

COPD 并发呼吸衰竭患者血清 14-3-3 β , CC16 水平表达及与预后的关系研究

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摘要: 目的 探讨慢性阻塞性肺疾病(COPD)并发呼吸衰竭患者血清酪氨酸3-单加氧酶/色氨酸5-单加氧酶激活蛋白 β (14-3-3 β), 克拉拉细胞分泌蛋白16(CC16)水平表达及与预后的关系。方法 选取2020年4月~2023年10月南方科技大学盐田医院收治的COPD并发呼吸衰竭患者232例纳入COPD并发呼吸衰竭组, 根据病情程度分为轻度组($n=67$)、中度组($n=73$)和重度组($n=92$); 根据28天预后分为死亡组($n=73$)和存活组($n=159$); 另选择同时时间段单纯COPD患者80例(COPD组)和80例体检健康者(对照组), 采用酶联免疫吸附法(ELISA)检测血清14-3-3 β , CC16表达。通过多因素Logistic回归分析COPD并发呼吸衰竭患者死亡的因素, 受试者工作特征(ROC)曲线分析血清14-3-3 β , CC16表达对COPD并发呼吸衰竭患者死亡的预测价值。结果 COPD并发呼吸衰竭组血清14-3-3 β 表达高于COPD组和对照组($U=3.894, 11.417$), CC16表达低于COPD组和对照组($t=5.845, 14.306$), 差异具有统计学意义(均 $P<0.05$)。重度组血清14-3-3 β 表达高于中度组和轻度组($U=5.179, 8.234$), CC16表达低于中度组和轻度组($t=4.090, 9.281$), 差异具有统计学意义(均 $P<0.05$)。232例COPD并发呼吸衰竭患者28天死亡率为31.47%(73/232)。死亡组血清14-3-3 β 表达高于存活组, CC16表达低于存活组, 差异具有统计学意义($U/t=6.790, 8.265$, 均 $P<0.05$)。死亡组年龄大于存活组, 气流受限程度、1年内急性加重次数高于存活组, 差异具有统计学意义($t/\chi^2/U=3.895, 7.202, 3.360$, 均 $P<0.05$)。年龄增加、重度气流受限、极重度气流受限、1年内急性加重次数增加、14-3-3 β 升高为COPD并发呼吸衰竭患者死亡的独立危险因素(Wald $\chi^2=3.914\sim 22.668$, 均 $P<0.05$), CC16升高为独立保护因素(Wald $\chi^2=23.675$, $P<0.05$)。血清14-3-3 β , CC16表达联合预测COPD并发呼吸衰竭患者死亡的曲线下面积(AUC)大于血清14-3-3 β , CC16表达单独预测, 差异具有统计学意义($Z=3.995, 3.813$, 均 $P<0.01$)。结论 COPD并发呼吸衰竭患者血清14-3-3 β 表达升高和CC16表达降低与病情加重、不良预后密切相关, 血清14-3-3 β , CC16表达联合预测COPD并发呼吸衰竭患者死亡的价值较高。

关键词: 慢性阻塞性肺疾病; 呼吸衰竭; 酪氨酸3-单加氧酶/色氨酸5-单加氧酶激活蛋白 β ; 克拉拉细胞分泌蛋白16

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Study on the Expression of Serum 14-3-3 β , CC16 Levels in Patients with COPD Complicated with Respiratory Failure and Their Relationship with Prognosis

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Abstract: **Objective** To investigate the expression levels of serum tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein β (14-3-3 β) and clara's cell secretory protein 16 (CC16) in patients with chronic obstructive pulmonary disease (COPD) complicated by respiratory failure, and their relationship with prognosis. **Methods** A total of 232 patients with COPD complicated with respiratory failure admitted to Yantian Hospital of Southern University of Science and Technology from April 2020 to October 2023 were enrolled in the COPD complicated with respiratory failure group. According to the severity of the disease, they were divided into mild group ($n=67$), moderate group ($n=73$) and severe group ($n=92$). According to the 28-day prognosis, they were divided into death group ($n=73$) and survival group ($n=159$). In addition, 80 patients with simple COPD (COPD group) and 80 healthy subjects (control group) were selected at the same time. Enzyme-linked immunosorbent assay (ELISA) was used to detect the expression of serum 14-3-3 β and CC16. Multivariate Logistic regression analysis

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was used to analyze the factors of death in patients with COPD complicated with respiratory failure. The receiver operating characteristic (ROC) curve was used to analyze the predictive value of serum 14-3-3 β and CC16 expression on the death of patients with COPD complicated with respiratory failure. **Results** The expression of serum 14-3-3 β in COPD complicated with respiratory failure group was higher than that in COPD group and control group ($U = 3.894, 11.417$), the expression of CC16 was lower than that in COPD group and control group ($t = 5.845, 14.306$), and the differences were statistically significant (all $P < 0.05$), respectively. The expression of serum 14-3-3 β in severe group was higher than that in moderate group and mild group ($U = 5.179, 8.234$), the expression of CC16 was lower than that of moderate group and mild group ($t = 4.090, 9.281$), and the differences were statistically significant (all $P < 0.05$), respectively. The 28-day mortality rate of 232 COPD patients with respiratory failure was 31.47% (73/232). The expression of serum 14-3-3 β in the death group was higher than that in the survival group, and the expression of CC16 was lower than that in the survival group, the differences were statistically significant ($U/t = 6.790, 8.265$, all $P < 0.05$). The age of the death group was older than that of the survival group, the degree of airflow limitation and the number of acute exacerbations within 1 year were higher than those of the survival group, and the differences were statistically significant ($t/\chi^2/U = 3.895, 7.202, 3.360$, all $P < 0.05$). Age, severe airflow limitation, extremely severe airflow limitation, and the number of acute exacerbations within 1 year, elevated 14-3-3 β were independent risk factors for death in patients with COPD complicated with respiratory failure (Wald $\chi^2 = 3.914 \sim 22.668$, all $P < 0.05$), and elevated CC16 was an independent protective factor (Wald $\chi^2 = 23.675$, $P < 0.05$). The area under the curve (AUC) of serum 14-3-3 β combined and CC16 expression in predicting the death of patients with COPD complicated with respiratory failure which was greater than that of serum 14-3-3 β and CC16 expression alone, the differences were statistically significant ($Z = 3.995, 3.813$, all $P < 0.01$). **Conclusion** The increase of serum 14-3-3 β expression and the decrease of CC16 expression in patients with COPD complicated by respiratory failure are closely related to the aggravation of the disease and poor prognosis. The combination of serum 14-3-3 β and CC16 expression is of high value in predicting the death of patients with COPD complicated with respiratory failure.

Keywords: chronic obstructive pulmonary disease; respiratory failure; tyrosine 3-monooxygenase/tryptophan5-monooxygenase activation protein β ; clara's cell secretory protein-16

慢性阻塞性肺疾病(chronic obstructive pulmonary disease, COPD)是一种常见的慢性气道炎症性疾病,以持续性、进行性加重的气流受限和相应呼吸系统症状为主要特征,COPD发病率随年龄增长而增加,中国20岁以上人群COPD患者数量约有1亿,其中 ≥ 60 岁人群的COPD患病率高达27%,给家庭和社会带来了巨大负担^[1-2]。呼吸衰竭是COPD急性加重常见的并发症,也是导致患者死亡的重要原因^[3]。研究表明,炎症反应参与COPD发生发展^[4]。酪氨酸3-单加氧酶/色氨酸5-单加氧酶激活蛋白(tyrosine 3-monooxygenase/tryptophan5-monooxygenase activation protein, 14-3-3) β 是一种可溶性酸性蛋白,能通过与多种靶标相互作用参与炎症反应过程^[5]。WANG等^[6]报道,血清14-3-3 β 表达有助于稳定期COPD诊断。克拉拉细胞分泌蛋白16(clara's cell secretory protein-16, CC16)是一种分泌珠蛋白,具有广泛的免疫调节、抗炎、抗纤维化等作用^[7]。白燕等^[8]报道,血清CC16表达降低与COPD急性加重有关。然而关于COPD并发呼吸衰竭患者血清14-3-3 β ,CC16表达及与预后的关系仍缺乏报道,基于此,本研究报道如下,以期改善COPD并发呼吸衰竭患者预后提供更多依据。

1 材料与方法

1.1 研究对象 选取2020年4月~2023年10月南方科技大学盐田医院收治的COPD并发呼吸衰竭患者232例纳入COPD并发呼吸衰竭组,按气流受限程度^[9]分为:轻度者52例,中度者63例,重度者46例,极重度者71例,其中男性148例,女性84例,年龄 62.74 ± 10.85 岁。另选择同期收治的单纯COPD患者80例纳入COPD组,男性51例,女性29例,年龄 62.52 ± 10.57 岁。同期80例体检健康者纳入对照组,男性50例,女性30例,年龄 62.40 ± 10.42 岁。三组年龄和性别比较,差异无统计学意义($F/\chi^2 = 0.035, 0.045$,均 $P > 0.05$)。纳入标准:①年龄18岁及以上;②资料完整;③COPD符合《慢性阻塞性肺疾病诊治指南(2021年修订版)》^[10]诊断标准;④COPD并发呼吸衰竭为II型呼吸衰竭[动脉血氧分压(arterial partial pressure of oxygen, PaO₂) < 60mmHg且动脉血二氧化碳分压(arterial partial pressure of carbon dioxide, PaCO₂) > 50mmHg];⑤患者或家属自愿签署知情同意书。排除标准:①肺部胸廓外伤、肺部手术史或合并其他肺疾病如肺结核、哮喘、肺源性心脏病;②自身免疫系统疾病;③活动性内脏出血、脑卒中;④严重凝血功能障碍;⑤精神病史如帕金森病、癫痫、阿尔兹海默病;⑥妊娠及哺乳期妇女;⑦恶性肿瘤;⑧近1个月内进行手术治疗或使用免疫抑制

剂; ⑨严重肝肾功能损害。本研究经医院伦理委员会批准(伦理批号: KF2020G0076)。

1.2 仪器与试剂 14-3-3 β , CC16酶联免疫吸附法(ELISA)试剂盒(武汉菲恩生物科技有限公司, 批号: 207454, 206385); 多功能酶标仪(英国珀金埃尔默公司, 型号: EnVision); 瑞士罗氏Cobas b 123 血气分析仪; 深圳迈瑞BC5310全自动血液分析仪。

1.3 方法

1.3.1 资料收集: 收集并统计COPD并发呼吸衰竭患者一般资料, 包括性别、年龄、COPD病程、气流受限程度、吸烟史、疾病史、1年内急性加重次数、抗生素使用时间、机械通气时间、血气指标(PaO_2 , $PaCO_2$)、血尿素氮、血肌酐、血红蛋白、血小板计数和白细胞计数。

1.3.2 血清14-3-3 β , CC16表达检测: 采集COPD并发呼吸衰竭患者入院次日和单纯COPD患者、体检健康者体检时静脉血2ml, 静置2h, 以3 500r/min离心5min(离心半径13.5cm), 分离血清后用ELISA检测14-3-3 β , CC16表达。

1.3.3 病情和预后分组: COPD并发呼吸衰竭患者入院后根据病情程度分为轻度组(PaO_2 为61~80mmHg, $n=67$)、中度组(PaO_2 为41~60mmHg, $n=73$)、重度组($PaO_2 \leq 40$ mmHg, $n=92$)^[11]; 参考《慢性阻塞性

肺疾病诊治指南(2021年修订版)^[10]接受相关治疗, 根据28天预后将COPD并发呼吸衰竭分为死亡组($n=73$)和存活组($n=159$)。

1.4 统计学分析 采用SPSS28.0软件进行统计分析。计数资料用 $n(\%)$ 表示, 使用 χ^2 检验; 偏态计量资料用 $M(P_{25}, P_{75})$ 表示, 行 U 检验或 H 检验, 组间两两比较采用 U 检验; 正态资料行 t 检验或单因素方差分析, 组间两两比较行 t 检验; 多因素Logistic回归分析COPD并发呼吸衰竭患者死亡的因素; 受试者工作特征(receiver operating characteristics, ROC)曲线分析血清14-3-3 β , CC16表达对COPD并发呼吸衰竭患者死亡的预测价值, Delong检验比较血清14-3-3 β , CC16表达单独和联合预测的曲线下面积(area under the curve, AUC); 检验水准 $\alpha = 0.05$ 。

2 结果

2.1 三组血清14-3-3 β , CC16表达比较 见表1。COPD并发呼吸衰竭组血清14-3-3 β 表达高于COPD组和对照组($U=3.894, 11.417$), CC16表达低于COPD组和对照组($t=5.845, 14.306$), 差异具有统计学意义(均 $P < 0.05$); COPD组血清14-3-3 β 表达高于对照组, CC16表达低于对照组, 差异具有统计学意义($U/t=6.197, 5.485$, 均 $P < 0.05$)。

表1 三组血清14-3-3 β , CC16表达比较 [$\bar{x} \pm s, M(P_{25}, P_{75})$]

项目	COPD并发呼吸衰竭组 ($n=232$)	COPD组 ($n=80$)	对照组 ($n=80$)	F/H 值	P 值
14-3-3 β (ng/ml)	54.63 (45.14, 63.01)	37.47 (25.49, 55.31)	27.22 (20.01, 36.60)	140.588	< 0.01
CC16 (ng/ml)	80.48 \pm 16.21	93.99 \pm 21.88	111.16 \pm 17.47	91.984	< 0.01

2.2 不同病情程度COPD并发呼吸衰竭患者血清14-3-3 β , CC16表达比较 见表2。重度组血清14-3-3 β 表达高于中度组和轻度组($U=5.179, 8.234$), CC16表达低于中度组和轻度组($t=4.090, 9.281$), 差

异具有统计学意义(均 $P < 0.05$); 中度组血清14-3-3 β 表达高于轻度组, CC16表达低于轻度组, 差异具有统计学意义($U/t=3.707, 4.373$, 均 $P < 0.05$)。

表2 不同病情程度COPD并发呼吸衰竭患者血清14-3-3 β , CC16表达比较 [$\bar{x} \pm s, M(P_{25}, P_{75})$]

项目	重度组 ($n=92$)	中度组 ($n=73$)	轻度组 ($n=67$)	F/H 值	P 值
14-3-3 β (ng/ml)	59.02 (51.67, 72.66)	55.18 (43.95, 64.01)	44.13 (35.47, 52.17)	74.425	< 0.01
CC16 (ng/ml)	71.61 \pm 13.63	81.56 \pm 15.55	91.48 \pm 12.91	38.997	< 0.01

2.3 不同预后COPD并发呼吸衰竭患者一般资料和血清14-3-3 β , CC16表达比较 见表3。随访28天, 232例COPD并发呼吸衰竭患者死亡73例, 28天死亡率为31.47%(73/232)。死亡组年龄大于存活组, 气流受限程度、1年内急性加重次数、血清14-3-3 β 表达高于存活组, CC16表达低于存活组, 差异具有统计学意义(均 $P < 0.05$); 两组性别、COPD病程、吸烟史、病史等资料比较, 差异无统计学意义(均 $P > 0.05$)。

2.4 COPD并发呼吸衰竭患者死亡的多因素Logistic回归分析 见表4。以COPD并发呼吸衰竭预后(死亡=1, 存活=0)为因变量, 以年龄、气流受限程度(轻度

=1, 中度=2, 重度=3, 极重度=4)、1年内急性加重次数、14-3-3 β , CC16(连续变量均原值录入)为自变量, 进行Logistic回归分析。结果显示: 年龄增加、重度/极重度气流受限、1年内急性加重次数增加、14-3-3 β 升高为COPD并发呼吸衰竭患者死亡的独立危险因素(均 $P < 0.05$), CC16升高为独立保护因素($P < 0.05$)。

2.5 血清14-3-3 β , CC16表达对COPD并发呼吸衰竭患者死亡的预测价值 见表5和图1。通过Logistic回归拟合血清14-3-3 β , CC16表达联合预测概率 $[\ln(P/1-P) = 0.141 + 0.100 \times 14-3-3 \beta - 0.085 \times CC16]$ 。绘制血清14-3-3 β , CC16表达单独与联合预

测 COPD 并发呼吸衰竭患者死亡的 ROC 曲线。结果显示:血清 14-3-3 β , CC16 表达联合预测的 AUC 为 0.880, 大于血清 14-3-3 β , CC16 表达单独预测的 0.778, 0.788, 差异具有统计学意义 ($Z=3.995, 3.813$, 均 $P < 0.01$)。

表 3 不同预后 COPD 并发呼吸衰竭患者一般资料比较 [n (%), M (P_{25}, P_{75})]

类别	死亡组 ($n=73$)	存活组 ($n=159$)	$\chi^2/t/U$	P	
性别	男	45 (61.64)	103 (64.78)	0.213	0.644
	女	28 (38.36)	56 (35.22)		
年龄 (岁)		66.71 \pm 11.30	60.91 \pm 10.17	3.895	< 0.01
COPD 病程 (年)		5.00 (5.00, 6.00)	5.00 (4.00, 6.00)	1.898	0.058
气流受限程度	轻度	0 (0)	56 (35.22)	7.202	< 0.01
	中度	16 (21.92)	52 (32.70)		
	重度	25 (34.25)	29 (18.24)		
	极重度	32 (43.84)	22 (13.84)		
吸烟史		31 (42.47)	62 (38.99)	0.251	0.616
病史	高血压	37 (50.68)	62 (38.99)	2.795	0.095
	糖尿病	29 (39.73)	45 (28.30)	3.006	0.083
	冠心病	40 (54.79)	66 (41.51)	3.558	0.059
	慢性肾脏病	14 (19.18)	19 (11.95)	2.143	0.143
1年内急性加重次数 (次)		1.00 (0.00, 1.00)	1.00 (0.00, 1.00)	3.360	0.001
抗生素使用时间 (天)		10.00 (8.00, 12.00)	10.00 (7.50, 11.00)	0.970	0.332
机械通气时间 (天)		7.00 (6.00, 9.00)	6.50 (5.50, 9.00)	0.878	0.380
PaO ₂ (mmHg)		51.00 (45.50, 55.00)	52.00 (48.00, 55.00)	1.573	0.116
PaCO ₂ (mmHg)		55.00 (54.00, 56.00)	56.00 (54.00, 56.00)	0.630	0.529
血尿素氮 (mmol/L)		8.31 (5.86, 11.25)	7.66 (3.68, 11.76)	1.821	0.069
血肌酐 (μ mol/L)		72.44 (27.29, 116.97)	62.46 (32.31, 89.88)	0.955	0.339
血红蛋白 (g/L)		118.12 \pm 26.49	119.35 \pm 27.37	0.321	0.748
血小板计数 ($\times 10^9/L$)		288.69 \pm 123.20	262.83 \pm 113.15	1.572	0.117
白细胞计数 ($\times 10^9/L$)		12.83 \pm 4.35	12.26 \pm 3.99	0.987	0.329
14-3-3 β (ng/ml)		61.09 (54.52, 74.89)	49.47 (40.06, 59.33)	6.790	< 0.01
CC16 (ng/ml)		69.05 \pm 14.55	85.73 \pm 14.14	8.265	< 0.01

表 4 COPD 并发呼吸衰竭患者死亡的多因素 Logistic 回归分析

因素	β 值	SE 值	Wald χ^2 值	P 值	OR	95%CI	
年龄增加	0.071	0.023	9.685	0.002	1.074	1.027 ~ 1.123	
气流受限程度	轻度 (参照)	-	7.772	0.051	-	-	
	中度	0.030	0.561	0.003	0.958	1.030	0.343 ~ 3.095
	重度	1.151	0.582	3.914	0.048	3.160	1.011 ~ 9.879
	极重度	1.251	0.600	4.349	0.037	3.493	1.078 ~ 11.317
1年内急性加重次数增加	1.688	0.729	5.354	0.021	5.408	1.295 ~ 22.588	
14-3-3 β 升高	0.115	0.024	22.668	< 0.01	1.122	1.070 ~ 1.177	
CC16 升高	-0.094	0.019	23.675	< 0.01	0.910	0.877 ~ 0.946	

表 5 血清 14-3-3 β , CC16 表达对 COPD 并发呼吸衰竭患者死亡的预测价值

因素	AUC	95%CI	P 值	cut-off	敏感度 (%)	特异度 (%)	Youden 指数
14-3-3 β	0.778	0.719 ~ 0.830	< 0.01	56.48 ng/ml	100.00	40.88	0.409
CC16	0.788	0.730 ~ 0.839	< 0.01	74.93 ng/ml	84.93	60.38	0.453
二者联合	0.880	0.832 ~ 0.919	< 0.01	-	75.34	83.02	0.584

3 讨论

呼吸衰竭是各种原因引起的肺换气 and / 或通气功能障碍, 其引起的缺氧可严重损害心、肝、肾、脑等重要器官功能, 进而危及生命安全^[12]。COPD 患

者由于气道和 / 或肺泡异常引起气流严重受限, 这些病理生理变化使气体在呼吸过程中无法有效地进入和排出肺部, 导致气体交换障碍、缺氧和二氧化碳潴留, 最终导致呼吸衰竭^[3]。截止目前, 机械通气仍然

是COPD并发呼吸衰竭最有效的治疗措施, 尽管近年来吸氧疗法、支持性治疗和呼吸机辅助等措施不断改进, 但针对COPD并发呼吸衰竭仍然缺乏个体化和综合性治疗方案, 总体预后仍然较差^[13-14]。本组COPD并发呼吸衰竭患者死亡率为31.47%, 与国内学者报道的30.51%相近^[15], 说明COPD并发呼吸衰竭患者预后较差。及时预测COPD并发呼吸衰竭患者预后, 以便临床及时针对治疗, 改善预后。

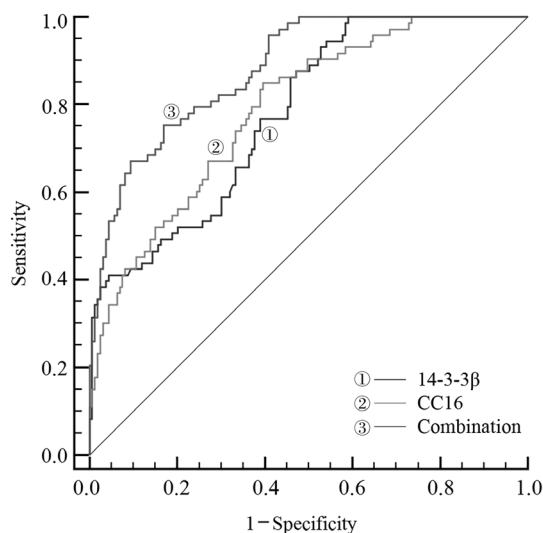


图1 血清14-3-3 β , CC16表达预测COPD并发呼吸衰竭患者死亡的ROC曲线

气道重塑是COPD发生发展的根本病理改变, 涉及炎症反应、细胞外基质沉积等机制, 其中持续炎症不仅能损伤气道和影响修复驱动气道重塑, 还能诱导细胞外基质过度沉积导致气道重塑, 引起气流受限、肺泡破坏等功能障碍, 进而促进呼吸衰竭发生发展^[4]。14-3-3是一类能通过建立蛋白-蛋白相互作用与多种靶标相互作用的蛋白家族, 14-3-3 β (14-3-3 α 为其磷酸化类型)是14-3-3家族首个成员, 在所有真核细胞中广泛存在, 在炎症反应调节中发挥至关重要的作用^[16]。肺表面活性物质缺乏所致的炎症反应, 是气道重塑的重要机制, 也是COPD的重要病理特征^[17]。实验报道^[6], 14-3-3亚型 β , γ , ϵ , η , σ 和 τ 能特异性结合肺表面活性物质相关蛋白A的外显子B, 导致肺表面活性物质相关蛋白A水平降低。哮喘细胞模型中, 14-3-3 β 能与肺成纤维细胞、气道成纤维细胞相互作用, 增强基质金属蛋白1表达以促进气道重塑^[18]。这些研究均支持笔者推测14-3-3 β 参与COPD过程。近期有学者报道, 血清14-3-3 β 水平升高与哮喘患者气道炎症加重相关^[19]。稳定期COPD患者血清14-3-3 β 水平升高, 并与全身炎症反应相关^[8]。因此推测血清14-3-3 β 可能与COPD并发呼吸衰竭患者预后有关。本研究结果显示, COPD并发呼吸衰竭患者血清14-3-3 β 水平升

高, 并随着病情加重而升高, 是死亡的独立危险因素, 说明血清14-3-3 β 水平升高与COPD并发呼吸衰竭患者病情加重有关, 并会增加COPD并发呼吸衰竭患者死亡风险。分析原因可能如下: 14-3-3 β 能与磷脂酰肌醇3-激酶/蛋白激酶B(PI3K/AKT)相互作用激活NF- κ B信号通路, 诱导大量炎症介质表达, 加剧气道、肺组织结构和功能破坏, 进而加重病情和增加死亡风险^[20]; 14-3-3 β 能上调基质金属蛋白表达诱导细胞外基质过度沉积, 促进气道重塑进展而导致病情加重和死亡风险增加^[19]; 14-3-3 β 能下调肺表面活性物质相关蛋白表达, 破坏肺部免疫调节功能和肺泡-气液界面, 加剧肺组织结构、功能损害和呼吸衰竭, 加重病情和增加死亡风险^[17]。

CC16是由呼吸道上皮克拉拉细胞分泌的一种具有抗炎、抗氧化、抗纤维化等作用的分泌蛋白, 因CC16具有肺组织特异性, 因此被广泛报道与肺部疾病发生和进展有关系^[7]。肺炎克雷伯菌感染支气管上皮细胞中, 上调CC16能抑制NF- κ B信号通路和降低活性氧水平, 以保护支气管上皮免受炎症和氧化应激诱导的凋亡^[21]。香烟烟雾诱导的CC16基因缺陷小鼠中, NF- κ B信号通路显著活化, 补充CC16能抑制肺中NF- κ B信号通路活化, 减轻肺部过度炎症反应^[22]。同时提高CC16表达水平能抑制转化生长因子(transforming growth factor, TGF) β 1/小母系抗肢瘫同系物(small mothers against decapentaplegic homolog, SMAD)信号通路激活, 抑制肺组织纤维化^[23]。这些研究说明CC16具有重要的肺部保护作用。近年有学者指出, 血清CC16水平降低与COPD患者肺功能降低和气流受限程度加重有关, 并且有助于COPD早期诊断^[24]。外周血CC16水平有助于评估急性加重COPD患者预后^[25]。然而关于血清CC16与COPD并发呼吸衰竭患者预后的报道较少。本研究结果显示, COPD并发呼吸衰竭患者血清CC16水平降低, 并随着病情加重而降低, CC16升高是死亡的独立保护因素, 说明血清CC16水平升高能降低COPD并发呼吸衰竭病情程度和死亡风险。分析原因可能如下: CC16能抑制NF- κ B信号通路和活性氧产生, 减少炎症和氧化应激对气道及肺组织结构功能的损害, 改善呼吸衰竭症状, 降低病情程度和死亡风险^[21-22]; CC16能抑制TGF- β 1/SMAD信号通路, 抑制肺组织纤维化发展, 保护肺组织结构和功能, 进而改善病情和预后^[23,26]。

本研究结果还发现, 年龄增加、重度/极重度气流受限、1年内急性加重次数增加的COPD并发呼吸衰竭患者死亡风险更高, 分析原因: 高龄患者多病共存和肺功能更差, 因此死亡风险更高; 重度/极重度气流受限和1年内急性加重次数增加的患者病情更加严重, 肺功能持续降低, 故死亡风险更高。ROC

曲线显示,血清14-3-3 β ,CC16表达联合预测COPD并发呼吸衰竭患者死亡的AUC大于血清14-3-3 β ,CC16表达单独预测。提示血清14-3-3 β ,CC16表达有助于COPD并发呼吸衰竭患者预后预测,同时检测血清14-3-3 β ,CC16表达能更准确地预测COPD并发呼吸衰竭患者预后。

综上所述,血清14-3-3 β 表达升高和CC16表达降低与COPD并发呼吸衰竭患者病情加重、不良预后有关,血清14-3-3 β ,CC16表达联合检测对COPD并发呼吸衰竭患者死亡有较高的预测价值。但本研究结果仍需进一步多中心研究验证。

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