·临床研究·

肾上腺髓质素原联合降钙素原对老年重症社区获得性肺炎患者预后的预测价值

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【摘 要】 目的 探讨肾上腺髓质素原（pro-ADM）和降钙素原（PCT）在老年重症社区获得性肺炎（SCAP）患者中的变化及其预测预后的价值。**方法** 回顾性分析2016年1月至2017年9月海南省儋州市人民医院急诊科收治的老年SCAP患者162例，根据患者28 d死亡或存活情况分为存活组（$n=114$）和死亡组（$n=48$），监测患者确诊SCAP第1，3，7天时的血清pro-ADM和PCT水平变化。采用SPSS 19.0统计软件对数据进行分析。根据数据类型，组间比较采用成组t检验或χ^2检验，组内比较采用重复测量的方差分析；受试者工作特征（ROC）曲线分析各时间点pro-ADM、PCT以及两者联合对老年SCAP患者预后预测的价值。**结果** 死亡组的CURB-65评分、肺炎严重度指数（PSI）评分及急性生理学与慢性健康状况评分Ⅱ（APACHEⅡ）分值明显高于存活组，差异具有统计学意义（$P<0.05$）。死亡组患者确诊第1天[（4.66±1.83）*vs*（3.04±1.31）nmol/L]、第3天[（5.47±1.96）*vs*（2.95±1.34）nmol/L]、第7天时[（6.81±2.17）*vs*（1.53±0.82）nmol/L]血清pro-ADM水平明显高于存活组患者；死亡组患者确诊第3天[（3.28±1.24）*vs*（1.05±0.53）ng/ml]和第7天[（5.62±1.83）*vs*（0.26±0.12）ng/ml]时血清PCT水平高于存活组患者；死亡组患者确诊第7天时的pro-ADM[（6.81±2.17）*vs*（5.47±1.96）nmol/L]和PCT[（5.62±1.83）*vs*（3.28±1.24）ng/ml]水平明显高于第3天水平，差异均具有统计学意义（$P<0.05$）。第3天血清pro-ADM联合PCT预测老年SCAP患者28 d预后的ROC曲线下面积（AUC）是0.942（0.883～0.998），明显高于pro-ADM的0.892（0.830～0.951）和PCT的0.857（0.793～0.924），灵敏度为95.2%，特异度为86.4%，预测价值较好。**结论** pro-ADM及PCT水平变化与老年SCAP患者的病情严重程度及预后相关，第3天血清pro-ADM联合PCT对患者28 d预后的预测价值较好。

【关键词】 肺炎；社区获得性感染；降钙素；肾上腺髓质素；预后
【中图分类号】 R563；R592 **【文献标志码】** A **【DOI】** 10.11915/j.issn.1671-5403.2018.03.044

Prognostic value of proadrenomedullin combined with procalcitonin in the elderly with severe community-acquired pneumonia

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【Abstract】 Objective To investigate the changes of proadrenomedullin (pro-ADM) and procalcitonin (PCT) in the elderly patients with severe community-acquired pneumonia (SCAP), and assess their prognostic value. **Methods** A total of 162 elderly SCAP patients who were admitted in Emergency Department of our hospital from January 2016 to September 2017 were retrospectively enrolled in this study. According to the 28-day survival, they were divided into survival group ($n=114$) and death group ($n=48$). The serum pro-ADM and PCT levels in the patients were measured in 1, 3 and 7 d after SCAP diagnosis. SPSS statistics 19.0 was used to perform the statistical analysis. Student's t test or Chi-square test was employed for comparison between the 2 groups, and repeated measures analysis of variance for intragroup comparison. Receiver operating characteristic (ROC) curve was adopted to analyze the prognostic value of pro-ADM, PCT and combination for SCAP at various time points. **Results** The CURB-65 score, pneumonia severity index (PSI), and the score of acute physiology and chronic health evaluation Ⅱ (APACHE Ⅱ) were significantly higher in the death group than the survival group ($P<0.05$). When compared with the survival group, the serum pro-ADM level was significantly higher in the death group on 1st day [(4.66±1.83) *vs* (3.04±1.31) nmol/L], 3rd day [(5.47±1.96) *vs* (2.95±1.34) nmol/L] and 7th day [(6.81±2.17) *vs* (1.53±0.82) nmol/L, all $P<0.05$], but such diffe-rences of serum PCT level were only found on the 3rd day [(3.28±1.24) *vs* (1.05±0.53) ng/ml] and 7th day [(5.62±1.83) *vs* (0.26±0.12) ng/ml,

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both $P<0.05$]. The serum pro-ADM and PCT levels on the 7th day were obviously higher than those on the 3rd day in the death group [(6.81±2.17) *vs* (5.47±1.96) nmol/L, (5.62±1.83) *vs* (3.28±1.24) ng/ml, $P<0.05$]. The area under ROC curve of combined diagnosis was 0.942 (0.883–0.998) for 28-day prognosis in elderly SCAP patients, significantly higher than that by pro-ADM alone (0.892, 0.830–0.951) or by PCT alone (0.857, 0.793–0.924). The sensitivity and specificity were 95.2% and 86.4% respectively, suggesting good predictive value. **Conclusion** The changes in pro-ADM and PCT levels are associated with the severity of the disease and prognosis in elderly patients with SCAP, and combination of serum pro-ADM and PCT levels on the 3rd day shows good predictive value for 28-day prognosis.

【Key words】 pneumonia; community acquired infection; calcitonin; adrenomedullin; prognosis

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重症社区获得性肺炎(severe community-acquired pneumonia, SCAP)是重症监护室中的常见疾病,老年患者往往病情进展迅速、病死率高、预后差。SCAP已成为感染性疾病的主要死因[1,2],研究表明肾上腺髓质素原(proadrenomedullin, pro-ADM)是一种预测肺部感染的新型指标,pro-ADM水平高低与肺部感染的严重程度密切相关[3]。降钙素原(procalcitonin, PCT)是预测细菌感染的有效指标,在感染性疾病尤其是重症感染方面具有较高的诊断价值[4]。然而,关于pro-ADM联合PCT和老年SCAP患者预后的相关研究尚未见报道。本研究通过观察血清pro-ADM和PCT在老年SCAP患者中的变化情况,探讨两者对老年SCAP患者预后的预测价值,旨在为该病的早期治疗提供依据。

1 对象与方法

1.1 研究对象

回顾性分析2016年1月至2017年9月海南省儋州市人民医院急诊科收治的老年SCAP患者162例,根据患者28 d死亡或存活情况分为存活组和死亡组。其中存活组114例,男性71例,女性43例,年龄(74.2±9.8)岁;死亡组48例,男性31例,女性17例,年龄(77.8±10.6)岁。所有患者均按照SCAP治疗指南进行治疗,SCAP的诊断符合中华医学会呼吸病分会制定的社区获得性肺炎(community-acquired pneumonia, CAP)诊断标准[5]。纳入标准:符合SCAP诊断标准的初诊患者,由细菌感染引起,年龄≥65岁,病历资料完整。排除标准:存在医院获得性肺炎、肺结核及肺栓塞等呼吸系统疾病者;严重肝肾功能不全、恶性肿瘤者及家属放弃治疗者。

1.2 观察指标

记录2组患者的血氧分压(partial pressure of oxygen, PO_2)、血二氧化碳分压(partial pressure of carbon dioxide, PCO_2),以及CURB-65、肺炎严重度指数(pneumonia severity index, PSI)和急性生理学与慢性健康状况评分Ⅱ(acute physiology and chronic health evaluation Ⅱ, APACHE Ⅱ)。APACHE Ⅱ分值为急性生理学变量、年龄和慢性健康状况分值的总和,总分值0~71分,分值越大预后越差。CURB-65评分包括5项指标,每项指标分值为1分,依次为意识障碍(confusion, C)、血尿素氮(Urea, U)>7 mmol/L、呼吸频率(respiratory rate, RR)>30次/min、收缩压(systolic blood pressure, SBP)<90 mmHg(1 mmHg=0.133 kPa)或舒张压(diastolic blood pressure, DBP)<60 mmHg、年龄>65岁。

所有患者均于确诊SCAP后第1天、第3天、第7天分别抽取静脉血3 ml,检测患者血清pro-ADM及PCT水平。pro-ADM的测定采用双抗体夹心法,试剂盒购自华美生物工程有限公司;PCT的测定采用酶联免疫吸附法,使用全自动多功能酶标仪检测(美国Thermo公司),试剂盒为美国Rapidbio公司产品。操作过程均严格按照试剂盒说明书进行。

1.3 统计学处理

采用SPSS 19.0统计软件对数据进行分析。计量资料用均数±标准差($\bar{x}\pm s$)表示,组间比较采用成组t检验,组内比较采用重复测量的方差分析。计数资料用百分率表示,组间比较用χ^2检验。绘制受试者工作特征(receiver operating characteristic, ROC)曲线分析pro-ADM及PCT对老年SCAP患者预后预测的价值,曲线下面积(area under ROC curve, AUC)比较采用Z检验。$P<0.05$为差异有统计学意义。

2 结 果

2.1 2组患者基线资料比较

存活组与死亡组的性别、年龄、体质量指数(body mass index, BMI)、SBP、DBP、心率(heart rate, HR)、RR、体温、PO_2、PCO_2、糖尿病、高血压、高脂血症、吸烟比例差异无统计学意义($P>0.05$)。死亡组的CURB-65、PSI及APACHE Ⅱ评分明显高于存活组,差异具有统计学意义($P<0.05$;表1)。

2.2 2 组患者血清 pro-ADM 和 PCT 水平比较

相比存活组患者,死亡组患者确诊第 3 天和第 7 天时的 pro-ADM 和 PCT 水平以及第 1 天 pro-ADM 水平明显增高,差异具有统计学意义($P < 0.05$)。存活组患者确诊第 7 天时的 pro-ADM 和 PCT 水平明显低于第 1 天,死亡组患者确诊第 3 天和第 7 天时的 pro-ADM 和 PCT 水平明显高于第 1 天,且第 7 天时的 pro-ADM 和 PCT 水平明显高于第 3 天,差异均具有统计学意义($P < 0.05$;表 2)。

2.3 pro-ADM 联合 PCT 对老年 SCAP 患者预后预测的价值

第 1 天血清 pro-ADM 联合 PCT 预测老年 SCAP 患者 28 d 预后的 AUC(95% *CI*)是 0.784(0.716 ~ 0.849),明显高于 pro-ADM 的 0.683(0.621 ~ 0.746)和 PCT 的 0.642(0.584 ~ 0.705),差异具有统计学意义($Z = 5.812$, $Z = 6.274$; $P < 0.05$)。第 3 天血清pro-ADM联合 PCT 预测老年 SCAP 患者 28 d 预后的 AUC(95% *CI*)是 0.942(0.883 ~ 0.998),明显高于 pro-ADM 的 0.892(0.830 ~ 0.951)和 PCT 的 0.857(0.793 ~ 0.924),差异有统计学意义($Z = 3.516$, $Z = 5.348$; $P < 0.05$)。第 7 天血清 pro-ADM 联合 PCT 预测老年 SCAP 患者 28 d 预后的 AUC(95% *CI*)为 0.906(0.845 ~ 0.967),明显高于 pro-ADM 的 0.846(0.781 ~ 0.908)和 PCT 的 0.812(0.749 ~ 0.875),差异具有统计学意义($Z = 3.702$, $Z = 5.507$; $P < 0.05$)。第 3 天血清 pro-ADM 联合 PCT 预测老年 SCAP 患者 28 d 预后的灵敏度为 95.2%,特异度为 86.4%,预测价值较好(图 1 ~ 3)。

3 讨 论

SCAP 是老年人群较为常见的感染性疾病,具有起病急、病情进展迅速和预后差等特点[6]。近年老年 SCAP 的发病率及病死率呈明显升高趋势,给社会及家庭带来了沉重的负担[7]。尽管常规抗生素、机械通气治疗能够缓解患者病情,但大多数患者救

表 1 2 组患者基线资料比较

Table 1 Comparison of baseline data between two groups

Item	Survival group($n = 114$)	Death group($n = 48$)	t/χ^2	P value
Gender(male/female, n)	71/43	31/17	0.077	0.782
Age(years, $\bar{x} \pm s$)	74.2 ± 9.8	77.8 ± 10.6	1.802	0.096
BMI (kg/m^2, $\bar{x} \pm s$)	23.4 ± 4.5	23.8 ± 4.6	0.658	0.362
Diabetes mellitus[n(%)]	33(28.9)	16(33.3)	0.308	0.579
Hypertension[n(%)]	45(39.5)	22(45.8)	0.563	0.453
Hyperlipidemia[n(%)]	42(36.8)	19(39.6)	0.108	0.742
Smoking[n(%)]	48(42.1)	17(35.4)	0.629	0.428
SBP(mmHg, $\bar{x} \pm s$)	128.2 ± 32.0	126.5 ± 33.4	0.519	0.536
DBP(mmHg, $\bar{x} \pm s$)	68.0 ± 16.3	70.3 ± 16.8	0.384	0.715
Heart rate(times/min, $\bar{x} \pm s$)	117.2 ± 10.6	117.5 ± 10.4	0.305	0.824
RR(times/min, $\bar{x} \pm s$)	26.4 ± 7.5	27.3 ± 7.8	0.582	0.403
Body temperature(℃, $\bar{x} \pm s$)	37.0 ± 1.5	37.4 ± 1.3	0.563	0.526
PO_2(mmHg, $\bar{x} \pm s$)	56.3 ± 11.4	54.2 ± 10.7	0.702	0.305
PCO_2(mmHg, $\bar{x} \pm s$)	58.6 ± 10.5	57.3 ± 8.6	0.448	0.609
CURB-65(score, $\bar{x} \pm s$)	2.4 ± 0.9	3.3 ± 1.2	7.813	< 0.001
PSI(score, $\bar{x} \pm s$)	98.6 ± 12.5	130.4 ± 18.2	9.624	< 0.001
APACHE Ⅱ(score, $\bar{x} \pm s$)	19.2 ± 6.8	24.3 ± 7.6	4.416	0.012

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; RR: respiratory rate; PO_2: partial pressure of oxygen; PCO_2: partial pressure of carbon dioxide; PSI: pneumonia severity index; APACHE Ⅱ: acute physiology and chronic health evaluation Ⅱ. 1 mmHg = 0.133 kPa

表 2 2 组患者血清 pro-ADM 和 PCT 水平比较

Table 2 Comparison of serum pro-ADM and PCT levels between two groups ($\bar{x} \pm s$)

Group	n	pro-ADM(nmol/L)			PCT(ng/ml)		
		Day 1	Day 3	Day 7	Day 1	Day 3	Day 7
Survival	114	3.04 ± 1.31	2.95 ± 1.34	1.53 ± 0.82$^{\#}$	1.36 ± 0.64	1.05 ± 0.53	0.26 ± 0.12$^{\#}$
Death	48	4.66 ± 1.83*	5.47 ± 1.96$^{*\#}$	6.81 ± 2.17$^{*\#\triangle}$	1.52 ± 0.72	3.28 ± 1.24$^{*\#}$	5.62 ± 1.83$^{*\#\triangle}$

pro-ADM: proadrenomedullin; PCT: procalcitonin. Compared with survival group, $^{*}P < 0.05$; comapred with day 1, $^{\#}P < 0.05$; comapred with day 3, $^{\triangle}P < 0.05$

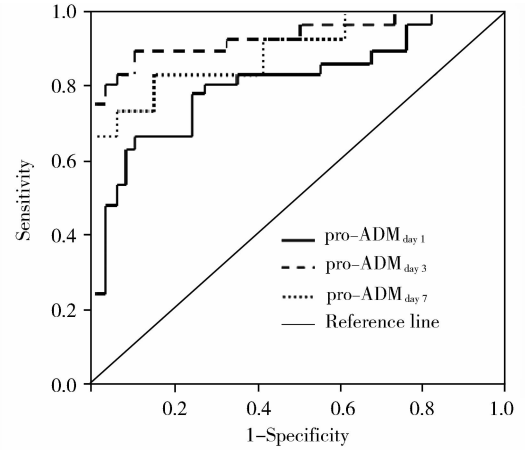


图1 pro-ADM预测老年SCAP患者预后的ROC曲线

Figure 1 ROC curve for predicting the prognosis of elderly patients with SCAP by pro-ADM

pro-ADM: proadrenomedullin; SCAP: severe community-acquired pneumonia; ROC: receiver operating characteristic

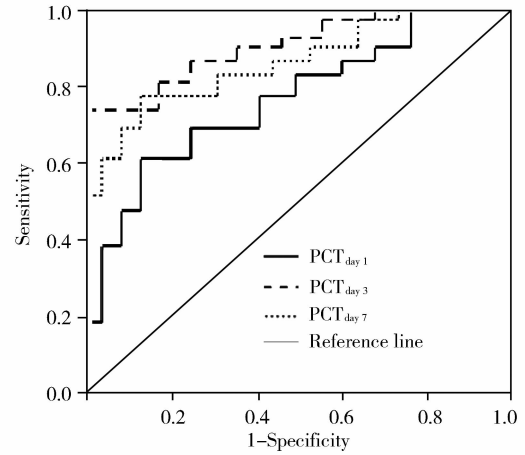


图2 PCT预测老年SCAP患者预后的ROC曲线

Figure 2 ROC curve for predicting the prognosis of elderly patients with SCAP by PCT

PCT: procalcitonin; SCAP: severe community-acquired pneumonia; ROC: receiver operating characteristic

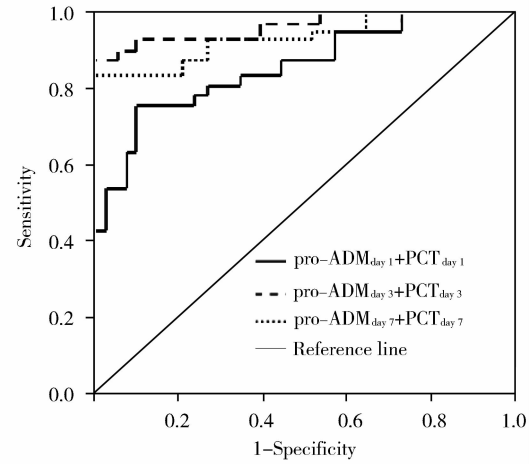


图3 pro-ADM联合PCT预测老年SCAP患者预后的ROC曲线

Figure 3 ROC curve for predicting prognosis of elderly patients with SCAP by pro-ADM combined with PCT

pro-ADM: proadrenomedullin; PCT: procalcitonin; SCAP: severe community-acquired pneumonia; ROC: receiver operating characteristic

治时往往病情危重,治疗效果不理想,因而寻找一种有效评估老年SCAP预后的指标,对其救治有着重要意义。

肾上腺髓质素(adrenomedullin,ADM)由血管内皮细胞产生,具有调节免疫、代谢和扩张血管等多种生物学效应。pro-ADM是ADM的前体物质,可作为细菌感染及脓毒症严重程度和危险分层的生物标志物[8,9]。PCT是降钙素的前肽物质,在严重感染及全身炎症反应患者中水平显著升高,有研究表明PCT是早期鉴别脓毒症以及评价感染严重程度的敏感指标[10]。本研究结果表明,死亡组患者确诊第3天、第7天时的血清pro-ADM和PCT水平均明显高于存活组患者,且第1天的血清pro-ADM水平明显高于存活组。死亡组患者血清pro-ADM和PCT水平呈升高趋势,而存活组患者呈下降趋势,提示血清pro-ADM和PCT水平与老年SCAP患者病情严重程度相关。倪菊平等[11]观察pro-ADM在呼吸机相关性肺炎患者中的变化,结果发现第1天、第3天、第5天死亡组患者血清pro-ADM水平分别为(4.18±1.78)、(4.51±1.88)和(5.15±1.89)nmol/L,存活组患者血清pro-ADM水平分别为(3.19±1.39)、(2.98±1.35)和(1.65±0.88)nmol/L,死亡组患者水平明显增高,差异具有统计学意义($P<0.05$),表明pro-ADM是反映患者病情严重程度的有效指标。Courtais等[12]通过研究表明,pro-ADM可用于急诊CAP患者的危险分层和预后评估,能有效判断患者的死亡风险。Stolz[13]认为PCT与老年SCAP患者病情程度及预后密切相关,动态监测血清PCT水平能反映患者病情的发展情况。

研究表明,指标AUC≤0.5为无诊断价值,0.5<AUC≤0.7为诊断准确性较低,0.7<AUC≤0.9为诊断准确性较好,AUC≥0.9表示诊断准确性最高[14]。本研究结果表明,确诊第3天时血清pro-ADM联合PCT预测老年SCAP患者预后的准确性最高,其AUC为0.942(0.883~0.998);确诊第3天血清pro-ADM预测老年SCAP患者预后的准确性较好,AUC为0.892(0.830~0.951)。提示第3天血清pro-ADM及PCT水平升高可能是老年SCAP患者发生死亡的早期预警信号,临床上应尽早采取有效治疗措施阻止病情进一步发展。陈云霞等[15]研究表明,ADM可作为预测CAP患者预后不良的独立危险因素($OR=1.084$,95% CI 1.060~1.108;$P<0.001$),用于急诊CAP患者的危险分层和预后评估。Suberviola等[16]对49例因CAP而发生的重症脓毒症或脓毒性休克患者进行研究,结果发现

pro-ADM 预测患者死亡的 AUC(0.72)明显优于 C-反应蛋白(AUC=0.44)和 PCT(AUC=0.40),提示pro-ADM水平与疾病严重程度和死亡相关,高pro-ADM水平的患者死亡风险较大。Zhydkov 等[17]研究表明,PCT 对预测 CAP 患者病死率有较高的临床价值,其灵敏度和特异度均超过 C-反应蛋白。另有研究表明,PCT 水平变化对预测急诊 CAP 患者病情严重程度和病死率有重要价值,可作为 CAP 患者预后评估的通用指标[18]。

综上所述,血清 pro-ADM 及 PCT 水平变化与 SCAP 患者病情严重程度及预后相关,第 3 天时的血清 pro-ADM 和 PCT 水平能预测老年 SCAP 患者 28 d 的病死率。临床医师可在实际工作中监测血清 pro-ADM 及 PCT 水平初步评估老年 SCAP 患者的病情严重程度,对于 pro-ADM 及 PCT 水平明显升高的患者,要采取相应的治疗措施,及早控制病情,以降低患者的病死率。

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