con los pacientes a los que se les hace un seguimiento estándar.
8. HEPACONTROL reduce el gasto económico del reingreso precoz y el coste global de la atención en urgencias posterior al alta, permitiendo una mejor optimización de los recursos sanitarios.

BIBLIOGRAFÍA

8. BIBLIOGRAFIA

[1] Schuppan D, Afdhal NH. Liver cirrhosis. Lancet. 2008; 371:838-851.

[2] Bernal V, Bosch J (2012). Cirrosis hepática. Montori M, García Pagan J., editores. Gastroenterología y Hepatología; Problemas comunes en la práctica clínica 2º edición. Pag: 867-892. Madrid, Jarpyo Editores, S.A.

[3] Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380: 2095–2128

[4] Blachier M, Leleu H, Peck-Radosavljevic M, Valla D, Roudot-Thoraval F. The burden of liver disease in Europe:

A review of available epidemiological data. J Hepatol 2013; 58:593-608

[5] Zatonski WA, Sulkowska U, Manczuk M, Rehm J, Boffetta P, Lowenfels AB,et al. Liver cirrhosis mortality in Europe, with special attention to Central and Eastern Europe. Eur Addict Res 2010;16:193–201.

[6] Wong RJ, Aguilar M, Cheung R, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. Gastroenterology 2015;148:547.

[7] Wen-Ce Zhou, Quan-Bao Zhang, Liang Qiao. Pathogenesis of liver cirrosis. World J Gastroenterol 2014 June 21; 20(23): 7312-7324

[8] Muir A.J. Understanding the Complexities of Cirrhosis. Clin Ther. 2015;37(8):1822-36

[9] Bataller R, Brenner DA. Liver fibrosis. J Clin Invest. 2005; 115:209–218

[10] Garcia-Tsao G,Friedman S, Iredale J, Pinzani M. Now There Are Many (Stages) Where Before There Was One: In Search of a Pathophysiological Classification of Cirrhosis. Hepatology. 2010 Apr;51(4):1445-1449

[11] D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol. 2006;44: 217–231

[12] Gomez EV, Rodriguez YS, Bertot LC, Gonzalez AT, Perez YM, et al. The natural history of compensated HCV-related cirrhosis: a prospective long-term study. J Hepatol. 2013 Mar; 58(3): 434-44

[13] D'Amico G, Pasta L, Morabito A, et al. Competing risks and prognostic stages of cirrhosis: a 25-year inception cohort study of 494 patients. Aliment Pharmacol Ther. 2014; 39:1180–1193

[14] Zipprich A, Garcia-Tsao G, Rogowsky S, et al. Prognostic indicators of survival in patients with compensated and decompensated cirrhosis. Liv Int 2012; 32: 1407–14

[15] De Franchis R, Baveno VI Faculty. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. J Hepatol. 2015;63:743-52.

[16] Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. Hepatology. 2017 Jan;65(1):310-335.

[17] Bruno S, Zuin M, Crosignani A, Rossi S, Zadra F, et al. Predicting mortality risk in patients with compensated HCV-induced cirrhosis: a long term prospective study. Am J Gastroenterol. 2009; 104:1147–58

[18] 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

[19] D'Amico G, Villanueva C, Burroughs AK, Dollinger M, Planas R, et al. Clinical stages of cirrhosis a multicenter study of 1858 patients. Hepatology. 2010;52(S1):329

[20] Planas R, Ballesté B, Alvarez MA, Rivera M, Montoliu S, Galeras JA, et al. Natural history of decompensated hepatitis C virus-related cirrhosis. A study of 200 patients. J Hepatol 2004;40:823-30

[21] Gines P, Quintero E, Arroyo V. Compensated cirrhosis: natural history and prognosis. Hepatology. 1987;7:122–8

[22] D'Amico G, Morabito A, Pagliaro L, Marubini E. Survival and prognostic indicators in compensated and decompensated cirrhosis. Dig Dis Sci. 1986;31:468–75

[23] Sammy Saab. Evaluation of the impact of rehospitalization in the management of hepatic encephalopathy. Int J Gen Med. 2015; 8: 165–173

[24] Tapper E, Halbert B, Mellinger J. Rates of and Reason for Hospital Readmissions in Patients With Cirrhosis: A Multistate Population-based Cohort Study. Clin Gastroenterol Hepatol. 2016 Aug;14(8):1181-1188

[25] Bajaj J, Rajender K, Tandon P, Wong F, Kamath P, Garcia-Tsao G, et al. The 3-Month Readmission Rate Remains Unacceptably High in a Large North American

Cohort of Patients With Cirrhosis. Hepatology 2016; Vol. 64, No. 1;200-208

[26] Volk ML, Tocco RS, Bazick J, Rakoski MO, Lok AS. Hospital readmissions among patients with decompensated cirrhosis. Am J Gastroenterol. 2012;107(2):247–252

[27] Rakoski MO, McCammon RJ, Piette JD, et al. Burden of cirrhosison older Americans and their families: analysis of the health and retirement study. Hepatology 2012; 55:184–191

[28] Kanwal F, Volk ML, Singal AG, Angeli P, Talwalkar JA. Improving quality of health care for patients with cirrosis. Gastroenterology 2014;147:1204–1207

[29] Agency for Healthcare Research and Quality. Healthcare cost and utilization project HCUPnet. Available at:

Healthcare Cost and Utilization Project http://hcupnet.ahrq. gov/. Accessed September 2014.

[30] Guy W Neff, Nyingi Kemmer, Christopher Duncan and Angel Alsina. Update on the management of cirrhosis – focus on cost-effective preventative strategies. Clinicoecon Outcomes Res. 2013; 5: 143–152

[31] Marchesini G, Bianchi G, Amodio P, et al. Factors associated with por health-related quality of life of patients with cirrhosis. Gastroenterology 2001;120:170–178

[32] Bhanji RA, Carey EJ, Watt KD. Review article: maximising quality of life while aspiring for quantity of life in end-stage liver disease. Aliment Pharmacol Ther. 2017;46:16–25.

[33] Pellicoro A, Ramachandran P, Iredale J, Fallowfield J. Liver fibrosis and repair: immune regulation of wound healing in a solid organ. Nat Rev Immunol. 2014;14(3):181-194.

[34] Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. N Engl J Med 2009 Apr 2;360(14):1418-1428.

[35] Dharmarajan K, Hsieh AF, Lin Z, Bueno H, Ross JS, Horwitz LI, et al. Diagnoses and timing of 30-day readmissions after hospitalization for heart failure, acute myocardial infarction, or pneumonia. JAMA 2013 Jan 23;309(4):355-363

[36] Ashton C, Kuykendall D, Johnson M, et al. The association between the quality of inpatient care and early readmission. Ann Intern Med. 1995; 122:415–421.

[37] Balla U, Malnick S, Schattner A. Early readmissions to the department of medicine as a screening tool for monitoring quality of care problems. Medicine. 2008;87:294–300.

[38] Benbassat J, Taragin M. Hospital readmissions as a measure of quality of health care: advantages and limitations. Arch Intern Med. 2000; 160:1074–1081.

[39] Nolte E, Roland M, Guthrie S, Brereton L. Preventing emergency readmissions to hospital. A scoping review. RAND Corporation 2012. www.rand.org

[40] Medicare Payment Advisory Commission. Report to the Congress: promoting greater efficiency in Medicare. http://www.medpac.gov/documents/jun07_entirereport.pdf

[41] Colleen K. McIlvennan, Zubin J. Eapen, Larry A. Allen. Hospital readmissions reduction program. Circulation. 2015 May 19;131(20):1796-803.

[42] Ross JS, Mulvey GK, Stauffer B, et al. Statistical models and patient predictors of readmission for heart failure: a systematic review. Arch Intern Med 2008;168:1371-1386

[43] Jasti H, Mortensen E, Obrosky D, et al. Causes and risk factors for rehospitalization of patients hospitalized with community-acquired pneumonia. Clin Infect Dis. 2008; 46:550–556

[44] Gudmundsson G, Gislason T, Janson C, et al. Risk factors for rehospitalisation in COPD: role of health status, anxiety and depression. Eur Respir J. 2005; 26:414.

[45] Roberts C, Lowe D, Bucknall C, et al. Clinical audit indicators of outcome following admission to hospital with acute exacerbation of chronic obstructive pulmonary disease. BMJ. 2002; 57:137

[46] Rubin DJ, Golden SH, McDonnell ME, Zhao H. Predicting readmission risk of patients with diabetes hospitalized for cardiovascular disease: a retrospective cohort study. J Diabetes Complications. 2017 Aug;31(8):1332-1339

[47] Amarasingham R, Moore BJ, Tabak YP, et al. An automated model to identify heart failure patients at risk for 30-day readmission or death using electronic medical record data. Med Care 2010;48:981–988

[48] Chin MH, Goldman L. Correlates of early hospital readmission or death in patients with congestive heart failure. Am J Cardiol 1997;79:1640–1644.

[49] Krumholz HM, Parent EM, Tu N, et al. Readmission after hospitalization for congestive heart failure among Medicare beneficiaries. Arch Intern Med 1997;157:99–104

[50] Krumholz H, Chen Y, Wang Y, et al. Predictors of readmission among elderly survivors of admission with heart failure. Am Heart J. 2000; 139:72–77.

[51] Berman K, Tandra S, Forssell K, et al. Incidence and predictors of 30-day readmission among patients

hospitalized for advanced liver disease. Clin Gastroenterol Hepatol 2011; 9:254-259.

[52] Singal A, Rahimi R, Clark C, et al. An automated Model Using Electronic Medical Record Data Identifies Patients with Cirrhosis at High Risk for Readmission. Clin Gastroenterol Hepatol 2013; 11: 1335-41

[53] Morando F, Maresio G, Piano S, et al. How to improve care in outpatients with cirrhosis and ascites: a new model of care coordination by consultant hepatologists. J Hepatol 2013;59:257–264

[54] Riegel B, Naylor M, Stewart S, et al. Interventions to prevent readmission for congestive heart failure. JAMA 2004;291:2816.

[55] Hernandez AF, Greiner MA, Fonarow GC, et al. Relationship between early physician follow-up and 30-

day readmission among Medicare beneficiaries hospitalized for heart failure. JAMA. 2010;303:1716–1722

[56] Rich MW , Beckham V , Wittenberg C et al. A multidisciplinary intervention to prevent the readmission of elderly patients with congestive heart failure. N Engl J Med 1995 ; 333 : 1190 – 5

[57] Naylor MD, Brooten DA, Campbell RL, Maislin G, McCauley KM, Schwartz JS. Transitional care of older adults hospitalized with heart failure: a randomized, controlled trial. J Am Geriatr Soc 2004;52: 675-684

[58] Gohler A, Januzzi JL, Worrell SS, et al. A systematic meta-analysis of the efficacy and heterogeneity of disease management programs in congestive heart failure. J Card Fail2006;12:554-567

[59] Van Walraven C, Seth R, Austin PC, Laupacis A. Effect of discharge summary availability during post-discharge

visits on hospital readmission. J Gen Intern Med. 2002;17:186–92.

[60] Coleman EA, Parry C, Chalmers S, Min SJ. The care transitions intervention: results of a randomized controlled trial. Arch Intern Med. 2006;166:1822–8.

[61] Naylor MD, Brooten D, Campbell R, Jacobsen BS, Mezey MD, Pauly MV, et al. Comprehensive discharge planning and home follow-up of hospitalized elders: a randomized clinical trial. JAMA. 1999;281:613–20

[62] Anderson C, Deepak BV, Amoateng-Adjepong Y, Zarich S. Benefits of comprehensive inpatient education and discharge planning combined with outpatient support in elderly patients with congestive heart failure. Congest Heart Fail. 2005;11:315–21

[63] Dudas V, Bookwalter T, Kerr KM, Pantilat SZ. The impact of follow-up telephone calls to patients after hospitalization. Am J Med. 2001;111:26S–30S

[64] Andersen HE, Schultz-Larsen K, Kreiner S, Forchhammer BH, Eriksen K, Brown A. Can readmission after stroke be prevented? Results of a randomized clinical study: a postdischarge follow-up service for stroke survivors. Stroke. 2000;31:1038–45

[65] Feltner C, Jones CD, Cene CW, et al. Transitional care interventions to prevent readmissions for persons with heart failure: a systematic review and meta-analysis. Ann Intern Med 2014 Jun 3;160(11):774-784

[66] Hess CN, Shah BR, Peng SA, et al. Association of early physician follow-up and 30-day readmission after non-ST-segment-elevation myocardial infarction among older patients. Circulation 2013 Sep 10;128(11):1206-1213.

[67] Sharma G, Kuo YF, Freeman JL, et al. Outpatient follow-up visit and 30-day emergency department visit and readmission in patients hospitalized for chronic obstructive pulmonary disease. Arch Intern Med 2010 Oct 11;170(18):1664-1670

[68] McAlister FA, Youngson E, Bakal JA, et al. Impact of physician continuity on death or urgent readmission after discharge among patients with heart failure. CMAJ 2013 Oct 1;185(14):E681-E689

[69] Hansen LO, Young RS, Hinami K, Leung A, Williams MV. Interventions to reduce 30-day rehospitalization: a systematic review. Ann Intern Med 2011; 155:520-528

[70] Leppin AL, Gionfriddo MR, Kessler M, et al. Preventing 30-day hospital readmissions: a systematic review and meta-analysis of randomized trials. JAMA Intern Med. 2014;174(7):1095-1107

[71] PYALeadership Briefing: Providing and Billing Medicare for Transitional Care Management. http://www.pyapccom/resources/collateral/white-papers/TCM-whitepaper-PYA pdf. 2014 Nov 1

[72] Centers for Medicare and Medicaid Services. [Accessed May 25, 2014] Community-based care transitions program. http://innovation.cms.gov/initiatives/CCTP

[73] Johnson E, Spier B, Leff J, et al. Optimising the care of patients with cirrhosis and gastrointestinal haemorrhage: a quality improvement study. Aliment Pharmacol Ther 2011;34:76–82

[74] Wigg AJ, McCormick R, Wundke R, et al. Efficacy of a chronic disease management model for patients with chronic liver failure. Clin Gastroenterol Hepatol 2013;11:850–858

[75] Ghaoui R, Friderici J, Desilets D, Lagu T, Visintainer P, Belo A, et al. Outcomes associated with a mandatory gastroenterology consultation to improve the quality of care of patients hospitalized with decompensated cirrhosis J Hosp Med. 2015 April ; 10(4): 236–241

[76] Tapper EB, Finkelstein D, Mittleman MA, et al. A quality improvement initiative reduces 30-day rate of readmission for patients with cirrhosis. Clin Gastroenterol Hepatol 2016; 14:753–759

[77] Kanwal F, Asch SM, Kramer JR, et al. Early Outpatient Follow-up and 30-day Outcomes in Patients Hospitalized with Cirrhosis. Hepatology 2016;64(2):569-81