-Dariana Carla Maggi

IMPACTO PROGNÓSTICO DA AVALIAÇÃO SERIADA DA ENCEFALOPATIA HEPÁTICA EM PACIENTES HOSPITALIZADOS POR DESCOMPENSAÇÃO AGUDA DE CIRROSE

Trabalho apresentado à Universidade Federal de Santa Catarina, como requisito para a obtenção do título de Mestre Profissional em Cuidados Intensivos e Paliativos.

Orientador: Prof. Dr. Leonardo de Lucca Schiavon

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Dariana Carla Maggi

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Esta Dissertação foi julgada adequada para obtenção do Título de "Mestre", e aprovada em sua forma final pelo Programa de Mestrado Profissional em Cuidados Intensivos e Paliativos da Universidade Federal de Santa Catarina

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À Universidade Federal de Santa Catarina, por servir de base e ponte para a realização deste projeto.

Todos grandes avanços da ciência nasceram
de uma nova audácia da imaginação.

(John Dewey)

RESUMO

Introdução: A encefalopatia hepática (EH) é uma das complicações mais comuns da cirrose, porém o significado clínico e prognóstico da progressão do estado mental em cirróticos hospitalizados ainda é desconhecido. **Objetivos:** investigar o significado prognóstico da avaliação seriada da EH em pacientes hospitalizados por descompensação aguda (DA) da cirrose. **Métodos:** Os pacientes (n = 293) foram submetidos a avaliações seriadas da EH durante a internação (primeiro e terceiro dia) e classificados da seguinte forma: 1) evolução favorável: EH ausente na admissão e no terceiro dia ou qualquer melhora da EH; 2) evolução desfavorável: aparecimento da EH no terceiro dia ou EH presente na admissão e estável/pior no terceiro dia. **Resultados**: Evolução desfavorável da EH foi observada em 31% da amostra e foi associada na análise de regressão logística à antecedente de EH (OR 1.919, IC 95% 1,116-3,299, P = 0,018), Child-Pugh C (OR 1.851, IC 95% 1,044 - 3,157, P= 0,035) e insuficiência hepática crônica agudizada (IHCA) (OR 2.982, IC 95% 1,646 - 5,404, P < 0,001). Evolução desfavorável da EH (OR 2.318, IC 95% 1,237 - 4,342, P = 0,009) e MELD (OR 1.203, IC 95% 1,141 - 1,269, P < 0,001) foram associados de forma independente à mortalidade em 90 dias. A probabilidade de sobrevida de Kaplan-Meier em 90 dias foi de 91% nos pacientes com MELD < 18 e progressão favorável da EH contra apenas 31% naqueles com MELD ≥ 18 e progressão desfavorável da EH. Progressão desfavorável da EH também foi associada à menor sobrevida entre pacientes com ou sem IHCA. Piora da escala de coma de Glasgow no terceiro dia foi observada em 11% da amostra e também foi associada com elevada mortalidade (69% *vs.* 27%, P < 0,001). **Conclusão:** Em cirróticos hospitalizados por DA, evolução desfavorável da EH durante a internação foi associada à elevada mortalidade no curto prazo e pode auxiliar no avaliação do prognóstico.

Palavras-chave: Cirrose Hepática. Encefalopatia Hepática. Prognóstico.

ABSTRACT

Background & Aims: Hepatic encephalopathy (HE) is a frequent complication of cirrhosis, but the clinical and prognostic significance of the progression of mental status in hospitalized cirrhotics is unknown. We aimed at investigate the prognostic significance of serial evaluation of hepatic encephalopathy in patients hospitalized for acute decompensation (AD) of cirrhosis. **Methods**: Patients (n = 293) were evaluated for HE (West-Haven criteria) at admission and third day and classified in two groups: 1) Favorable progression: HE absent at admission and at third day or any improvement at third day; 2) Unfavorable progression: Development of HE or HE present at admission and stable/worse at third day. **Results:** Unfavorable progression of HE was observed in 31% of patients and was independently associated with previous HE (OR 1.919, 95% CI 1.116-3.299, P = 0,018), Child-Pugh C (OR 1.851, 95% CI 1.044 – 3.157, P= 0,035) and acute-on-chronic liver failure (ACLF) (OR 2.982, 95% CI 1.646 – 5.404, P < 0,001). MELD score (OR 1.203, 95% CI 1.141 – 1.269, P < 0,001) and unfavorable progression of HE (OR 2.318, 95% CI 1.237 – 4.342, P = 0,009) were independently associated with 90-day mortality. The Kaplan-Meier survival probability at 90-day was 91% in patients with MELD < 18 and favorable progression of HE and only 31% in subjects with both MELD ≥ 18 and unfavorable progression of HE. Unfavorable progression of HE was also related to lower survival in patients with or without ACLF. Worsening of GCS at third day was observed in only 11% of the sample and was related with significantly high mortality (69% vs. 27%, P < 0.001). **Conclusion:** Among cirrhotics hospitalized for AD, unfavorable progression of HE was associated with high short-term mortality and therefore can be used for prognostication and to individualize clinical care.

Keywords: Liver Cirrhosis. Hepatic encephalopathy. Prognosis.

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LISTA DE ABREVIATURAS E SIGLAS

DA	Descompensação aguda
DP	Desvio Padrão
EASL-CLIF	*European Association for the Study of the Liver – Chronic Liver Failure*
ECG	Escala de Coma Glasgow
EH	Encefalopatia hepática
HCV	Vírus da Hepatite C
HDA	Hemorragia digestiva alta
IC	Intervalo de confiança
IHCA	Insuficiência hepática crônica agudizada
MELD	*Model for end-stage liver disease*
OR	*Odds Ratio*
PBE	Peritonite bacteriana espontânea
PCR	Proteína C reativa
RNI	Relação normatizada internacional
SPSS	*Statistical Package for the Social Sciences*
TAP	Tempo de protrombina
UTI	Unidade de Terapia Intensiva
WH	Critérios de West Haven

SUMÁRIO

ARTIGO CIENTÍFICO

Título: Impacto prognóstico da avaliação seriada da encefalopatia hepática em pacientes hospitalizados por descompensação aguda da cirrose

Artigo submetido à revista *Liver International* (Official Journal Of The International Association For The Study Of The Liver)

1 INTRODUÇÃO

A encefalopatia hepática (EH) é definida como uma disfunção cerebral ocasionada por insuficiência hepática e/ou *shunts* portossistêmicos, e é uma das complicações mais comuns da cirrose, resultando em prejuízo significativo da qualidade de vida e hospitalizações frequentes (1). EH está presente em até metade dos pacientes hospitalizados por descompensação aguda (DA) da cirrose e a recorrência é comum após um episódio de EH clinicamente aparente (2-4). A fisiopatologia da EH é complexa e inclui vários fatores que podem afetar a função neurológica. Entre esses fatores destacam-se as alterações no metabolismo da amônia, compostos similares à benzodiazepínicos, citocinas inflamatórias, e acúmulo de manganês (5).

O diagnóstico da EH permanece essencialmente clínico. Os pacientes podem apresentar desorientação progressiva, comportamento inapropriado, e estado confusional agudo com agitação ou sonolência, estupor, e, eventualmente, coma (1). Um amplo espectro de desordens motoras podem ser observadas na EH, incluindo asterixis, hipertonia, hiperreflexia e disfunção extrapiramidal (1). A encefalopatia hepática episódica é frequentemente relacionada a fatores precipitantes, como infecção, sangramento gastrointestinal, uso de diuréticos, distúrbios eletrolíticos e constipação (6). O manejo adequado da EH episódica consiste principalmente no reconhecimento e controle dessas condições precipitantes, juntamente com medidas gerais e específicas como controle da via aérea, admissão em UTI em casos graves e uso de dissacarídeos não absorvíveis (7).

É reconhecido que a EH está associada à elevada mortalidade e é considerada um dos principais componentes para o diagnóstico da insuficiência hepática crônica agudizada (IHCA) (3, 7). Embora a avaliação periódica da EH em pacientes hospitalizados por complicações da cirrose seja habitualmente recomendada, existem poucos dados sobre o significado clínico e prognóstico da progressão do estado mental neste cenário.

A ausência de melhora ou surgimento de EH durante os primeiros dias de hospitalização pode indicar um episódio mais grave de descompensação aguda ou falha no controle dos fatores precipitantes que podem afetar o prognóstico. Portanto, nosso objetivo foi investigar o significado prognóstico da avaliação seriada da encefalopatia hepática em pacientes hospitalizados por descompensação aguda de cirrose.

2 MÉTODOS

2.1 PACIENTES

Trata-se de estudo de coorte que incluiu pacientes admitidos no Serviço de Emergência de um hospital universitário terciário brasileiro devido a descompensação aguda (DA) de cirrose hepática entre janeiro de 2011 e novembro de 2015. Os pacientes nas seguintes situações foram excluídos: hospitalização para procedimentos eletivos, admissões não relacionadas com complicações da cirrose hepática, admissão por menos de 48 horas, o uso de sedativos nos três primeiros dias de internação, carcinoma hepatocelular fora dos critérios de Milão, os pacientes com perda de seguimento e diagnóstico duvidoso de cirrose hepática. Todos os pacientes foram inicialmente admitidos em unidade de emergência. A decisão de transferir o paciente para a enfermaria ou unidade de terapia intensiva (UTI) foi feita a critério do médico assistente de acordo com a gravidade da DA.

O diagnóstico de cirrose foi estabelecido histologicamente (quando disponível) ou pela combinação de achados clínicos, de imagem e laboratoriais em pacientes com evidência de hipertensão portal.

O protocolo do estudo está em conformidade com os princípios éticos da Declaração de Helsinski e foi aprovado pelo Comitê de Ética em Pesquisa com Seres Humanos da Universidade Federal de Santa Catarina (Anexo A). Termo de consentimento livre e esclarecido foi obtido de pacientes ou seus substitutos legais antes da sua avaliação (Apêndice A).

2.2 MÉTODOS

Todos os pacientes admitidos por DA, definida pelo desenvolvimento rápido de encefalopatia hepática, ascite volumosa, hemorragia gastrointestinal, infecção bacteriana, ou qualquer combinação destes, foram avaliados. As seguintes variáveis clínicas foram coletadas: idade, sexo, etiologia da cirrose, complicações prévias e atuais da cirrose. Todos os indivíduos foram submetidos à avaliação laboratorial na admissão, e os seguintes testes foram realizados para este estudo: leucócitos totais, sódio sérico, creatinina, relação normalizada internacional (RNI), albumina, proteína C-reativa (PCR), e bilirrubina total.

Alcoolismo ativo foi definido como um consumo médio de 21 ou mais doses por semana para homens e 14 ou mais doses por semana para as mulheres durante as quatro semanas anteriores à avaliação (uma dose padrão equivale a 12 g de álcool absoluto) (8). Os pacientes foram acompanhados durante a internação e a mortalidade em trinta e 90 dias foi avaliada por telefonema, em caso de alta hospitalar. As taxas de mortalidade de noventa dias foram estimadas como mortalidade livre de transplante.

Indivíduos com suspeita de infecção na admissão hospitalar foram submetidos a exame clínico para confirmar o diagnóstico e determinar a fonte primária de infecção. A paracentese diagnóstica foi realizada em todos os pacientes com ascite na admissão. Peritonite bacteriana espontânea (PBE) foi diagnosticada quando a contagem de neutrófilos do líquido ascítico foi ≥ 250 neutrófilos/mm^3, na ausência de fonte intra-abdominal da infecção, independentemente de cultura negativa (9). Todos os pacientes com PBE receberam ceftriaxona associada à albumina intravenosa baseada no peso corpóreo no primeiro e no terceiro dia após o diagnóstico. Todos os indivíduos com sangramento agudo por varizes receberam octreotide intravenoso, um antibiótico (norfloxacina oral ou ceftriaxona intravenosa) e foram submetidos à endoscopia terapêutica urgente após a estabilização. O sistema de classificação de Child-Pugh (10), a escala *Model for End-Stage Liver Disease* (MELD) (11) e *Chronic Liver Failure-Sequential Organ Failure Assessment* (CLIF-SOFA) (3), foram calculados com base em exames laboratoriais e nas avaliações clínicas realizadas na admissão. IHCA foi definida como proposto pelo Consórcio EASL-CLIF (3).

2.3 AVALIAÇÃO DA ENCEFALOPATIA HEPÁTICA

EH foi diagnosticada como um comprometimento da cognição, consciência, ou da função motora em pacientes com cirrose sem outras causas aparentes de distúrbios mentais. EH foi classificada de acordo com os critérios clássicos de West-Haven (WH) (6) (Apêndice B) . No caso de presença da EH, um evento desencadeante foi ativamente investigado e foi iniciado lactulose, com ajuste de dose conforme necessário. Os pacientes foram avaliados clinicamente no primeiro e terceiro dias de hospitalização por um dos pesquisadores envolvidos no estudo. Para minimizar o impacto da variabilidade inter-observador, a primeira e segunda avaliação para um dado paciente foram realizadas pelo mesmo investigador. Todos os examinadores eram residentes de

quarto ano com pelo menos um ano de experiência em hepatologia clínica e treinados especificamente para o uso da classificação de WH. Os pacientes foram divididos em dois grupos de acordo com a classificação de WH: 1) evolução favorável de EH - EH ausente na admissão e no terceiro dia ou qualquer melhora na EH no terceiro dia; 2) progressão desfavorável da EH - aparecimento de EH no terceiro dia ou EH presente na admissão e estável/pior no terceiro dia. A melhora da EH foi definida como qualquer regressão nos Critérios de WH e o agravamento da EH como qualquer aumento $\geq$ 1 grau na mesma classificação. A escala de coma Glasgow (ECG) (12) (Apêndice C) também foi aplicada na admissão e no terceiro dia. Agravamento da ECG no terceiro dia foi definido como qualquer diminuição na pontuação da ECG.

2.4 ANÁLISE ESTATÍSTICA

A normalidade da distribuição das variáveis foi determinada pelo teste de Kolmogorov-Smirnov. As variáveis contínuas foram comparadas pelo teste t de Student no caso de distribuição normal ou teste de Mann-Whitney nos demais casos. As variáveis categóricas foram avaliadas por meio do teste do qui-quadrado ou teste exato de Fisher, conforme apropriado. A análise de regressão logística múltipla (*stepwise forward*) foi utilizada para investigar os fatores independentemente associados com a progressão desfavorável da EH e com a mortalidade em 90 dias. O melhor ponto de corte do escore MELD para predição de mortalidade em 90 dias foi escolhido com base na curva ROC. A curva de sobrevida foi calculada usando o método de Kaplan-Meier e a sobrevida entre os grupos foi comparada pelo teste de Log-rank. A correlação entre duas variáveis ordinais (WH e ECG) foi avaliada pelo teste de correlação de Spearman. Todos os testes foram realizados pelo software SPSS, versão 22.0 (SPSS, Chicago, IL, EUA). Um valor P inferior a 0,05 foi considerado estatisticamente significativo.

3 RESULTADOS

3.1 CARACTERÍSTICAS DA CASUÍSTICA

Quatrocentos e sessenta e sete internações por descompensação aguda de cirrose hepática foram relatados entre janeiro de 2011 e novembro de 2015. Destes, 174 foram excluídos pelas seguintes razões: admissão por menos de 48 horas (n = 46), perda de seguimento (n = 12) e hospitalização repetida (n = 116). Um total de 293 indivíduos compôs a amostra final do estudo.

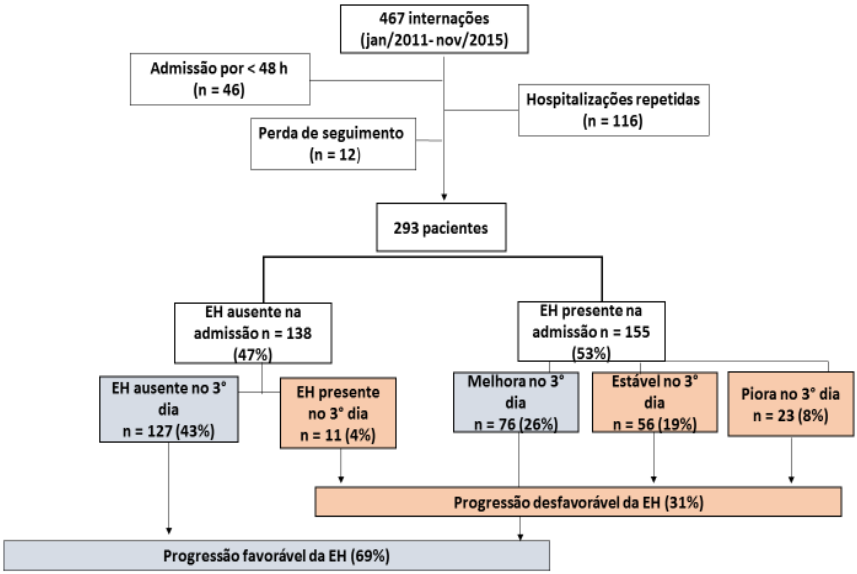
A Tabela 1 apresenta as características dos pacientes incluídos. A idade média foi de 54,78 ± 11,32 anos e 72% eram do sexo masculino. História prévia de descompensação da cirrose foi observada em 69% da amostra e 31% dos indivíduos relataram alcoolismo ativo durante os últimos trinta dias. A etiologia mais comum de cirrose foi hepatite C (38%), seguida pelo abuso de álcool (35%) e criptogênica (8%).

No momento da admissão, hemorragia digestiva alta foi observada em 42% dos casos, ascite em 52%, IHCA em 25% e infecções bacterianas em 36%. As infecções bacterianas mais comuns foram PBE (10%), infecção do trato urinário (10%), pneumonia (7%), e infecções de pele (4%). Quarenta e cinco por cento dos indivíduos foram classificados como Child-Pugh C e a média do escore MELD foi 17,34 ± 6,71.

3.2 FATORES ASSOCIADOS À PROGRESSÃO DA EH DURANTE OS TRÊS PRIMEIROS DIAS DE INTERNAÇÃO

Na primeira avaliação, 155 pacientes (53%) apresentaram EH (Graus I, II, III ou IV, em 17%, 26%, 8% e 1%, respectivamente). A progressão da EH durante os três primeiros dias de internação ocorreu da seguinte forma: 43% - EH ausente na admissão e no terceiro dia; 4% - EH ausente na admissão e presente no terceiro dia; 26% - EH presente na admissão e melhora no terceiro dia; 19% - EH presente na admissão e estável no terceiro dia; 8% - EH presente na admissão e piora no terceiro dia. Os pacientes foram divididos em dois grupos: 1) evolução favorável da EH - EH ausente na admissão e no terceiro dia ou qualquer melhoria na EH no terceiro dia (69%); 2) progressão desfavorável da EH - desenvolvimento de EH no terceiro dia ou EH presente na admissão e estável/pior no terceiro dia (31%) (Figura 1).

Figura 1 – Distribuição dos pacientes incluídos no estudo de acordo com a presença de EH na admissão e progressão da EH durante os três primeiros dias de internação



Fonte: elaborado pela autora.

Evolução desfavorável da EH foi associada na análise bivariada com EH anterior (47% *vs*. 30%, P = 0,006), ascite (63% vs. 47%, P = 0,011), uso de benzodiazepínicos (18% *vs*. 1%, P = 0,001) ou disfunção renal (47% *vs*. 26%, P = 0,008) como fatores precipitantes de EH, maior mediana da contagem de leucócitos (8260 cels/mm^3 *vs*. 6560 cels/mm^3, P = 0,010), níveis de creatinina (1,25 mg/dL *vs*. 1,00 mg/dL; P = 0,001), PCR (20,90 mg/L *vs*. 11,00 mg/L, P = 0,010) e a bilirrubina total (2,80 mg/dL *vs*. 2,10 mg/dL; P = 0,009). Evolução desfavorável da EH também foi relacionada a maior média de MELD (19,70 ± 7,70 *vs*. 16,29 ± 5,95, P < 0,001), CLIF-SOFA (8,24 ± 3,15 *vs*. 5,98 ± 2,94, P < 0,001), maior proporção de Child-Pugh C (71% *vs*. 38%, P < 0,001) e ACLF (43% *vs*. 17%, P < 0,001) (Tabela 1).

Foi realizada análise de regressão logística para investigar fatores independentemente associados à progressão desfavorável da EH, incluindo as seguintes variáveis com P ≤ 0,010 na análise bivariada: EH prévia, ACLF, Child-Pugh C, MELD e contagem de leucócitos. Outras variáveis laboratoriais já presentes nos modelos prognósticos não foram

incluídas para evitar redundância. PCR também não foi incluída devido à elevada percentagem de dados faltantes (11%). Evolução desfavorável da EH foi independentemente associada com EH anterior (OR 1,919, IC 95% 1,116-3,299, P = 0,018), Child-Pugh C (OR 1,851, IC 95% 1,044-3,157, P = 0,035) e IHCA (OR 2.982, 95% CI 1,646-5,404, P < 0,001).

Tabela 1 - Características dos pacientes incluídos e fatores associados à progressão desfavorável da EH (desenvolvimento precoce, persistência ou agravamento de HE)

Variáveis	Total (n = 293)	Progressão favorável da EH (n = 203)	Evolução desfavorável da HE (n = 90)	P
Idade (anos), média ± DP	54,78 ± 11,32	54,93 ± 11,95	54,45 ± 9,80	0,746
Sexo masculino, n (%)	211 (72)	143 (70)	68 (76)	0,369
Etiologia da cirrose, n (%)				
Álcool	104 (35)	65 (32)	39 (43)	0,062
Hepatite C	110 (38)	77 (39)	33 (37)	0,837
Hepatite B	17 (6)	10 (5)	7 (8)	0,335
Criptogênica	23 (8)	20 (10)	3 (3)	0,056
Outra	39 (13)	31 (15)	8 (9)	0,138
Descompensação prévia, n (%)	200 (69)	138 (68)	62 (71)	0,718
EH prévia, n (%)	103 (35)	61 (30)	42 (47)	0,006
Alcoolismo ativo, n (%)	89 (31)	58 (29)	31 (34)	0,326
Complicações na admissão, n (%)				
Ascite	153 (52)	96 (47)	57 (63)	0,011
Sangramento gastrointestinal	122 (42)	85 (42)	37 (41)	0,903
PBE	30 (10)	21 (10)	9 (10)	0,918
Infecção bacteriana*	105 (36)	67 (33)	38 (42)	0,129
EH na admissão, n (%)				
Qualquer grau	155 (53)	76 (37)	79 (88)	< 0,001
Grau I	51 (17)	25 (12)	26 (29)	0,001
Grau II	76 (26)	34 (17)	42 (47)	< 0,001
Grau III	24 (8)	16 (8)	8 (9)	0,772

Variáveis	Total (n = 293)	Progressão favorável da EH (n = 203)	Evolução desfavorável da HE (n = 90)	P
Grau IV	4 (1)	1 (1)	3 (3)	0,088
Fator precipitante da EH, n (%)[#]				
Sangramento gastrointestinal	60 (39)	25 (33)	35 (44)	0,145
Infecção	58 (37)	24 (32)	34 (43)	0,141
Constipação	24 (16)	14 (18)	10 (13)	0,321
Benzodiazepínicos	15 (10)	1 (1)	14 (18)	0,001
Distúrbios hidro-eletrolíticos	32 (21)	13 (17)	19 (24)	0,286
Disfunção renal	57 (37)	20 (26)	37 (47)	0,008
Diuréticos	100 (34)	68 (34)	32 (36)	0,648
Outros	9 (6)	5 (7)	4 (5)	0,743
Não identificado	7 (5)	5 (7)	2 (3)	0,270
Dados laboratoriais				
Leucócitos (cels/mm^3), mediana	7.090,00	6.560,00	8.260,00	0,010
Sódio (mEq/L), média ± DP	134,88 ± 5,50	135,14 ± 5,33	134,31 ± 5,83	0,239
Creatinina (mg/dL), mediana	1,10	1,00	1,25	0,001
INR, mediana	1,45	1,42	1,50	0,056
Albumina (g/dL), media ± DP	2,36 ± 0,65	2,38 ± 0,63	2,31 ± 0,71	0,411
PCR (mg/L),mediana	14,20	11,00	20,90	0,010
Bilirubina total (mg/dL), mediana	2,20	2,10	2,80	0,009
Child-Pugh score, média ± DP	9,35 ± 1,94	9,01 ± 1,87	10,10 ± 1,90	< 0,001
Child-Pugh C, n (%)	130 (45)	76 (38)	54 (71)	< 0,001
Score MELD média ± DP	17,34 ± 6,71	16,29 ± 5,95	19,70 ± 7,70	< 0,001
CLIF-SOFA, média ± DP	6,63 ± 2,85	5,98 ± 2,94	8,24 ± 3,15	< 0,001

Variáveis	Total (n = 293)	Progressão favorável da EH (n = 203)	Evolução desfavorável da HE (n = 90)	P
IHCA, n (%)	74 (25)	35 (17)	39 (43)	< 0,001

IHCA = Insuficiência hepática crônica agudizada; DP = Desvio padrão; AST = aspartato aminotransferase; ALT = alanina aminotransferase; GGT = gamaglutamiltransferase INR = Relação normatizada internacional; PCR = Proteína C reativa; MELD = Model for End-stage Liver Disease; [#]Dentre os Pacientes com EH na admissão; *Incluindo PBE

Fonte: elaborado pela autora.

3.3 PROGRESSÃO DA EH DURANTE OS TRÊS PRIMEIROS DIAS DE INTERNAÇÃO COMO FATOR PROGNÓSTICO

A mortalidade global em 30 e 90 dias foi de 26% e 31%, respectivamente. A análise bivariada (Tabela 2) mostrou que a mortalidade em 90 dias foi diretamente associada à ascite (82% *vs.* 39%, P < 0,001), infecção bacteriana (50% *vs.* 30%, P = 0,001), Child-Pugh C (74% *vs.* 32%, P < 0,001), ACLF (54% *vs.* 12%, P < 0,001) e progressão desfavorável da EH (50% *vs.* 22%, P < 0,001). A mortalidade em noventa dias também foi relacionada à maior MELD (22,42 ± 6,95 *vs.* 15,05 ± 5,18, P < 0,001), CLIF-SOFA (8,78 ± 2,82 *vs.* 5,73 ± 2,33, P < 0,001), maior mediana de contagem de leucócitos (8090 cels/mm^3 *vs.* 6650 cels/mm^3, P = 0,011), creatinina (1,60 mg/dL *vs.* 1,00 mg/dL, P < 0,001), RNI (1,62 *vs.* 1,39, P < 0,001), PCR (25,10 mg/L *vs.* 9,00 mg/L, P < 0,001), bilirrubina (3,40 mg/dL *vs*. 1,80 mg/dL; P < 0,001), menores níveis de sódio (133,22 ± 5,91 mEq/L *vs.* 135,63 ± 5,14 mEq/L, P < 0,001) e albumina (2,05 ± 0,61 g/dL *vs.* 2,49 ± 0,62 g/dL, P < 0,001).

Tabela 2 - Fatores associados à mortalidade de 90 dias entre os pacientes com cirrose internados por descompensação aguda

Características	Sobreviventes (n = 202)	Óbitos (n = 91)	P
Idade (anos), média ± DP	54,55 ± 11,34	55,29 ± 11,32	0,608
Sexo masculino, n (%)	150 (74)	61 (67)	0,202
Etiologia da cirrose, n (%)			
Álcool	74 (37)	30 (33)	0,544
Hepatite C	76 (38)	34 (37)	0,966
Hepatite B	11 (5)	6 (7)	0,697
Criptogênica	16 (8)	7 (8)	0,946
Descompensação prévia, n (%)	136 (68)	64 (72)	0,471
EH prévia, n (%)	67 (33)	36 (40)	0,289
Alcoolismo ativo, n (%)	61 (30)	28 (31)	0,942
Complicações na admissão, n (%)			
Ascite	78 (39)	75 (82)	< 0,001
Sangramento gastrointestinal	94 (47)	28 (31)	0,011
PBE	19 (10)	11 (12)	0,491
Infecção bacteriana*	60 (30)	45 (50)	0,001
Dados laboratoriais			
Leucócitos (cel/mm^3), mediana	6.650,00	8.090,00	0,011
Sódio (mEq/L), média ± DP	135,63 ± 5,14	133,22 ± 5,91	< 0,001
Creatinina (mg/dL), mediana	1,00	1,60	< 0,001
RNI, mediana	1,39	1,62	< 0,001
Albumina (g/dL), média ± DP	2,49 ± 0,62	2,05 ± 0,61	< 0,001
PCR (mg/L),mediana	9,00	25,10	< 0,001
Bilirrubina total (mg/dL), mediana	1,80	3,40	< 0,001
Score Child-Pugh, média ± DP	8,76 ± 1,76	10,70 ± 1,65	< 0,001
Child-Pugh C, n (%)	65 (32)	65 (74)	< 0,001
Score MELD, média ± DP	15,05 ± 5.18	22,42 ± 6,95	< 0,001
CLIF-SOFA, média ± DP	5,73 ± 2,33	8,78 ± 2,82	< 0.001
IHCA, n (%)	25 (12)	49 (54)	< 0.001
Progressão desfavorável da EH, n (%)	45 (22)	45 (50)	< 0.001

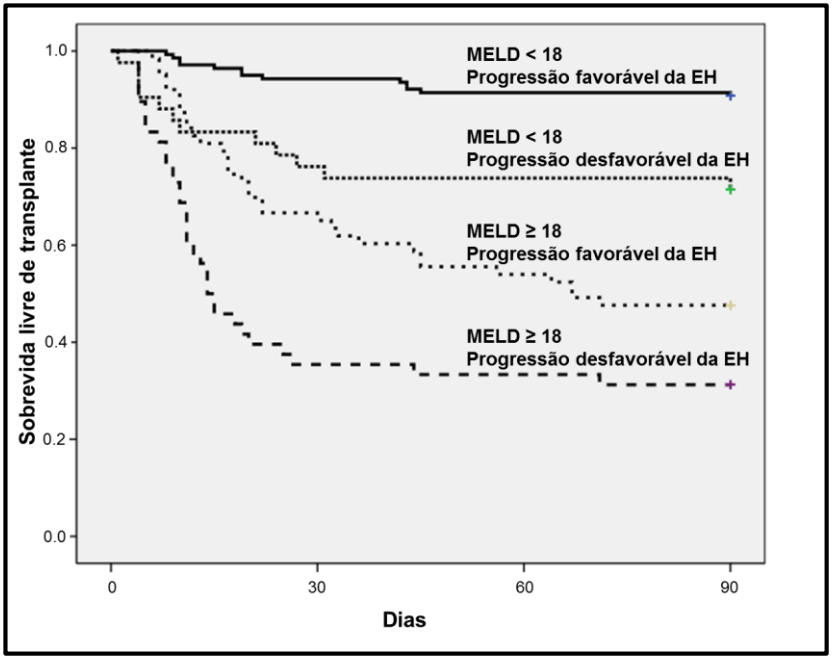
IHCA = Insuficiência hepática crônica agudizada; EH = Encefalopatia hepatica DP = Desvio-padrão; RNI = Relação normatizada internacional; PCR = Proteína C reativa; MELD = Model for End-stage Liver Disease; *Incluindo PBE.

Fonte: elaborado pela autora.

Análise de regressão logística para investigar fatores independentemente associados à mortalidade em 90 dias foi realizada incluindo variáveis com valor de P < 0,010 na análise bivariada (níveis de sódio, infecção bacteriana, Child-Pugh C, MELD, ACLF e progressão desfavorável da EH). Outras variáveis laboratoriais já presentes nos modelos não foram incluídas na análise de regressão para evitar redundância. Os parâmetros que foram independentemente associados à mortalidade em 90 dias foram MELD (OR 1,203, IC 95% 1,141 - 1,269, P < 0,001) e progressão desfavorável de HE (OR 2,318, IC 95% 1.237 - 4,342, P = 0,009).

O melhor ponto de corte do escore MELD para predição de mortalidade de 90 dias foi escolhido com base na curva ROC. A Figura 2 mostra as curvas de Kaplan-Meier para a mortalidade de acordo com a progressão da EH e categorias MELD. A probabilidade de sobrevida de Kaplan-Meier em 90 dias foi de 91% em pacientes com MELD <18 e progressão favorável da EH, 71% naqueles com MELD <18 mas com progressão desfavorável da EH, 48% em pacientes com MELD ≥ 18 e progressão favorável da EH, e apenas 31% em indivíduos com MELD ≥ 18 e progressão desfavorável da EH (P < 0,001, long-rank test).

Figura 2 - Curvas de Kaplan-Meier para a mortalidade de acordo com a progressão da EH e categorias MELD



Fonte: elaborado pela autora.

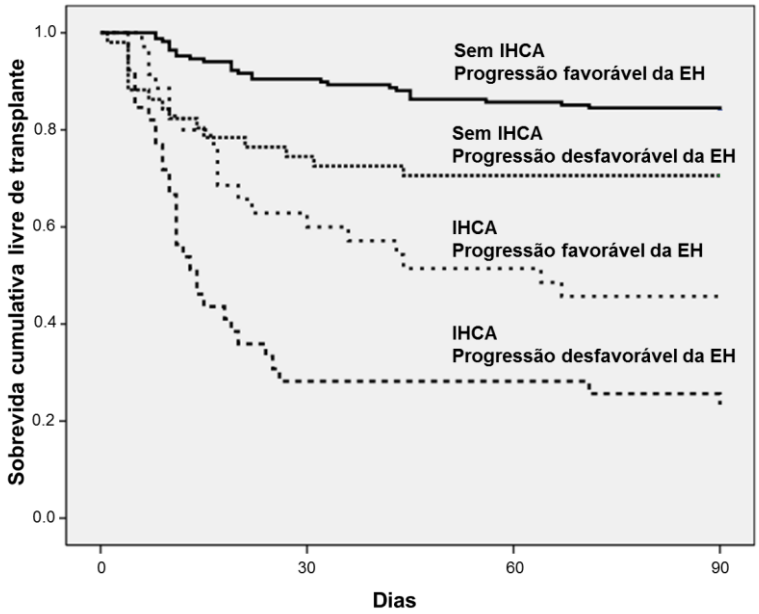
3.4 INFLUÊNCIA DA IHCA NA PROGRESSÃO E PROGNÓSTICO DA EH

Dentre os 219 pacientes sem IHCA e EH na admissão, EH permaneceu ausente no terceiro dia em 50% e se desenvolveu em 4%. Naqueles sem IHCA mas com EH na admissão, EH melhorou em 27%, manteve-se estável em 14% e agravou-se em 6%. Entre aqueles com IHCA e sem EH na admissão, EH permaneceu ausente em 23%, desenvolvendo em 3%. Em indivíduos com IHCA e EH na admissão, EH melhorou em 24%, manteve-se estável em 35% e agravou-se em 15%. No geral, uma maior proporção de pacientes apresentaram evolução desfavorável da EH entre os pacientes com IHCA na admissão (53% *vs.* 23%, P < 0,001).

A figura 3 exibe as curvas de Kaplan-Meier para a mortalidade de acordo com a progressão da EH e a presença de IHCA. Pacientes sem IHCA que apresentaram evolução desfavorável da EH apresentaram

menor probabilidade de sobrevivência de Kaplan-Meier, em comparação aqueles que permaneceram sem EH ou com melhora no terceiro dia (71% *vs.* 84%, P = 0,016). Do mesmo modo, entre aqueles com IHCA, a progressão desfavorável da EH foi associada com sobrevida significativamente menor (23% *vs.* 46%, P = 0,012).

Figura 3 - Curvas de Kaplan-Meier para a mortalidade de acordo com a progressão da EH e a presença de IHCA



Fonte: elaborado pela autora.

3.5 ESCALA DE COMA DE GLASGOW NA AVALIAÇÃO DA PROGRESSÃO DO ESTADO MENTAL EM PACIENTES CIRRÓTICOS

Na admissão, ECG era de 15 pontos em 205 pacientes (70%), 14 em 48 indivíduos (16%) e ≤ 13 em 40 (14%). Na avaliação do terceiro dia, a ECG era de 15 pontos em 228 pacientes (78%), 14 em 25 (9%) e ≤ 13 em 39 (13%). ECG não estava disponível no terceiro dia para um paciente. Uma correlação forte foi observada entre a ECG e a classificação de WH na admissão (r = -0,736, P < 0,001) e na avaliação

do terceiro dia (r = -0,730, P < 0,001). Na admissão, a ECG foi de 15 em todos os pacientes sem HE e de 3 nos pacientes com EH grau IV de acordo com os critérios WH. A mediana da ECG foi de 15,0, 14,0 e 12,0 entre os pacientes com HE graus 1, 2 e 3, respectivamente. As taxas de mortalidade foram de 25%, 38% e 53% entre os pacientes com GCS de 15, 14 e ≤ 13 na admissão, respectivamente (P = 0,002). Redução na pontuação da ECG no terceiro dia foi observada em apenas 32 pacientes (11%) e foi associado a maiores médias de MELD (21,04 ± 6,84 *vs.* 16,71 ± 6,62, P = 0,001) e CLIF-SOFA (8,38 ± 2,11 *vs.* 6,43 ± 2,83, P < 0,001), maiores proporções de pacientes Child-Pugh C (65% *vs.* 43%, P = 0,021) e de pacientes com EH diagnosticada pelos critérios WH na admissão (81% *vs.* 50%, P = 0,001). Piora da ECG no terceiro dia foi relacionada com aumento significativo da mortalidade em comparação com aqueles que tinham a pontuação da ECG estável ou melhor na segunda avaliação (69% *vs.* 27%, P < 0,001).

4 DISCUSSÃO

A encefalopatia hepática é uma das complicações mais comuns de cirrose, e tem sido associada a impacto significativo na qualidade de vida relacionada à saúde (13) e sobrevida, independente da gravidade da cirrose (7). No presente estudo, a maioria dos pacientes (69%) apresentaram uma progressão favorável da EH, seja por EH permanecendo ausente após três dias de internação, ou com melhora da EH presente no momento da admissão. No entanto, em quase um terço dos indivíduos houve aparecimento ou não melhora da EH no terceiro dia. Na análise bivariada, a progressão desfavorável da EH foi associada com variáveis relacionadas à gravidade da doença hepática, tais como EH prévia, ascite, Child-Pugh C, maior MELD e níveis de bilirrubina total. No entanto, também foi relacionada a fatores que refletem mais a gravidade do episódio de descompensação aguda e estado inflamatório, como maior contagem de leucócitos, PCR, níveis de creatinina e a presença de IHCA. Na análise de regressão, a progressão desfavorável da EH foi associada com EH prévia, Child-Pugh C e IHCA. Apesar de não terem sido encontrados estudos anteriores que avaliaram fatores associados à progressão da EH durante a hospitalização, estes resultados eram esperados já que a gravidade inical da EH produz impacto significativo sobre esses modelos prognósticos. Uma sub-análise recente do estudo CANONIC revelou diferenças significativas entre pacientes com EH relacionada ou não com IHCA (14). Com base em seus resultados, os autores propuseram duas apresentações distintas de HE nas quais EH relacionada a IHCA está normalmente associado com idade mais jovem, disfunção hepática mais intensa, infecções bacterianas, alcoolismo ativo ou hiponatremia dilucional (14). Outra característica importante da EH relacionada com a IHCA é o achado consistente com uma reação inflamatória sistêmica exagerada que pode desempenhar um papel na disfunção cerebral (14). Os resultados observados no presente estudo provavelmente complementam os do estudo CANONIC, indicando que IHCA e resposta inflamatória mais intensa no início do quadro também estão associadas a um maior risco de progressão desfavorável da EH durante os primeiros dias de hospitalização.

A evolução desfavorável da EH e MELD foram independentemente associados à mortalidade em 90 dias entre pacientes hospitalizados por DA da cirrose. EH é considerada um importante fator prognóstico na cirrose hepática, seja no regime extra ou intra-hospitalar (14-17). Na análise recente derivada da coorte CANONIC, a EH foi

associada com maior probabilidade de mortalidade que aumentou significativamente conforme a piora do grau da EH (14). Em outro estudo que avaliou o impacto a longo prazo da EH em pacientes com cirrose, EH graus 2 ou 3 foram associados com alta mortalidade na coorte de indivíduos hospitalizados, mesmo após o ajuste para o escore MELD (17). Nenhum estudo anterior que avaliou o impacto prognóstico das mudanças no grau da EH durante a hospitalização foi encontrado. Embora seja possível que a progressão desfavorável da EH apenas reflita a gravidade da doença hepática de base ou do fator precipitante, ela permaneceu associada a elevada mortalidade em 90 dias, mesmo após o controle para vários fatores prognósticos importantes. Além disso, ausência de melhora ou surgimento de EH durante a internação representa um desafio clínico, e saber a relação desse evento com o prognóstico pode permitir a individualização na condução dos casos.

O significado prognóstico da progressão da EH foi avaliado de acordo com o score MELD. Os pacientes com evolução favorável da EH e baixa pontuação de MELD (<18) apresentaram bom prognóstico (sobrevida em 90 dias ≈ 91%). No entanto, mesmo em indivíduos com baixo MELD, a progressão desfavorável da EH foi associada com pior prognóstico e uma sobrevida em 90 dias de 71%. Da mesma forma, naqueles com MELD elevado, a progressão favorável da EH foi associada à sobrevida de 90 dias de 48% *vs.* 31% para aqueles com MELD elevado e progressão desfavorável da EH. Estes resultados indicam que unindo a avaliação clínica da progressão da EH ao longo dos três primeiros dias de hospitalização e escore MELD obtem-se uma estratificação de quatro níveis bem definida para o prognóstico de curto prazo em pacientes hospitalizados por DA da cirrose.

Como mencionado acima, a IHCA relacionada à EH tem características específicas e recentemente foi proposto que fosse considerada como uma entidade distinta da EH isolada (14). Por essa razão, o impacto da progressão da EH no prognóstico foi avaliado em pacientes com e sem IHCA. A evolução desfavorável da EH teve impacto negativo no prognóstico, independentemente da presença de IHCA. A pior sobrevida em 90 dias foi observada para pacientes com IHCA que apresentaram evolução desfavorável da EH (23%). Esses achados reforçam a utilidade da avaliação seriada da EH, independentemente do tipo de EH, se isolada ou associada à IHCA.

A ECG foi utilizada como uma alternativa aos critérios de West Haven para avaliar a progressão das alterações cognitivas durante a hospitalização. Embora a ECG tenha se correlacionado fortemente com a classificação de WH, a grande maioria dos pacientes com EH graus 1 e

2 mostrou GCS ≥ 14. A piora da ECG no terceiro dia foi fortemente relacionada com mortalidade, apesar de ter sido observada em apenas 32 pacientes (11%). A ECG é uma ferramenta útil para a avaliação objetiva e monitoramento contínuo de mudanças no estado mental do paciente não-cirrótico (18). Há poucos dados sobre a utilização da ECG em pacientes com cirrose. A versão original e uma modificada da ECG foram utilizadas em ensaios terapêuticos de flumazenil para EH (19-21). Um estudo norte-americano que teve como objetivo descrever uma versão modificada da classificação de WH, chamada Score Algorítmico EH (HESA), mostrou que a ECG diferiu entre os quatro estágios de WH, mas as diferenças entre os graus I e II foram pequenas e não clinicamente úteis (22). Estes dados sugerem que a ECG pode ser útil em pacientes com EH mais severa e que o agravamento da ECG, embora infrequente, está associada à pior prognóstico.

Algumas limitações do presente estudo merecem ser discutidas. Em primeiro lugar, a utilização dos critérios de WH foi criticada devido à sua subjetividade e variabilidade inter-observador, especialmente para o grau 1 (23). No entanto, tais critérios ainda são recomendados como padrão-ouro na prática clínica (23). Além disso, o impacto da variabilidade inter-observador foi provavelmente minimizado no presente estudo porque a primeira e a segunda avaliações para um dado paciente foram realizadas pelo mesmo investigador. No que diz respeito à dificuldade em distinguir entre ausência de EH e EH grau 1, foi realizada uma análise considerando apenas EH grau ≥ 2 como EH clinicamente aparente e EH grau 1 como ausente e não foi observada qualquer vantagem na capacidade prognóstica (dados não mostrados). Em segundo lugar, o nosso estudo foi realizado fora do contexto de um ensaio clínico e incluiu uma população muito heterogênea, em cenários clínicos distintos. Portanto, variações na abordagem de casos específicos são esperadas. Ainda, não existem estudos definindo o tempo ideal para a reavaliação de forma dinâmica da encefalopatia hepática, e a escolha do terceiro dia no nosso trabalho foi empírica, porém retrata experiência prévia do serviço. Finalmente, este foi um estudo de um único centro e os dados aqui apontados não podem ser extrapolados para outras coortes. Estudos multicêntricos maiores, incluindo mais pacientes com EH graus 3 e 4 seriam úteis para validar os nossos resultados e prosseguir na investigação do impacto das mudanças dinâmicas na ECG entre os pacientes com cirrose.

É possível concluir que a evolução desfavorável da EH durante os primeiros dias de hospitalização por DA da cirrose foi mais frequente em pacientes com história prévia de EH e naqueles que se apresentam

com disfunção hepática mais intensa e IHCA. A evolução desfavorável da EH foi associada a maior mortalidade no curto prazo e, portanto, pode ser usada para prognosticar e individualizar os cuidados clínicos com os portadores de cirrose hepática.

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APÊNDICES

APÊNDICE A - TERMO DE CONSENTIMENTO LIVRE ESCLARECIDO

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

AVALIAÇÃO DE MARCADORES PROGNÓSTICOS EM PORTADORES DE CIRROSE HEPÁTICA DESCOMPENSADA

Você está sendo convidado para participar de um projeto de pesquisa: *Avaliação de marcadores prognósticos em portadores de cirrose hepática descompensada*. Este projeto tem o objetivo de identificar dados da avaliação médica ou de exames laboratoriais que possam nos ajudar a identificar os pacientes com doença mais grave. Os resultados desta pesquisa poderão permitir a criação de ferramentas para a identificação rápida dos pacientes com doença mais grave, permitindo assim um tratamento mais adequado.

Caso você concorde em participar deste estudo, será feita uma avaliação clínica (entrevista e exame físico) no primeiro dia da sua internação e 48 horas depois. Além disso, uma coleta de sangue será realizada por punção periférica na veia do antebraço também nestes dois momentos. Parte do material será destinada aos exames de rotina (que são necessários para avaliação do seu caso durante a internação) e uma outra porção será armazenadas em freezer a -80º C para a posterior dosagem dos exames referentes a este estudo, que são: Anti-HEV IgG, procalcitonina, GST-α, neoepítopos da CK-18 e queratina 18 solúvel. Além disso, uma amostra de fezes será coletada para realização da dosagem de calprotectina.

Não existem riscos importantes relacionados a tais procedimentos, podendo ocorrer, como consequência da coleta de sangue, dor no local da punção e/ou formação de hematoma local.

Não há benefício direto para o participante. Em qualquer etapa do estudo, você terá acesso aos profissionais responsáveis pela pesquisa para esclarecimento de eventuais dúvidas. Os principais investigadores envolvidos são o Dr. Marcelo Ronsoni, o Dr. Cesar Lazzarotto e o Dr. Leonardo de Lucca Schiavon que podem ser encontrados no endereço: Departamento de Clínica Médica, Hospital Universitário/Campus Universitário – Trindade - Cep 88040-970 - Florianópolis – SC Fone (48) 37219149/37219014; e-mail: cesarlazzarotto@ig.com.br ou marceloronsoni@terra.com.br. Se você tiver alguma consideração ou

dúvida sobre a ética da pesquisa, entre em contato com o Comitê de Ética em Pesquisa (CEP): Universidade Federal de Santa Catarina; Pró-Reitoria de Pesquisa e Extensão - Campus Universitário - Trindade - Florianópolis/SC; Tel: (48) 3721-9206.

É garantida a liberdade da retirada de consentimento a qualquer momento e deixar de participar do estudo, sem qualquer prejuízo à continuidade de seu tratamento na Instituição.

As informações obtidas serão analisadas em conjunto com outros pacientes, não sendo divulgada a identificação de nenhum paciente.

Você tem o direito de ser mantido atualizado sobre os resultados parciais das pesquisas, assim que os mesmos forem de conhecimento dos pesquisadores.

Não há despesas pessoais para o participante em qualquer fase do estudo, incluindo exames e consultas. Também não há compensação financeira relacionada à sua participação. Se existir qualquer despesa adicional, ela será absorvida pelo orçamento da pesquisa.Em caso de dano pessoal, diretamente causado pelos procedimentos propostos neste estudo (nexo causal comprovado), o participante tem direito a tratamento médico na Instituição, bem como às indenizações legalmente estabelecidas.

Segue abaixo os termos da declaração para poder participar do estudo:

Acredito ter sido suficientemente informado a respeito do estudo "**Avaliação de marcadores prognósticos em portadores de cirrose hepática descompensada**".

Eu discuti com os pesquisadores responsáveis sobre a minha decisão em participar nesse estudo. Ficaram claros para mim quais são os propósitos do estudo, os procedimentos a serem realizados, seus desconfortos e riscos, as garantias de confidencialidade e de esclarecimentos permanentes. Ficou claro também que minha participação é isenta de despesas e que tenho garantia do acesso a tratamento hospitalar, caso seja necessário. Concordo voluntariamente em participar deste estudo e poderei retirar o meu consentimento a qualquer momento: antes ou durante o mesmo, sem penalidades, prejuízo, perda de qualquer benefício que eu possa ter adquirido, ou no meu atendimento neste Serviço.

Nome do participante Assinatura

Data _____

ou

Responsável legal Assinatura

Data _____

Responsável pelo estudo Assinatura

Data _____

APÊNDICE B – Critérios de West Haven

Grau I	Alterações leves de comportamento e de funções biorregulatórias, como alternância do ritmo do sono, distúrbios discretos do comportamento como riso e choro “fácil”, hálito hepático
Grau II	Letargia ou apatia, lentidão nas respostas, desorientação no tempo e espaço, alterações na personalidade e comportamento inadequado, presença de flapping
Grau III	Sonolência e torpor com resposta aos estímulos verbais, desorientação grosseira e agitação psicomotora, flapping presente
Grau IV	Coma não responsivo aos estímulos verbais e com resposta flutuante à dor

GED gastroenterol. endosc. dig.2011

APÊNDICE C – Escala de Coma Glasgow

Abertura ocular	4 - espontânea 3 - ao chamado 2 - ao estímulo doloroso 1 - ausente
Resposta verbal	5 - orientada 4 - confusa 3 - palavras inapropriadas 2 - sons incompreensíveis 1 - ausente
Resposta motora	6 - obedece a comandos 5 - localiza a dor 4 - retirada à dor 3 - decorticação 2 – descerebração 1 - ausente

TEASDALE G., JENNETT, B. *Assessment of coma and impaired consciousness.* Lancet, 1974

APÊNDICE D – Artigo Científico (Versão Língua Inglesa)

TITLE PAGE

Manuscript title:

Prognostic impact of serial assessment of hepatic encephalopathy in patients hospitalized for acute decompensation of cirrhosis

Running Head:

Serial assessment of hepatic encephalopathy

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List of abbreviations: HE: Hepatic encephalopathy; AD: acute decompensation; INR: international normalized ratio, CRP: C-reactive protein; SBP: Spontaneous bacterial peritonitis; MELD: Model for End-Stage Liver Disease; CLIF-SOFA: Chronic Liver Failure-Sequential Organ Failure Assessment; ACLF: Acute-on-chronic liver failure; WHC: West-Haven criteria; GCS: Glasgow Coma Scale; ROC: Receiver operating characteristic. HESA: HE Scoring Algorithm

Key points:

- Although periodical assessment of hepatic encephalopathy (HE) in patients hospitalized for complications of cirrhosis is advised, there are very few data about the clinical and prognostic significance of the progression of mental status in this setting
- Unfavorable progression of HE (development of HE or HE present at admission and stable/worse at third day) was seen in 31% of patients and was independently associated with higher 90-day mortality
- Unfavorable progression of HE was related to lower survival in patients with or without ACLF
- Worsening of Glasgow Coma Scale at third day was also related with high short-term mortality

ABSTRACT

Background & Aims: Hepatic encephalopathy (HE) is a frequent complication of cirrhosis, but the clinical and prognostic significance of the progression of mental status in hospitalized cirrhotics is unknown. We aimed at investigate the prognostic significance of serial evaluation of hepatic encephalopathy in patients hospitalized for acute decompensation (AD) of cirrhosis. **Methods:** Patients (n = 293) were evaluated for HE (West-Haven criteria) at admission and third day and classified in two groups: 1) Favorable progression: HE absent at admission and at third day or any improvement at third day; 2) Unfavorable progression: Development of HE or HE present at admission and stable/worse at third day. **Results:** Unfavorable progression of HE was observed in 31% of patients and was independently associated with previous HE, Child-Pugh C and acute-on-chronic liver failure (ACLF). MELD score and unfavorable progression of HE were independently associated with 90-day

mortality. The Kaplan-Meier survival probability at 90-day was 91% in patients with MELD < 18 and favorable progression of HE and only 31% in subjects with both MELD ≥ 18 and unfavorable progression of HE. Unfavorable progression of HE was also related to lower survival in patients with or without ACLF. Worsening of GCS at third day was observed in only 11% of the sample and was related with significantly high mortality (69% vs. 27%, P < 0.001). **Conclusion:** Among cirrhotics hospitalized for AD, unfavorable progression of HE was associated with high short-term mortality and therefore can be used for prognostication and to individualize clinical care.

Keywords: Liver Cirrhosis. Hepatic encephalopathy. Prognosis.

Introduction

Hepatic encephalopathy (HE) is defined as a brain dysfunction caused by liver insufficiency and/or portosystemic shunts and is one of the most common complications of liver cirrhosis, resulting in significant impairment in quality of life and frequent hospitalizations.[1] HE is present in one third to half patients hospitalized for acute decompensation (AD) of cirrhosis and recurrence is common following an episode of overt HE.[2-4] Pathophysiology of HE is complex and include several factors that may impair neuronal function. These factors include ammonia, benzodiazepine-like compounds, inflammatory cytokines, and manganese deposition.[5]

The diagnosis of HE remains essentially clinical. Patients may present with progressive disorientation, inappropriate behavior, and acute confusional state with agitation or somnolence, stupor, and, eventually, coma.[1] A wide spectrum of motor disorders can be observed in HE, including asterixis, hypertonia, hyperreflexia and

extrapyramidal dysfunction.[1] Episodic HE is usually related to precipitant factors, such as infection, gastrointestinal bleeding, diuretics use, electrolyte disorder and constipation.[6] Proper management of episodic HE consists primarily in the recognition and control of these precipitant conditions, along with general and specific measures such airway control, ICU admission in severe cases and non-absorbable disaccharides.[7]

It is well-known that HE is associated with higher mortality and that it is considered one of the major components for the diagnosis of acute-on-chronic liver failure.[3,7] Although periodical assessment of HE in patients hospitalized for complications of cirrhosis is advised, there are very few data about the clinical and prognostic significance of the progression of mental status in this setting. Absence of improvement or new-onset HE during the first days of hospitalization might indicate a more severe episode of acute decompensation or failure in controlling precipitant factors that may impact prognosis. Therefore, our aim was to investigate

the prognostic significance of serial assessment of hepatic encephalopathy in patients hospitalized for acute decompensation of cirrhosis.

METHODS

Patients

This was cohort study that included consecutive subjects admitted to the emergency room of a Brazilian tertiary hospital due to AD of liver cirrhosis between December 2010 and November 2015. Patients in the following situations were excluded: hospitalization for elective procedures, admissions not related to complications of liver cirrhosis, admission for less than 48 hours, use of sedative within the first three days of admission, hepatocellular carcinoma outside Milan criteria, patients who were lost to follow-up and doubtful diagnosis of liver cirrhosis. All patients were initially admitted in the emergency room. The decision to transfer the patient to the ward or the intensive care unit was made at the discretion of

the attending physician according to the severity of the AD.

The diagnosis of cirrhosis was established either histologically (when available) or by the combination of clinical, imaging, and laboratory findings in patients with evidence of portal hypertension.

The study protocol complies with the ethical principles of the Declaration of Helsinki and was approved by the Ethics Committee on Human Research of the Federal University of Santa Catarina. Written informed consent was obtained from patients or their legal surrogates before enrollment.

Methods

All patients admitted for AD as defined by the acute development of hepatic encephalopathy, large ascites, gastrointestinal bleeding, bacterial infection, or any combination of these were screened. The following clinical variables were collected: age, gender, etiology of cirrhosis, previous and current complications of cirrhosis. All subjects underwent laboratory evaluation at admission, and the

following tests were performed for this study: total leukocytes, serum sodium, creatinine, international normalized ratio (INR), albumin, C-reactive protein (CRP), and total bilirubin.

Active alcoholism was defined as an average overall consumption of 21 or more drinks per week for men and 14 or more drinks per week for women during the 4 weeks before enrolment (one standard drink is equal to 12 g absolute alcohol).[8] Patients were followed during their hospital stay and thirty and 90-day mortality was evaluated by phone call, in case of hospital discharge. Ninety-day mortality rates were estimated as transplant-free mortality.

Individuals with suspected infection at hospital admission were submitted to clinical examination to confirm this diagnosis and to establish the primary source of infection. A diagnostic paracentesis was performed in all patients with ascites at admission. Spontaneous bacterial peritonitis (SBP) was diagnosed when the neutrophil count of the ascitic fluid was $\geq$ 250 neutrophils/mm^3 in the absence of intra-abdominal

source of infection, regardless of negative culture.[9] All patients with SBP received ceftriaxone plus weight-based intravenous albumin in the first and third day after the diagnosis. All subjects with acute variceal bleeding received intravenous octreotide, an antibiotic (either oral norfloxacin or intravenous ceftriaxone) and underwent urgent therapeutic endoscopy after stabilization. Suspicion of alcoholic hepatitis was based on clinical and laboratory data. Child-Pugh classification system,[10] Model for End-Stage Liver Disease (MELD)[11] and Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA)[3] were calculated based on laboratory tests and clinical evaluation performed at admission. Acute-on-chronic liver failure (ACLF) was defined as proposed by the EASL-CLIF Consortium.[3]

Assessment of Hepatic Encephalopathy

HE was diagnosed as an impairment of cognition, consciousness, or motor function in patients with cirrhosis with no other apparent causes for mental disturbances. HE was

graded according to the classic West-Haven criteria (WHC)[6] and, if it was present, a precipitant event was actively investigated and lactulose was initiated and the dose adjusted as needed. Patients were clinically evaluated in the first and third days of hospitalization by one of the researchers involved in the study. To minimize the impact of inter-observer variability, the first and second evaluations for a given patient were performed by the same investigator. All examiners were fourth-year fellows with at least one year experience in clinical hepatology and trained by the senior investigators specifically for the use of WHC. Patients were divided in two groups according to the WHC: 1) Favorable progression of HE - HE absent at admission and at third day or any improvement in HE at third day; 2) Unfavorable progression of HE - Development of HE at third day or HE present at admission and stable/worse at third day. Improvement of HE was defined as any regression on the WHC and worsening of HE as any increase $\geq$ 1 degree on WHC. Glasgow Coma Scale (GCS)[12] was also applied at

admission and third day. Worsening of GCS at third day was defined as any decrease in GCS score.

Statistical analysis

The normality of the variable distribution was determined by the Kolmogorov–Smirnov test. Continuous variables were compared using Student's *t* test in the case of normal distribution or Mann-Whitney test in the remaining cases. Categorical variables were evaluated by chi-square test or Fisher's exact test as appropriate. Multiple logistic regression analysis (forward stepwise regression) was used to investigate the factors independently associated with unfavorable progression of HE and with 90-day mortality. The best cutoff of MELD score for predicting 90-day mortality was chosen based on Receiver operating characteristic (ROC) curve. The survival curve was calculated using the Kaplan-Meier method and survival differences between groups were compared using the log rank test. Correlation between two ordinal variables (WHC and GCS) was evaluated by the

Spearman's rank correlation analysis. All tests were performed by the SPSS software, version 22.0 (SPSS, Chicago, IL, USA). A P value of less than 0.05 was considered statistically significant.

RESULTS

Characteristics of the sample

Four hundred and sixty-seven admissions due to acute decompensation of liver cirrhosis were reported between January 2011 and November 2015. Of those, 174 were excluded for the following reasons: admission for less than 48 hours (n = 46), lost to follow-up (n = 12) and repeated hospitalization (n = 116). A total of 293 individuals composed the final sample of the study.

Table 1 exhibits the characteristics of the included patients. The mean age was 54.78 ± 11.32 years, 72% were males. Previous history of cirrhosis decompensation was observed in 69% of the sample and 31% of subjects reported active alcoholism during the past month. The most common

etiology of cirrhosis was hepatitis C (38%) followed by alcohol abuse (35%) and cryptogenic (8%).

Upon admission, upper gastrointestinal bleeding was observed in 42% of cases, ascites in 52%, ACLF in 25% and bacterial infections in 36%. The most common bacterial infections were spontaneous bacterial peritonitis (10%), urinary tract infection (10%), pneumonia (7%), and skin infections (4%). Forty-five percent of the subjects were classified as Child-Pugh C and the mean MELD score was 17.34 ± 6.71.

Factors associated with progression of HE during the first three days of hospitalization

At the first evaluation, 155 patients (53%) presented with HE (grades I, II, III or IV in 17%, 26%, 8% and 1%, respectively). The progression of HE during the first three days of hospitalization was at follows: 43% - HE absent at admission and at third day; 4% - HE absent at admission and present at third day; 26% - HE present at admission and improved at third day; 19% - HE present at admission and

stable at third day; 8% - HE present at admission and worsened at third day. Patients were then divided into two groups: 1) Favorable progression of HE - HE absent at admission and at third day or any improvement in HE at third day (69%); 2) Unfavorable progression of HE - Development of HE at third day or HE present at admission and stable/worse at third day (31%) (Figure 1).

Unfavorable progression of HE was associated in the bivariate analysis with previous HE (47% vs. 30%, P = 0.006), ascites (63% vs. 47%, P = 0.011), benzodiazepine (18% vs. 1%, P = 0.001) or kidney dysfunction (47% vs. 26%, P = 0.008) as precipitant factors of HE, higher median leukocyte count (8.26 $x10^9$ vs. 6.56 $x10^9$, P = 0.010), creatinine levels (1.25 mg/dL vs. 1.00 mg/dL, P = 0.001), CRP (20.90 mg/L vs. 11.00 mg/L, P = 0.010) and total bilirubin (2.80 mg/dL vs. 2.10 mg/dL, P = 0.009). Unfavorable progression of HE was also related to higher mean MELD (19.70 ± 7.70 vs. 16.29 ± 5.95, P < 0.001), CLIF-SOFA (8.24 ± 3.15 vs. 5.98 ± 2.94, P < 0.001),

higher proportion of Child-Pugh C (71% vs. 38%, P < 0.001) and ACLF (43% vs. 17%, P < 0.001) (Table 1).

A logistic regression analysis to investigate factors independently associated with unfavorable progression of HE was performed including the following variables with P ≤ 0.010 in the bivariate analysis: previous HE, ACLF, Child-Pugh C, MELD and leukocyte count. Other laboratory variables already present in the models were not included to avoid redundancy. CRP was also not included given the high proportion of missing values (11%). Unfavorable progression of HE was independently associated with previous HE (OR 1.919, 95% CI 1.116 – 3.299, P = 0.018), Child-Pugh C (OR 1.851, 95% CI 1.044 – 3.157, P = 0.035), ACLF (OR 2.982, 95% CI 1.646 – 5.404, P < 0.001).

Progression of HE during the first three days of hospitalization as a prognostic factor

Overall 30-day and 90-day mortality was 26% and 31%, respectively. Bivariate analysis (table 2) showed that 90-day

mortality was directly associated with ascites (82% vs. 39%, P < 0.001), bacterial infection (50% vs. 30%, P = 0.001), Child-Pugh C (74% vs. 32%, P < 0.001), ACLF (54% vs. 12%, P < 0.001) and unfavorable progression of HE (50% vs. 22%, P < 0.001). Ninety-day mortality was also related to higher MELD (22.42 ± 6.95 vs. 15.05 ± 5.18, P < 0.001), CLIF-SOFA (8.78 ± 2.82 vs. 5.73 ± 2.33, P < 0.001), higher median leukocyte count (8.09 $x10^9$ vs. 6.65 x 10^9, P = 0.011), creatinine (1.60 mg/dL vs. 1.00 mg/dL, P < 0.001), INR (1.62 vs. 1.39, P < 0.001), CRP (25.10 mg/L vs. 9.00 mg/L, P < 0.001), bilirubin (3.40 mg/dL vs. 1.80 mg/dL, P < 0.001), and lower sodium (133.22 ± 5.91 mEq/L vs. 135.63 ± 5.14 mEq/L, P < 0.001) and albumin (2.05 ± 0.61 g/dL vs. 2.49 ± 0.62 g/dL, P < 0.001).

Logistic regression analysis to investigate factors independently associated with 90-day mortality was performed including variables with P-value < 0.010 in the bivariate analysis (sodium levels, bacterial infection, Child-Pugh C, MELD, ACLF and unfavorable progression of HE). Other

laboratory variables already present in the models were not included in the regression analysis to avoid redundancy. The parameters that were independently associated with 90-day mortality were MELD score (OR 1.203, 95% CI 1.141 – 1.269, P < 0.001) and unfavorable progression of HE (OR 2.318, 95% CI 1.237 – 4.342, P = 0.009).

The best cutoff of MELD score for predicting 90-day mortality was chosen based on ROC curve. Figure 2 shows the Kaplan-Meier curves for death according to the progression of HE and MELD categories. The Kaplan-Meier survival probability at 90-day was 91% in patients with MELD < 18 and favorable progression of HE, 71% in those with MELD < 18 but unfavorable progression of HE, 48% in patients with MELD ≥ 18 and favorable progression of HE, and only 31% in subjects with both MELD ≥ 18 and unfavorable progression of HE (P < 0.001, long-rank test).

Influence of ACLF on HE progression and prognosis

Among the 219 patients without ACLF and HE at admission, HE remained absent at third day in 50% and developed in 4%. In those without ACLF but with HE at admission, HE improved in 27%, was stable in 14% and worsened in 6%. Among those with ACLF and without HE at admission, HE remained absent in 23%, developed in 3%. In subjects with ACLF and HE at admission, HE improved in 24%, was stable in 35% and worsened in 15%. Overall, a higher proportion of patients exhibited unfavorable progression of HE among patients with ACLF at admission (53% vs. 23%, $P < 0.001$).

Figure 3 exhibited the Kaplan-Meier curves for death according to the progression of HE and the presence of ACLF. Patients without ACLF who showed unfavorable progression of HE exhibited lower Kaplan-Meier survival probability as compared to those who remained without HE or improved (71% vs. 84%, $P = 0.016$). Similarly, among those with ACLF,

unfavorable progression of HE was associated with significantly lower survival (23% vs. 46%, P = 0.012).

Glasgow Coma Scale in the assessment of progression of mental status in cirrhotic patients

At admission, GCS was 15 in 205 patients (70%), 14 in 48 subjects (16%) and ≤ 13 in 40 (14%). At third day evaluation, GCS was 15 in 228 patients (78%), 14 in 25 (9%) and ≤ 13 in 39 (13%). GCS was not available at third day for one patient. GCS was strongly correlated with WHC at admission (r = -0.736, P < 0.001) and at third day evaluation (r = -0.730, P < 0.001). At admission, GCS was 15 in all patients without HE and 3 in those with grade 4 HE according to WHC. Median GCS was 15.0, 14.0 and 12.0 among patients with HE grades 1, 2 and 3, respectively. Mortality rates were 25%, 38% and 53% among patients with GCS of 15, 14 and ≤ 13 at admission, respectively (P = 0.002). Worsening of GCS at third day was observed in only 32 patients (11%) and was associated with higher mean MELD (21.04 ± 6.84 vs. 16.71 ± 6.62, P =

0.001) and CLIF-SOFA scores (8.38 ± 2.11 vs. 6.43 ± 2.83, P < 0.001), higher proportion of Child-Pugh C patients (65% vs. 43%, P = 0.021) and of patients with HE diagnosed by the WHC at admission (81% vs. 50%, P = 0.001). Worsening of GCS at third day was related with significantly high mortality as compared to those who had the GCS stable or improved at second evaluation (69% vs. 27%, P < 0.001).

Discussion

Hepatic encephalopathy is one of the most common complications of cirrhosis, and it has been associated with significant impact in patients' health-related quality of life[13] and on survival independent of the severity of cirrhosis.[7] In the present study, the majority of patients (69%) exhibited a favorable progression of HE, with either HE remaining absent after three days of hospitalization, or with improvement of HE present at admission. However, almost one third of subjects developed HE at third day or failed to improve. In the bivariate

analysis, unfavorable progression of HE was associated with variables related to the severity of liver disease such as previous HE, ascites, Child-Pugh C, higher MELD score and total bilirubin levels. However, it was also related to factors that mostly reflect the severity of the episode of acute decompensation and inflammatory state, such as higher leukocyte count, CRP, creatinine levels and the presence of ACLF. In the regression analysis, unfavorable progression of HE was associated with previous HE, Child-Pugh C and ACLF. Although we were not able to find previous studies evaluating factors associated with progression of HE during hospitalization, these findings are expected as the severity of HE at baseline impact on these models. A recent subanalysis of the CANONIC study revealed significant differences between patients HE related or not to ACLF.[14] Based on their results, the authors proposed two distinct presentations of HE in which ACLF-related HE are usually associated with younger age as a consequence of impairment in liver function and bacterial

infections, active alcoholism or dilutional hyponatremia.[14] Other important features of ACLF-related HE are findings consistent with an exaggerated generalized inflammatory reaction that may play a role in brain dysfunction.[14] The findings observed in the present study probably complement those of the CANONIC study, indicating that ALCF and more intense inflammatory response at baseline are also associated with a higher risk of development or failure to improve HE during the first days of hospitalization.

Unfavorable progression of HE and MELD score were independently associated with 90-day mortality among patients hospitalized for AD of cirrhosis. HE is regarded as an important prognostic factor in liver cirrhosis, either in out- or inpatient setting.[14-17] In the recent analysis derived from the CANONIC cohort, HE was associated with higher mortality probability that increased significantly as the HE grade worsened.[14] In another study that evaluated long-term impact of HE in patients with cirrhosis, grades 2 or 3 HE were

associated with high mortality in the cohort of hospitalized subjects, even after adjusting for MELD score.[17] No previous study evaluating the prognostic impact of changes in HE grade during hospitalization were found. Although it is possible that the unfavorable progression of HE in those patients merely reflect the baseline severity of cirrhosis or of the precipitant factor, it remained associated with high 90-day mortality even after controlling for several important prognostic factors. In addition, a patient who fail to improve or with new-onset HE posed a clinical challenge and knowing the relationship of this event with prognosis may allow individualization of care.

The prognostic significance of HE progression was evaluated according to MELD score categories. Patients with favorable progression of HE and low MELD scores (< 18) showed good prognosis (90-day survival ≈ 91%). However, even in subjects with low MELD, unfavorable progression of HE was associated with worse prognosis and a 90-day survival of 71%. Similarly, in those with high MELD, favorable

progression of HE was associated with 90-day survival of 48% versus 31% for those with both high MELD and unfavorable progression of HE. These results indicate that combining clinical assessment of HE progression over the first three days of hospitalization and MELD score provided a well-defined four-level stratification for short-term prognosis in patients with cirrhosis hospitalized for AD.

As mentioned above, ACLF-related HE have specific features and it has been recently proposed that it should regarded as a distinct entity from isolated HE.[14] For that reason, the impact of HE progression on prognosis was evaluated in patients with and without ACLF. Unfavorable progression of HE negatively impact prognosis regardless of the presence of ACLF. The worst 90-day survival was observed among patients with ACLF who exhibited an unfavorable progression of HE (23%). These findings reinforce the utility of serial assessment of HE, regardless of the HE type, isolated or ALCF-related.

GCS was used as an alternative to WHC to evaluate the progression of cognitive changes during hospitalization. Although GCS strongly correlated with WHC, the vast majority of patients with grades 1 and 2 HE showed GCS ≥ 14. Worsening of GCS at third day was strongly related to mortality, even though it was observed in only 32 patients (11%). GCS is a useful tool for objective evaluation and continued monitoring of changes in the mental status of non-cirrhotic patient.[18] There few data regarding GCS utility in patients with cirrhosis. Original and modified version of GCS was used in therapeutic trials of flumazenil for HE.[19-21] A North-American study aimed to describe a modified version of WHC, named HE Scoring Algorithm (HESA), showed that GCS differed among the four stages of the WHC, but the differences between grades I and II were small and not clinically useful.[22] These data suggest that GCS might be useful in patients with more severe HE and that the worsening

of GCS, although uncommon, is associated with poor prognosis.

We acknowledge some limitation of our analysis. First, the use of WHC criteria has been criticized given its subjectiveness and limited inter-observer reliability, especially for grade 1.[23] However, WHC still recommended as the gold standard in clinical practice.[23] In addition, the impact of inter-observer variability was probably minimized in the present study because the first and second evaluations for a given patient were performed by the same investigator. Regarding the difficulty to distinguish among absence of HE and HE grade 1, we performed an analysis considering only grades ≥ 2 as overt HE and no advantage in prognostication was observed (data not shown). Secondly, our study was performed outside the context of a clinical trial, and included a very heterogeneous population in distinct clinical scenarios. Therefore, variation in the approach of specific cases is to be expected. Finally, this was a single-center study; thus, the results might be difficult to

extrapolate to other cohorts. Larger multicenter studies, including more patients with HE grades 3 and 4 would be useful in order to validate our results e further investigate dynamic changes in GCS among patients with cirrhosis.

In conclusion, unfavorable progression HE during the first days of hospitalization for AD of cirrhosis was more frequent in patients with previous history of HE and in those who present with more severe liver impairment and ACLF. Unfavorable progression of HE was associated with short term mortality and therefore can be used for prognostication and to individualize clinical care.

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FIGURE LEGENDS

Fig 1. Distribution of patients included in the study in relation to the presence of HE at admission and the progression over the first three days of hospitalization.

Fig. 2. Kaplan-Meier survival of 293 hospitalized patients with cirrhosis stratified according to the progression of HE and MELD score dichotomized in 18. The survival probability at 90-day was 91% in patients with MELD < 18 and favorable progression of HE, 71% in those with MELD < 18 but unfavorable progression of HE, 48% in patients with MELD ≥ 18 and favorable progression of HE, and 31% in subjects with both MELD ≥ 18 and unfavorable progression of HE ($P < 0.001$, long-rank test).

Fig. 3. Kaplan-Meier survival of 293 hospitalized patients with cirrhosis stratified according to the progression of HE and the presence of ACLF at admission. Patients without ACLF who showed unfavorable progression of HE exhibited lower Kaplan-Meier survival probability as compared to those

who remained without HE or improved (71% vs. 84%, P = 0.016). Among those with ACLF, unfavorable progression of HE was also associated with significantly lower survival (23% vs. 46%, P = 0.012).

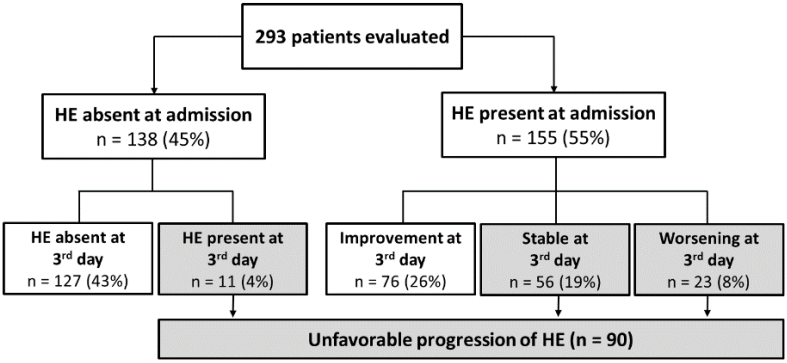

Fig 1. Distribution of patients included in the study in relation to the presence of HE at admission and the progression over the first three days of hospitalization.

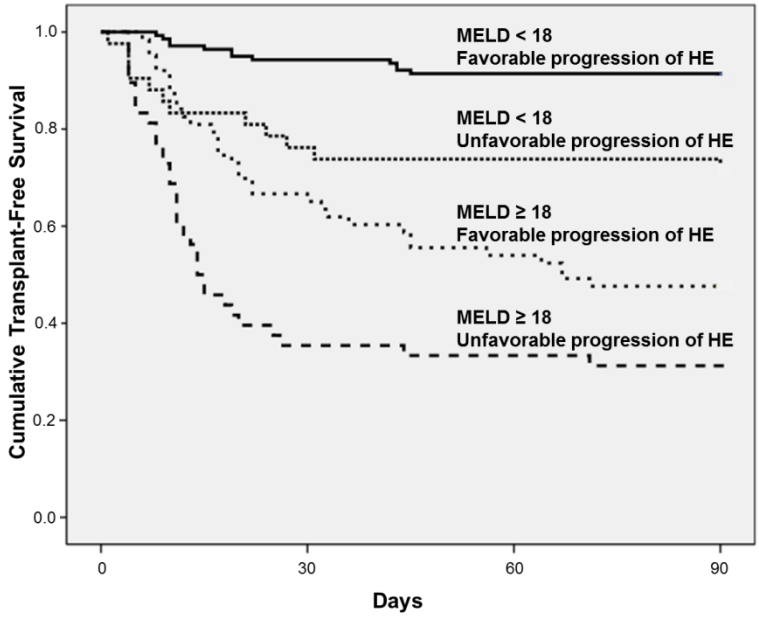

Fig. 2. Kaplan-Meier survival of 293 hospitalized patients with cirrhosis stratified according to the progression of HE and MELD score dichotomized in 18.

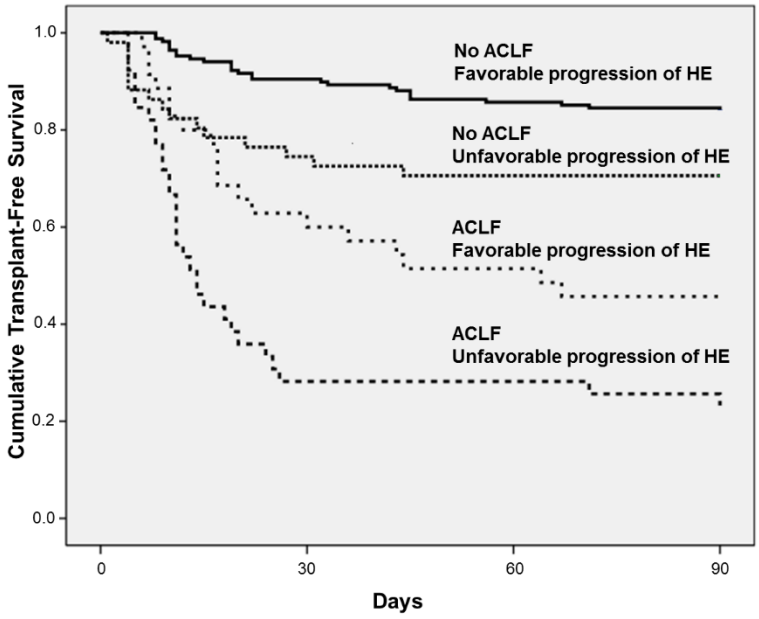

Fig. 3. Kaplan-Meier survival of 293 hospitalized patients with cirrhosis stratified according to the progression of HE and the presence of ACLF at admission.

Table 1. Characteristics of included patients and factors associated with unfavorable progression of HE (early development, persistence or worsening of HE)

	All (n = 293)	Favorable progression of HE (n = 203)	Unfavorable progression of HE (n = 90)	P
Age (years), mean ± SD	54.78 ± 11.32	54.93 ± 11.95	54.45 ± 9.80	0.746
Male Gender, n (%)	211 (72)	143 (70)	68 (76)	0.369
Etiology of cirrhosis, n (%)				
Alcohol	104 (35)	65 (32)	39 (43)	0.062
Hepatitis C	110 (38)	77 (39)	33 (37)	0.837
Hepatitis B	17 (6)	10 (5)	7 (8)	0.335
Cryptogenic	23 (8)	20 (10)	3 (3)	0.056
Other	39 (13)	31 (15)	8 (9)	0.138
Previous decompensation, n (%)	200 (69)	138 (68)	62 (71)	0.718
Previous HE, n (%)	103 (35)	61 (30)	42 (47)	0.006
Active alcoholism, n (%)	89 (31)	58 (29)	31 (34)	0.326
Complication at admission, n (%)				
Ascites	153 (52)	96 (47)	57 (63)	0.011
Gastrointestinal bleeding	122 (42)	85 (42)	37 (41)	0.903
SBP	30 (10)	21 (10)	9 (10)	0.918
Bacterial infection*	105 (36)	67 (33)	38 (42)	0.129
HE at admission, n (%)				
Any grade	155 (53)	76 (37)	79 (88)	<0.001
Grade I	51 (17)	25 (12)	26 (29)	0.001
Grade II	76 (26)	34 (17)	42 (47)	<0.001
Grade III	24 (8)	16 (8)	8 (9)	0.772
Grade IV	4 (1)	1 (1)	3 (3)	0.088
Precipitating factor for HE, n (%)#				
Digestive bleeding	60 (39)	25 (33)	35 (44)	0.145
Infection	58 (37)	24 (32)	34 (43)	0.141
Constipation	24 (16)	14 (18)	10 (13)	0.321
Benzodiazepines	15 (10)	1 (1)	14 (18)	0.001
Hydroelectrolytic disturbances	32 (21)	13 (17)	19 (24)	0.286
Kidney dysfunction	57 (37)	20 (26)	37 (47)	0.008
Diuretics	100 (34)	68 (34)	32 (36)	0.648
Other	9 (6)	5 (7)	4 (5)	0.743
Not identified	7 (5)	5 (7)	2 (3)	0.270
Laboratory data				
Leukocyte count (x10^9), median	7.09	6.56	8.26	0.010
Sodium (mEq/L), mean ± SD	134.88 ± 5.50	135.14 ± 5.33	134.31 ± 5.83	0.239
Creatinine (mg/dL), median	1.10	1.00	1.25	0.001
INR, median	1.45	1.42	1.50	0.056
Albumin (g/dL), mean ± SD	2.36 ± 0.65	2.38 ± 0.63	2.31 ± 0.71	0.411
CRP (mg/L),median	14.20	11.00	20.90	0.010
Total bilirubin (mg/dL), median	2.20	2.10	2.80	0.009
Child-Pugh score, mean ± SD	9.35 ± 1.94	9.01 ± 1.87	10.10 ± 1.90	<0.001
Child-Pugh C, n (%)	130 (45)	76 (38)	54 (71)	<0.001
MELD score, mean ± SD	17.34 ± 6.71	16.29 ± 5.95	19.70 ± 7.70	<0.001
CLIF-SOFA, mean ± SD	6.63 ± 2.85	5.96 ± 2.94	8.24 ± 3.15	<0.001
ACLF, n (%)	74 (25)	35 (17)	39 (43)	<0.001

ACFL = Acute-on-chronic liver failure; SD = Standard deviation; AST = aspartate aminotransferase; ALT = alanine aminotransferase; GGT = Gamma-glutamyltransferase; INR = international normalised ratio; CRP = C-reactive protein; MELD = Model for End-stage Liver Disease

#Within patients with HE at admission

*Including SBP

Table 2. Factors associated with 90-day mortality among patients with cirrhosis admitted for acute decompensation

	Survivors (n = 202)	Deaths (n = 91)	P
Age (years), mean ± SD	54.55 ± 11.34	55.29 ± 11.32	0.608
Male Gender, n (%)	150 (74)	61 (67)	0.202
Etiology of cirrhosis, n (%)			
Alcohol	74 (37)	30 (33)	0.544
Hepatitis C	76 (38)	34 (37)	0.966
Hepatitis B	11 (5)	6 (7)	0.697
Cryptogenic	16 (8)	7 (8)	0.946
Previous decompensation, n (%)	136 (68)	64 (72)	0.471
Previous HE, n (%)	67 (33)	36 (40)	0.289
Active alcoholism, n (%)	61 (30)	28 (31)	0.942
Complication at admission, n (%)			
Ascites	78 (39)	75 (82)	**<0.001**
Gastrointestinal bleeding	94 (47)	28 (31)	**0.011**
SBP	19 (10)	11 (12)	0.491
Bacterial infection*	60 (30)	45 (50)	**0.001**
Laboratory data			
Leukocyte count (x10^9), median	6.65	8.09	**0.011**
Sodium (mEq/L), mean ± SD	135.63 ± 5.14	133.22 ± 5.91	**<0.001**
Creatinine (mg/dL), median	1.00	1.60	**<0.001**
INR, median	1.39	1.62	**<0.001**
Albumin (g/dL), mean ± SD	2.49 ± 0.62	2.05 ± 0.61	**<0.001**
CRP (mg/L),median	9.00	25.10	**<0.001**
Total bilirubin (mg/dL), median	1.80	3.40	**<0.001**
Child-Pugh score, mean ± SD	8.76 ± 1.76	10.70 ± 1.65	**<0.001**
Child-Pugh C, n (%)	65 (32)	65 (74)	**<0.001**
MELD score, mean ± SD	15.05 ± 5.18	22.42 ± 6.95	**<0.001**
CLIF-SOFA, mean ± SD	5.73 ± 2.33	8.78 ± 2.82	**<0.001**
ACLF, n (%)	25 (12)	49 (54)	**<0.001**
Unfavorable progression of HE, n (%)	45 (22)	45 (50)	**<0.001**

ACFL = Acute-on-chronic liver failure; HE = Hepatic encephalopathy; SD = Standard deviation; INR = international normalised ratio; CRP = C-reactive protein; MELD = Model for End-stage Liver Disease
*Including SBP

ANEXO

ANEXO A – PARECER CONSUBSTANCIADO COMITÊ DE ÉTICA E PESQUISA

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Pró-Reitoria de Pesquisa e Extensão
Comitê de Ética em Pesquisa com Seres Humanos

CERTIFICADO Nº 1822

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APROVADO

PROCESSO: 1822 **FR:** 402205

TÍTULO: AVALIAÇÃO DE MARCADORES PROGNÓSTICOS EM PORTADORES DE CIRROSE HEPÁTICA DESCOMPENSADA

AUTOR: Leonardo de Lucca Schiavon, Esther Buzaglo Dantas Correa, Janaina Luz Narciso Schiavon, Maria Luiza Bazzo, Marcelo Ronsoni, César Lazzarotto

FLORIANÓPOLIS, 28 **de** Fevereiro **de** 2011.

Coordenador do CEPSH/UFSC

ANEXO B – Normas para Publicação na Revista Liver International

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The abstract must be organized as follows: - Background & Aims

- Methods
- Results
- Conclusions

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[15] Groszmann RJ, Wongcharatrawee S. The hepatic venous pressure gradient: anything worth doing should be done right. Hepatology 2004;39:280-282.

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