

· 临床研究 ·

## 老年重叠综合征患者早期肾损伤临床研究

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**【摘要】** **目的** 探讨重叠综合征(OS)早期肾损伤情况及相关指标分析。**方法** 选取2014年1月至2018年8月南京市第一医院呼吸与危重症医学科收治的16例OS患者(OS组)及42例慢性阻塞性肺疾病(COPD)患者(COPD组),另选取同期不伴有缺氧性疾病的健康体检者30名(对照组)。分别测定各组肺功能指标1秒钟用力呼气容积占预计值百分比(FEV1%)、用力肺活量占预计值百分比(FVC%)和1秒钟用力呼气容积/用力肺活量(FEV1/FVC),血气分析指标氧分压(PaO<sub>2</sub>)及二氧化碳分压(PaCO<sub>2</sub>),肾功能指标血清尿素氮(BUN)、血肌酐(SCr)、内生肌酐清除率(Ccr)、胱抑素C(Cys-C)及β<sub>2</sub>微球蛋白(β<sub>2</sub>-MG)水平。比较各组指标差异。采用SPSS 22.0软件进行统计分析。根据数据类型,组间比较采用方差分析、LSD两两比较或χ<sup>2</sup>检验。Spearman秩相关法对Cys-C和β<sub>2</sub>-MG与其他指标进行相关性分析。**结果** 与对照组比较,OS和COPD组患者COPD评估测试(CAT)评分、PaCO<sub>2</sub>、Cys-C及β<sub>2</sub>-MG显著升高,PaO<sub>2</sub>、FEV1%、FVC%和FEV1/FVC显著降低,差异有统计学意义( $P<0.05$ ),但3组BUN及SCr及Ccr差异无统计学意义( $P>0.05$ )。与COPD组比较,OS组患者CAT、Cys-C及β<sub>2</sub>-MG显著升高,差异有统计学意义( $P<0.05$ )。相关性分析显示,Cys-C和β<sub>2</sub>-MG与CAT评分呈正相关(Cys-C: $r=0.722, P=0.000$ ; β<sub>2</sub>-MG: $r=0.287, P=0.029$ ),与PaO<sub>2</sub>呈负相关(Cys-C: $r=-0.355, P=0.006$ ; β<sub>2</sub>-MG: $r=-0.471, P=0.000$ ),差异均有统计学意义。**结论** 通过检验OS患者血清Cys-C和β<sub>2</sub>-MG水平可以监测早期肾损伤程度,并且Cys-C和β<sub>2</sub>-MG水平和缺氧密切相关。

**【关键词】** 肺疾病,慢性阻塞性;重叠综合征;胱抑素C;β<sub>2</sub>微球蛋白;早期肾损伤

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## Clinical study of early renal injury in elderly patients with overlap syndrome

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**【Abstract】** **Objective** To investigate early renal injury in overlap syndrome (OS) and related indicators. **Methods** Enrolled in the study were 16 patients with OS (OS group) and 42 with chronic obstructive pulmonary disease (COPD; COPD group) treated in the Department of Respiratory and Critical Care Medicine of Nanjing First Hospital from January 2014 to August 2018. During the same period, 30 healthy people without hypoxic diseases were enrolled as control group. Measurement was made of the pulmonary indicators [percentage of predicted forced expiratory volume in 1 second (FEV1%), percentage of predicted forced vital capacity (FVC%), forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC)], blood gas analysis [partial pressure of oxygen (PaO<sub>2</sub>) and partial pressure of carbon dioxide (PaCO<sub>2</sub>)], indicators of renal function [blood urea nitrogen (BUN), serum creatinine (SCr), endogenous creatinine clearance rate (Ccr), cystatin C (Cys-C) and β<sub>2</sub>-microglobulin (β<sub>2</sub>-MG)]. The difference of the parameters among groups was observed. SPSS statistics 22.0 was used for statistical analysis. According to the data type, analysis of variance (ANOVA), LSD pairwise comparison or χ<sup>2</sup> test was used for comparison among groups, and Spearman rank correlation for the correlation between Cys-C or β<sub>2</sub>-MG and other indicators. **Results** The OS and COPD groups scored significantly higher than the control group in COPD assessment test (CAT), PaCO<sub>2</sub>, Cys-C and β<sub>2</sub>-MG but significantly lower in PaO<sub>2</sub>, FEV1%, FVC% and FEV1/FVC ( $P<0.05$ ), but there were no significant differences in BUN, SCr and Ccr among the three groups ( $P>0.05$ ). Compared with the COPD group, CAT, Cys-C and β<sub>2</sub>-MG in the OS group were significantly higher ( $P<0.05$ ). The correlation analysis showed that Cys-C and β<sub>2</sub>-MG were positively correlated with CAT score (Cys-C:  $r=0.722, P=0.000$ ; β<sub>2</sub>-MG:  $r=0.287, P=0.029$ ) and negatively correlated with PaO<sub>2</sub> (Cys-C:  $r=-0.355, P=0.006$ ; β<sub>2</sub>-MG:  $r=-0.471, P=0.000$ ), all with statistical significance ( $P<0.05$ ).

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**Conclusion** Measurement of serum Cys-C and  $\beta_2$ -MG in OS patients can help monitor the degree of early renal injury, and Cys-C and  $\beta_2$ -MG are closely associated with hypoxia.

**【Key words】** pulmonary disease, chronic obstructive; overlap syndrome; cystatin C;  $\beta_2$ -microglobulin; early renal injury

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慢性阻塞性肺疾病(chronic obstructive pulmonary disease, COPD)是一种具有气流阻塞特征的慢性支气管炎和(或)肺气肿,且可进一步发展为肺心病和呼吸衰竭的常见慢性疾病,可以合并全身性疾病以及伴随重要的合并症<sup>[1]</sup>。阻塞性睡眠呼吸暂停综合征(obstructive sleep apnea syndrome, OSAS)是指睡眠过程中反复发作上呼吸道阻塞,引起呼吸暂停和(或)低通气,出现间歇低氧等病理改变的临床综合征<sup>[2]</sup>。COPD是下气道疾病,OSAS是上气道疾病,当临床上发现上述两种疾病共存于一例患者时,称之为重叠综合征(overlap syndrome, OS)<sup>[3]</sup>。中重度COPD经常伴有低氧血症和(或)高碳酸血症,而OS患者伴上述症状更为明显<sup>[4]</sup>。有研究表明,慢性间歇低氧可造成肾小管上皮细胞损伤<sup>[5]</sup>。若肾功能损害到了中晚期,并发症会增多,且花费巨大,死亡率高,故肾功能损害的早期诊断越来越受到重视。胱抑素C(cystatin C, Cys-C)和 $\beta_2$ 微球蛋白( $\beta_2$ -microglobulin,  $\beta_2$ -MG)做为肾功能损害的早期筛查指标已被国内外很多学者证实。其中针对COPD进行筛查Cys-C和 $\beta_2$ -MG的研究较多<sup>[6,7]</sup>,而对OS尚无报道。本研究拟对比早期OS和COPD患者及不伴有缺氧性疾病的健康人群血清Cys-C和 $\beta_2$ -MG水平及相关临床特征,分析Cys-C和 $\beta_2$ -MG与OS患者早期肾损伤的关系,为临床积极制定应对措施提供参考。

## 1 对象与方法

### 1.1 研究对象

选取2014年1月至2018年8月南京市第一医院呼吸与危重症医学科收治的OS患者16例(OS组)、COPD患者42例(COPD组)及同期来本院进行体检的不伴有缺氧性疾病的人群30名(对照组)。纳入标准:(1)COPD符合中华医学会呼吸病学分会COPD学组制定的《慢性阻塞性肺疾病诊治指南(2013年修订版)》诊断标准<sup>[8]</sup>;(2)OSAS符合2011年中华医学会颁布的诊断标准<sup>[9]</sup>;(3)年龄>60岁;(4)OS及COPD患者1秒钟用力呼气容积占预计值百分比(percentage of predicted forced expiratory volume in 1 second, FEV1%)<80%,且血气分析氧分

压(partial pressure of oxygen, PaO<sub>2</sub>)<80 mmHg(1 mmHg=0.133 kPa)。排除标准:(1)支气管哮喘、支气管扩张及间质性肺病等其他阻塞或限制性肺病;(2)各种原因导致的急慢性肾脏疾病(如糖尿病肾病、高血压肾病及自身免疫性肾病等)、急慢性心力衰竭、肝功能不全、糖尿病及恶性肿瘤等;(3)中枢性睡眠呼吸暂停、单纯鼾症、肥胖低通气综合征、发作性睡病;(4)资料不全。本研究经南京市第一医院医学伦理委员会批准。

### 1.2 方法

受试者入院当天抽取股动脉或桡动脉血1 ml,使用RAPIDPOINT500血气分析仪(西门子,德国)进行动脉血气指标PaO<sub>2</sub>及PaCO<sub>2</sub>分析。第2天清晨抽取外周静脉血5 ml,采用AU5800全自动生化分析仪(贝克曼库尔特,美国)进行肾功能指标血清尿素氮(blood urine nitrogen, BUN)、血肌酐(serum creatinine, SCr)、Cys-C和 $\beta_2$ -MG的测定;受试者内生肌酐清除率(endogenous creatinine clearance rate, Ccr)采用公式计算:男性Ccr=[(140-年龄)×体重(kg)]/[0.818×SCr(μmol/L)],女性Ccr=[(140-年龄)×体重(kg)]/[0.818×SCr(μmol/L)×0.85]。采用肺功能仪(耶格,德国)检测受试者肺功能指标FEV1%、用力肺活量占预计值百分比(percentage of predicted forced vital capacity, FVC%)及1秒钟用力呼气容积/用力肺活量(forced expiratory volume in one second/forced vital capacity ratio, FEV1/FVC)等。明确有无合并OSAS通过多导睡眠图检测(polysomnography, PSG)仪器(飞利浦伟康Alice5,美国)测定呼吸暂停低通气指数(apnea-hypopnea index, AHI)进行判断。COPD严重程度评估采用COPD评估测试<sup>[10]</sup>(COPD assessment test, CAT)量表,内容包括咳嗽、胸闷、咳痰程度、睡眠、精神情况、日常生活受限程度、活动量增加后的困难程度以及在室外活动信心程度等8个方面,每个方面按照严重程度分为0~5分,总计40分,分值越高表示患者的病情越严重。

### 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,组间比较采用方差分析,差异有统计学意义再进行LSD两两比较;计数

资料以例数(百分率)表示,组间比较采用 $\chi^2$ 检验。采用 Spearman 秩相关法对 Cys-C 和  $\beta_2$ -MG 与其他指标进行相关性分析。 $P < 0.05$  为差异有统计学意义。

## 2 结果

### 2.1 3组受试者一般资料比较

3组受试者年龄、性别、吸烟、病程及伴发高血压、冠心病比例比较,差异均无统计学意义( $P > 0.05$ ;表1)。

### 2.2 3组受试者临床特点比较

与对照组比较,OS 和 COPD 组患者 CAT 评分、 $\text{PaCO}_2$ 、Cys-C 及  $\beta_2$ -MG 显著升高, $\text{PaO}_2$ 、FEV1%、FVC%和 FEV1/FVC 显著降低,差异有统计学意义( $P < 0.05$ );与 COPD 组比较,OS 组患者 CAT、Cys-C 及  $\beta_2$ -MG 显著升高,差异有统计学意义( $P < 0.05$ ;表2)。

### 2.3 OS 临床指标与 Cys-C 及 $\beta_2$ -MG 的 Spearman 秩相关分析

分析显示,Cys-C 和  $\beta_2$ -MG 与 CAT 呈正相关,与

$\text{PaO}_2$  呈负相关,差异有统计学意义( $P < 0.05$ ;表3)。

## 3 讨论

在 GOLD(2017 版)指南中<sup>[11]</sup>,COPD 全球倡议对 COPD 的定义增加了“呼吸道症状”,把呼吸道症状提高到和气道阻塞同样的地位,即突出了呼吸道症状的地位。目前评价 COPD 症状的评分最常用的是 CAT 量表,CAT $\geq 10$ 分,表明症状多,COPD 严重程度较大。本研究发现 OS 患者 CAT 评分明显大于单纯 COPD 患者( $P < 0.05$ ),提示 OS 患者较单纯 COPD 症状更加严重。Gjerde 等<sup>[12]</sup>通过回顾性分析 433 例 COPD 患者发现,高龄、恶病质等与患者存在肾衰竭的高风险独立相关,指出老年 COPD 患者发生肾衰竭是一个值得关注的问题。Yoshizawa 等<sup>[13]</sup>对比了 108 例 COPD 患者及 73 名健康人群发现,COPD 患者中慢性肾脏疾病的发病率显著增加。另外,两大流行病学研究<sup>[14,15]</sup>及一个横断面研究<sup>[16]</sup>均发现 OSAS 患者存在慢性肾脏疾病的高发病率。故我们考虑 COPD 合并 OSAS 即 OS 患者产生肾脏损害的风险可能更大,并展开了此项研究。

表 1 3组受试者一般资料比较

Table 1 Comparison of baseline data among three groups

Item	Control group (n=30)	COPD group (n=42)	OS group (n=16)
Age(years, $\bar{x} \pm s$ )	73.0 $\pm$ 7.5	72.4 $\pm$ 9.1	76.8 $\pm$ 8.6
Male[n(%)]	20(66.7)	25(57.5)	9(56.2)
Smoking[n(%)]	16(53.3)	24(57.1)	9(56.2)
Course of disease(year, $\bar{x} \pm s$ )	-	16.50 $\pm$ 11.07	17.19 $\pm$ 13.63
Hypertension[n(%)]	12(40.0)	17(40.5)	7(43.8)
Coronary heart disease[n(%)]	11(36.7)	15(35.7)	6(37.5)

COPD: chronic obstructive pulmonary disease; OS: overlap syndrome.

表 2 3组受试者临床特点比较

Table 3 Comparison of clinical characteristics among three groups

( $\bar{x} \pm s$ )

Item	Control group (n=30)	COPD group (n=42)	OS group (n=16)
CAT(score)	2.90 $\pm$ 1.21	12.81 $\pm$ 2.86*	15.31 $\pm$ 3.48*#
$\text{PaO}_2$ (mmHg)	77.65 $\pm$ 5.43	55.82 $\pm$ 15.07*	53.70 $\pm$ 11.20*
$\text{PaCO}_2$ (mmHg)	41.37 $\pm$ 5.83	55.33 $\pm$ 11.90*	62.98 $\pm$ 17.74*
FEV1%	78.93 $\pm$ 4.08	45.32 $\pm$ 13.78*	43.13 $\pm$ 11.81*
FVC%	83.19 $\pm$ 3.03	57.61 $\pm$ 14.76*	60.29 $\pm$ 13.23*
FEV1/FVC	80.53 $\pm$ 3.36	52.30 $\pm$ 12.22*	56.78 $\pm$ 10.76*
Cys-C(mg/L)	0.95 $\pm$ 0.19	1.21 $\pm$ 0.24*	1.40 $\pm$ 0.20*#
$\beta_2$ -MG(mg/L)	1.65 $\pm$ 0.39	1.86 $\pm$ 0.50*	2.35 $\pm$ 0.52*#
BUN(mmol/L)	5.21 $\pm$ 0.94	5.90 $\pm$ 2.01	6.39 $\pm$ 2.16
SCr( $\mu\text{mol/L}$ )	68.70 $\pm$ 13.51	69.54 $\pm$ 14.43	73.89 $\pm$ 13.63
Ccr(ml/min)	75.25 $\pm$ 19.08	70.05 $\pm$ 16.47	68.94 $\pm$ 18.82

COPD: chronic obstructive pulmonary disease; OS: overlap syndrome; CAT: COPD assessment test;  $\text{PaO}_2$ : partial pressure of oxygen;  $\text{PaCO}_2$ : partial pressure of carbon dioxide; FEV1%: percentage of predicted forced expiratory volume in 1 second; FVC%: percentage of predicted forced vital capacity; FEV1/FVC: forced expiratory volume in one second/forced vital capacity; Cys-C: cystatin C;  $\beta_2$ -MG:  $\beta_2$ -microglobulin; BUN: blood urea nitrogen; SCr: serum creatinine; Ccr: endogenous creatinine clearance rate. Compared with control group, \* $P < 0.05$ ; compared with COPD group, # $P < 0.05$ . 1 mmHg=0.133 kPa.

**表3 Cys-C、 $\beta_2$ -MG 与 CAT、血气分析及肺功能参数相关性分析**

Table 3 Correlation analysis of Cys-C and  $\beta_2$ -MG with CAT, blood gas analysis and pulmonary function

Item	Cys-C		$\beta_2$ -MG	
	r	P value	r	P value
CAT	0.722	0.000	0.287	0.029
PaO <sub>2</sub>	-0.355	0.006	-0.471	0.000
PaCO <sub>2</sub>	0.251	0.058	0.437	0.061
FEV1%	-0.091	0.496	-0.122	0.363
FVC%	-0.113	0.399	-0.289	0.056
FEV1/FVC	-0.002	0.987	0.013	0.925

CAT: COPD assessment test; Cys-C: cystatin C;  $\beta_2$ -MG:  $\beta_2$ -microglobulin; PaO<sub>2</sub>: partial pressure of oxygen; PaCO<sub>2</sub>: partial pressure of carbon dioxide; FEV1%: percentage of predicted forced expiratory volume in 1 second; FVC%: percentage of predicted forced vital capacity; FEV1/FVC: forced expiratory volume in one second/forced vital capacity.

判定肾脏疾病最常用的方法是检查 BUN、SCr、肾小球滤过率(glomerular filtration rate, GFR)或 Ccr 等,但上述指标出现异常时,表明肾功能已到不可逆阶段,不能反映早期肾功能异常。Cys-C 是半胱氨酸蛋白酶抑制剂,表达于所有有核细胞,其血浆浓度较稳定,和 SCr 相比能更好地反映肾小球滤过功能; $\beta_2$ -MG 是一种单链多肽低分子蛋白,和 Cys-C 类似,均可以自由通过肾小球滤过膜,被完全重吸收而不被近曲小管分泌,为目前公认的反映 GFR 变化及肾功能早期损伤的内源性标志物之一<sup>[17,18]</sup>。罗红艳等<sup>[19]</sup>通过对比老年 COPD 和健康对照者发现, COPD 患者 Cys-C 及  $\beta_2$ -MG 明显升高,认为二者可以作为检测早期肾损伤的指标。本研究结果表明, 3 组受试者 BUN、SCr 和 Ccr 差异无统计学意义,但 OS 组和 COPD 组的 Cys-C 及  $\beta_2$ -MG 都较对照组显著升高,且 OS 组 Cys-C 及  $\beta_2$ -MG 显著高于 COPD 组 ( $P < 0.05$ ),表明 2 组患者皆存在早期肾损伤,且 OS 患者早期肾损伤比 COPD 更严重。

FEV1%是评估气流受限严重程度的重要指标。庞志刚等<sup>[20]</sup>通过统计稳定期 COPD 患者肺功能严重程度和 Cys-C 关系,发现气流受限越严重,Cys-C 水平越高,COPD 患者早期肾损伤也更严重。COPD 患者随着病情进展逐渐出现缺氧和(或)二氧化碳潴留,根本原因是不可逆性气流受限所致。当 PaO<sub>2</sub> 低于正常值时,FEV1 常在 50% 预计值以下,所以 FEV1% 和缺氧密切相关,故 FEV1% 引起 Cys-C 升高的根本原因和缺氧有关。本研究未发现 Cys-C 或  $\beta_2$ -MG 与 FEV1%、FVC% 或 FEV1/FVC 等肺功能指标的相关性。笔者考虑本研究样本量可能偏小产生了偏倚,如果按照肺功能严重程度进行亚组分析并

探讨和 Cys-C 及  $\beta_2$ -MG 的关系可能会得到不同的结果,因此后期需大样本研究。

钟红珍等<sup>[21]</sup>指出慢性缺氧和肾小管间质损伤在慢性肾脏疾病的发生发展中起关键作用。有研究发现,中年 OSAS 患者 Cys-C 水平和氧减饱和度、血氧饱和度和  $< 90\%$  的时间及平均血氧饱和度相关<sup>[22]</sup>。而赵素芝等<sup>[23]</sup>探讨 PaO<sub>2</sub> 对老年 COPD 患者早期肾损伤的诊断价值,将入组 COPD 缺氧患者分为 3 个级别,结果显示缺氧程度越重,Cys-C 和  $\beta_2$ -MG 水平越高,并且通过相关性分析显示,Cys-C 水平与缺氧程度呈显著正相关。本研究相关性分析显示 Cys-C 及  $\beta_2$ -MG 和 PaO<sub>2</sub> 呈负相关,结合文献分析原因可能为 OS 患者夜间血氧饱和度下降程度较明显,在夜间低氧血症常导致低水平 PaO<sub>2</sub>,而慢性间歇低氧可造成肾小管上皮细胞损伤<sup>[5]</sup>,从而导致 Cys-C 及  $\beta_2$ -MG 的升高。诚然,OS 和 COPD 引起肾损伤的机制较多,并不仅仅和缺氧有关。肖亚军等<sup>[24]</sup>指出除缺氧和高碳酸血症外,COPD 患者的系统性炎症、神经及体液调节系统、吸烟和氧化应激等都会促进肾损伤的发生,而 OS 患者肾损伤机制和 COPD 有相似,也有不同的地方,有待我们进一步去探讨。

综上,通过对作为早期肾损伤指标的 Cys-C 和  $\beta_2$ -MG 水平的检验可以监测 OS 患者肾损伤程度,且 Cys-C 和  $\beta_2$ -MG 水平和缺氧密切相关。本研究不足之处在于样本量偏小,需扩大样本进一步求证。此外,OS 或 COPD 多为老年患者,伴发疾病较多,其中高血压及冠心病也可以引起 Cys-C 的升高。虽然本研究 3 组受试者基线资料差异无统计学意义,仍不能排除 Cys-C 的升高和慢性缺氧协同导致的肾脏损害,未来研究需尽可能排除混杂因素的影响,并结合其它肾损伤指标如尿微量白蛋白、尿微量白蛋白/肌酐比值等进行联合检测以获取更多可靠依据。

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