

· 其他肝病 ·

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COSSH-ACLF II 评分对HBV相关慢加急性肝衰竭 合并肝性脑病患者短期预后的预测价值

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摘要: **目的** 探讨中国重症乙型肝炎研究学组-慢加急性肝衰竭评分(COSSH-ACLF II)对HBV相关慢加急性肝衰竭(HBV-ACLF)合并肝性脑病(HE)患者短期预后的预测价值。**方法** 回顾性分析2019年1月—2024年10月山西医科大学第一医院收治并确诊的134例HBV-ACLF合并HE患者,根据随访90 d患者的生存状态分为生存组($n=60$)和死亡组($n=74$)。分别计算COSSH-ACLF II评分、COSSH-ACLF评分、终末期肝病模型(MELD)评分、终末期肝病模型联合血清钠(MELD-Na)评分和MELD 3.0评分,比较两组基础临床资料、实验室指标、并发症及各模型评分等。计数资料两组间比较采用 χ^2 检验;计量资料两组间比较采用成组 t 检验或者Mann-Whitney U 检验。采用受试者操作特征曲线(ROC曲线)分析各评分对HBV-ACLF合并HE患者预后预测的临床效能。**结果** 死亡组年龄[(56.09 $\pm$ 10.52)岁]明显大于生存组[(49.23 $\pm$ 11.57)岁]($t=2.720, P=0.007$)。死亡组中并发症发生率(上消化道出血、腹水)、实验室指标(白细胞计数、中性粒细胞计数、总胆红素、国际标准化比值、血肌酐、血尿素氮)均明显高于生存组(P 值均 <0.05)。死亡组COSSH-ACLF II、COSSH-ACLF、MELD、MELD-Na和MELD 3.0评分均高于生存组(P 值均 <0.001)。将患者以COSSH-ACLF II评分危险分层的3个区间分为低危组、中危组和高危组,比较发现,COSSH-ACLF II评分分值越高,患者病死率越高($\chi^2=44.371, P<0.001$)。根据ROC曲线分析结果,COSSH-ACLF II评分评价HBV-ACLF合并HE患者90 d死亡的ROC曲线下面积(AUC)为0.883, 95%CI为0.837~0.919。截断值为7.25时,敏感度90.5%,特异度78.7%,预测准确度85.07%。COSSH-ACLF II的AUC(0.883)优于COSSH-ACLF(0.841)、MELD 3.0(0.733)、MELD-Na(0.723)、MELD(0.716)(P 值均 <0.05)。**结论** 采用COSSH-ACLF II评分可提高预测HBV-ACLF合并HE患者90 d预后的准确度,COSSH-ACLF II危险分层有助于简化患者病情分级。

关键词: 乙型肝炎病毒;慢加急性肝功能衰竭;肝性脑病;预后

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Value of Chinese Group on the Study of Severe Hepatitis B-acute-on-chronic liver failure II score in predicting the short-term prognosis of patients with acute-on-chronic liver failure comorbid with hepatic encephalopathy

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Abstract: Objective To investigate the value of Chinese Group on the Study of Severe Hepatitis B-acute-on-chronic liver failure II (COSSH-ACLF II) score in predicting the short-term prognosis of patients with hepatitis B virus-related acute chronic liver failure (HBV-ACLF) comorbid with hepatic encephalopathy (HE). **Methods** A retrospective analysis was performed for 134 patients who were admitted to The First Hospital of Shanxi Medical University from January 2019 to October 2024 and were diagnosed with HBV-ACLF and HE, and according to the survival status of the patients on day 90 of follow-up, they were divided into survival group with 60 patients and death group with 74 patients. Related scores were calculated, including COSSH-ACLF II score, COSSH-

ACLF score, Model for End-Stage Liver Disease (MELD) score, MELD combined with serum sodium concentration (MELD-Na) score, and MELD 3.0 score, and the two groups were compared in terms of basic clinical data, laboratory markers, complications, and the scores of each model. The chi-square test was used for comparison of categorical data between two groups, and the *t*-test or the Mann-Whitney *U* test was used for comparison of continuous data between two groups. The receiver operating characteristic (ROC) curve was used to assess the performance of each score in predicting the prognosis of patients with comorbidity of HBV-ACLF and HE. **Results** The death group had a significantly higher age than the survival group (56.09 ± 10.52 years vs 49.23 ± 11.57 years, $t=2.720$, $P=0.007$). Compared with the survival group, the death group had significantly higher incidence rate of complications (upper gastrointestinal bleeding and ascites) and laboratory markers (white blood cell count, neutrophil count, total bilirubin, international normalized ratio, serum creatinine, and blood urea nitrogen) (all $P<0.05$). The death group had significantly higher COSSH-ACLF II, COSSH-ACLF, MELD, MELD-Na, and MELD 3.0 scores than the survival group (all $P<0.001$). The patients were stratified into low-, moderate-, and high-risk groups based on COSSH-ACLF II score, and comparison between groups showed that the mortality rate of patients increased with the increase in COSSH-ACLF II score ($\chi^2=44.371$, $P<0.001$). The ROC curve analysis showed that COSSH-ACLF II score had an area under the ROC curve (AUC) of 0.883 (95% confidence interval: 0.837—0.919) in predicting the 90-day mortality of patients with comorbidity of HBV-ACLF and HE, with a sensitivity of 90.5%, a specificity of 78.7%, and a predictive accuracy of 85.07% at the cut-off value of 7.25. COSSH-ACLF II score had a better performance than COSSH-ACLF (AUC=0.841, $P<0.05$), MELD 3.0 (AUC=0.733, $P<0.05$), MELD-Na (AUC=0.723, $P<0.05$), and MELD (AUC=0.716, $P<0.05$). **Conclusion** COSSH-ACLF II score can improve the accuracy of predicting 90-day prognosis in patients with comorbidity of HBV-ACLF and HE, and COSSH-ACLF II risk stratification can help to simplify the grading of patients.

Key words: Hepatitis B Virus; Acute-on-Chronic Liver Failure; Hepatic Encephalopathy; Prognosis

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慢加急性肝功能衰竭(ACLF)是指慢性肝病的基础上,由于急性损伤因素致肝功能短期内恶化的临床综合征,病死率高且预后差,据报道早期病死率达50%~90%^[1]。肝性脑病(HE)是一种因严重功能障碍或异常门-体分流引起的以代谢紊乱为基础的神经精神异常综合征。据报道,出现发作性HE后,ACLF患者的病死率可高达70%~90%^[2-4]。目前,唯一被证实对ACLF患者有益的治疗方法是肝移植,但存在肝源缺乏及费用等问题^[5]。因此,监测疾病进展、早期诊断、评估ACLF患者预后对制定临床最佳治疗方案至关重要。

目前临床常用的肝病预后评估方法包括终末期肝病模型(MELD)评分, MELD-Na评分和MELD 3.0评分,但特异度和灵敏度存在局限性^[6-7]。这可能与评分系统基于外国人种建立、遗传背景不同,且未考虑年龄、肝脏细胞再生等影响HBV-ACLF患者预后的关键因素有关。中国重症乙型肝炎研究学组-慢加急性肝衰竭评分(Chinese group on the study of severe hepatitis B-acute on chronic liver failure II, COSSH-ACLF II),对HBV-ACLF预后评估更具代表性^[7],但该评分系统对HE患者预后评估的研究国内报道较少。本研究旨在评估该评分系统对HBV-ACLF合并HE患者短期预后的价值。

1 资料与方法

1.1 研究对象 本研究为病例对照研究,共纳入2019年1月—2024年10月在山西医科大学第一医院接受检查与治疗的134例HBV-ACLF且确诊为HE的患者。其中,男116例,女18例,平均年龄(51.98 ± 7.65)岁。纳入标准:(1)符合《肝衰竭诊治指南(2018年版)》中ACLF的诊断标准^[8];(2)HBV-ACLF同时确诊HE患者,HE分级采用West-Haven分级标准^[9];(3)患者与家属同意参与本研究。排除标准:(1)除HBV外合并其他病毒感染,或合并自身免疫性肝病、药物性和/或酒精性肝损伤等其他疾病;(2)妊娠或哺乳期妇女;(3)合并严重精神疾病或神经系统严重疾病、酒精戒断综合征、终末期肝癌的患者;(4)患者的一般资料不完整。

1.2 研究方法 收集所有患者在本院住院期间出现HE时的基础临床资料和检验指标。基础临床资料包括:性别,年龄,是否有肝硬化、腹水、消化道出血等。检验指标包括:白细胞计数、中性粒细胞计数(NEUT)、总胆红素(TBil)、白蛋白、血清肌酐、血清钠离子浓度、凝血酶原活动度(INR)等。90 d后观察患者预后,治疗后病情好转出院者纳入生存组,病情恶化死亡者纳入死亡组。

1.3 预后评分系统 COSSH-ACLF II = $1.649 \times \ln(\text{INR}) + 0.457 \times \text{HE 评分} + 0.425 \times \ln[\text{NEUT} (\times 10^9/\text{L})] + 0.396 \times \ln[\text{TBil} (\mu\text{mol/L})] + 0.576 \times \ln[\text{血尿素氮} (\text{mmol/L})] + 0.033 \times \text{年龄}$; COSSH-ACLF II 危险分层包括低危(<7.4)、中危(7.4~8.4)和高危(>8.4)^[7]。COSSH-ACLF^[10]、MELD、MELD-Na、MELD 3.0 评分按照最新指南公式进行计算^[11]。

1.4 统计学方法 采用 R 语言 4.2.3 版本和 SPSS 26.0 软件进行统计学分析。计数资料组间比较采用 χ^2 检验。呈正态分布的计量资料以 $\bar{x} \pm s$ 表示,两组间比较采用成组 t 检验;呈偏态分布的计量资料以 $M(P_{25} \sim P_{75})$ 表示,两组间比较采用 Mann-Whitney U 检验。绘制受试者操作特征曲线(ROC 曲线),通过曲线下面积(AUC)评估模型评分对患者 90 d 及随访截止时生存结局的预测价值,AUC 的组间比较用 Delong 检验, $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 两组患者基本特征、实验室指标比较 死亡组年龄 $[(56.09 \pm 10.52) \text{岁}]$ 明显大于生存组 $[(49.23 \pm 11.57) \text{岁}]$,

差异有统计学意义($P = 0.007$)。两组性别、基础疾病(肝硬化、高血压、糖尿病)差异均无统计学意义(P 值均 > 0.05)。死亡组中并发症发生率(上消化道出血、腹水)、白细胞计数、NEUT、TBil、INR、血肌酐、血尿素氮亦明显高于生存组(P 值均 < 0.05)。死亡组 COSSH-ACLF II、COSSH-ACLF、MELD、MELD-Na 和 MELD 3.0 评分均高于生存组,差异均有统计学意义(P 值均 < 0.05)(表 1)。

2.2 病死率与 COSSH-ACLF II 评分危险分层的关系 根据 COSSH-ACLF II 评分危险分层分为低危组(63 例)、中危组(33 例)、高危组(38 例),观察患者 90 d 内的病死率。COSSH-ACLF II 评分越高,病死率显著上升($\chi^2 = 44.37, P < 0.001$)。中危组的病死率显著高于低危组(75.76% vs 19.05%, $\chi^2 = 15.62, P < 0.001$),高危组的病死率远高于低危组(97.37% vs 19.05%, $\chi^2 = 38.74, P < 0.001$),危险分层越高,死亡风险越大。高危组的病死率亦高于中危组($\chi^2 = 8.93, P = 0.003$)。

2.3 不同评分对 HBV-ACLF 合并 HE 患者短期预后的评估 ROC 曲线分析结果显示,COSSH-ACLF II、COSSH-

表 1 两组患者基线特征及预后评分比较

Table 1 Comparison of baseline characteristics and prognostic scores between the two groups

指标	生存组($n=60$)	死亡组($n=74$)	统计值	P 值
年龄(岁)	49.23±11.57	56.09±10.52	$t=2.720$	0.007
男[例(%)]	55(91.67)	61(82.43)	$\chi^2=0.182$	0.669
基础疾病[例(%)]				
肝硬化	47(78.33)	62(83.78)	$\chi^2=0.527$	0.462
高血压	8(13.33)	14(18.91)	$\chi^2=0.935$	0.333
糖尿病	5(8.33)	8(10.81)	$\chi^2=0.081$	0.774
并发症[例(%)]				
上消化道出血	16(26.67)	56(75.68)	$\chi^2=41.518$	<0.001
腹水	40(66.67)	60(81.08)	$\chi^2=4.331$	0.035
实验室指标				
白细胞计数($\times 10^9/\text{L}$)	6.43(4.01~8.11)	8.30(4.57~10.73)	$Z=-4.134$	<0.001
NEUT($\times 10^9/\text{L}$)	3.78(2.73~5.37)	6.53(3.03~8.72)	$Z=-5.512$	<0.001
血小板计数($\times 10^9/\text{L}$)	109(82~143)	90(62~115)	$Z=-1.962$	0.051
INR	1.82(1.65~2.06)	2.36(1.75~2.88)	$Z=-4.121$	<0.001
TBil($\mu\text{mol/L}$)	228.70(113.81~362.71)	294.45(241.72~365.15)	$Z=-2.233$	0.023
丙氨酸转氨酶(U/L)	490(192~981)	391(119~995)	$Z=-0.127$	0.882
白蛋白(g/L)	29.28(26.91~32.34)	29.14(27.67~33.93)	$Z=-0.049$	0.972
血肌酐($\mu\text{mol/L}$)	63(52~78)	75(60~108)	$Z=-3.172$	0.001
血尿素氮(mmol/L)	4.08(3.02~6.64)	7.64(5.43~12.06)	$Z=-6.371$	<0.001
血清钠(mmol/L)	137(135~142)	138(132~141)	$Z=-0.271$	0.272
MELD 评分(分)	22.31±6.02	25.98±8.58	$t=-5.431$	<0.001
MELD-Na 评分(分)	24.15±5.67	27.03±7.11	$t=-5.633$	<0.001
MELD 3.0 评分(分)	23.97±5.57	27.19±8.12	$t=-5.720$	<0.001
COSSH-ACLF 评分(分)	4.33(3.73~4.27)	6.09(4.66~7.32)	$Z=-6.498$	<0.001
COSSH-ACLF II 评分(分)	6.32(5.72~7.33)	7.64(7.11~8.68)	$Z=-8.472$	<0.001

ACLF、MELD、MELD-Na和MELD 3.0评分均对HBV-ACLF患者90 d预后具有一定的预测价值(P 值均 <0.001),其中COSSH-ACLF II评分预测患者90 d死亡的AUC最大(0.883)(95%CI:0.837~0.919),截断值为7.25时,敏感度90.5%,特异度78.7%,预测准确度85.07%。而COSSH-ACLF、MELD、MELD-Na、MELD 3.0评分的AUC分别为0.841、0.716、0.723、0.733(图1,表2)。

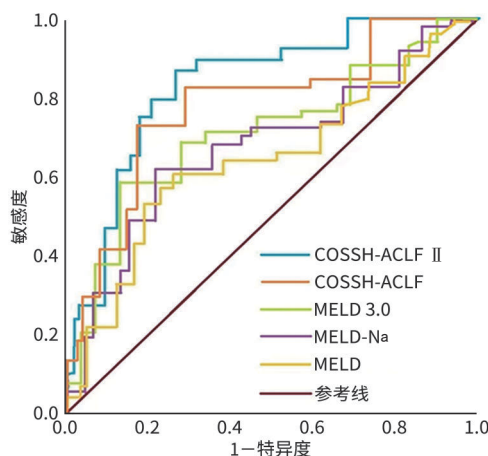


图1 90 d不同评分预后判断的ROC曲线

Figure 1 ROC curves for prognostic assessment at 90 days with different scores

3 讨论

HBV-ACLF约占我国肝衰竭患者总数的80%,是指肝功能相对稳定的慢性肝病患者,在急性损伤因素作用下,短期内迅速恶化的肝衰竭综合征^[12]。尽管内科医疗水平的进步改善了慢性肝病患者的预后,但ACLF,尤其是合并HE患者短期预后仍然很差,早期评估这类患者的预后将有助于降低短期病死率和指导患者的临床管理^[13]。

本研究表明,死亡组年龄明显高于生存组,而两组性别无明显差异。死亡组的腹水、消化道出血发生率明显高于生存组,说明腹水、消化道出血为严重并发症,提示预后不良,病死率高。本研究中死亡组INR、血肌酐、

血尿素氮等实验室指标明显高于生存组,提示患者合并肾功能不全、凝血功能障碍,表明该类患者合并多系统衰竭,短期预后不良,与国内外既往研究一致^[14]。

预后评分的敏感度和准确性对于决定强化治疗策略、评估ACLF患者的预后非常重要。本研究显示,COSSH-ACLF II评分对患者90 d预后的预测价值优于COSSH-ACLF等其他4种评分模型。COSSH-ACLF II评分预测患者90 d预后的AUC亦大于其他评分,差异有统计学意义(P 值均 <0.05)。临床常用的肝病预后评估方法为MELD评分,其敏感度偏低,因人种、饮食习惯、文化差异,肝损伤病因不同等,预后判断和诊断也存在差异性^[6],2017年COSSH提出的针对国内HBV-ACLF患者建立的COSSH-ACLF评分预测模型,纳入了年龄、循环、呼吸、HE分级等指标,更能反映HBV-ACLF患者预后状态,其次COSSH-ACLF是针对HBV-ACLF人群设计的,因此对HBV-ACLF预后评估更具代表性^[7]。

COSSH-ACLF评分涉及6种器官衰竭评估和超过10项评分指标,不利于临床医师进行快速的预后评估和病情分级。2021年推出的COSSH-ACLF评分2.0(COSSH-ACLF II)和简化版危险分层,显著提高了临床医师对ACLF患者进行快速预后评估和病情分级的效率。但该评分系统对HE患者预后评估的研究国内外报道较少。本研究旨在探讨该评分系统对ACLF合并HE患者短期预后的价值。

本研究结果显示:(1)死亡组患者的COSSH-ACLF II评分明显高于生存组,且COSSH-ACLF II评分越高,患者90 d内病死率越高,COSSH-ACLF II评分 >8.4 分,病死率高达97.37%,提示COSSH-ACLF II评分高低可反映HBV-ACLF合并HE患者病情严重程度及可用于判断患者的短期预后;(2)ROC曲线结果显示,COSSH-ACLF II评分评价患者预后的AUC为0.883,提示该评分系统对预后预测的准确性较好;(3)COSSH-ACLF II对HBV-ACLF合并HE患者90 d预后的预测效能高于MELD、MELD-Na、

表2 不同预后评分对HBV-ACLF合并HE患者90 d死亡的预测效能分析

Table 2 Analysis of the predictive efficacy of different prognostic scores for 90-days mortality in patients with HBV-ACLF complicated by HE

预后评分	AUC	95%CI	截断值	敏感度	特异度	预测准确度(%)	P 值
COSSH-ACLF II	0.883	0.837 ~ 0.919	7.25	0.905	0.787	85.07	<0.001
COSSH-ACLF	0.841 ¹⁾	0.786 ~ 0.876	6.79	0.881	0.693	79.85	<0.001
MELD 3.0	0.733 ¹⁾²⁾	0.670 ~ 0.789	29.40	0.873	0.621	76.12	<0.001
MELD-Na	0.723 ¹⁾²⁾	0.663 ~ 0.773	28.21	0.807	0.673	74.43	<0.001
MELD	0.716 ¹⁾²⁾	0.650 ~ 0.768	21.63	0.793	0.588	70.15	<0.001

注:1)与COSSH-ACLF II比较, $P<0.05$;2)与COSSH-ACLF比较, $P<0.05$ 。

MELD 3.0 和 COSSH-ACLF, 预测敏感度 90.5%, 特异度 78.7%, 预测准确度 85.07%。与经典 COSSH-ACLF 分级相比, COSSH-ACLF II 风险分层操作更为简易, 有助于简化 HBV-ACLF 患者病情分级以优化临床治疗策略。

本研究存在以下几点局限性: (1) 样本量较少, 可能导致统计偏倚; (2) 作为回顾性队列研究, 证据等级偏弱。应通过更大规模的前瞻性的队列研究进一步改善研究设计。

综上所述, 本研究通过回顾性分析 HBV-ACLF 患者的临床资料和生存信息, 验证了 COSSH-ACLF II 评分系统对 HBV-ACLF 合并 HE 患者短期预后的预测价值。此外, COSSH-ACLF II 风险分层评分在简化 HBV-ACLF 病情分级以改善患者转归方面具有一定的临床应用价值。

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