·临床研究·

早期血清白蛋白水平对重型颅脑损伤术后患者预后的预测价值

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【摘 要】 目的 评估早期血清白蛋白(ALB)水平用于预测重型颅脑损伤(STBI)术后患者预后的价值。**方法** 采用回顾性研究方法,选取2015年9月至2020年6月徐州医科大学附属医院重症医学科收治的年龄≥18岁、ICU住院时间>7 d的149例STBI术后患者为研究对象,根据28 d生存情况将其分为存活组和死亡组。收集患者一般资料,入ICU 1、3、5、7 d的血清ALB水平,1~3、4~5、6~7 d ALB补充量。采用多因素logistic回归分析影响预后的独立危险因素。通过动态ALB水平及急性生理和慢性健康状况Ⅱ(APACHEⅡ)评分绘制受试者工作特征曲线(ROC),评估其预测28 d预后的价值;基于相应时间点ALB临界值分组,通过Kaplan-Meier生存曲线分析累积生存率。**结果** 149例患者中,28 d内死亡41例,病死率为27.5%。治疗时间延长情况下,存活组血清ALB水平呈逐渐上升趋势,死亡组呈先下降后升高趋势,死亡组3 d血清ALB水平最低。相较存活组,死亡组入ICU 3、5、7 d血清ALB水平皆明显偏低[(35.22±0.54)和(25.99±0.60),(36.58±0.54)和(32.29±4.25),(36.70±0.49)和(34.66±0.79) mmol/L,均$P<0.05$)]。分析ROC曲线可知,在预测STBI术后患者28 d死亡方面,入ICU 3 d与5 d血清ALB具有较高的价值,ROC曲线下面积(AUC)依次是0.928和0.892(均$P<0.001$);APACHEⅡ评分及入ICU 7 d血清ALB水平次之,两者AUC依次是0.801和0.616(均$P<0.05$)。以3 d血清ALB 31.2 g/L当作预测28 d死亡的临界值时,其灵敏度为95.12%,特异度为81.48%,阳性似然比为3.02,阴性似然比为0.07。分析Kaplan-Meier生存曲线可知,入ICU不同时间点,高于血清ALB临界值者28 d存活率明显比低于临界值者高,且生存期更长。3 d时血清ALB>31.2 g/L者28 d存活率明显高于血清ALB≤31.2 g/L者,且生存期显著延长[28 d存活率:96.7%(89/92)和32.8%(19/57),$\chi^2=68.068$,$P<0.001$;生存期(d):26.46(23.96,30.11)和24.26(19.93,28.46),$Z=3.423$,$P=0.001$]。**结论** 血清ALB水平下降代表STBI术后患者预后不佳;入ICU 3 d血清ALB水平对STBI术后患者预后预测价值最高。

【关键词】 颅脑损伤;血清白蛋白;预后;APACHEⅡ评分
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Predictive value of early serum albumin level on prognosis of patients after severe traumatic brain injury

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【Abstract】 Objective To evaluate the value of early serum albumin (ALB) levels for predicting the prognosis of patients with severe traumatic brain injury (STBI). **Methods** A retrospective study was of 149 postoperative STBI patients who were aged over 18 and stayed over 7 days in the Intensive Care Unit of the Affiliated Hospital of Xuzhou Medical University from September 2015 to June 2020. Based on 28-day survival, the patients were divided into survival group and death group. Data were collected of the patient's basic information, serum albumin levels at d 1, 3, 5 and 7, and supplementary albumin volume at d 1-3, d 4-5, d 6-7. Multivariate logistic regression analysis was performed for independent risk factors affecting prognosis. Receiver operating characteristic (ROC) curve was drawn based on dynamic ALB levels and acute physiology and chronic health evaluation Ⅱ (APACHEⅡ) score to evaluate the predictive value for 28-day survival. The patients were grouped based on the ALB cut-off value at the corresponding time point, and Kaplan-Meier survival curve was used for analyzing the cumulative survival rate. **Results** Of 149 patients, 41 died in 28 days, with a fatality rate of 27.5%. With the prolonged treatment, the ALB level of the survival group showed a trend of gradual increase. The death group showed a decrease-increase trend of ALB levels, reaching the lowest at d 3. On d 3, 5, and 7 of ICU stay, the ALB levels in the death group were significantly lower than that in the survival group [(35.22±0.54) *vs* (25.99±0.60), (36.58±0.54)

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vs (32.29±4.25), (36.70±0.49) *vs* (34.66±0.79) mmol/L, $P<0.05$ for all). Analysis of the ROC curve showed that in predicting the 28-day death of patients with severe brain injury, the ALB levels at d 3 and d 5 of ICU stay had the highest value, and the area under the ROC curve (AUC) was 0.928 and 0.892 (both $P<0.001$). APACHE Ⅱ score and the ALB level at d 7 of ICU stay were the second, and the AUC of the two were 0.801 and 0.616 ($P<0.05$ for both). Using the ALB of 31.2 g/L at d 3 as the critical value for predicting 28-d death, it yielded a sensitivity of 95.12%, a specificity of 81.48%, a positive likelihood ratio of 3.02, and a negative likelihood ratio of 0.07. Analysis of the Kaplan-Meier survival curve showed that, at different time points in the ICU, the 28-d survivalrate of those above the cut-off value of ALB was significantly higher than that of those below, and the survival was longer. The 28-d survival rate was significantly higher in the patients with ALB>31.2 g/L at d 3 than that of those with ALB≤31.2 g/L, and the survival was significantly prolonged [28-d survival rate: 96.7% (89/92) *vs* 32.8% (19/57), $\chi^2=68.068$, $P<0.001$; survival period (d): 26.46 (23.96,30.11) *vs* 24.26 (19.93, 28.46), $Z=3.423$, $P=0.001$]. **Conclusion** A decrease in ALB represents a poor prognosis for STBI patients, and the ALB level at d 3 in ICU has the highest prognostic value for those patients.

【Key words】 traumatic brain injury; serum albumin; prognosis; APACHE Ⅱ

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重型颅脑损伤(severe traumatic brain injury, STBI)是存在于世界范围的健康问题。全球每年因颅脑损伤入院的患者比例高达 108~332 例/10 万人[1],其中格拉斯哥昏迷评分(Glasgow coma scale, GCS)≤8 分的 STBI 患者,病死率高达 35%~45%[2]。我国颅脑创伤资料库统计结果表明,47 所医疗机构 13 000 多例急性颅脑创伤住院患者中,STBI 患者的重残率、死亡率分别在 50%以上与 20%以上[3]。STBI 指头部受到暴力直接(或间接)作用,导致颅脑组织受损,同时伤后昏迷时间超过 6 h 或出现再昏迷。近年来虽然在创伤性颅脑损伤的病理生理研究方面取得一些进展,但并未在患者预后方面带来实质的进步[4,5]。此类患者入院时病情相对危重,诸多因素与预后相关,在预测预后方面存在较高难度[6]。目前国内外针对血清白蛋白(albumin, ALB)水平对 STBI 术后患者预后影响的研究较少,多局限于单一时间点,未能动态监测血清 ALB 水平变化。本研究对早期血清 ALB 进行监测,分析其对 STBI 术后患者预后的预测价值。

1 对象与方法

1.1 研究对象

回顾性分析 2015 年 9 月至 2020 年 6 月就诊于徐州医科大学附属医院重症监护病房(intensive care unit, ICU)的 149 例 STBI 患者的临床资料。纳入标准:年龄≥18 岁;明确诊断颅脑损伤(入院时 GCS 评分 3~8 分),外伤后 24 h 内入院并进行手术治疗;住院时间>7 d。排除标准:住院期间再次手术;曾患感染性疾病与慢性消耗性疾病(心脑血管疾病、肾脏疾病、糖尿病、肝炎);血液系统疾病;使用免疫抑制剂;多器官功能衰竭,发生颅脑损伤前有日常活动能力受限与营养不良问题;临床资料不完整。

1.2 治疗方法

患者入院后立即进行手术治疗,手术方式包括开颅血肿清除术、去骨瓣减压术、脑室外引流术与视神经管减压术。术后患者收住 ICU,并于术后 24 h 内复查头颅及胸部 CT。对患者生命体征进行监测,包括瞳孔、意识、血压、脉搏等。根据患者神志及瞳孔变化,及时复查头颅 CT 及床边胸片。常规治疗包括甘露醇降低颅内压防治脑水肿,肠内外营养支持,维持酸碱平衡及血糖的平稳,营养脑神经等对症干预。控制感染,体温保持正常水平。同本研究相关的治疗,若患者 ALB 在 35 g/L 以下,根据公式进行补充:所需剂量(g)=(期望达到白蛋白水平-现有水平)(g/L)×2×血浆容量(L)。若在 35 g/L 以上,通常可不做处理。

1.3 研究方法及分组

收集患者基本资料,性别、体质量、年龄、入 ICU 24 h 内相关实验室参数、ICU 入住天数与转归、有创机械通气时间等;收集急性生理和慢性健康状况评估Ⅱ(acute physiology and chronic health evaluation Ⅱ, APACHE Ⅱ)评分;对患者的预后进行电话随访,对入 ICU 1、3、5、7 d 血清 ALB 水平进行记录(1 d 血清 ALB 为入院 24 h 内最低值),同时记录 1~3、4~5、6~7 d 的 ALB 补充量。基于 28 d 预后,将患者分为存活组(108 例)和死亡组(41 例)。

1.4 统计学处理

采用 SPSS 26.0 和 GraphPad Prism 5.0 进行统计学处理和制图。正态性检验采用 Shapiro-Wilk 法,若计量资料符合正态分布,用均数±标准差($\bar{x}\pm s$)表示,组间比较采用独立样本 t 检验;非正态分布用中位数(四分位数间距)[$M(Q_1, Q_3)$]表示,组间比较采用非参数检验(Mann-Whitney U)。计数资料用例数(百分率)表示,采用 χ^2 检验。通过单因素 logistic 回归分析影响预后的有统计学意义的参

数,进行多因素 logistic 回归分析。以不同时间点 ALB 水平和 APACHE Ⅱ 评分绘制受试者工作特征(receiver operating characteristic, ROC)曲线,计算 ROC 曲线下面积(area under the curve, AUC)。采用 Kaplan-Meier 法进行生存曲线分析。$P<0.05$ 为差异有统计学意义。

2 结果

2.1 2组患者临床资料比较

入选 149 例患者中,男性 106 例,女性 43 例;年龄 19~86 岁,中位年龄 52(42,64)岁;28 d 存活 108 例,死亡 41 例,28 d 病死率为 27.5%。存活组和死亡组患者性别、体质量、年龄比较差异均无统计学意义(均 $P>0.05$),表示基线资料均衡,2 组具有可比性。与存活组比较,死亡组血小板与 GCS 显著偏低(均 $P<0.05$);APACHE Ⅱ评分、乳酸、机械通气时间、血糖、ICU 入住天数、凝血酶原时间(prothrombin time, PT)及活化部分凝血酶原时间(activated partial thromboplastin time, APTT),死亡组皆明显偏高(均 $P<0.05$);但血红蛋白、白细胞、淋巴细胞、血钠及血钾差异均无统计学意义(均 $P>0.05$;表 1)。

2.2 2组患者血清 ALB 动态变化比较

149 例患者中发生低白蛋白血症 62 例(41.6%)。存活组和死亡组入 ICU 1 d 血清 ALB 水平接近,维持在 30 mmol/L 左右。存活组血清 ALB 水平随病情控制和及时补充 ALB 后呈逐渐上升趋势,而死亡组则随治疗时间延长呈先下降后升高趋势,其中死亡组 3 d 血清 ALB 水平最低。死亡组 3、5、7 d 血清 ALB 水平显著低于存活组(均 $P<0.05$;图 1)。

2.3 患者预后的影响因素

通过单因素 logistic 回归分析确定影响 28 d 病死率有统计学意义的变量,最后通过多因素 logistic 回归分析进行校正,发现 GCS、APACHE Ⅱ评分、血清 ALB 为影响预后的独立危险因素(表 2)。

2.4 ALB、APACHEⅡ评分对患者预后的预测价值

ROC 曲线分析显示,入 ICU 3 d 血清 ALB 水平对 STBI 术后患者 28 d 死亡的预测价值较大,AUC 为 0.928($P<0.001$);以 3 d 血清 ALB 31.2 g/L 作为预测 28 d 死亡的临界值时,灵敏度为 95.12%,特异度为 81.48%,阳性似然比为 3.02,阴性似然比为 0.07(图 2,表 3)。

表 1 2组患者临床资料比较

Table1 Comparison of clinical data between two groups

Item	Survival group($n=108$)	Death group($n=41$)	$\chi^2/Z/t$	P value
Age[years, $M(Q_1,Q_3)$]	50(35,62)	53(46,70)	1.086	0.073
Male[n(%)]	75(69.4)	31(75.6)	0.500	0.458
Body mass[kg, $M(Q_1,Q_3)$]	62(57,67)	62(57,65)	0.043	0.966
GCS[points, $M(Q_1,Q_3)$]	7(6,7)	4(4,5)	7.778	0.000
APACHE Ⅱ [points, $M(Q_1,Q_3)$]	13(12,15)	18(17,20)	7.978	0.000
Mechanical ventilation time[d, $M(Q_1,Q_3)$]	2.00(0.00,5.00)	6.00(0.75,9.50)	2.972	0.003
Length of ICU stay[d, $M(Q_1,Q_3)$]	8.50(5.00,13.75)	12.00(9.00,17.00)	3.542	0.000
Hb(g/L, $\bar{x}\pm s$)	106.06±21.71	98.46±24.84	1.833	0.069
PLT[$\times10^9$/L, $M(Q_1,Q_3)$]	166.00(113.50,211.50)	125.00(87.00,181.50)	2.323	0.020
WBC[$\times10^9$/L, $M(Q_1,Q_3)$]	13.30(9.35,16.18)	13.30(10.55,15.35)	0.055	0.956
Lymphocytes[$\times10^9$/L, $M(Q_1,Q_3)$]	0.80(0.53,1.30)	0.70(0.50,1.15)	0.771	0.441
PT[s, $M(Q_1,Q_3)$]	13.05(11.90,14.48)	14.10(12.65,15.40)	2.691	0.007
APTT[s, $M(Q_1,Q_3)$]	29.20(25.83,34.23)	34.40(28.30,42.25)	3.292	0.001
Na^+[mmol/L, $M(Q_1,Q_3)$]	141.00(138.35,144.83)	142.40(138.25,148.35)	0.634	0.526
K^+[mmol/L, $M(Q_1,Q_3)$]	3.70(3.42,4.14)	3.80(3.33,4.17)	0.259	0.795
Blood glucose[mmol/L, $M(Q_1,Q_3)$]	8.60(7.13,10.10)	10.40(7.55,14.05)	2.769	0.006
Lactate[mmol/L, $M(Q_1,Q_3)$]	1.40(1.03,2.50)	2.30(1.15,3.50)	2.257	0.024

GCS: Glasgow coma scale; APACHE Ⅱ: acute physiology and chronic health evaluation Ⅱ; Hb: hemoglobin; PLT: platelet; WBC: white blood cell; PT: prothrombin time; APTT: activated partial thromboplastin time.

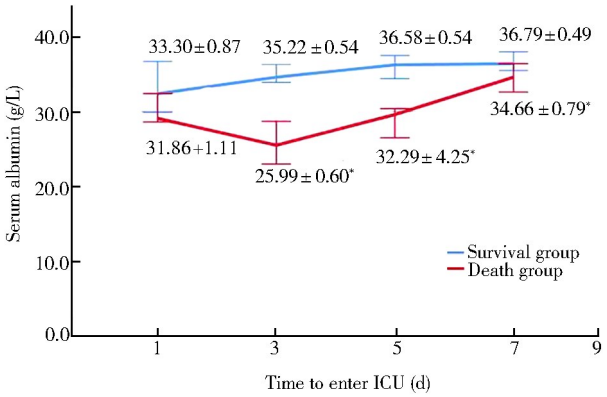

图 1 2 组患者入 ICU 后血清 ALB 水平动态变化

Figure 1 Dynamic changes of serum albumin levels in two groups of patients after entering ICU

ICU: intensive care unit; ALB: albumin. Compared with survival group, * $P<0.05$.

表 2 患者 28 d 病死率多因素 logistic 回归分析

Table 2 Multivariate logistic regression analysis of 28-day mortality

Factor	*B*	*SE*	*Wald*	*OR*	95% *CI*	*P* value
GCS	−2.876	1.162	6.126	0.056	0.060−0.550	0.013
APACHE Ⅱ	1.667	0.695	5.753	5.295	1.356−20.669	0.016
3 d ALB	−0.998	0.391	6.493	0.369	0.171−0.794	0.011
6 d ALB	−0.067	0.043	2.403	0.935	0.858−1.018	0.121
1−3 d ALB	−0.154	0.067	5.286	0.857	0.751−0.978	0.021

GCS: Glasgow coma scale; APACHE Ⅱ: acute physiology and chronic health evaluation Ⅱ; ALB: albumin.

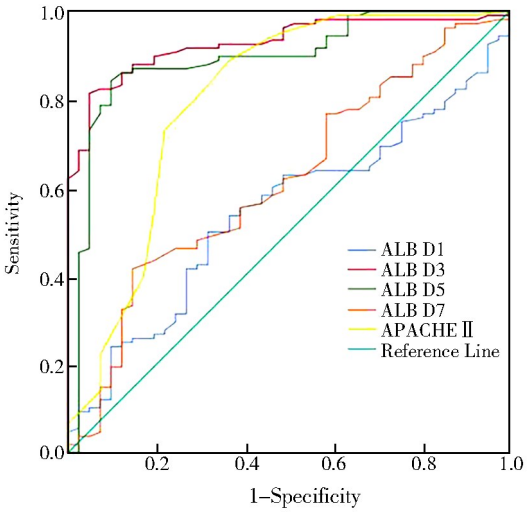

图 2 血清 ALB 水平及 APACHE Ⅱ 评分预测患者 28 d 死亡 ROC 曲线

Figure 2 ROC curve of ALB level and APACHE Ⅱ score predicting 28-day death of patients

ALB: albumin; APACHE Ⅱ: acute physiology and chronic health evaluation Ⅱ; ROC: receiver operating characteristic.

2.5 Kaplan-Meier 生存曲线分析

根据入 ICU 后不同时间点相应的血清 ALB 预后临界值将患者分组,以存活 50 d 为上限。结果显示高于 ALB 临界值组患者 28 d 存活率明显高于低于临界值组,且生存期更长(均 $P<0.05$;图 3,表 4)。

表 3 血清 ALB 水平及 APACHE Ⅱ 评分对患者 28 d 死亡的预测价值

Table 3 Predictive value of ALB level and APACHE Ⅱ score for 28-day death of patients

Factor	AUC	95% *CI*	*P* value	Cut-off value	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio
1 d ALB	0.545	0.462−0.627	0.368	32.4	68.29	50.00	1.37	0.63
3 d ALB	0.928	0.874−0.964	0.000	31.2	95.12	81.48	3.02	0.07
5 d ALB	0.892	0.831−0.937	0.000	31.5	90.24	84.26	5.73	0.12
7 d ALB	0.616	0.533−0.694	0.024	37.8	85.37	41.67	1.46	0.35
APACHE Ⅱ	0.801	0.728−0.862	0.000	17.0	63.41	88.89	5.71	0.41

ALB: albumin; APACHE Ⅱ: acute physiology and chronic health evaluation scoring system; AUC: area under the curve.

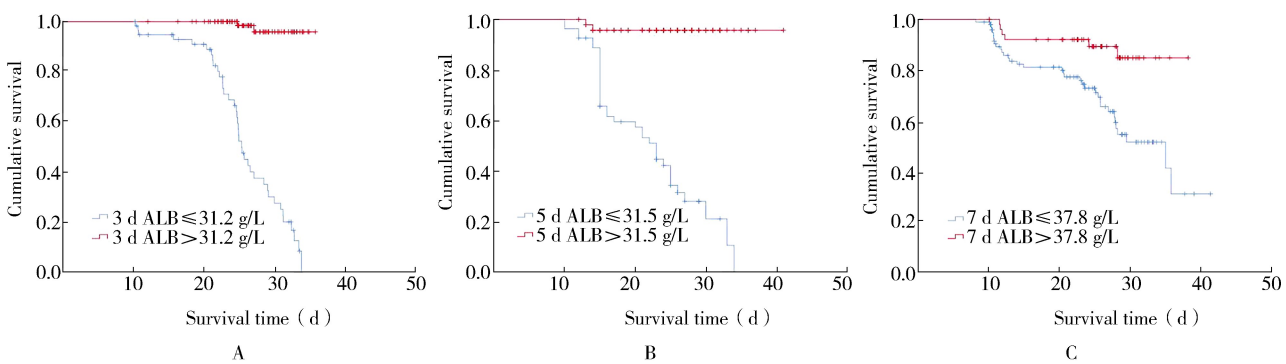

图 3 不同时间点血清 ALB 预后临界值分组患者 Kaplan-Meier 生存曲线

Figure 3 Kaplan-Meier survival curve of patients grouped by the prognostic critical value of serum albumin at different time points

ALB: albumin.

表4 不同时间点血清ALB预后临界值分组的患者存活情况

Table 4 Survival of patients grouped by prognostic threshold of serum albumin at different time points

Time	ALB(g/L)	n	28 d survival			Lifetime		
			[n(%)]	χ^2	P value	[d, $M(Q_1,Q_3)$]	Z	P value
3 d	>31.2	92	89(96.7)	78.511	<0.001	26.46(23.96,30.11)	3.423	0.001
	≤31.2	57	19(33.3)			24.26(19.93,28.46)		
5 d	>31.5	95	92(96.8)	76.848	<0.001	26.00(22.00,30.00)	4.071	0.000
	≤31.5	54	17(31.5)			20.50(15.00,25.00)		
7 d	>37.8	51	45(88.2)	10.151	0.001	25.84(22.51,28.91)	2.160	0.031
	≤37.8	98	62(63.3)			23.45(12.73,28.05)		

ALB: albumin.

3 讨 论

颅脑损伤是影响人类健康最严重的疾病之一,目前原发性颅脑损伤和继发性脑损害预后均不佳,给家庭及社会带来沉重负担。ALB为一类可溶性生物大分子,其合成场所为肝细胞,转移到肝外后使用。在维持血浆胶体渗透压、运输机体重要物质、参与球蛋白胶体保护、调解机体代谢等方面发挥重要作用[7]。如果机体ALB低于正常水平,可引发若干病理生理改变,血浆胶体渗透压降低,出现组织水肿,严重的水电解质失衡,伤及肝脏代谢机能[8]。STBI患者常出现低白蛋白血症,其机制包括STBI后机体呈高分解代谢水平,打破了能量供应方面的平衡,会加剧ALB的消耗与分解。肝细胞合成能力不足,同时尿氮排出增加,机体出现负氮平衡,处于营养失衡状态[9]。在神经内分泌系统与众多炎性介质协同刺激下,ALB mRNA表达下降,阻碍ALB合成,导致体内蛋白分解代谢失控[10]。

目前国内外关于低白蛋白血症对STBI患者预后影响的研究均局限于单一时间点,未能动态监测早期血清ALB水平[11]。严重的低白蛋白血症可导致STBI患者病死率增高,且低白蛋白血症可作为患者死亡的独立预测因素[12, 13]。本研究评估动态血清ALB水平对STBI术后患者预后的预测价值。入院时2组血清ALB水平无显著差异,入院后存活组血清ALB水平随病情控制和及时补充ALB后呈逐渐上升趋势,而死亡组则随治疗时间延长呈先下降后升高趋势,其中死亡组3 d血清ALB水平最低。3、5、7 d时,对比存活组,死亡组ALB水平皆明显偏低。ALB的半衰期较长,为20 d左右,同时存在极大的血清库,这意味着在营养治疗期间和从压力中恢复的患者中ALB浓度会缓慢升高。采用补充ALB方式使ALB水平上调需经历一定时间,存活组脑功能受损较死亡组相对较轻,及时补充ALB后,其水平逐渐上升;死亡组由于颅脑创伤更严重,3~4 d达脑水肿高峰期,体内ALB损耗更严重,虽补充ALB,但仍有一段下降趋势,3 d达最低水平,后通过补充ALB逐渐上升。因此,动态监测早期血清ALB水平能使临床医师及时了解STBI术后患者的病情变化,为评估预后提供依据。

进一步通过ROC曲线分析显示,入ICU 3 d血清ALB水平对患者28 d死亡的预测价值最大(AUC=0.928)。以3 d血清ALB>31.2 g/L作为临界值时,其灵敏度为95.12%,特异度为81.48%。根据3 d血清ALB是否>31.2 g/L将患者分为2组,结果显示高血清ALB组患者28 d存活率显著高于低血清ALB组,并且生存期明显延长。5、7 d血清ALB水平对于患者预后有一定预测价值,但1 d血清ALB水平不能用来预测预后。

对于APACHE Ⅱ评分,临床领域用其评价危重疾病的严重程度及危重患者面临死亡和严重并发症的危险,其分值和病死率直接相关,有公认的可靠性及实用性,可以预测ICU患者预后[14]。本研究中死亡组APACHE Ⅱ评分显著高于存活组,说明APACHE Ⅱ评分和STBI患者病情及预后密切相关;ROC曲线分析结果表明,在预测STBI术后患者28 d死亡方面,APACHE Ⅱ评分体现出较高的价值(AUC=0.801)。

综上所述,本研究结果显示,在血清ALB上升趋势方面,相比STBI死亡患者,存活患者更为明显,此项指标下降表明患者预后不良,缺乏良好治疗反应,需对治疗方案合理与否及时做出判断。现今依然需要通过更多样本量、设计规范的前瞻性多中心研究,更为深入地求证早期血清ALB水平在治疗STBI术后患者中的应用价值。

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致“一带一路”沿线国家和地区医学机构

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