·临床研究·

降钙素原和D-二聚体变化率对老年重症肺炎患者临床预后的评估

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【摘 要】 **目的** 探索降钙素原(PCT)与D-二聚体(D-D)的动态变化对老年重症肺炎患者预后的评估作用。**方法** 选取2019年1月至2020年6月航天中心医院收治的78例老年重症肺炎患者作为研究对象,记录入组患者的预后,治疗前、治疗第3天、第7天,及转出ICU(或死亡)前PCT、D-D水平。计算降钙素原变化率(PCTc)和D-二聚体变化率(D-Dc)值,同时记录患者急性生理学与慢性健康状况评分Ⅱ(APACHEⅡ)。绘制受试者工作特征曲线(ROC),分析PCTc及D-Dc对老年重症肺炎患者临床转归的评估作用。采用SPSS 22.0软件进行数据分析。根据数据类型,组间比较分别采用χ^2检验、t检验或者方差分析。**结果** 78例老年重症肺炎患者中31例(39.7%)经治疗后好转并转出监护室,47例(60.2%)病情恶化死亡;生存组的年龄[(77.30±6.72)岁]及APACHE Ⅱ[(19.29±2.69)分]明显低于死亡组[(83.84±5.54)岁、(21.02±2.72)分],差异均有统计学意义(均$P<0.05$)。生存组及死亡组患者PCT水平在治疗前和3 d时,差异无统计学意义($P>0.05$);存活组患者治疗7 d、转出或死亡前PCT水平低于死亡组,差异均有统计学意义[(2.57±0.65)和(7.18±1.91)ng/ml,(0.62±0.25)和(10.37±2.47)mg/ml;均$P<0.01$]。2组患者D-D水平在治疗前和3 d时比较,差异均无统计学意义(均$P>0.05$);存活组D-D呈逐渐下降趋势,但在死亡组呈逐渐升高趋势,治疗7 d、转出或死亡前存活组患者的D-D水平明显低于死亡组,差异有统计学意义[(0.75±0.15)和(3.78±0.85)mg/L,(0.40±0.09)和(4.98±0.69)mg/L;$P<0.001$]。存活组和死亡组PCTc在治疗3、7 d及转出或死亡前比较,差异均有统计学意义[5.56(3.28, 8.22)和-3.17(-4.55, 0.00),53.73(49.12, 58.93)和-31.75(-40.91,-21.05),89.29(86.36,91.78)和-96.86(-119.40,-68.00),均$P<0.001$]。D-Dc在生存组始终维持在高水平,并随病情好转升高,D-Dc在死亡组中则相对较低,并随病情恶化逐渐下降,2组在治疗3、7 d,转出或死亡前比较,差异均有统计学差异[0.00(0.00, 6.25)和0.00(-7.69,0.00),58.33(55.29, 64.21)和-95.24(-128.50,-60.87),77.22(74.29,83.64)和-161.10(-218.70,-114.20),均$P<0.001$]。ROC曲线结果显示,PCTc,D-Dc,APACHEⅡ对老年重症肺炎预后具有评估意义[曲线下面积(AUC)=0.974,0.779,0.337; $P<0.05$],其中PCTc对老年重症肺炎患者住院期间死亡预测的AUC为0.974,95%*CI*为(0.940,1.010),最佳截断点为0.658,灵敏度为93.5%,特异度为97.9%。**结论** PCTc及D-Dc可以评估老年重症肺炎患者的临床预后,具有良好的临床应用价值。

【关键词】 老年人;重症肺炎;降钙素原;降钙素原变化率;D-二聚体;D-二聚体变化率
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Prognostic values of procalcitonin and D-dimer for severe pneumonia in the elderly

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【**Abstract**】 **Objective** To explore the dynamic changes of procalcitonin (PCT) and D-dimer (D-D) and investigate their values in the prognosis for severe pneumonia in the elderly patients. **Methods** A total of 78 elderly patients with severe pneumonia admitted in our hospital from January 2019 to June 2020 were recruited in this study. Their clinical outcome, PCT and D-D levels before treatment on the 3rd and 7th days of treatment, and immediately before out of ICU (or death) were recorded, and change rate of PCT (PCTc) and D-D (D-Dc) were calculated. Their score of Acute Physiology Age Chronic Health Evaluation Ⅱ (APACHEⅡ) were also recorded. Receiver operating characteristic (ROC) curve was drawn to assess the values of PCTc and D-Dc on the clinical outcome of the severe pneumonia patients. SPSS statistics 22.0 was used for statistical analysis. Data comparison between two groups was perfomed using χ^2 test, t test or Fisher exact test depending on date type. **Results** Among the 78 elderly patients, 31 cases (39.7%) were transferred out of ICU after treatment, and the other 47 (60.2%) patients died. The survival group had significantly younger age [(77.30±6.72) years] and lower APACHE Ⅱ score [(19.29±2.69) points] than the death group [(83.84±5.54) years, (21.02±2.72) points; $P<0.05$]. There were no obvious differences in PCT level between the survival group and the death group before and in 3 d after treatment

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(P>0.05). But the level was statistically lower in the survival group than the death group in 7 d after treatment and before transference from ICU or death [(2.57±0.65) *vs* (7.18±1.91) ng/ml, (0.62±0.25) *vs* (10.37±2.47) ng/ml; P<0.01]. Before and in 3 d after treatment, no significant difference was seen in D-D level between the 2 groups (P>0.05). Its level was in a decreasing trend in the survival group but in an increasing trend in the death group, and the former group had obviously lower level than the latter group in 7 d after treatment and transference from ICU or before death [(0.75±0.15) *vs* (3.78±0.85) mg/ml, (0.40±0.09) *vs* (4.89±0.69) mg/ml, P<0.001]. Statistical difference was seen in PCTc level between the 2 groups in 3 and 7 d after treatment and before out of ICU or death [5.56 (3.28, 8.22) *vs* −3.17 (−4.55, 0.00), 53.73 (49.12, 58.93) *vs* −31.75 (−40.91, −21.05), 89.29 (86.36, 91.78) *vs* −96.86 (−119.40, −68.00), all P<0.001]. The D-Dc level maintained at a high level and gradually turned to elevation with the condition better in the survival group. But the level differed from the 2 groups in 3 and 7 d after treatment and before out of ICU or death [0.00 (0.00, 6.25) *vs* 0.00 (−7.69, 0.00), 58.33 (55.29, 64.21) *vs* −95.24 (−128.50, −60.87), 77.22 (74.29, 83.64) *vs* −161.10 (−218.70, −114.20); all P<0.001]. ROC curve analysis showed that PCTc, D-Dc and APACHE Ⅱ were of prognostic significances for the elderly with severe pneumonia [area under curve (AUC) = 0.974, 0.779, 0.337; P<0.05]. PCTc had an AUC of 0.974, a 95% confidence interval of 0.940 to 1.010, cutoff value of 0.658, a sensitivity of 93.5%, and a specificity of 97.9%. **Conclusion** PCTc and D-Dc could predict the clinical prognosis of elderly patients with severe pneumonia, and show good value in clinical application.

【Key words】 aged; severe pneumonia; procalcitonin; change rate of procalcitonin; D-dimer; change rate of D-dimer

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肺炎是呼吸系统常见的感染性疾病,而老年人慢性基础疾病较多,免疫功能低下,呼吸道防疫能力降低,肺炎发病率较高,并常因症状不典型或就诊不及时发展为重症肺炎。据报道,重症肺炎患病率在60岁以上人群中约10%,而我国60岁以上人群患病率和死亡率逐年增高[1]。重症肺炎病死率高,早期识别重症肺炎并加强治疗,可以降低重症肺炎患者死亡率。近年来,降钙素原(procalcitonin, PCT)与D-二聚体(D-dimer, D-D)在感染性疾病的诊治及预后评估中受到了广泛关注[2,3],但有关两者在重症肺炎患者中表达水平及动态变化对预后的评估作用的研究相对较少。本研究旨在探讨老年重症肺炎患者血浆PCT、D-D的表达水平及动态变化情况与预后的关系,分析其在重症肺炎患者临床转归中的评估价值,为临床评估老年重症肺炎患者的预后提供新的思路,从而及早调整诊治方案,进一步降低老年重症肺炎的死亡率。

1 对象与方法

1.1 研究对象

选取2019年1月至2020年6月航天中心医院重症监护室(intensive care unit, ICU)收治的老年重症肺炎患者78例作为研究对象。其中男性44例,女性34例;年龄72~86岁。根据确诊后第28天生存情况将患者分为生存组(31例)和死亡组(47例)。本研究符合医院医学伦理学标准,所有检测均获得患者及家属知情同意。

纳入标准:年龄>60岁;符合中华医学会呼吸病分会制订的重症肺炎诊断标准[4];首次发病且入组前未给予任何治疗。排除标准:合并肺癌、肺结核及肺栓塞等其他肺部疾病;需长期应用糖皮质激素或免疫抑制剂;病原学证实以非细菌感染为主;入院48 h内死亡;依从性较差,不能配合治疗。

1.2 方法

入组患者均进行病原菌检查并实施对症治疗,以诊断重症肺炎的时间为研究起点,在治疗前、治疗第3和7天及转出ICU(或死亡)前分别进行PCT和D-D水平检验。

采用双抗体夹心免疫发光法检测患者血清PCT水平,酶联免疫法测定D-D。并计算降钙素原变化率(change rate of procalcitonin, PCTc)和D二聚体变化率(change rate of D-dimer, D-Dc)。PCTc=(初始血清PCT值-检测当日PCT值)/初始血清PCT值×100%。D-Dc=(初始血清D-D值-检测当日D-D值)/初始血清D-D值×100%。同时,入组患者在确诊为重症肺炎24 h内由ICU医师进行急性生理学与慢性健康状况评分Ⅱ(acute physiology and ahronic health evaluation Ⅱ, APACHE Ⅱ)并记录。

1.3 统计学处理

采用SPSS 22.0软件进行统计分析。计量资料以均数±标准差($\bar{x}\pm s$)表示,2组间比较采用独立样本t检验,多组间比较采用单因素方差分析。计数资料用例数(百分率)表示,采用χ^2检验。非正态分布的计数资料以中位数(四分位数间距)[$M(Q_1, Q_3)$]表示,采用Mann-Whitney U检验。采用受试者工作特征(receiver operating characteristic, ROC)曲线判断PCT、PCTc、D-D、D-Dc及APACHE Ⅱ评分对老年重症肺炎患者临床转归的评估价值,ROC曲线下面积(area under the curve, AUC)越大,诊断准确性越高。P<0.05为差异有统计学意义。

2 结 果

2.1 2组患者一般临床资料比较

2组患者性别、体温、白细胞(white blood cell, WBC)、血沉(erythrocyte sedimentation rate, ESR)及C-反应蛋白(C-reactive protein, CRP)比较,差异均无统计学意义(均 $P>0.05$);生存组年龄及APACHE Ⅱ评分明显低于死亡组,差异均有统计学意义(均 $P<0.05$;表1)。

死亡组患者肺炎克雷伯菌感染19例,铜绿假单胞菌感染15例,鲍曼不动杆菌感染10例,金黄色葡萄球菌3例;生存组肺炎克雷伯菌感染15例,铜绿假单胞菌感染8例,鲍曼不动杆菌感染6例,金黄色葡萄球菌2例,差异无统计学意义($P=0.910$)。

2.2 2组患者不同时间段血清PCT和D-D水平比较

生存组及死亡组患者PCT水平在治疗前和3 d时,差异均无统计学意义(均 $P>0.05$);存活组患者治疗7 d、转出或死亡前PCT水平低于死亡组,差异均有统计学意义(均 $P<0.05$)。2组患者D-D水平在治疗前和3 d时比较,差异均无统计学意义(均 $P>0.05$);存活组D-D呈逐渐下降趋势,但在死亡组呈逐渐升高趋势,治疗7 d、转出或死亡前存活组患者的D-D水平明显低于死亡组,差异均有统计学意义(均 $P<0.05$;表2)。

2.3 2组患者不同时段血清PCTc及D-Dc比较

2组PCTc在治疗3、7 d及转出或死亡前比较,差异均有统计学意义(均 $P<0.05$)。D-Dc在生存组始终维持在高水平,并随病情好转升高,D-Dc在死亡组中则相对较低,并随病情恶化逐渐下降,2组在治疗3、7 d,转出或死亡前比较,差异均有统计学意义(均 $P<0.05$;表3)。

2.4 PCTc、D-Dc和APACHE Ⅱ评分对重症肺炎患者死亡预测价值分析

采用ROC曲线分析老年重症肺炎治疗第3天PCTc、D-Dc、PCT、D-D和APACHE Ⅱ对重症肺炎患者临床转归的预测效果,结果显示PCTc、D-Dc及APACHE Ⅱ对老年重症肺炎预后具有评估意义($P<0.05$)。其中PCTc对老年重症肺炎患者住院期间死亡预测AUC为0.974,对老年重症肺炎患者的死亡预测评估价值最高(表4,图1)。

表1 2组患者一般临床资料比较

Table 1 Comparison of general clinical data between two groups

Group	n	Gender (male/female, n)	Age (years, $\bar{x}\pm s$)	Body temperature (℃, $\bar{x}\pm s$)	White blood cell ($\times10^9$/L, $\bar{x}\pm s$)	ESR (mm/h, $\bar{x}\pm s$)	CRP (mg/L, $\bar{x}\pm s$)	APACCHE Ⅱ (points, $\bar{x}\pm s$)
Survival	31	18/13	77.30±6.72	38.34±1.65	11.34±4.21	39.8±9.60	102.40±39.53	19.29±2.69
Death	47	26/21	83.84±5.54	38.52±1.68	12.08±5.14	41.4±10.58	116.52±43.65	21.02±2.72
χ^2/t		0.057	6.207	0.185	0.289	0.035	0.283	7.659
P value		0.498	0.037	0.678	0.605	0.856	0.609	0.007

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; APACCHE Ⅱ: acute physiology and chronic health evaluation Ⅱ.

表2 2组患者不同时段血清PCT和D-D水平比较

Table 2 Comparison of PCT levels and D-D levels in different time periods between two groups ($\bar{x}\pm s$)

Item	PCT (ng/ml)				D-D (mg/L)			
	Survival group (n=31)	Death group (n=47)	t	P value	Survival group (n=31)	Death group (n=47)	t	P value
Before treatment	5.39±1.05	5.46±1.12	−0.672	0.796	1.85±0.36	1.90±0.39	−0.489	0.626
Treatment 3 d	5.12±2.02	5.60±1.08	−1.965	0.053	1.81±0.32	1.96±0.37	−1.877	0.064
Treatment 7 d	2.57±0.65	7.18±1.91	−24.231	<0.001	0.75±0.15	3.78±0.85	−23.869	<0.001
Treatment out of ICU (or die)	0.62±0.25	10.37±2.47	−44.591	<0.001	0.40±0.09	4.89±0.69	−44.412	<0.001

PCT: procalcitonin; D-D: D-dimer; ICU: intensive care unit.

表3 2组患者不同时段血清PCTc及D-Dc比较

Table 3 Comparison of PCTcand D-Dc in different time periods between two groups [$M(Q_1, Q_3)$]

Treatment time	PCTc				D-Dc			
	Survival group (n=31)	Death group (n=47)	Z	P value	Survival group (n=31)	Death group (n=47)	Z	P value
3 d	5.56 (3.28, 8.22)	−3.17 (−4.55, 0.00)	−7.092	<0.001	0.00 (0.00, 6.25)	0.00 (−7.69, 0.00)	−4.650	<0.001
7 d	53.73 (49.12, 58.93)	−31.75 (−40.91, −21.05)	−7.439	<0.001	58.33 (55.29, 64.21)	−95.24 (−128.50, −60.87)	−6.339	<0.001
Out of ICU (or die)	89.29 (86.36, 91.78)	−96.86 (−119.40, −68.00)	−8.657	<0.001	77.22 (74.29, 83.64)	−161.10 (−218.70, −114.20)	−9.127	<0.001

PCTc: change rate of procalcitonin; D-Dc: change rate of D-dimer; ICU: intensive care unit.

表 4 预测重症肺炎患者死亡的效能指标

Table 4 Indicators for predicting death of patients with severe pneumonia

Item	AUC	95%*CI*	*P* value	Best cut-off	Sensitivity(%)	Specificity(%)
PCTc	0.974	0.940–1.010	<0.001	0.658	93.5	97.9
D-Dc	0.779	0.673–0.885	<0.001	−2.273	93.5	46.8
PCT	0.380	0.253–0.507	0.075	3.55	96.8	2.1
D-D	0.375	0.240–0.491	0.064	1.35	90.3	8.5
APACHE Ⅱ	0.337	0.211–0.463	0.015	18.5	54.8	21.3

PCTc: change rate of procalcitonin; D-Dc: change rate of D-dimer; PCT: procalcitonin; D-D: D-dimer; APACHE Ⅱ: acute physiology and chronic health evaluation Ⅱ; AUC: area under the curve.

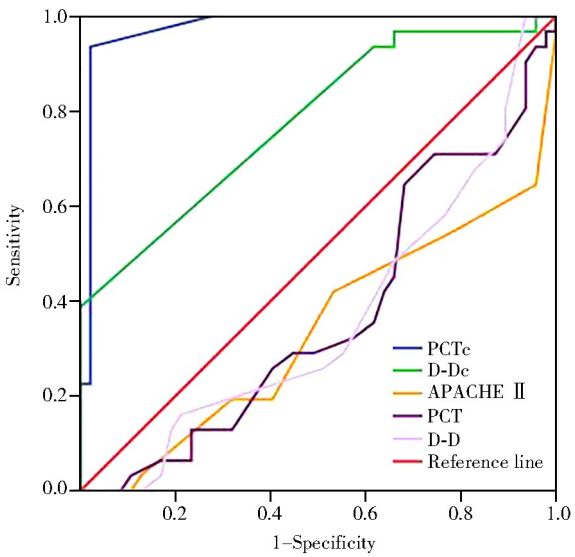

图 1 重症肺炎患者死亡预测效果 ROC 曲线

Figure 1 ROC curve analysis of prediction effect on death prediction

PCTc: change rate of procalcitonin; D-Dc: change rate of D-dimer; PCT: procalcitonin; D-D: D-dimer; APACHE Ⅱ: acute physiology and chronic health evaluation Ⅱ; ROC: receiver operating characteristic.

3 讨 论

重症肺炎是一种严重的呼吸系统感染性疾病，由多种病原菌直接损伤或机体免疫防御机制异常启动引起的肺实质炎症反应，发病急骤且病情进展迅速，易出现各种并发症，病死率高，尤以老年人多见[5]。老年重症肺炎的发病率及死亡率非常高，故早期准确评估及预测老年重症肺炎的预后，对疾病的诊治及临床转归具有重要意义[6]。

PCT 在正常情况下由甲状腺滤泡旁细胞分泌，在细胞内全部酶解为降钙素和其他片段，几乎不被释放入血，但在机体发生全身感染时，其他组织器官也可释放 PCT，所以在严重感染时 PCT 会明显升高。多项研究表明[7,8]，PCT 能反映重症肺炎的严重程度，并随病情好转下降。重症肺炎多由细菌感染引起，因此感染后 PCT 水平明显升高，这是 PCT 作为重症肺炎患者预后预测指标的理论依据[9]。PCT 在感染疾病的早期筛选、治疗效果监测、预后评估及合理使用抗菌药物等方面具有较高的应用价值[10]。但 PCT 易受感染时间和抗菌药物等治疗措施因素影响，因此用疾病某一时期的 PCT 来评价病情具有很大局限性。持续动态观察 PCT 并进行 PCTc 分析比仅仅关注某一时期 PCT 更具优势，且越来越多的研究表明[11,12]，危重及急性呼吸道感染患者用降钙素原的动态变化作为抗生素更换及停药的指标具有较好的临床意义。并有研究表明[13]，PCTc 可作为重症肺炎患者病情发展预后判断的一项指标。在本研究中，我们动态监测了老年重症肺炎患者血清 PCT 水平，并观察 PCT 和 PCTc 的变化情况与疾病预后的关系，进一步评估其对老年重症肺炎患者临床转归中的评估价值。研究结果表明，PCT 及 PCTc 均随着老年重症肺炎患者疾病转归发生变化，这有助于临床医师对疾病发展进行评估，及时调整治疗方案。进一步我们发现，在治疗好转组及死亡组患者治疗 3 d 时 PCT 比较，差异无统计学意义，但 PCTc 已经呈现出明显的差异，这提示 PCTc 相对于 PCT 能更早地反映患者对治疗的反应情况，对判断重症肺炎患者预后的价值更高，且更准确，可以为临床治疗方案的调整提供及时可靠依据。

D-二聚体是纤维蛋白经纤溶酶交联水解后形成的产物中最小片段，D-D 可反映机体高凝状态及纤溶亢进状态，大量研究已证实凝血、纤溶系统功能障碍在炎症发生、发展过程中发挥的重要作用[14]。在本研究中，我们同样证实 D-D 在老年重症肺炎中高表达，并随着病情的好转逐渐降低，而在死亡组患者中 D-D 持续在较高水平，这与既往的研究结果一致[7,15]，提示 D-D 可作为重症肺炎预后判断指标。本研究同样发现 D-Dc 相对于 D-D 能更早地反映老年重症肺炎的预后情况。D-Dc 可以更及时地帮助临床医师掌握病情变化及判断感染控制情况，进而更好地指导治疗方案的调整及疗效评价，对预后具有很高的预测价值。

APACHE Ⅱ评分是目前应用最广泛且最权威的疾病评价系统,包括急性主动脉夹层、感染性休克及老年社区获得性肺炎等急慢性疾病,但缺乏特异性,不能单独作为某疾病诊断和预后的独立指标[16]。在本研究中,我们进一步用ROC曲线分析了治疗第3天PCT、D-D、PCTc及D-Dc对老年重症肺炎患者死亡预测效果,结果显示,治疗第3天PCTc和D-Dc评估预后的AUC均远远超过了APACHE Ⅱ、PCT及D-D评分,其中第3天PCTc的AUC高达0.974、D-Dc的AUC为0.779,这说明PCT、D-D的变化率相对于APACHE Ⅱ评分能更准确地预测老年重症肺炎的预后。其中,第3天PCTc对死亡预测灵敏度可达93.5%,特异度为97.9%。以上研究结果均表明连续动态观察PCT和D-D水平变化,不仅与患者疾病严重程度有关,还可以帮助我们早期准确地判断预后,从而针对老年重症肺炎患者进行早期干预、治疗,及时调整治疗方案,降低死亡率。

综上,PCT及D-D在老年重症肺炎疾病转归中变化明显,PCTc及D-Dc动态监测可以帮助临床医师对老年重症肺炎的预后作出更早期、更准确的预测,从而为及时调整治疗方案赢得治疗时间,提高老年重症肺炎患者的生存率。

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