急性呼吸窘迫综合征患者血清 IL-18 和组织因子水平与预后的关系

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摘要 目的:探讨急性呼吸窘迫综合征(ARDS)患者血清白细胞介素-18(IL-18)和组织因子(TF)水平变化及其与预后的关系。方法:选取92例ARDS患者,根据病情严重程度将其分为轻度组(26例)、中度组(36例)和重度组(30例);根据患者的预后分为存活组(50例)和死亡组(42例),另选择同期健康体检者80例作为对照组。采用酶联免疫吸附法(ELISA)检测受试者血清IL-18及TF水平,观察各组血清IL-18及TF水平变化及其对ARDS患者预后的临床预测价值。结果 :ARDS组患者血清IL-18及TF水平高于对照组(均 $P<0.05$)。重度组、中度组患者血清IL-18及TF水平高于轻度组,且重度组高于中度组(均 $P<0.05$);死亡组患者血清IL-18及TF水平明显高于存活组(均 $P<0.05$)。受试者工作特征曲线(ROC)分析显示,IL-18的曲线下面积(AUC)为0.755,截断值为110 pg/mL,敏感性为75.00%,特异性为81.67%;TF的AUC为0.725,截断值为2.13 U/L,敏感性为65.00%,特异性为76.67%。经COX多因素回归分析显示,年龄、急性生理学与慢性健康评估(APACHE II)评分、血清IL-18及TF是影响ARDS患者预后的独立危险因素(均 $P<0.05$)。结论:ARDS患者血清IL-18及TF水平升高,与患者疾病严重程度相关,可作为ARDS患者预后不良的检测指标。

关键词 急性呼吸窘迫综合征;白细胞介素-18;组织因子;严重程度;预后

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Changes of serum IL-18 and tissue factor levels in patients with acute respiratory distress syndrome and their relationships with prognosis *DUAN Ya-nan, MI Ting*. Xi'an Central Hospital, Xi'an 710003, China*

Abstract Objective: To investigate the changes of serum interleukin-18 (IL-18) and tissue factor (TF) levels in patients with acute respiratory distress syndrome (ARDS) and their relationships with prognosis. Methods: Ninety-two patients were selected for the study, among them, there were 26 mild cases (mild group), 36 moderate cases (moderate group), and 30 severe cases (severe group). According to prognosis, patients were divided into survival group (50 cases) and death group (42cases). Eighty healthy persons in the same period were selected as control group. Levels of serum IL-18 and TF were measured by enzyme-linked immunosorbent assay (ELISA). The changes of serum IL-18 and TF levels in each group and their clinical predictive values for the prognosis of ARDS patients were observed. Results: The levels of serum IL-18 and TF in ARDS group were significantly higher than those in control group (all $P<0.05$). Levels of serum IL-18 and TF in severe group and moderate group were significantly higher than those in mild group, and those in severe group were significantly higher than those in moderate group (all $P<0.05$). The levels of serum IL-18 and TF in the death group were significantly higher than those in the survival group (all $P<0.05$). ROC curve analysis showed that the AUC of IL-18 was 0.755, the truncation value was 110 pg/mL, the sensitivity was 75.00%, and the specificity was 81.67%; AUC of TF was 0.725, truncation value was 2.13 U/L, sensitivity was 65.00%, specificity was 76.67%. COX multivariate regression analysis showed that age, APACHEII score, serum IL-18 and TF were independent risk factors influencing the prognosis of ARDS patients (all $P<0.05$). Conclusion: Serum IL-18 and TF levels in patients with ARDS increase, which is related to the severity of the disease, and can be used as a prognostic indicator of ARDS patients.

Key words Acute respiratory distress syndrome; Interleukin-18; Tissue factor; Severity; Prognosis

急性呼吸窘迫综合征(acute respiratory distress syndrome,ARDS)是临床常见多病因引起的急性炎症性弥漫性肺损伤,主要临床表现为进行性呼吸困难、难治性低氧血症、双肺弥漫性浸润阴影等,死亡率高[1]。炎症反应在ARDS发病过程中发挥重要作用,而白细胞介素-18(interleukin-18,IL-18)是重要炎症因子,在多种感染性疾病中高表达[2]。肺血管微血栓形成是ARDS患者关键病理学变化,凝血因子在其发病中发挥重要作用,而组织因子(tissue factor,TF)能增强凝血因子蛋白酶活性,促进凝血[3]。本研究探讨ARDS患者血清IL-18及TF水平的变化及其与预后的关系。

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资料与方法

一般资料 选取2016年1月~2018年12月西安市中心医院收治的ARDS患者92例(男52,女40),根据病情严重程度将其分为轻度组(26例)、中度组(36例)和重度组(30例);根据患者的预后分为存活组(50例)和死亡组(42例)。ARDS患者年龄23~75岁,平均(48.21±4.15)岁;体重指数(body mass index,BMI)20.83~25.77 kg/m^2,平均(21.38±1.06)kg/m^2。原发病:重症肺炎65例,创伤21例,急性胰腺炎6例。急性生理学与慢性健康评估(acute physiology and chronic health evaluation,APACHE Ⅱ)评分为(16.25±5.12)分;Murray肺损伤评分为(2.87±0.94)分。另选择同期健康体检者80例(男46,女34)作为对照组,年龄25~76岁,平均(49.52±4.27)岁;BMI 20.68~25.93 kg/m^2,平均(22.14±1.13)kg/m^2。受试者性别、年龄、BMI等一般资料比较,差异无统计学意义(均$P>0.05$)。

纳入与排除标准 纳入标准:①符合ARDS诊断标准[4];②1周内发病患者;③氧合指数≤300 mmHg。排除标准:①年龄<18岁者;②合并其他器官功能障碍者;③合并免疫功能障碍者;④合并恶性肿瘤患者;⑤合并妊娠者;⑥依从性差者。本研究经医院伦理委员会批准,患者或家属知情并签署同意书。

方法 采集3组受试者入组24 h内清晨空腹静脉血5 mL,室温静置25 min,3 000 r/min离心10 min,取上层血清,-80℃冻存待检。采用酶联免疫吸附法(ELISA)检测受试者血清IL-18及TF水平,试剂盒购自美国ADL公司,Infinite 20 PRO多功能酶标仪购自瑞士Tecan公司,实验步骤如下:室温平衡试剂、样品20 min,1:20蒸馏水稀释洗涤液,1:4稀释液稀释样本。①加样:取板,设置标准品孔、待检样品孔及空白孔,标准品孔加不同浓度标准品各50 μL,样品孔加稀释后样品各50 μL,空白孔不加,振荡器上混匀,封膜室温孵育40 min;②洗板:去除孔内液体,甩干,加清洗液静止1 min,滤纸上拍干,反复洗板4~5次;③加标记抗体:加辣根过氧化物酶标记抗体工作液100 μL(空白孔不加),振荡器上混匀,封膜37℃水浴锅孵育60 min;④洗板:去除孔内液体,甩干,加清洗液静止1 min,滤纸上拍干,反复洗板4~5次;⑤加底物:各孔加入底物A和底物B工作液各50 μL,封膜37℃避光反应15 min;⑥终止反应:各孔加终止液50 μL终止反应,15 min内检测;⑦结果检测:采用酶标仪在450 nm波长处读取光密度(OD)值,以OD值为纵坐标,标准品浓度为横坐标绘制标准曲线,计算各样品浓度。

统计学处理 采用SPSS 18.0统计学软件,计量资料以($\bar{x}\pm s$)表示,采用t检验,计数资料以百分比(%)表示,采用卡方检验,多组间比较采用方差分析,采用受试者工作特征(ROC)曲线预测血清IL-18及TF水平对ARDS预后死亡的预测价值,采用COX回归分析影响预后的危险因素,以$P<0.05$为差异有统计学意义。

结 果

血清IL-18及TF水平 ARDS组患者血清IL-18及TF水平高于对照组(均$P<0.05$),见表1。重度组、中度组患者血清IL-18及TF水平高于轻度组,且重度组高于中度组(均$P<0.05$),见表2。死亡组患者血清IL-18及TF水平明显高于存活组(均$P<0.05$),见表3。

表1 ARDS组与对照组血清IL-18及TF水平比较 ($\bar{x}\pm s$)

组别	例	IL-18(pg/mL)	TF(U/L)
对照组	80	14.38±4.26	1.04±0.28
ARDS组	92	76.35±7.42*	1.75±0.51*

注:与对照组比较,*$P<0.05$

表2 不同严重程度患者血清IL-18及TF水平比较 ($\bar{x}\pm s$)

组别	例	IL-18(pg/mL)	TF(U/L)
轻度组	26	46.85±6.37	1.34±0.31
中度组	36	82.64±8.33*	1.71±0.47*
重度组	30	104.51±18.29*△	2.01±0.66*△

注:与轻度组比较,*$P<0.05$;与中度组比较,△$P<0.05$

表3 不同预后患者血清IL-18及TF水平比较 ($\bar{x}\pm s$)

组别	例	IL-18(pg/mL)	TF(U/L)
存活组	50	85.36±8.26	1.75±0.33
死亡组	42	118.73±3.54*	2.21±0.35*

注:与存活组比较,*$P<0.05$

血清IL-18、TF水平对ARDS患者预后的预测价值 ROC曲线显示,IL-18的曲线下面积(AUC)为0.755,截断值为110 pg/mL,敏感性为75.00%,特异性为81.67%,约登指数为0.5667;TF的AUC为0.725,截断值为2.13 U/L,敏感性为65.00%,特异性为76.67%,约登指数为0.4167,见图1。

影响ARDS预后独立危险因素分析 经COX多因素回归分析显示,年龄、APACHEII评分、IL-18、TF是影响ARDS患者预后的独立危险因素(均$P<0.05$),见表4。

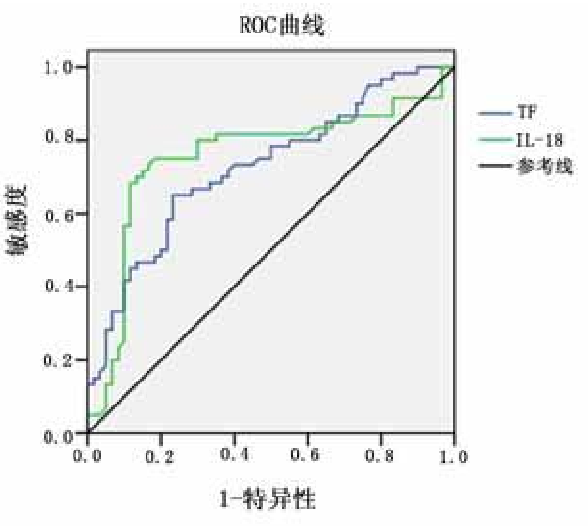

图 1 血清 IL-18 及 TF 预测 ARDS 患者预后的 ROC 曲线

讨 论

炎症反应在 ARDS 发生发展中起关键作用，全身炎症反应聚集肺部，使炎性递质呈瀑布样释放，抗炎因子与促炎因子平衡失调，升高肺微血管通透性，引起肺水肿，形成透明膜及肺泡出血等病理变化，当病情发展到一定程度可导致肺纤维化，造成患者死亡[5]。IL-18 是近年新发现的一种属于 IL-1 家族的重要促炎因子，与 IL-12 功能相似，由单核细胞、巨噬细胞及淋巴细胞等分泌。当发生炎症反应时，患者血清 IL-18 水平显著升高，与肺部炎症反应及肺纤维化形成紧密相关[6]。柯耀棋等[7]报道慢性阻塞性肺疾病患者血清 IL-18 水平升高，且急性加重期高于稳定期，证实 IL-18 参与气道炎症反应，与疾病严重程度相关。本文结果显示，ARDS组患者血清 IL-18 水平高于对照组（$P < 0.05$），与袁雪丰等[8]研究结果相似，提示 IL-18 在 ARDS 患者血清中高表达，可能参与其致病过程。

TF 又名凝血因子Ⅲ，是一种跨膜糖蛋白，为外源性凝血途径关键启起始因子，与血液循环和血管壁状态相关。正常生理状态下，TF 仅在血管外细胞表达，当血管内皮受各种刺激发生损伤时，血管内皮细胞及机体多种正常细胞均可分泌 TF，在血液中，TF 与凝血酶原Ⅶ结合后形成活化凝血因子Ⅶa（FⅦa），进而结合成 TF-FⅦa 复合物，激活 FX，形成凝血酶并放大，导致纤维蛋白沉淀，活化血小板，启动凝血途径[9]。张春玲等[10]报道 TF 在肺栓塞大鼠肺组织中高表达，并随栓塞时间加长而升高，与本研究结果相似。

本研究显示，重度组及中度组患者血清 IL-18 及 TF 水平高于轻度组，且重度组高于中度组（均 $P < 0.05$），提示血清 IL-18 及 TF 可能参与 ARDS 发生发展，且与疾病严重程度相关，病情越严重，血清 IL-18 及 TF 水平越高。进一步研究分析显示，死亡组患者血清 IL-18、TF 水平明显高于存活组，与 Makabe 等[11]研究结果相似，提示血清 IL-18、TF 水平可能与 ARDS 患者预后不良有关。ROC 曲线分析显示，IL-18 预测 ARDS 的 AUC 为 0.755，截断值为 110 pg/mL，敏感性为 75.00%，特异性为 81.67%；TF 的 AUC 为 0.725，截断值为 2.13 U/L，敏感性为 65.00%，特异性为 76.67%，与 Borthwick 等[12]研究结果相似。最后经 COX 多因素分析显示，年龄、APACHE Ⅱ 评分、血清 IL-18、TF 是影响 ARDS 患者预后的独立危险因素，提示年龄大、APACHE Ⅱ 评分高、血清 IL-18 及 TF 水平高，患者死亡风险增高。

表 4 影响 ARDS 预后 COX 多因素回归分析

因素	*B*	*S. E*	*Wald*	*HR*	95% *CI*	*P*
年龄	0.067	0.375	0.816	1.069	1.005 ~ 1.138	0.047
APACHEII 评分	0.342	0.296	2.335	1.408	1.185 ~ 1.673	0.009
IL-18	0.264	0.281	1.939	1.302	1.137 ~ 1.492	0.016
TF	0.199	0.302	1.625	1.221	1.069 ~ 1.394	0.035

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可使肾小管上皮细胞停留在 G1 期加重肾损害。高 IGFBP-7 水平反应了更加严重的肾损伤[16]。IGFBP-7 的下调可以减轻炎性反应,从而降低 HMBG1 水平。动物实验研究发现 HMBG1 或促进缺氧-复氧介导的肾小管上皮细胞凋亡[17]。这说明乌司他丁可通过直接作用于多种水解酶减少炎性反应,也可直接或间接降低尿 IGFBP-7 和 HMGB1 水平,从而保护肾脏细胞,对 AKI 具有更好的疗效。

综上所述,乌司他丁对脓毒症 AKI 的肾功能具有保护作用,可降低炎性因子,这可能与乌司他丁可降低尿 IGFBP-7 和 HMGB1 的水平有关。

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