

· 临床研究 ·

慢性阻塞性肺疾病合并肺动脉高压患者的临床特征与危险因素分析

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【摘要】目的 探讨慢性阻塞性肺疾病(COPD)合并肺动脉高压(PH)患者的临床特征及相关危险因素。**方法** 回顾性分析2015年1月至2016年1月自贡市第四人民医院呼吸科住院COPD患者702例,根据是否并发PH分为PH组279例和无PH组423例,PH组患者根据收缩期肺动脉压(SPAP)又分为轻度PH亚组188例和重度PH亚组91例,分别比较PH组和无PH组以及亚组患者间的体质指数(BMI)、B型脑钠肽(BNP)、红细胞沉降率(ESR)、红细胞压积(HCT)、C-反应蛋白(CRP)、白蛋白(ALB)、氧合指数(OI)、D-二聚体(D-D)、纤维蛋白原(FIB)、乳酸(LA)、第1秒用力呼气末容积(FEV1)和糖类抗原125(CA125)的差异。利用SPSS 18.0统计软件对数据进行分析。组间比较采用 t 检验或 χ^2 检验。Pearson相关分析SPAP的影响因素,采用多因素logistic回归分析危险因素。**结果** PH组患者相比无PH组患者FEV1/预计值 $[(46.4 \pm 16.5)\% \text{ vs } (67.6 \pm 15.4)\%]$ 和OI值 $[(226.7 \pm 56.9) \text{ vs } (352.0 \pm 49.9) \text{ mmHg } (1 \text{ mmHg} = 0.133 \text{ kPa})]$ 下降,BNP $[(575.9 \pm 53.2) \text{ vs } (297.8 \pm 84.8) \text{ pg/ml}]$ 、CA125 $[(39.9 \pm 14.5) \text{ vs } (15.8 \pm 12.2) \text{ U/L}]$ 和SPAP $[(59.2 \pm 16.3) \text{ vs } (30.4 \pm 9.1) \text{ mmHg}]$ 增高,差异具有统计学意义($P < 0.05$)。重度相比轻度PH组患者FEV1/预计值 $[(37.4 \pm 16.7)\% \text{ vs } (59.8 \pm 14.1)\%]$ 和OI值 $[(156.0 \pm 80.5) \text{ vs } (267.7 \pm 98.9) \text{ mmHg}]$ 下降,BNP $[(698.0 \pm 125.6) \text{ vs } (495.9 \pm 118.2) \text{ pg/ml}]$ 、D-D $[(2.9 \pm 1.2) \text{ vs } (1.3 \pm 1.2) \text{ mg/L}]$ 、FIB $[(4.9 \pm 1.4) \text{ vs } (3.7 \pm 1.5) \text{ g/L}]$ 、LA $[(3.5 \pm 1.8) \text{ vs } (1.8 \pm 1.1) \text{ mmol/L}]$ 、CA125 $[(52.8 \pm 38.2) \text{ vs } (32.9 \pm 17.5) \text{ U/L}]$ 和SPAP $[(68.3 \pm 16.1) \text{ vs } (55.2 \pm 14.3) \text{ mmHg}]$ 增高,差异具有统计学意义($P < 0.05$)。Pearson相关分析结果表明SPAP与OI($r = -0.459, P = 0.021$)、FEV1/预计值呈负相关($r = -0.442, P = 0.035$),与BNP($r = 0.507, P = 0.012$)、CA125($r = 0.375, P = 0.048$)和D-D($r = 0.401, P = 0.030$)呈正相关。多因素logistic回归分析结果表明BNP、CA125、D-D、FEV1/预计值和OI是PH的危险因素。**结论** PH是COPD患者常见并发症,检测BNP、CA125、D-D、FEV1/预计值和OI等指标有助于临床诊疗。

【关键词】 慢性阻塞性肺疾病;危险因素;肺动脉高压**【中图分类号】** R563.9**【文献标志码】** A**【DOI】** 10.11915/j.issn.1671-5403.2018.05.083

Clinical features and risk factors of patients with chronic obstructive pulmonary disease complicated with pulmonary hypertension

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【Abstract】 Objective To investigate the clinical features and related risk factors of chronic obstructive pulmonary disease (COPD) complicated with pulmonary hypertension (PH). **Methods** A retrospective analysis was carried out on 702 COPD patients admitted to our department of respiratory diseases from January 2015 to January 2016. According to complicated with PH or not, they were assigned into PH group ($n = 279$) and non-PH group ($n = 423$). The former group was further divided into mild PH subgroup ($n = 188$) and severe PH subgroup ($n = 91$) based on their systolic pulmonary arterial pressure (SPAP). Body mass index (BMI), type B brain natriuretic peptide (BNP), erythrocyte sedimentation rate (ESR), hematocrit (HCT), C-reactive protein (CRP), albumin (ALB), oxygenation index (OI), D-dimer (D-D), fibrinogen (FIB), lactic acid (LA), first second forced expiratory volume (FEV1) and carbohydrate antigen 125 (CA125) were compared between the PH and non-PH groups and between the mild PH and severe PH subgroups. SPSS statistics 18.0 was used to analyze the data. Student's t test or Chi-square test was employed for the comparison between groups. Pearson correlation analysis was used for the influencing factors for SPAP, and multivariate logistic regression analysis for risk factors. **Results** Compared with the non-PH patients, the PH patients had significantly lower FEV1/predictive value $[(46.4 \pm 16.5)\% \text{ vs } (67.6 \pm 15.4)\%]$ and OI $[(226.7 \pm 56.9) \text{ vs } (352.0 \pm 49.9) \text{ mmHg}]$, and increased BNP $[(575.9 \pm 53.2) \text{ vs } (297.8 \pm 84.8) \text{ pg/ml}]$, CA125 $[(39.9 \pm 14.5) \text{ vs } (15.8 \pm 12.2) \text{ U/L}]$ and SPAP $[(59.2 \pm 16.3) \text{ vs } (30.4 \pm 9.1) \text{ mmHg}]$. In severe PH subgroup compared with mild PH subgroup, FEV1/predictive value $[(37.4 \pm 16.7)\% \text{ vs } (59.8 \pm 14.1)\%]$ and OI $[(156.0 \pm 80.5) \text{ vs } (267.7 \pm 98.9) \text{ mmHg}]$ were lower, BNP $[(698.0 \pm 125.6) \text{ vs } (495.9 \pm 118.2) \text{ pg/ml}]$, D-D $[(2.9 \pm 1.2) \text{ vs } (1.3 \pm 1.2) \text{ mg/L}]$, FIB $[(4.9 \pm 1.4) \text{ vs } (3.7 \pm 1.5) \text{ g/L}]$, LA $[(3.5 \pm 1.8) \text{ vs } (1.8 \pm 1.1) \text{ mmol/L}]$, CA125 $[(52.8 \pm 38.2) \text{ vs } (32.9 \pm 17.5) \text{ U/L}]$ and SPAP $[(68.3 \pm 16.1) \text{ vs } (55.2 \pm 14.3) \text{ mmHg}]$ were higher, and the differences were statistically significant ($P < 0.05$). Pearson correlation analysis showed that SPAP was negatively correlated with OI ($r = -0.459, P = 0.021$) and FEV1/predictive value ($r = -0.442, P = 0.035$), and positively correlated with BNP ($r = 0.507, P = 0.012$), CA125 ($r = 0.375, P = 0.048$) and D-D ($r = 0.401, P = 0.030$). Multivariate logistic regression analysis showed that BNP, CA125, D-D, FEV1/predictive value and OI were risk factors for PH. **Conclusion** PH is a common complication of COPD, and the detection of BNP, CA125, D-D, FEV1/predictive value and OI can help clinical diagnosis.

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(297.8 ± 84.8) pg/ml], CA125 [(39.9 ± 14.5) vs (15.8 ± 12.2) U/L] and SPAP [(59.2 ± 16.3) vs (30.4 ± 9.1) mmHg] (all $P < 0.05$). The ratio of FEV1/predictive value [$(37.4 \pm 16.7)\%$ vs $(59.8 \pm 14.1)\%$] and OI [(156.0 ± 80.5) vs (267.7 ± 98.9) mmHg] were obviously higher, while the levels of BNP [(698.0 ± 125.6) vs (495.9 ± 118.2) pg/ml], D-D [(2.9 ± 1.2) vs (1.3 ± 1.2) mg/L], FIB [(4.9 ± 1.4) vs (3.7 ± 1.5) g/L], LA [(3.5 ± 1.8) vs (1.8 ± 1.1) mmol/L], CA125 [(52.8 ± 38.2) vs (32.9 ± 17.5) U/L], and SPAP [(68.3 ± 16.1) vs (55.2 ± 14.3) mmHg] were elevated in the severe PH group than the mild PH group (all $P < 0.05$). Pearson correlation analysis showed that SPAP was negatively correlated with OI ($r = -0.459$, $P = 0.021$) and FEV1/predictive value ($r = -0.442$, $P = 0.035$), and positively correlated with BNP ($r = 0.507$, $P = 0.012$), CA125 ($r = 0.375$, $P = 0.048$) and D-D ($r = 0.401$, $P = 0.030$). Multivariate logistic regression analysis indicated that BNP, CA125, D-D, FEV1/predictive value and OI were risk factors for PH. **Conclusion** PH is a common complication of COPD. The detection of BNP, CA125, D-D, FEV1/predictive value and OI is helpful to its diagnosis and treatment.

[Key words] chronic obstructive pulmonary disease; risk factors; pulmonary hypertension

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慢性阻塞性肺疾病 (chronic obstructive pulmonary disease, COPD) 是目前发病率和病死率极高的慢性呼吸系统疾病, 而肺动脉高压 (pulmonary hypertension, PH) 是 COPD 患者并发症之一, 它可导致患者住院时间延长以及病死率上升, 本研究旨在探讨 COPD 患者合并 PH 患者的临床特征及危险因素。

1 对象与方法

1.1 研究对象

回顾性分析 2015 年 1 月至 2016 年 1 月自贡市第四人民医院呼吸科住院 COPD 患者 702 例, 根据是否并发 PH 分为 PH 组 279 例和无 PH 组 423 例, 其中 PH 组男性 255 例, 女性 24 例, 年龄 $40 \sim 88$ (64.4 ± 23.8) 岁; 无 PH 组男性 380 例, 女性 43 例, 年龄 $41 \sim 84$ (61.5 ± 20.1) 岁。纳入标准: 符合《中国 COPD 诊治指南 (2013 年修订版)》COPD 诊断标准^[1]。超声心动图显示患者有 PH, 病程 $5 \sim 30$ 年。排除标准: 肺栓塞、间质性肺病、特发性肺动脉高压 (idiopathic pulmonary arterial hypertension, IPAH)、左心疾病、活动性肺结核、免疫缺陷性疾病以及先天性心脏病等。世界卫生组织定义 PH 为收缩期肺动脉压 (systolic pulmonary arterial pressure, SPAP) > 40 mmHg ($1 \text{ mmHg} = 0.133 \text{ kPa}$, 彩色多普勒超声三尖瓣反流速度 $> 3.0 \text{ m/s}$)^[2-4]。PH 组患者根据 SPAP 值又分为轻度 PH 亚组 188 例 ($40 \text{ mmHg} < \text{SPAP} \leq 60 \text{ mmHg}$) 和重度 PH 亚组 ($\text{SPAP} > 60 \text{ mmHg}$) 91 例。其中轻度 PH 亚组男性 170 例, 女性 18 例, 重度 PH 亚组男性 85 例, 女性 6 例。

1.2 监测指标

收集患者性别、年龄、体质量指数 (body mass index, BMI)、B 型脑钠肽 (type B brain natriuretic peptide, BNP)、红细胞沉降率 (erythrocyte sedimenta-

tion rate, ESR)、红细胞压积 (hematocrit, HCT)、C-反应蛋白 (C-reactive protein, CRP)、白蛋白 (albumin, ALB)、氧合指数 (oxygenation index, OI)、D-二聚体 (D-dimer, D-D)、纤维蛋白原 (fibrinogen, FIB)、乳酸 (lactic acid, LA)、第 1 秒用力呼气末容积 (first second forced expiratory volume, FEV1)、糖类抗原 125 (carbohydrate antigen 125, CA125) 以及超声心动图检查结果。

1.3 统计学处理

利用 SPSS 18.0 统计软件对数据进行分析。计量资料用均数 $\pm$ 标准差 ($\bar{x} \pm s$) 表示, 2 组比较采用 t 检验。计数资料用百分率表示, 组间比较用 χ^2 检验。Pearson 相关分析 SPAP 的影响因素, 采用多因素 logistic 回归分析危险因素。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 PH 组和无 PH 患者临床特征比较

PH 组和无 PH 组患者 BMI、HCT、ALB、CRP、ESR、D-D、FIB 和 LA 差异无统计学意义 ($P > 0.05$)。相比无 PH 组患者, PH 组患者 FEV1/预计值和 OI 值下降, BNP、CA125 和 SPAP 值增高, 差异具有统计学意义 ($P < 0.05$; 表 1)。

2.2 轻度和重度 PH 组患者临床特征比较

轻度和重度 PH 组患者 BMI、HCT、ALB、CRP 和 ESR 差异无统计学意义 ($P > 0.05$)。相比轻度 PH 组患者, 重度 PH 组患者 FEV1/预计值和 OI 值下降, BNP、D-D、FIB、LA、CA125 和 SPAP 值增高, 差异具有统计学意义 ($P < 0.05$; 表 2)。

2.3 Pearson 相关分析 SPAP 的影响因素

Pearson 相关分析结果表明 SPAP 与 OI ($r = -0.459$, $P = 0.021$)、FEV1/预计值呈负相关 ($r = -0.442$, $P = 0.035$), 与 BNP ($r = 0.507$, $P = 0.012$)、CA125

($r=0.375, P=0.048$) 和 D-D($r=0.401, P=0.030$) 呈正相关。

2.4 多因素 logistic 回归分析

以是否存在 PH 为因变量,以年龄、BNP、ESR、

CRP、OI、D-D、FIB、CA125、FEV1/预计值、BMI、HCT、LA 为自变量建立 logistic 回归模型,结果表明 BNP、CA125、D-D、FEV1/预计值和 OI 是 PH 的危险因素,具体结果见表 3。

表 1 PH 和无 PH 组患者临床特征比较

Table 1 Comparison of clinical characteristics between PH and non-PH groups

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

Item	PH group ($n=279$)	Non-PH group ($n=423$)	t/χ^2	P value
FEV1/predictive value(%)	46.4 ± 16.5	67.6 ± 15.4	2.518	0.012
BMI(kg/m ²)	21.6 ± 5.4	22.8 ± 6.7	1.189	0.235
HCT(%)	50.8 ± 10.6	43.5 ± 12.3	1.320	0.187
ALB(g/L)	30.4 ± 5.9	31.7 ± 7.7	0.303	0.762
BNP(pg/ml)	575.9 ± 53.2	297.8 ± 84.8	4.054	0.000
CRP(mg/L)	49.1 ± 19.5	57.2 ± 27.1	1.134	0.257
ESR(mm/h)	54.0 ± 20.4	42.6 ± 30.9	1.413	0.158
OI(mmHg)	226.7 ± 56.9	352.0 ± 49.9	2.816	0.005
D-D(mg/L)	1.9 ± 0.7	0.6 ± 0.5	1.714	0.087
FIB(g/L)	4.2 ± 1.1	3.5 ± 1.2	1.692	0.091
LA(mmol/L)	2.4 ± 2.2	1.7 ± 1.4	1.309	0.191
CA125(U/L)	39.9 ± 14.5	15.8 ± 12.2	3.102	0.002
SPAP(mmHg)	59.2 ± 16.3	30.4 ± 9.1	3.962	0.000

PH: pulmonary hypertension; FEV1: first second forced expiratory volume; BMI: body mass index; HCT: hematocrit; ALB: albumin; BNP: type B brain natriuretic peptide; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; OI: oxygenation index; D-D: D-dimer; FIB: fibrinogen; LA: lactic acid; CA125: carbohydrate antigen 125; SPAP: systolic pulmonary arterial pressure. 1 mmHg = 0.133 kPa

表 2 轻度和重度 PH 组患者临床特征比较

Table 2 Comparison of clinical characteristics between mild and severe PH groups

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

Item	Mild PH group ($n=188$)	Severe PH group ($n=91$)	t/χ^2	P value
FEV1/predictive value(%)	59.8 ± 14.1	37.4 ± 16.7	2.994	0.003
BMI(kg/m ²)	22.6 ± 2.1	21.9 ± 1.8	0.235	0.814
HCT(%)	38.6 ± 10.0	46.5 ± 8.9	1.594	0.112
ALB(g/L)	31.5 ± 7.2	29.0 ± 6.8	0.846	0.398
BNP(pg/ml)	495.9 ± 118.2	698.0 ± 125.6	4.817	0.000
CRP(mg/L)	47.8 ± 16.3	51.6 ± 15.5	1.219	0.224
ESR(mm/h)	53.3 ± 19.7	55.6 ± 28.2	0.501	0.617
OI(mmHg)	267.7 ± 98.9	156.0 ± 80.5	4.933	0.000
D-D(mg/L)	1.3 ± 1.2	2.9 ± 1.2	2.063	0.040
FIB(g/L)	3.7 ± 1.5	4.9 ± 1.4	2.155	0.032
LA(mmol/L)	1.8 ± 1.1	3.5 ± 1.8	2.208	0.028
CA125(U/L)	32.9 ± 17.5	52.8 ± 38.2	2.074	0.039
SPAP(mmHg)	55.2 ± 14.3	68.3 ± 16.1	4.283	0.000

PH: pulmonary hypertension; FEV1: first second forced expiratory volume; BMI: body mass index; HCT: hematocrit; ALB: albumin; BNP: type B brain natriuretic peptide; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; OI: oxygenation index; D-D: D-dimer; FIB: fibrinogen; LA: lactic acid; CA125: carbohydrate antigen 125; SPAP: systolic pulmonary arterial pressure. 1 mmHg = 0.133 kPa

表 3 多因素 logistic 回归分析 PH 影响因素

Table 3 Multivariate logistic regression analysis of factors influencing PH

Factor	β	SE	$Wald$	$OR(95\% CI)$	P value
BNP	0.276	0.119	2.326	1.342(1.057 - 1.690)	0.020
OI	-0.375	0.149	-2.512	0.473(0.112 - 0.926)	0.012
D-D	0.076	0.038	2.014	1.605(1.011 - 2.235)	0.044
CA125	0.256	0.119	2.157	1.042(1.003 - 2.073)	0.031
FEV1/predictive value	-0.298	0.120	-2.483	0.532(0.103 - 1.086)	0.013

PH: pulmonary hypertension; BNP: type B brain natriuretic peptide; OI: oxygenation index; D-D: D-dimer; CA125: carbohydrate antigen 125; FEV1: first second forced expiratory volume

3 讨 论

本研究分析的均是住院患者,不包括非住院患者,且均采用多普勒超声诊断仪计算肺动脉压力,未能行右心导管检查,因此 COPD 合并 PH 患者的比例为 39.7% (279/702),高于 Cuttica 等^[5]通过右心导管评估得出的 30.4% 及 Gologanu 等^[6]通过彩色多普勒超声评估得出的 36.7%。

COPD 合并 PH 患者早期无明显临床表现,仅有血流动力学改变,随着疾病进展,患者逐渐出现呼吸困难^[7,8]。目前研究表明长期大量吸烟、持续性气道慢性炎症和低氧血症等可造成肺血管损伤、收缩、形成血栓和重塑,从而使肺动脉内膜增厚,平滑肌细胞增生,毛细血管缺失,细胞外基质合成及沉积,最终进展为 PH^[9]。严重时造成右心室肥厚及扩张,右心负荷增加可使 BNP 代偿性分泌增加,最终导致慢性肺源性心脏病发生^[10]。Chen 等^[11]发现 COPD 合并 PH 患者 BNP 值显著高于单纯 COPD 患者,且与 PH 的严重程度相关,这与我们的研究结果一致。

CA125 属于膜结合型黏蛋白,呼吸道杯状上皮细胞和黏膜下黏液腺细胞可分泌。气道炎症可促使杯状上皮细胞增生和黏液腺细胞增生,从而导致 CA125 合成和分泌增加^[12]。研究表明 COPD 患者血清 CA125 值高于健康人群^[13]。同时研究亦证实,COPD 合并 PH 患者体内炎症因子的水平更高^[14]。本研究表明 COPD 合并 PH 患者 CA125 值明显高于无 PH 患者,且随 PH 严重程度增加而显著升高,其机制可能与炎症因子过度表达及黏液腺细胞合成与分泌 CA125 增加有关。

D-D 是纤维蛋白降解的最终衍生物之一,是机体呈高凝状态及纤溶系统亢进的标志。研究表明 COPD 患者血液处于高凝状态,合并 PH 时则更突出^[15],其机制可能与患者肺血管微小血栓形成有关^[16]。亦有研究表明上述机制可能是 PH 形成和发展的重要因素^[17]。本研究亦表明重度 PH 组比轻度 PH 组患者 D-D 值高,这可能预示患者的危险程度。总之,COPD 合并 PH 患者治疗时间长,预后差,动态检测和评估患者的 BNP、CA125、D-D、FEV1/预计值和 OI 对临床诊疗具有一定的指导意义。

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· 消 息 ·

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示例:

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