

六种预测模型对人工肝治疗的慢加急性肝衰竭 患者短期预后的评估价值*

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【摘要】目的 对接受人工肝治疗的慢加急性肝衰竭(ACLF)患者应用6种预测模型,比较它们对患者短期预后的评估价值。**方法** 自四川大学华西医院建立的人工肝治疗临床数据库中筛选2018年1月-2019年12月期间接受人工肝治疗的ACLF患者258例,收集临床资料和90 d预后信息。运用Cox比例风险模型估计6种预测模型(COSSH ACLF评分、CLIF-C ACLF评分、CLIF-C OF评分、AARC ACLF评分、MELD评分和sMELD评分)与患者90 d病死(含死亡或接受肝移植)的关系。以受试者工作特征(ROC)曲线下面积(AUC)、Harrell's C指数和Brier分数等评价模型预测效能。**结果** 共纳入ACLF患者258例,年龄(46.2±11.7)岁,女性37例(14.3%),肝硬化202例(78.3%),随访90 d时病死107例(41.5%),存活151例(58.5%)。病死患者的6种预测模型评分均高于存活患者(全部 $P<0.001$)。6种预测模型均是人工肝治疗的ACLF患者90 d病死的独立危险因素(校正的风险比 >1 , $P<0.001$)。COSSH ACLF评分的AUC[0.806, 95%可信区间(CI): 0.753~0.853]和Harrell's C指数(0.772, 95%CI: 0.727~0.816)均高于其余5种预测模型的AUC(5种AUC均 <0.750 , $P<0.01$)和Harrell's C指数(5种Harrell's C指数均 <0.750 , $P\leq 0.001$)。COSSH ACLF评分的Brier分数为0.18(95%CI: 0.15~0.20)。基于COSSH ACLF评分风险分层的低危、中危和高危组患者的90 d病死率分别为22.2%、56.3%和90.2%。**结论** COSSH ACLF评分可更准确地预测人工肝治疗的ACLF患者的短期预后,有助于临床决策。

【关键词】 慢加急性肝衰竭 人工肝治疗 预测模型 预后

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【Abstract】 Objective To apply 6 predictive models on acute-on-chronic liver failure (ACLF) patients treated with artificial liver support system (ALSS), and to compare their assessment values for the short-term prognosis of patients. **Methods** A total of 258 ACLF patients who underwent ALSS therapy between January 2018 and December 2019 were selected from the ALSS clinical database established by West China Hospital, Sichuan University, and their clinical data and 90-day prognosis information were collected. Cox proportional hazards model was used to estimate the association between the six predictive models, including Chinese Group on the Study of Severe Hepatitis B-ACLF (COSSH ACLF), European Association for the Study of the Liver--Chronic Liver Failure-Consortium (CLIF-C) ACLF, CLIF-C Organ Failure (OF), Asian Pacific Association for the Study of the Liver (APASL) ACLF Research Consortium (AARC) ACLF, Model for End-Stage Liver Disease (MELD) and Simplified MELD (sMELD), and 90-day mortality, which included death or receiving liver transplantation. The area under the receiver operating characteristic (ROC) curve (AUC), Harrell's C-index and Brier scores were calculated and compared to evaluate the predictive power. **Results** A total of 258 ACLF patients were enrolled. Of these patients, who had a mean age of (46.2±11.7) years old, 37 (14.3%) patients were female, 202 (78.3%) patients had a diagnosis of liver cirrhosis, and 107 (41.5%) patients died during the 90-day follow-up period. The six predictive models all yielded higher scores for patients who died than those for patients who survived (all $P<0.001$). The six predictive models were all independent risk factors for the short-term prognosis of ACLF patients treated with ALSS (all adjusted hazard ratio [HR] >1 , all $P<0.001$). The AUC (0.806, 95% confidence interval [CI]: 0.753-0.853) and Harrell's C-index (0.772, 95% CI: 0.727-0.816) of COSSH ACLF were much higher than those of the five other predictive models (all AUCs <0.750 , $P<0.01$; all Harrell's C-indices <0.750 , $P<0.001$). The Brier score of COSSH ACLF was 0.18 (95% CI: 0.15-0.20). The 90-day mortality of patients defined as having low risk, moderate risk, and high risk according to the risk stratification of COSSH ACLF were 22.2%, 56.3%, and 90.2%, respectively. **Conclusion** The COSSH ACLF could more accurately predict short-term prognosis in ACLF patients who received ALSS therapy, and

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could facilitate clinical decision-making.

【Key words】 Acute-on-chronic liver failure Artificial liver support system therapy Predictive model Prognosis

慢加急性肝衰竭(acute-on-chronic liver failure, ACLF)是临床常见的严重肝病症候群,病情进展快,病死率高^[1]。及早准确评估ACLF病情和可能预后,有助于临床决策^[2]。近年来,中国重症乙型病毒性肝炎研究小组(COSSH)、欧洲肝病学会慢性肝衰竭联盟(CLIF-C)、亚太肝病学会ACLF研究联盟(AARC)分别建立了能较准确地评估ACLF患者病情与预后的COSSH ACLF评分^[3]、CLIF-C ACLF评分^[4]、CLIF-C器官衰竭(OF)评分^[4]、AARC ACLF评分^[5]等预测模型用于临床决策,但这些预测模型能否准确地评估人工肝治疗的ACLF患者预后尚不明确。本研究旨在人工肝治疗的ACLF患者中验证上述模型的预测效能,为临床合理选择预测模型提供参考。

1 对象和方法

1.1 研究对象

自四川大学华西医院感染性疾病中心连续性纳入病例建立的“人工肝治疗临床数据库”中筛选2018年1月–2019年12月期间接受人工肝治疗的乙型肝炎相关性ACLF(HBV-ACLF)患者进行回顾性分析。本研究经四川大学华西医院生物医学伦理委员会批准(批准号:2020-262)。

纳入标准:①患者基础肝病为慢性乙型肝炎病毒感染;②HBV-ACLF诊断符合COSSH ACLF诊断标准^[3];慢性乙型肝炎病毒感染病史至少6个月,出现急性肝功能异常,总胆红素 $\geq 205 \mu\text{mol/L}$ 且凝血酶原时间国际标准化值 ≥ 1.5 ,伴或不伴肝硬化;③均接受了内科综合治疗基础上的人工肝治疗,人工肝治疗方案为局部枸橼酸抗凝法双重血浆分子吸附系统治疗序贯血浆置换治疗。④随访至首次人工肝治疗后90 d。

排除标准:确诊或疑似肝癌,曾接受肝移植手术或肝部分切除术。

1.2 研究方法

收集患者的基本信息、首次人工肝治疗时疾病数据与治疗数据、人工肝治疗总次数、随访90 d时的预后(存活或病死)。纳入病例若在随访期间接受肝移植手术,则将该病例视为病死病例。

根据预测模型报告文献提供的计算公式或评分系统分别计算每例ACLF患者人工肝治疗前的COSSH ACLF评

分^[3]、CLIF-C ACLF评分^[4]、CLIF-C OF评分(范围:5~15)^[4]、AARC ACLF评分(范围:5~15)^[5]、终末期肝病模型(MELD)评分^[6]及简化的MELD(sMELD)评分(范围:0~6)^[7]的分值。以上预测模型的分值越高,提示病情越严重。

1.3 统计学方法

正态分布的定量资料采用 $\bar{x} \pm s$ 表示,非正态分布的定量资料采用中位数($P_{25} \sim P_{75}$)表示,组间比较均采用Mood中位数检验;分类变量采用例数和构成比表示,组间比较采用卡方检验;预测模型与患者预后的关系采用Cox比例风险模型计算风险比(HR)估计。预测模型的区分度采用受试者工作特征(ROC)曲线下面积(AUC)和Harrell's C指数评估,AUC的比较采用Z检验,Harrell's C指数的比较采用t检验。预测模型的校准度通过计算Brier分数评估,并应用GraphPad Prism v9.0制作校准度图展现。AUC和Harrell's C指数均 ≥ 0.75 且Brier分数在0~0.25的预测模型具有临床应用价值^[8]。使用X-tile v3.6确定具有临床应用价值的预测模型的最佳临界值,并依据最佳临界值将患者分为病死风险低危、中危、高危3组^[9]。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 患者临床特征

共纳入满足入排标准的ACLF患者258例,年龄(46.2 ± 11.7)岁,范围21~77岁,女性37例(14.3%),肝硬化202例(78.3%),随访90 d时病死107例(41.5%),存活151例(58.5%)。病死组患者的COSSH ACLF评分、CLIF-C ACLF评分、CLIF-C OF评分、AARC ACLF评分、MELD评分及sMELD评分均高于存活组患者(P 均 < 0.001 ,表1)。

2.2 预测模型与患者预后的关系

经校正年龄、性别、有无肝硬化、HBV DNA水平、有无合并肝病、有无合并慢性疾病、人工肝治疗次数后,COSSH ACLF评分[校正HR(aHR):2.73,95%可信区间(CI):2.24~3.32, $P < 0.001$]、CLIF-C ACLF评分(aHR :1.16,95%CI:1.12~1.21, $P < 0.001$)、CLIF-C OF评分(aHR :1.75,95%CI:1.49~2.04, $P < 0.001$)、AARC ACLF评分(aHR :1.74,95%CI:1.52~1.99, $P < 0.001$)、MELD评分(aHR :1.18,95%CI:1.13~1.22, $P < 0.001$)及sMELD评分(aHR :2.02,95%CI:1.72~2.38, $P < 0.001$)均是人工肝治疗的ACLF患者90 d病死的独立危险因素(表2)。

表 1 患者临床特征
Table 1 Clinical data of patients

Characteristic	All patients (n=258)	90-day prognosis		P
		Mortality (n=107)	Survival (n=151)	
Female/case (%)	37 (14.3)	22 (20.6)	15 (9.9)	0.016
Age/yr., $\bar{x} \pm s$	46.2 $\pm$ 11.7	49.2 $\pm$ 11.4	44.1 $\pm$ 11.5	0.058
Liver cirrhosis/case (%)	202 (78.3)	95 (88.8)	107 (70.9)	0.001
HBV DNA [#] /(log10 IU/mL)	4.76 (3.50-6.57)	4.68 (3.47-6.26)	4.80 (3.51-6.68)	0.800
Causes of liver disease/case (%)				0.874
HBV infection only	194 (75.2)	81 (75.7)	113 (74.8)	
Coexisting with other causes [*]	64 (24.8)	26 (24.3)	38 (25.2)	
Comorbidities [*] /case (%)				0.006
No	215 (83.3)	81 (75.7)	134 (88.7)	
Yes	43 (16.7)	26 (24.3)	17 (11.3)	
Disease severity assessment				
COSSH ACLF score ($\bar{x} \pm s$)	6.53 $\pm$ 0.94	7.10 $\pm$ 0.95	6.12 $\pm$ 0.68	<0.001
CLIF-C ACLF score ($\bar{x} \pm s$)	34.5 $\pm$ 7.2	38.1 $\pm$ 7.0	32.0 $\pm$ 6.2	<0.001
CLIF-C OF score [#]	9 (8-10)	10 (9-10)	9 (8-9)	<0.001
AARC ACLF score ($\bar{x} \pm s$)	9.9 $\pm$ 1.6	10.6 $\pm$ 1.4	9.4 $\pm$ 1.5	<0.001
MELD score ($\bar{x} \pm s$)	26.9 $\pm$ 4.8	29.3 $\pm$ 5.3	25.2 $\pm$ 3.6	<0.001
sMELD score [#]	1 (1-2)	2 (1-3)	1 (0-2)	<0.001
Sessions of ALSS therapy [#]	4.0 (3.0-6.0)	4.0 (2.0-6.0)	4.0 (3.0-6.0)	0.959

HBV: Hepatitis B virus; ACLF: Acute-on-chronic liver failure; COSSH: Chinese Group on the Study of Severe Hepatitis B; CLIF-C: European Association for the Study of the Liver--Chronic Liver Failure-Consortium; OF: Organ failure; AARC: Asian Pacific Association for the Study of the Liver (APASL) ACLF Research Consortium; MELD: Model for End-Stage Liver Disease; sMELD: Simplified MELD; ALSS: Artificial liver support system. #: Those with HBV infection plus any one of other co-existing liver diseases were classified in this subgroup. *: Those with any one of comorbidities were classified in the comorbidity group. #: Data were shown as median (P₂₅-P₇₅).

表 2 与慢加急性肝衰竭患者90 d病死风险相关的因素
Table 2 Factors associated with risks for 90-day mortality in ACLF patients

Factor	Adjusted HR [▲] (95% CI)					
	COSSH ACLF score	CLIF-C ACLF score	CLIF-C OF score	AARC ACLF score	MELD score	sMELD score
Age	0.99 (0.97-1.01)	0.96 (0.94-0.98)**	1.02 (1.00-1.04)*	1.02 (1.00-1.04)	1.01 (0.99-1.03)	1.02 (1.00-1.04)
Gender						
Male	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Female	1.32 (0.79-2.19)	1.25 (0.76-2.06)	1.10 (0.66-1.83)	1.56 (0.94-2.57)	1.95 (1.18-3.23)**	1.39 (0.84-2.31)
Liver cirrhosis						
No	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Yes	1.68 (0.91-3.12)	2.09 (1.13-3.85)*	1.89 (1.02-3.49)*	2.16 (1.17-4.01)	2.00 (1.08-3.70)*	1.91 (1.04-3.54)*
HBV DNA	1.04 (0.93-1.15)	1.01 (0.91-1.12)	0.97 (0.87-1.08)	1.02 (0.92-1.14)	1.02 (0.91-1.14)	1.05 (0.94-1.17)
Etiology						
HBV infection only	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Coexisting with other causes [*]	1.09 (0.69-1.72)	1.09 (0.69-1.71)	1.04 (0.66-1.64)	1.09 (0.69-1.71)	0.82 (0.52-1.30)	0.96 (0.61-1.51)
Comorbidities [*]						
No	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Yes	1.72 (1.04-2.83)*	1.54 (0.94-2.51)	1.49 (0.91-2.43)	1.61 (0.99-2.62)	1.71 (1.03-2.82)*	1.72 (1.72-2.83)*
Disease severity	2.73 (2.24-3.32)***	1.16 (1.12-1.21)***	1.75 (1.49-2.04)***	1.74 (1.52-1.99)***	1.18 (1.13-1.22)***	2.02 (1.72-2.38)***
Sessions of ALSS therapy	0.91 (0.83-0.99)*	0.90 (0.83-0.98)*	0.92 (0.85-1.00)*	0.85 (0.78-0.93)***	0.90 (0.82-0.98)*	0.86 (0.78-0.95)**

ACLF, HBV, ALSS, ■, ◆: The notes are the same as those for table 1. HR: Hazard ratio; CI: Confidence interval. ▲: Multivariate Cox regression analysis includes age (continuous years), gender (female vs. male), liver cirrhosis (yes vs. no), HBV DNA (continuous log10 IU/mL), other co-existing liver diseases (viral infections other than hepatitis B virus, alcoholic liver disease, non-alcoholic fatty liver, immune related liver disease, drug induced liver injury, and other liver diseases), comorbidities (chronic obstructive pulmonary disease, diabetes mellitus, coronary heart disease, primary hypertension, chronic kidney disease, and other chronic diseases), disease severity (COSSH ACLF score, CLIF-C ACLF score, CLIF-C OF score, AARC ACLF score, MELD score, sMELD score), and sessions of ALSS therapy (continuous values). *** P<0.001, ** P<0.01, * P<0.05.

2.3 预测模型的预测效能

2.3.1 预测模型的区分度 COSSH ACLF评分预测人工肝治疗的ACLF患者90 d病死的AUC为0.806(95%CI: 0.753 ~ 0.853, P<0.001)。CLIF-C ACLF评分、CLIF-C OF评分、AARC ACLF评分、MELD评分及sMELD评分的

AUC均<0.750。COSSH ACLF评分的AUC明显高于其余5种预测模型的AUC(P均<0.01, 图1、表3)。COSSH ACLF评分预测人工肝治疗的ACLF患者90 d预后的Harrell's C指数为0.772(95%CI: 0.727 ~ 0.816, P<0.001)。CLIF-C ACLF评分、CLIF-C OF评分、AARC ACLF评分、

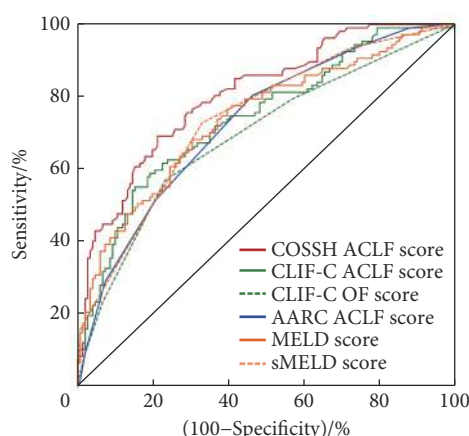


图1 预测模型预测慢加急性肝衰竭患者90 d病死的ROC曲线

Fig 1 Receiver operating characteristic curves of predictive models for 90-day mortality of ACLF patients

ACLF, COSSH, CLIF-C, OF, AARC, MELD, and sMELD: The notes are the same as those for table 1.

MELD评分及sMELD评分的Harrell's C指数均 <0.750 。COSSH ACLF评分的Harrell's C指数高于其余5种预测模型的Harrell's C指数(P 均 <0.001 , 表3)。因此, COSSH ACLF评分具有更好的预测人工肝治疗的ACLF患者

90 d预后的区分度。

2.3.2 预测模型的校准度 使用COSSH ACLF评分预测的ACLF患者90 d病死率与实际病死率所作校准度图的散点沿45°斜线排列(校准斜率为1.07, 图2); COSSH ACLF评分的Brier分数为0.18(95%CI: 0.15~0.20)。因此, COSSH ACLF评分具有较好的预测人工肝治疗的ACLF患者90 d预后的校准度。

2.3.3 预测模型的风险分层 基于X-tile软件确定的COSSH ACLF评分的最佳临界值(6.59和7.33), 可将患者分为COSSH ACLF分级低危、中危、高危3组(图3)。经校正年龄、性别、有无肝硬化、HBV DNA水平、有无合并肝病、有无合并慢性疾病、人工肝治疗次数后, 和COSSH ACLF分级低危组相比, 中危组(aHR : 3.47, 95%CI: 2.10~5.77, $P<0.001$)和高危组(aHR : 12.89, 95%CI: 7.49~22.18, $P<0.001$)ACLF患者的90 d病死风险明显增加。低危组、中危组和高危组患者的90 d病死率依次明显增加, 分别为22.2%(95%CI: 15.6%~28.9%)、56.3%(95%CI: 43.8%~68.7%)和90.2%(95%CI: 80.8%~99.7%)。

表3 预测模型预测慢加急性肝衰竭患者90 d病死的区分度

Table 3 Discrimination of models for 90-day mortality of ACLF patients

C-index	COSSH ACLF score	CLIF-C ACLF score	CLIF-C OF score	AARC ACLF score	MELD score	sMELD score
AUC (95% CI)	0.806 (0.753-0.853)	0.741 (0.683-0.793)	0.692 (0.632-0.748)	0.729 (0.671-0.783)	0.739 (0.681-0.792)	0.740 (0.682-0.792)
Z		3.07	4.63	3.21	2.74	3.03
P*		0.002	<0.001	0.001	0.006	0.002
Harrell's C (95% CI)	0.772 (0.727-0.816)	0.710 (0.658-0.761)	0.677 (0.625-0.729)	0.711 (0.663-0.750)	0.698 (0.645-0.750)	0.707 (0.660-0.754)
t		3.61	4.71	3.26	3.65	3.58
P*		<0.001	<0.001	0.001	<0.001	<0.001

ACLF, COSSH, CLIF-C, OF, AARC, MELD, sMELD: The notes are the same as those of table 1. CI: Confidence interval. Area under the ROC curves (AUCs) were compared using the Z test (Delong's method). Harrell's C-indices were compared using the t test. *: Comparisons between COSSH ACLF score and five other models.

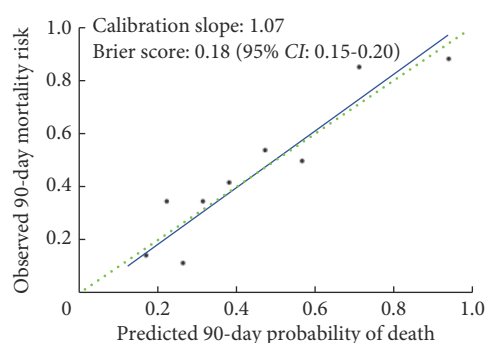


图2 COSSH ACLF评分预测慢加急性肝衰竭患者90 d病死的校准度

Fig 2 Calibrating COSSH ACLF score for predicting 90-day mortality of ACLF patients

COSSH, ACLF: The notes are the same as those for table 1.

2.4 人工肝治疗次数与患者预后

经校正年龄、性别、有无肝硬化、HBV DNA水平、有无合并肝病、有无合并慢性疾病、疾病严重程度后, 人工肝治疗次数是ACLF患者90 d预后的独立保护因素(全部 $aHR<1.0$, 全部 $P<0.05$, 表2)。与人工肝治疗1~2次相比, 治疗3~5次的ACLF患者的90 d病死风险更低(aHR : 0.59, 95%CI: 0.36~0.95, $P=0.030$); 但与人工肝治疗3~5次相比, 治疗 ≥ 6 次未进一步降低患者病死风险(aHR : 0.68, 95%CI: 0.44~1.05, $P=0.082$)。

3 讨论

COSSH ACLF评分是近年来新开发并被证明可较准

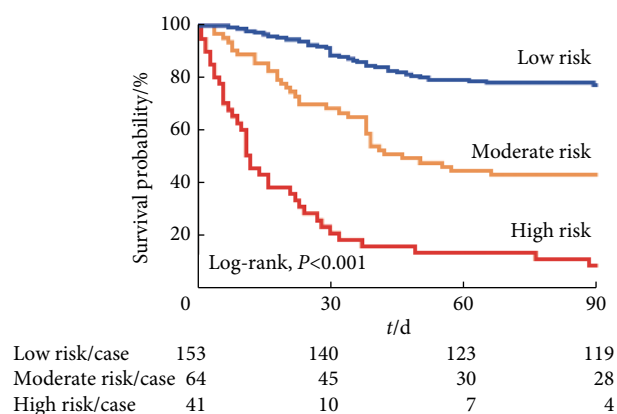


图3 基于COSSH ACLF评分风险分层的慢加急性肝衰竭患者的生存曲线

Fig 3 Survival curves of ACLF patients based on risk stratification of COSSH ACLF score

COSSH, ACLF: Note the same as table 1.

确地预测HBV-ACLF患者预后的预测模型^[3, 10-11]。以COSSH ACLF评分为代表的ACLF疾病严重程度评分分值越高, ACLF患者预后越差^[3-7, 12];在等待肝移植的ACLF患者中的研究结果也是如此^[13]。本研究把人工肝治疗的HBV-ACLF患者作为研究对象,验证了COSSH ACLF评分等6种预测模型的预后预测效能。本研究发现COSSH ACLF评分预测人工肝治疗的HBV-ACLF患者短期预后的AUC(0.806)和Harrell's C指数(0.772)均显著高于其余5种预测模型的AUC和Harrell's C指数(均<0.750)。因此, COSSH ACLF评分的区分度较好,在6种预测模型中最好。结合其较好的校准度(校准斜率1.07, Brier分数0.18),在临床实践中应优先考虑应用COSSH ACLF评分作为人工肝治疗的HBV-ACLF患者的预后评估指标。运用COSSH ACLF评分持续动态评估可能有助于更准确地预测患者预后^[5, 14-16]。

准确预测ACLF患者预后,有助于临床决策和选择治疗方案^[2]。目前,肝衰竭的主要治疗手段有内科综合治疗、人工肝治疗和肝移植治疗^[1-2]。其中,人工肝治疗是一种以对症支持为主的治疗方案,可为肝细胞再生及肝功能恢复创造条件,也可作为肝移植前的桥接^[1, 17]。近年来的研究还显示,人工肝治疗能显著改善肝衰竭患者的短期预后^[18-20]。临床实践中,可根据ACLF患者不同的病死风险制定个体化的治疗方案^[2]。在本研究关注的人工肝治疗的ACLF患者中,基于X-tile软件确定的COSSH ACLF评分的最佳临界值(6.59和7.33),可将患者分为低危、中危、高危3组;3组患者具有显著不同的短期病死风险和病死率。因此, COSSH ACLF评分也可用于指导人工肝治疗的ACLF患者的治疗决策:低危组可在内科综合

治疗基础上积极开展人工肝治疗;中危组在低危组治疗基础上,应做好肝移植准备;高危组尽管积极人工肝治疗,预期预后仍差,应尽早肝移植治疗。本研究发现的人工肝治疗次数是ACLF患者短期预后的独立保护因素和3~5次治疗相对最好等结果和既往文献报道的一致^[21-22]。因此, ACLF患者病情若在内科综合治疗和人工肝治疗3~5次后仍无改善,建议序贯肝移植治疗。序贯肝移植治疗可显著降低患者病死率^[23],若能在被列入肝移植等待名单后30 d内接受肝移植治疗, ACLF患者的5年肝移植存活率仍可达90%以上^[24]。运用COSSH ACLF评分持续动态评估获得更准确的患者预期预后,有利于优化临床决策,特别是指导肝移植治疗决策^[25]。

本研究仍具有一定的局限性。在国内外发布的多个ACLF诊断标准中^[1, 3-5],本研究采用了具有较高循证医学证据、更适合于慢性HBV感染患者的COSSH ACLF标准^[3],本研究结果因此可能不适用于无HBV感染病例和其他ACLF标准诊断病例。作为单中心非特大样本研究, COSSH ACLF评分风险分层的最佳临界值仍需要进一步研究确认。

综上所述,本研究在人工肝治疗的ACLF患者中发现COSSH ACLF评分可更准确地预测患者的短期预后。基于COSSH ACLF评分,可将人工肝治疗的ACLF患者分为低危、中危和高危3组,可分层采取个体化诊疗方案,有利于改善患者预后。

* * *

利益冲突 所有作者均声明不存在利益冲突

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