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## 慢性阻塞性肺疾病急性加重期患者血清 SAA 水平与肺功能、炎症因子的相关性及其诊断价值分析\*

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**摘要 目的:**探讨慢性阻塞性肺疾病急性加重期(AECOPD)患者血清淀粉样蛋白 A(SAA)水平与肺功能及炎症因子的相关性,并分析其诊断价值。**方法:**选取 2013 年 6 月-2018 年 6 月中国人民解放军第 970 医院收治的 204 例慢性阻塞性肺疾病(COPD)患者作为研究对象,其中 COPD 稳定期患者 132 例作为 COPD 稳定组,AECOPD 患者 72 例作为 AECOPD 组。另选取同期于中国人民解放军第 970 医院进行健康体检的 50 例健康体检者作为健康组。比较三组受试者血清 SAA 水平、白细胞介素-8(IL-8)、白细胞介素-6(IL-6)、C 反应蛋白(CRP)、降钙素原(PCT)水平及肺功能,采用 Pearson 相关性分析 AECOPD 患者血清 SAA 水平与肺功能及炎症因子的相关性,并分析 SAA 对 AECOPD 的诊断价值。**结果:**AECOPD 组患者血清 SAA、PCT、CRP、IL-6、IL-8 水平较 COPD 稳定组及健康组升高( $P<0.05$ ),COPD 稳定组患者血清 SAA、IL-6、IL-8、PCT、CRP 水平均高于健康组,差异有统计学意义( $P<0.05$ );AECOPD 组患者第一秒用力呼气容积( $FEV_1$ )、用力肺活量(FVC)、第一秒用力呼吸容积占用力肺活量的百分比( $FEV_1/FVC\%$ )、第一秒用力呼气容积占预计值百分比( $FEV_1\%$ )低于 COPD 稳定组及健康组,差异有统计学意义( $P<0.05$ ),COPD 稳定组患者  $FEV_1$ 、FVC、 $FEV_1/FVC\%$ 、 $FEV_1\%$ 低于健康组,差异有统计学意义( $P<0.05$ )。Pearson 相关性分析显示,AECOPD 患者血清 SAA 水平与 IL-8、IL-6、CRP、PCT 呈正相关,与  $FEV_1\%$ 、 $FEV_1/FVC\%$ 、 $FEV_1/FVC$  呈负相关( $P<0.05$ )。受试者工作特征(ROC)曲线结果显示,SAA 对 AECOPD 诊断的敏感度为 80.85%,特异度为 80.07%,曲线下面积为 0.832。**结论:**AECOPD 患者血清 SAA 水平明显升高,其与患者肺功能及炎症因子存在相关性,具有较高的诊断价值,可用于 AECOPD 患者病情的评估。

**关键词:**慢性阻塞性肺疾病;急性加重期;血清淀粉样蛋白 A;肺功能;诊断价值;炎症因子

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## Correlation and Diagnostic Value of Serum Amyloid A Level with Pulmonary Function and Inflammatory Factors in Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease\*

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**ABSTRACT Objective:** To investigate the correlation between serum amyloid A (SAA) level and pulmonary function, inflammatory factors in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD), and the diagnostic value was analyzed. **Methods:** 204 patients with chronic obstructive pulmonary disease (COPD) who were admitted to The 970th Hospital of People's Liberation Army from June 2013 to June 2018 were selected as COPD stable group, 72 patients with AECOPD were selected as AECOPD group. Another 50 healthy persons who underwent physical examination in The 970<sup>th</sup> Hospital of People's Liberation Army during the same period were selected as the health group. The levels of serum SAA, interleukin-8 (IL-8), interleukin-6 (IL-6), C-reactive protein (CRP), procalcitonin (PCT) and lung function were compared among the three groups. Pearson correlation was used to analyze the correlation between serum SAA level and pulmonary function and inflammatory factors in patients with AECOPD, and the diagnostic value of SAA in AECOPD was analyzed. **Results:** The serum levels of SAA, PCT, CRP, IL-6 and IL-8 in AECOPD group were higher than those in COPD stable group and healthy group ( $P<0.05$ ). The serum levels of SAA, IL-6, IL-8, PCT and CRP in COPD stable group were higher than those in healthy group, the difference were statistically significant ( $P<0.05$ ). The forced expiratory volume in one second ( $FEV_1$ ), forced vital capacity (FVC), the percentage of forced vital capacity occupied by the first second forced expiratory volume ( $FEV_1/FVC$ ), and the percentage of forced expiratory volume occupied by the first second forced expiratory volume ( $FEV_1\%$ ) in AECOPD group were lower than those in COPD stable group and healthy group, the difference was statistically significant ( $P<0.05$ ). The  $FEV_1$ , FVC,  $FEV_1/FVC\%$  and  $FEV_1\%$  in COPD stable group were lower than those in healthy group, the difference was statistically significant ( $P<0.05$ ). Pearson correlation analysis showed that serum SAA levels in AECOPD patients were positively correlated with IL-8, IL-6, CRP and

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PCT. It was negatively correlated with  $FEV_1\%$ ,  $FEV_1/FVC\%$ ,  $FEV_1$  and FVC ( $P<0.05$ ). The results of receiver operation characteristic (ROC) curve showed that the sensitivity of SAA to AECOPD diagnosis was 80.85%, the specificity was 80.07%, the area under the curve was 0.832. **Conclusion:** The serum SAA level in AECOPD patients is significantly increased, which is correlated with pulmonary function and inflammatory factors. It has high diagnostic value and could be used to evaluate the condition of patients with AECOPD.

**Key words:** Chronic obstructive pulmonary disease; Acute exacerbation; Serum amyloid A; Pulmonary function; Diagnostic value; Inflammatory factors

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## 前言

慢性阻塞性肺疾病(COPD)是具有气流阻塞性质的一种常见慢性支气管炎,常伴有肺气肿,其常见病因与有害气体、颗粒体吸入致异常炎症反应有关<sup>[1,2]</sup>。COPD 患者病情若控制不佳,在病毒或细菌感染下,病情易进展至慢性阻塞性肺疾病急性加重期(AECOPD),严重危害患者健康。目前部分研究表明,AECOPD 的发病机制除与气道高反应性、呼吸道平滑肌细胞的持续性痉挛等有关外,还与炎症反应存在密切关系,但尚无相关敏感性指标可以用于评估 AECOPD 疾病严重程度<sup>[3,4]</sup>。血清淀粉样蛋白 A(SAA)是具有免疫调理功能的一类载脂蛋白,其血清水平与呼吸道感染、败血症及呼吸机相关性肺炎等疾病预后密切相关<sup>[5,6]</sup>。本研究分析 AECOPD 患者血清 SAA 水平与炎症因子、肺功能的关系,并分析其对 AECOPD 的诊断价值,以期评估 AECOPD 病情提供依据。

## 1 资料与方法

### 1.1 临床资料

选取 2013 年 6 月 -2018 年 6 月中国人民解放军第 970 医院收治的 COPD 患者 204 例,纳入标准:(1)均符合《慢性阻塞性肺疾病诊治指南(2013 年修订版)》诊断标准<sup>[7]</sup>;(2)所有患者均可耐受呼吸功能检测;(3)患者及其家属均已签署知情同意书。排除标准:(1)合并有肺部肿瘤等恶性肿瘤者;(2)合并慢性支气管扩张、哮喘、肺结核等慢性肺病者;(3)近期服用糖皮质激素等药物者;(4)合并自身免疫病者;(5)严重肝肾功能不全者。其中 COPD 稳定期患者 72 例作为 COPD 稳定组,AECOPD 患者 132 例作为 AECOPD 组。另选同期于中国人民解放军第 970 医院进行健康体检的 50 例体检者作为健康组。中国人民解放军第 970 医院伦理委员会已批准本研究。各组受试者的一般临床资料比较差异无统计学意义( $P>0.05$ ),见表 1。

表 1 各组受试者临床资料比较

Table 1 Comparison of clinical data of subjects in each group

| Groups            | n   | Age (years) | Gender<br>(male/female) | Body mass index<br>(kg/m <sup>2</sup> ) | Diabetes[n(%)] | Smoke[n(%)] |
|-------------------|-----|-------------|-------------------------|-----------------------------------------|----------------|-------------|
| AECOPD group      | 132 | 62.35± 7.24 | 77/55                   | 22.15± 3.16                             | 26(19.70)      | 69(52.27)   |
| COPD stable group | 72  | 61.52± 6.42 | 40/32                   | 22.25± 4.12                             | 18(25.00)      | 38(52.78)   |
| Health group      | 50  | 60.36± 6.24 | 25/25                   | 22.14± 4.14                             | 10(20.00)      | 25(50.00)   |
| F/ $\chi^2$       |     | 1.253       | 1.027                   | 0.061                                   | 0.842          | 0.101       |
| P                 |     | 0.287       | 0.598                   | 0.941                                   | 0.656          | 0.951       |

### 1.2 血清 SAA 及炎症因子检测

所有受试者(COPD 患者于入院第 2d,健康体检者于体检时)采集空腹静脉血 5 mL,以 3000 r/min 的转速离心 5 min,取上清液保存备用。采用酶联免疫吸附法检测血清中白细胞介素-6(IL-6)、白细胞介素-8(IL-8)水平(试剂由深圳晶美公司提供);采用免疫胶体金法检测血清中 C 反应蛋白(CRP)、降钙素原(PCT)及 SAA 水平(试剂由上海奥普生物医药有限公司提供),试剂保存和使用严格遵循试剂盒说明书进行相关操作。

### 1.3 肺功能测定

所有受试者肺功能采用肺功能仪(德国耶格肺功能测定仪,型号 MasterScreen IOS)实行吹气检测,所有操作由同一医师进行,记录所有受试者第一秒用力呼气容积( $FEV_1$ )、用力肺活量(FVC)、第一秒用力呼气容积占用力肺活量的百分比( $FEV_1/FVC\%$ )、第一秒用力呼气容积占预计值百分比( $FEV_1\%$ )。

### 1.4 统计学方法

应用 SPSS24.0 统计软件分析,计数资料用率表示,组间比较行  $\chi^2$  检验。计量资料用  $\bar{x}\pm s$  表示,两组比较行独立样本 t 检验,多组对比行单因素方差分析。采用 Pearson 相关性分析指标间的关系。血清 SAA 水平对 AECOPD 的诊断价值采用受试者特征工作(Receiver operation characteristic,ROC)曲线分析。检验水准设置为 $\alpha=0.05$ 。

## 2 结果

### 2.1 各组受试者血清 SAA 水平及炎症指标比较

AECOPD 组患者血清 SAA、PCT、CRP、IL-6、IL-8 水平较 COPD 稳定组及健康组升高( $P<0.05$ ),COPD 稳定组患者血清 SAA、IL-6、IL-8、PCT、CRP 水平较健康组升高( $P<0.05$ ),见表 2。

### 2.2 各组受试者肺功能比较

AECOPD 组患者  $FEV_1$ 、FVC、 $FEV_1/FVC\%$ 、 $FEV_1\%$  低于

COPD 稳定组及健康组,差异有统计学意义( $P<0.05$ ),COPD 稳定组患者 FEV<sub>1</sub>、FVC、FEV<sub>1</sub>/FVC%、FEV<sub>1</sub>%低于健康组,差异有

表 2 各组受试者血清 SAA 水平及炎症指标比较( $\bar{x}\pm s$ )

Table 2 Comparison of serum SAA levels and inflammatory factors of subjects in each group( $\bar{x}\pm s$ )

| Groups            | n   | SAA(mg·L <sup>-1</sup> )  | IL-6 (μg·L <sup>-1</sup> ) | IL-8 (μg·L <sup>-1</sup> ) | PCT(μg·L <sup>-1</sup> ) | CRP(mg·L <sup>-1</sup> )  |
|-------------------|-----|---------------------------|----------------------------|----------------------------|--------------------------|---------------------------|
| AECOPD group      | 132 | 17.12± 4.24 <sup>ab</sup> | 27.64± 11.42 <sup>ab</sup> | 0.74± 0.35 <sup>ab</sup>   | 2.17± 0.42 <sup>ab</sup> | 20.51± 5.24 <sup>ab</sup> |
| COPD stable group | 72  | 11.14± 3.36 <sup>a</sup>  | 19.14± 7.41 <sup>a</sup>   | 0.53± 0.13 <sup>a</sup>    | 0.52± 0.13 <sup>a</sup>  | 12.42± 3.63 <sup>a</sup>  |
| Health group      | 50  | 8.25± 1.47                | 9.45± 4.83                 | 0.17± 0.03                 | 0.07± 0.02               | 5.73± 1.53                |
| F                 |     | 137.473                   | 70.991                     | 86.016                     | 1,149.899                | 238.268                   |
| P                 |     | 0.000                     | 0.000                      | 0.000                      | 0.000                    | 0.000                     |

Note: Compared with healthy group, <sup>a</sup> $P<0.05$ ; compared with COPD stable group, <sup>b</sup> $P<0.05$ .

表 3 各组受试者肺功能比较

Table 3 Comparison of pulmonary function of subjects in each group

| Groups            | n   | FEV <sub>1</sub> /FVC (%)  | FEV <sub>1</sub> (%)       | FEV <sub>1</sub> (L)     | FVC(L)                   |
|-------------------|-----|----------------------------|----------------------------|--------------------------|--------------------------|
| AECOPD group      | 132 | 40.25± 10.52 <sup>ab</sup> | 41.25± 13.63 <sup>ab</sup> | 1.59± 0.42 <sup>ab</sup> | 1.56± 0.35 <sup>ab</sup> |
| COPD stable group | 72  | 62.24± 12.14 <sup>a</sup>  | 63.25± 13.36 <sup>a</sup>  | 1.89± 0.46 <sup>a</sup>  | 1.75± 0.53 <sup>a</sup>  |
| Health group      | 50  | 83.14± 6.24                | 84.53± 7.25                | 2.42± 0.74               | 2.57± 0.82               |
| F                 |     | 336.593                    | 231.588                    | 242.11                   | 243.25                   |
| P                 |     | 0.000                      | 0.000                      | 0.000                    | 0.000                    |

Note: Compared with healthy group, <sup>a</sup> $P<0.05$ ; compared with COPD stable group, <sup>b</sup> $P<0.05$ .

### 2.3 AECOPD 患者 SAA 与肺功能及炎症因子的相关性分析

Pearson 相关性分析显示,AECOPD 患者 SAA 与 IL-8、IL-6、CRP、PCT 呈正相关关系,与 FEV<sub>1</sub>%、FEV<sub>1</sub>/FVC%、FVC、FEV<sub>1</sub> 呈负相关关系( $P<0.05$ ),见表 4。

表 4 AECOPD 患者 SAA 与肺功能及炎症因子的相关性分析

Table 4 The correlation between SAA and pulmonary function and inflammatory factors in patients with AECOPD

| Index                  | SAA    |       |
|------------------------|--------|-------|
|                        | r      | P     |
| IL-6                   | 0.671  | 0.001 |
| IL-8                   | 0.567  | 0.007 |
| CRP                    | 0.502  | 0.011 |
| PCT                    | 0.521  | 0.010 |
| FEV <sub>1</sub> /FVC% | -0.633 | 0.001 |
| FEV <sub>1</sub> %     | -0.521 | 0.013 |
| FVC                    | -0.525 | 0.009 |
| FEV <sub>1</sub>       | -0.561 | 0.004 |

断分析模型。经 ROC 分析可知:SAA 对 AECOPD 具有较高的诊断价值,在其理论阈值点处(14.8 mg/L),ROC-AUC 为 0.832,敏感度和特异度分别为 80.85%、80.07%。见图 1。

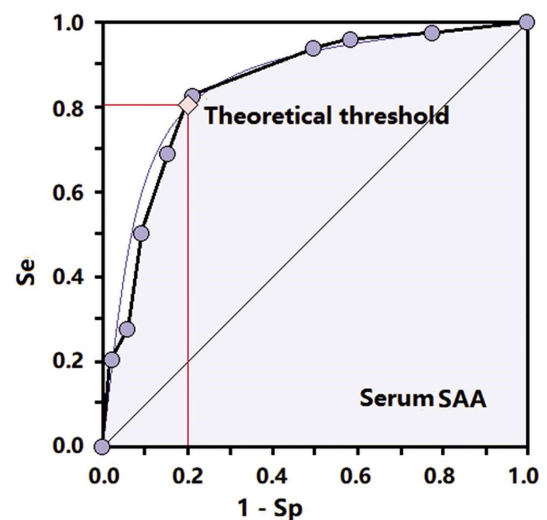


图 1 血清 SAA 对 AECOPD 诊断价值的 ROC 分析曲线

Fig. 1 ROC analysis curve of serum SAA for diagnostic value of AECOPD

### 2.4 血清 SAA 对 AECOPD 的诊断价值分析

以 AECOPD 组为阳性样本,以 COPD 稳定组及健康组为阴性样本,再将血清 SAA 水平划分成 9 个组段,分别为:~5 mg/L、~7.5 mg/L、~10 mg/L、~12.5 mg/L、~15 mg/L、~17.5 mg/L、~20 mg/L、~22.5 mg/L、22.5 mg/L~,建立 ROC 曲线诊

## 3 讨论

COPD 是由长期的肺部慢性炎症导致的肺泡上皮细胞及平滑肌上皮细胞重塑引起<sup>[8]</sup>,此类患者若伴随感染,在感染控制不佳的情况下其可在短期内进展至 AECOPD,而 AECOPD 患者早期易漏诊,从而导致患者体内炎症反应加重,肺功能急剧

恶化,进而影响患者预后<sup>[9-11]</sup>。AECOPD 的发病机制除与气道高反应性、呼吸道平滑肌细胞的持续性痉挛等有关外,还与炎症反应存在密切关系<sup>[12,13]</sup>,但目前尚无特异性的诊断指标,因此寻找相关特异性指标用于早期诊断 AECOPD 并及早对患者进行干预治疗,对改善 AECOPD 患者预后具有重大意义。

SAA 是肝脏合成的一类急性时相脂蛋白<sup>[14,15]</sup>,可清除病原微生物,在人体免疫系统中可发挥重要作用,但当病原微生物过多时,SAA 也会致炎症细胞增殖汇聚,并释放大量的炎症活性因子,从而加剧炎症反应<sup>[16,17]</sup>。SAA 具有高特异性及易于测量的优势,其血清学水平可在一定程度上反映患者机体炎症反应的剧烈程度<sup>[18,19]</sup>。CRP 为急性时相蛋白,是一种临床上判断感染以及炎症反应的经典炎症标志物<sup>[20-22]</sup>。PCT 是降钙素前体分子,其与细菌感染引起的炎症反应等密切相关<sup>[23]</sup>,而对病毒等非细菌因素诱发感染的敏感性不高,存在一定的局限性。虽有部分学者提出 CRP 联合 PCT 检测可用于评估 COPD 患者感染以及炎症反应程度,但评估效果并不理想<sup>[24]</sup>。IL-8、IL-6 作为细胞炎症因子,可作用于炎症反应细胞,如单核细胞、嗜酸性粒细胞、中性粒细胞等,而这些炎症细胞大量增殖浸润,引发支气管平滑肌痉挛,进一步导致小气道狭窄,阻塞性通气功能障碍加重。除上述机制外,IL-6、IL-8 还可使小气道出现高反应性,加重患者病情<sup>[25,26]</sup>。

本研究结果显示,AECOPD 组患者血清 SAA、PCT、CRP、IL-6、IL-8 水平均较 COPD 稳定组及健康组高,差异存在统计学意义 ( $P<0.05$ ),AECOPD 组患者 FVC、FEV<sub>1</sub>、FEV<sub>1</sub>/FVC%、FEV1% 低于 COPD 稳定组及健康组,差异存在统计学意义 ( $P<0.05$ ),提示患者病情进展至 AECOPD 时,血清 SAA 水平明显升高,机体炎症反应明显增强,与此同时,AECOPD 患者的肺功能也出现明显恶化。另外,Pearson 相关性分析显示,患者血清 SAA 水平与血清 IL-8、IL-6、CRP、PCT 呈正相关关系,与 FVC、FEV<sub>1</sub>、FEV<sub>1</sub>%,FEV<sub>1</sub>/FVC% 呈负相关关系,提示 AECOPD 患者血清 SAA 与炎症反应程度及肺功能存在相关性。孙万里等<sup>[27]</sup>也得出 SAA 可通过干扰脂氧素信号传导通路,维持炎症反应强度,其可使中性粒细胞持续活跃,机体炎症感染反应的加重,使得 AECOPD 患者病情趋于恶化。部分研究表明,IL-6、IL-8 等炎症因子水平失调可引起下游 SAA 分泌增加,从而对巨噬细胞募集及活化,进而使成纤维细胞活化,导致肺组织通气功能下降,加速 COPD 向 AECOPD 的发展<sup>[28-30]</sup>,而炎症反应加重也可致肺通气功能下降,患者肺功能也将出现相应恶化。另外,SAA 对 AECOPD 诊断的敏感度和特异度均高于 0.8,曲线下面积为 0.832,提示 SAA 诊断价值较高。

综上所述,AECOPD 患者血清 SAA 水平明显升高,可反映体内炎症反应程度与肺功能,且具有较高的诊断价值,其可用于评估 AECOPD 患者的病情,为 AECOPD 患者的早期诊断治疗提供参考。

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