

• 论著 •

毒蕈中毒患者 MELD 评分与预后的关系： 一项多中心临床研究

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【摘要】目的 探讨与急性毒蕈中毒患者预后相关的临床指标及其与预后的关系。**方法** 回顾性分析2015年8月至2017年8月中国医科大学附属第一医院、沈阳市第九人民医院、岫岩满族自治县中心人民医院、抚顺市中心医院收治的毒蕈中毒患者的临床资料。收集患者入院24 h内血生化指标、序贯器官衰竭评分(SOFA)、终末期肝病模型(MELD)评分、是否行血浆置换(PE)及28 d预后。根据预后将患者分为存活组和死亡组,比较两组间各指标的差异;采用Spearman或Pearson相关法分析MELD评分与预后指标的相关性,采用受试者工作特征曲线(ROC)分析MELD评分对预后的预测价值;并对其中接受PE治疗的患者进一步分析。**结果** 共纳入辽沈地区4家医院89例毒蕈中毒患者,28 d死亡6例、存活83例;其中17例严重肝功能损伤、凝血障碍患者接受了PE治疗,28 d死亡6例、存活11例。**①** 在89例患者中:与存活组比较,死亡组MELD评分、凝血酶原时间(PT)、活化部分凝血活酶时间(APTT)、总胆红素(TBil)、国际标准化比值(INR)、血糖(Glu)、丙氨酸转氨酶(ALT)、γ-谷氨酰转移酶(GGT)明显升高〔MELD评分(分):32.34(28.31, 41.06)比8.76(3.77, 21.19), PT(s):53.5(52.4, 113.2)比14.5(13.8, 19.5), APTT(s):58.6(48.9, 70.8)比36.9(34.4, 43.2), TBil(μmol/L):134.8(31.3, 155.6)比21.5(15.1, 41.4), INR:6.0(5.6, 14.7)比1.2(1.1, 1.5), Glu(mmol/L):9.2(9.0, 11.0)比6.6(5.7, 7.8), ALT(U/L):5923.0(1105.0, 6000.0)比35.0(18.0, 1767.0), GGT(U/L):49.0(32.0, 57.0)比25.0(16.0, 41.0), 均 $P<0.05$ 〕,凝血酶原活动度(PTA)、白蛋白(ALB)、Na⁺、Cl⁻明显降低〔PTA:13.0%(6.0%, 14.0%)比80.0%(61.0%, 87.0%), ALB(g/L):31.1(29.8, 39.0)比42.4(37.9, 44.3), Na⁺(mmol/L):126.5(122.4, 131.0)比137.0(134.9, 141.0), Cl⁻(mmol/L):93.5(87.6, 95.0)比104.0(101.3, 106.0), 均 $P<0.05$ 〕。Spearman相关分析显示,毒蕈中毒患者MELD评分与28 d病死率呈显著正相关($r=0.423$, $P=0.001$)。ROC曲线分析显示,MELD评分预测毒蕈中毒患者预后的ROC曲线下面积(AUC)为0.926;当截断值为27.30分时,敏感度为100%,特异度为84.3%。**②** 在17例PE患者中:与存活组比较,死亡组MELD评分、TBil、Glu、ALT明显升高〔MELD评分(分):36.81±5.18比29.01±5.23, TBil(μmol/L):145.2±13.9比93.2±44.0, Glu(mmol/L):9.1±1.9比6.0±2.7, ALT(U/L):5961.5±44.5比3932.9±1625.7, 均 $P<0.05$ 〕,Cl⁻明显降低(mmol/L:94.3±1.2比100.5±5.7, $P<0.05$),SOFA评分差异无统计学意义(分:5.83±2.71比5.91±1.58, $P>0.05$)。相关分析显示,进行PE治疗的毒蕈中毒患者MELD评分与28 d病死率呈显著正相关($r=0.355$, $P=0.001$),而与SOFA评分无相关性($r=0.427$, $P=0.087$)。ROC曲线分析显示,MELD评分预测进行PE治疗的毒蕈中毒患者预后的AUC为0.545;当截断值为32.19分时,敏感度为33.3%,特异度为100%。**结论** 毒蕈中毒患者,特别是接受PE治疗的患者,MELD评分越高,预后越差;MELD评分可用于评估急性毒蕈中毒患者的预后。

【关键词】 中毒; 毒蕈; 预后; 终末期肝病模型评分; 血浆置换**基金项目:** 辽宁省自然科学基金(2015020545)

**Correlation between model for end-stage liver disease score and prognosis in mushroom poisoning patients:
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【Abstract】Objective To find out the clinical indicators related to prognosis in patients with acute mushroom poisoning, and approach its correlation with prognosis. **Methods** Clinical data of patients with mushroom poisoning admitted to the First Hospital of China Medical University, the Ninth People's Hospital of Shenyang, Xiuyan Central People's Hospital, and Fushun Central Hospital from August 2015 to August 2017 were retrospectively analyzed. The

biochemical indicators within 24 hours after admission, sequential organ failure assessment (SOFA) score, model for end-stage liver disease (MELD) score, whether plasmapheresis (PE) was carried out or not and 28-day prognosis of patients were collected. According to prognosis, the patients were divided into death group and survival group, and the differences in above parameters between the two groups were compared. Spearman or Pearson correlation method was used to analyze the relationship between MELD score and prognosis. Receiver operating characteristic (ROC) curve was used to analyze the prognostic value of MELD score for prognosis. Further analysis of the patients receiving PE treatment was conducted. **Results** A total of four Liaoning hospitals with 89 patients with mushroom poisoning were enrolled, with 6 died within 28 days, and 83 survived. There were 17 patients with severely impaired liver and coagulant functions accepted PE treatment, with 6 patients died within 28 days, and 11 survived. ① In 89 patients, compared with survival group, MELD score, prothrombin time (PT), activated partial thromboplastin time (APTT), total bilirubin (TBil), international normalized ratio (INR), blood glucose (Glu), alanine aminotransferase (ALT), γ -glutamyltransferase (GGT) in death group were significantly increased [MELD score: 32.34 (28.31, 41.06) vs. 8.76 (3.77, 21.19), PT (s): 53.5 (52.4, 113.2) vs. 14.5 (13.8, 19.5), APTT (s): 58.6 (48.9, 70.8) vs. 36.9 (34.4, 43.2), TBil (μ mol/L): 134.8 (31.3, 155.6) vs. 21.5 (15.1, 41.4), INR: 6.0 (5.6, 14.7) vs. 1.2 (1.1, 1.5), Glu (mmol/L): 9.2 (9.0, 11.0) vs. 6.6 (5.7, 7.8), ALT (U/L): 5 923.0 (1 105.0, 6 000.0) vs. 35.0 (18.0, 1 767.0), GGT (U/L): 49.0 (32.0, 57.0) vs. 25.0 (16.0, 41.0), all $P < 0.05$], but the prothrombin activity (PTA), albumin (ALB), serum Na^+ , Cl^- were significantly decreased [PTA: 13.0% (6.0%, 14.0%) vs. 80.0% (61.0%, 87.0%), ALB (g/L): 31.1 (29.8, 39.0) vs. 42.4 (37.9, 44.3), Na^+ (mmol/L): 126.5 (122.4, 131.0) vs. 137.0 (134.9, 141.0), Cl^- (mmol/L): 93.5 (87.6, 95.0) vs. 104.0 (101.3, 106.0), all $P < 0.05$]. Spearman correlation analysis showed that MELD score of patients with mushroom poisoning was positively correlated with the 28-day mortality ($r = 0.423$, $P = 0.001$). ROC curve analysis showed that the area under ROC curve (AUC) of MELD score for prognosis of patients with mushroom poisoning was 0.926; when the cut-off value was 27.30, the sensitivity was 100%, and the specificity was 84.3%. ② In 17 patients who accepted PE treatment, compared with survival group, the MELD score, TBil, Glu, and ALT in the death group were significantly increased [MELD score: 36.81 \pm 5.18 vs. 29.01 \pm 5.23, TBil (μ mol/L): 145.2 \pm 13.9 vs. 93.2 \pm 44.0, Glu (mmol/L): 9.1 \pm 1.9 vs. 6.0 \pm 2.7, ALT (U/L): 5 961.5 \pm 44.5 vs. 3 932.9 \pm 1 625.7, all $P < 0.05$], and Cl^- was significantly lowered (mmol/L: 94.3 \pm 1.2 vs. 100.5 \pm 5.7, $P < 0.05$), but SOFA score showed no significant difference (5.83 \pm 2.71 vs. 5.91 \pm 1.58, $P > 0.05$). Correlation analysis showed that the MELD score in patients with mushroom poisoning who accepted PE treatment was positively correlated with 28-day mortality ($r = 0.355$, $P = 0.001$), but no correlation with SOFA score was found ($r = 0.427$, $P = 0.087$). ROC curve analysis showed that the AUC of MELD score in the prediction of mushroom poisoning patients undergoing PE treatment was 0.545; when the cut-off value was 32.19, the sensitivity was 33.3%, and the specificity was 100%. **Conclusions** In mushroom poisoning patients, especially those undergoing PE treatment, the higher the MELD score, the higher the mortality is. MELD score could assess the prognosis of patients with acute mushroom poisoning.

【Key words】 Poisoning; Mushroom; Prognosis; Model for end-stage liver disease score; Plasmapheresis

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辽沈地区每年7、8月份为毒蕈中毒高发期,目前治疗毒蕈中毒尚无特效药物,以血液净化或联合药物治疗为主^[1-2],病死率较高^[3]。根据毒蕈中毒的临床表现可分为胃肠炎型、中毒性肝炎型、急性肾衰竭型、中毒性溶血型、神经精神型^[4-5]。急诊医生在判断中毒类型后,并不能依据量化指标来判断患者的预后。近年来,国内外对终末期肝病模型(MELD)在重型肝炎/肝功能衰竭中的应用展开了广泛的研究^[6],但用于评估毒蕈中毒患者肝肾功能及预后的相关研究较少。本研究通过回顾性分析毒蕈中毒患者的生化指标,并进行MELD评分,探讨其对毒蕈中毒患者严重程度及预后的预测价值。

1 资料与方法

1.1 研究对象:选择2015年8月至2017年8月中国医科大学附属第一医院、沈阳市第九人民医院、岫岩满族自治县中心人民医院、抚顺市中心医院收治的毒蕈中毒患者。

1.1.1 纳入标准:明确食用过非养殖蕈类,并且出

现消化道症状者。

1.1.2 排除标准:既往有肝炎等肝脏疾病,或慢性心力衰竭、慢性肾功能不全者;生化指标不全者。

1.1.3 伦理学:本研究符合医学伦理学标准,并经医院伦理委员会批准(审批号:2017-11-01),所有诊疗均获得过患者或家属的知情同意。

1.2 观察指标:收集患者入院24 h内生化指标最差值,血浆置换(PE)者收集其PE前最后一次数据,包括血小板计数(PLT)、凝血酶原时间(PT)、活化部分凝血活酶时间(APTT)、凝血酶原活动度(PTA)、国际标准化比值(INR)、白蛋白(ALB)、丙氨酸转氨酶(ALT)、碱性磷酸酶(ALP)、总胆红素(TBil)、血肌酐(Scr)、血糖(Glu)、血 Cl^- 、血 Na^+ 、 γ -谷氨酰转移酶(GGT)等,计算序贯器官衰竭评分(SOFA)和MELD评分^[6];记录患者住院时间和28 d预后。

$$\begin{aligned} \text{MELD 评分} = & 3.8 \times \ln [\text{TBil}(\text{mg/dL})] + 11.2 \times \ln (\text{INR}) + \\ & 9.6 \times \ln [\text{Scr}(\text{mg/dL})] + 6.4 \times [\text{病因(胆汁}} \\ & \text{性或酒精性为 0, 其他为 1)}] \end{aligned}$$

1.3 分组及研究方法:根据28 d预后将所有患者分为死亡组和存活组,比较两组各指标的差异,分析MELD评分与预后指标的相关性,评估其预测价值;并对PE患者进一步分析。

1.4 统计学方法:应用SPSS 22.0软件分析数据。正态分布的计量资料以均数±标准差($\bar{x} \pm s$)表示,组间比较采用单因素方差分析;非正态分布的计量资料以中位数(四分位数)[$M(Q_L, Q_U)$]表示,组间比较采用Z检验。计数资料采用 χ^2 检验。采用Spearman或Pearson相关系数衡量生化指标与预后的相关性。预后评价采用受试者工作特征曲线(ROC)分析。 $P < 0.05$ 为差异有统计学意义。

2 结 果

2.1 一般资料(表1):共纳入4家医院89例毒蕈中毒患者,男性46例,女性43例;年龄16~84岁,平均(56.3 ± 8.1)岁;住院时间为(14.46 ± 10.32)d,MELD评分为8.22(4.50, 21.19)分;28 d死亡6例,病死率为6.7%。89例患者中有17例严重肝功能损伤、凝血障碍者接受了PE治疗,死亡6例。

2.2 所有毒蕈中毒患者资料分析

2.2.1 不同预后两组患者血生化指标和MELD评分比较(表2):与存活组比较,死亡组PT、APTT、TBil、INR、Glu、ALT、GGT、MELD评分明显升高,

PTA、ALB、Na⁺、Cl⁻明显降低(均 $P < 0.05$);PLT有降低趋势,SCr、ALP有升高趋势,但差异无统计学意义(均 $P > 0.05$)。

2.2.2 MELD评分与预后的相关性:Spearman相关分析显示,MELD评分与28 d病死率呈显著正相关($r=0.423, P=0.001$)。表明毒蕈中毒患者MELD评分越高,病死率就越高。

2.2.3 MELD评分对预后的预测价值(图1):ROC曲线分析显示,MELD评分预测毒蕈中毒患者预后的ROC曲线下面积(AUC)为0.926,95%可信区间(95%CI)为0.860~0.991;当截断值为27.30分时,敏感度为100%,特异度为84.3%,阳性预测值为0.316,阴性预测值为1,约登指数为0.843。说明MELD评分对毒蕈中毒患者的预后有预测价值。

2.3 进行PE治疗的毒蕈中毒患者资料分析

2.3.1 不同预后两组患者血生化指标和MELD评分比较(表3):经PE治疗后,死亡组患者TBil、Glu、ALT、MELD评分明显高于存活组,Cl⁻明显低于存活组(均 $P < 0.05$);两组其余生化指标、SOFA评分差异虽无统计学意义,但死亡组较存活组有异常趋势,存活组APTT有延长趋势。

2.3.2 进行PE治疗毒蕈中毒患者MELD评分与预后及SOFA评分的相关性:Spearman相关分析显示,

MELD评分与28 d病死率呈正相关($r=0.355, P=0.001$),表明进行PE治疗毒蕈中毒患者的预后也与MELD评分相关。Pearson相关分析显示,MELD评分与SOFA评分无相关性($r=0.427, P=0.087$)。

表1 不同28 d预后两组毒蕈中毒患者基本情况比较

组别	例数		性别(例)		年龄		中毒类型(例)					血浆置换 (例)
	(例)	男性	女性	(岁, $\bar{x} \pm s$)	胃肠 类型	中毒性 肝类型	急性肾 衰竭型	中毒性 溶血型	神经 精神型	混合 型		
存活组	83	44	39	56.6 ± 7.6	41	22	3	3	5	9	11	
死亡组	6	2	4	52.3 ± 13.2	0	1	0	1	0	4	6	
χ^2/t 值		0.868	0.043				47.780				27.250	
P值		0.352	0.966				0.000				0.000	

表2 不同28 d预后两组毒蕈中毒患者生化指标和MELD评分比较[$M(Q_L, Q_U)$]

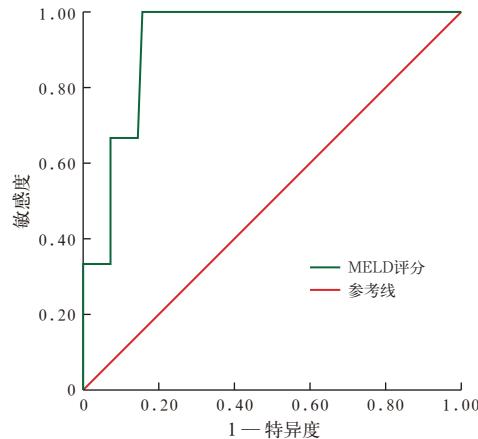
组别	例数		PLT	PT	APTT	PTA	ALB	TBil	SCr	INR
	(例)	($\times 10^9/L$)	(s)	(s)	(s)	(%)	(g/L)	($\mu mol/L$)	($\mu mol/L$)	
存活组	83	185.0(126.0, 217.0)	14.5(13.8, 19.5)	36.9(34.4, 43.2)	80.0(61.0, 87.0)	42.4(37.9, 44.3)	21.5(15.1, 41.4)	62.8(56.0, 79.0)	1.2(1.1, 1.5)	
死亡组	6	115.0(47.5, 234.0)	53.5(52.4, 113.2)	58.6(48.9, 70.8)	13.0(6.0, 14.0)	31.1(29.8, 39.0)	134.8(31.3, 155.6)	67.0(62.5, 92.0)	6.0(5.6, 14.7)	
Z值		1.183	2.023	1.909	2.023	1.738	1.567	0.888	2.020	
P值		0.122	0.001	0.001	0.001	0.005	0.015	0.409	0.001	
组别	例数	Glu	Na ⁺	Cl ⁻	ALT	GGT	ALP	MELD		
(例)	(mmol/L)	(mmol/L)	(mmol/L)	(mmol/L)	(U/L)	(U/L)	(U/L)	评分(分)		
存活组	83	6.6(5.7, 7.8)	137.0(134.9, 141.0)	104.0(101.3, 106.0)	35.0(18.0, 1767.0)	25.0(16.0, 41.0)	80.0(66.0, 100.0)	8.76(3.77, 21.19)		
死亡组	6	9.2(9.0, 11.0)	126.5(122.4, 131.0)	93.5(87.6, 95.0)	5923.0(1105.0, 6000.0)	49.0(32.0, 57.0)	112.0(63.0, 133.0)	32.34(28.31, 41.06)		
Z值		1.620	2.067	2.274	1.653	1.539	0.864	1.995		
P值		0.011	0.000	0.000	0.008	0.018	0.444	0.001		

注:MELD为终末期肝病模型,PLT为血小板计数,PT为凝血酶原时间,APTT为活化部分凝血活酶时间,PTA为凝血酶原活动度,ALB为白蛋白,TBil为总胆红素,SCr为血肌酐,INR为国际标准化比值,Glu为血糖,ALT为丙氨酸转氨酶,GGT为γ-谷氨酰转移酶,ALP为碱性磷酸酶。

表3 不同28 d预后两组进行血浆置换(PE)治疗的毒蕈中毒患者生化指标以及MELD评分和SOFA评分比较($\bar{x} \pm s$)

组别	例数(例)	PLT($\times 10^9/L$)	PT(s)	APTT(s)	PTA(%)	ALB(g/L)	TBil($\mu\text{mol}/L$)	Glu(mmol/L)	SCr($\mu\text{mol}/L$)
存活组	11	134.4 \pm 62.5	77.6 \pm 42.3	91.9 \pm 46.8	17.1 \pm 13.8	34.2 \pm 6.6	93.2 \pm 44.0	6.0 \pm 2.7	84.0 \pm 28.4
死亡组	6	78.5 \pm 66.5	83.8 \pm 35.0	64.0 \pm 25.2	11.0 \pm 3.9	35.0 \pm 4.7	145.2 \pm 13.9	9.1 \pm 1.9	73.3 \pm 15.0
<i>t</i> 值		-1.491	0.294	-1.543	1.042	0.272	3.709	2.547	-0.848
P值		0.199	0.779	0.154	0.314	0.793	0.002	0.037	0.410
组别	例数(例)	INR	Na^+ (mmol/L)	Cl^- (mmol/L)	ALT(U/L)	GGT(U/L)	ALP(U/L)	MELD(分)	SOFA(分)
存活组	11	5.7 \pm 2.1	132.7 \pm 5.2	100.5 \pm 5.7	3 932.9 \pm 1 625.7	43.1 \pm 21.0	106.9 \pm 21.2	29.01 \pm 5.23	5.91 \pm 1.58
死亡组	6	8.9 \pm 4.6	128.5 \pm 4.6	94.3 \pm 1.2	5 961.5 \pm 44.5	53.0 \pm 5.2	126.5 \pm 23.7	36.81 \pm 5.18	5.83 \pm 2.71
<i>t</i> 值		-1.996	-1.559	-3.668	4.494	1.555	1.484	2.614	0.074
P值		0.064	0.173	0.002	0.001	0.141	0.203	0.047	0.942

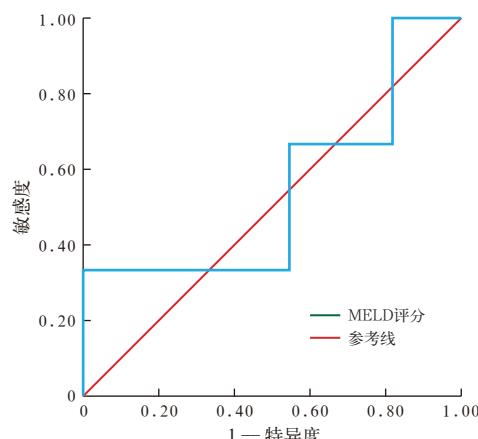
注:MELD为终末期肝病模型,SOFA为序贯器官衰竭评分,PLT为血小板计数,PT为凝血酶原时间,APTT为活化部分凝血活酶时间,PTA为凝血酶原活动度,ALB为白蛋白,TBil为总胆红素,Glu为血糖,SCr为血肌酐,INR为国际标准化比值,ALT为丙氨酸转氨酶,GGT为 γ -谷氨酰转移酶,ALP为碱性磷酸酶



注:MELD为终末期肝病模型,ROC曲线为受试者工作特征曲线

图1 MELD评分预测毒蕈中毒患者预后的ROC曲线

2.3.3 MELD评分对预后的预测价值(图2): ROC曲线分析显示,MELD评分预测进行PE治疗的毒蕈中毒患者预后的AUC为0.545,95%CI为0.228~0.863;当截断值为32.19分时,敏感度为33.3%,特异度为100%,阳性预测值为0.330,阴性预测值为1,约登指数为0.333。说明MELD评分对进行PE治疗的毒蕈中毒患者预后有一定预测价值。



注:MELD为终末期肝病模型,ROC曲线为受试者工作特征曲线

图2 MELD评分预测毒蕈中毒血浆置换(PE)患者预后ROC曲线

3 讨论

因大多数毒蕈中毒患者就诊时不能提供毒蕈标本,从而影响了对毒蕈种类的判断。研究表明,食用毒蕈的种类与预后明显相关^[7],故建议临床医生在接诊患者后应尽可能了解毒蕈种类,有助于判断预后;同时早期制定PE等治疗方案,改善患者预后。

用传统分类法可将毒蕈中毒分为肠胃炎型、中毒性肝炎型、中毒性溶血型、神经精神型、急性肾衰竭型^[8],但有些患者同时存在2种或以上类型的症状和体征,本研究将其归为混合型。本研究结果显示,死亡患者生化指标的异常程度明显高于存活患者;ROC曲线分析表明,在不确定哪一类毒蕈中毒的情况下,MELD评分对患者死亡有预测价值。研究表明,MELD评分不仅能评估肝损伤和肝衰竭的程度^[9],预测肝移植患者感染的发生风险^[10],同时在毒蕈中毒预后方面也有重要的评估作用。本研究结果显示,MELD评分与毒蕈中毒患者28 d病死率呈显著正相关。MELD评分中包含TBil、INR、SCr3项指标,高MELD评分可间接反映肝肾损伤严重程度。MELD评分在临床各级医院应用较为普遍,且涉及指标容易获得,甚至某些医院的急诊床旁检测(POCT)也能获得上述指标^[11],且POCT即时检测结果在数十分钟内即可获得^[12]。因此,用MELD评分评估毒蕈中毒患者预后可在临床进行尝试性推广。

本研究结果显示,SOFA评分不能很好地反映毒蕈中毒患者的病情严重程度,即使是死亡患者的均值也未超过9分。原因可能为:SOFA评分更适合于脓毒症导致的多器官功能衰竭(MOF)患者的病情评估^[13]。同时本研究中PE患者的相关分析显示,MELD评分与SOFA评分无相关性。研究表明,SOFA评分不能预测毒蕈中毒患者的预后^[14-15],与本研究结论一致。

研究显示,毒蕈中毒患者的 MELD 评分与住院时间存在相关性^[16-17]。但本研究中,一部分 MELD 评分较高的患者,出院后转入当地二甲医院或社区医院继续治疗,继续治疗的时间未算入住院时间。因此这部分数据不能准确反映毒蕈中毒患者的住院时间,未予统计。

本研究进一步分析显示,在进行 PE 的患者中,死亡组 MELD 评分、TBil、ALT 明显高于存活组。梁伟波等^[18]研究表明,中毒患者如果肝功能损害进一步加重,出现胆酶分离,提示预后不良。本研究中存活组 APTT 较死亡组更为异常,可能与 PE 前中心静脉置管术时给予肝素有关。研究表明,PE 可显著提高中毒性肝炎型毒蕈中毒患者的存活率,应尽早开展^[19]。我们建议,如怀疑患者是毒伞肽、毒肽类中毒,应尽早进行 PE 治疗,肝移植可以作为最后的治疗手段来考虑^[20]。

综上所述,本研究显示,毒蕈中毒患者的 MELD 评分越高,预后越差;经过 PE 治疗的毒蕈中毒患者的 MELD 评分也与预后有关。因此, MELD 评分可以评估急性毒蕈中毒患者的预后。

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