

· 临床研究 ·

盐酸氨溴索对老年肺炎患者氧合指数、D-二聚体和炎症指标的影响及对患者预后的预测效能

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【摘要】目的 探讨盐酸氨溴索对老年肺炎患者氧合指数、D-D聚体(D-D)和炎症指标的影响及对患者预后的预测效能。**方法** 选取2022年1月至2023年1月首都医科大学附属北京朝阳医院全科医学科收治的226例老年肺炎患者为研究对象。采用随机数字表法将患者分为对照组和盐酸氨溴索组各113例。去除脱落及换组病例后,两组最终各纳入患者110例。根据疾病严重程度,将对照组分为重症组36例及轻症组74例;盐酸氨溴索组分为重症组38例及轻症组72例。给予对照组吸氧支持、镇静和止咳祛痰等常规治疗方式,盐酸氨溴索组在对照组基础上给予盐酸氨溴索静脉滴注。观察各组患者治疗效果以及治疗前后氧合指数、D-D、C反应蛋白(CRP)和降钙素原(PCT)水平。采用受试者工作特征(ROC)曲线分析各指标的预测效能。使用Kaplan-Meier曲线绘制患者生存曲线。**结果** 盐酸氨溴索组治疗总有效率显著高于对照组,差异有统计学意义[98(89.09%)和78(70.91%);P<0.05]。与治疗前相比,治疗后对照组及盐酸氨溴索组的轻症患者氧合指数均显著升高[(275.69±27.82)和(153.26±11.89)mmHg, (297.19±23.53)和(156.87±12.47)mmHg],D-D水平平均显著降低[(1.79±0.66)和(2.43±0.91)mg/L,(1.34±0.47)和(2.41±0.88)mg/L];重症患者氧合指数均显著升高[(257.58±25.19)和(126.33±12.19)mmHg, (279.51±27.02)和(127.83±13.53)mmHg],D-D水平平均显著降低[(1.93±0.73)和(2.56±0.78)mg/L,(1.77±0.59)和(2.61±0.79)mg/L]。且盐酸氨溴索组轻症及重症患者氧合指数分别显著高于对照组轻症及重症患者[(297.19±23.53)和(275.69±27.82)mmHg,(279.51±27.02)和(257.58±25.19)mmHg],D-D水平分别显著低于对照组轻症及重症患者[(1.34±0.47)和(1.79±0.66)mg/L,(1.77±0.59)和(1.93±0.73)mg/L],差异均有统计学意义(均P<0.05)。与治疗前相比,治疗后对照组及盐酸氨溴索组轻症患者CRP[(54.35±9.27)和(87.55±8.19)mg/L,(41.56±9.57)和(88.49±9.17)mg/L]和PCT[(0.99±0.37)和(1.89±0.52)μg/L,(0.53±0.21)和(1.90±0.49)μg/L]水平均显著降低。且盐酸氨溴索组轻症和重症患者CRP[(41.56±9.57)和(54.35±9.27)mg/L,(55.12±7.58)和(60.58±9.82)mg/L]及PCT[(0.53±0.21)和(0.99±0.37)μg/L,(0.75±0.25)和(1.12±0.55)μg/L]水平分别显著低于对照组轻症和重症患者,差异均有统计学意义(均P<0.05)。对患者行28d的随访发现,盐酸氨溴索组患者28d累计生存率89.09%(98/110)显著高于对照组69.09%(76/110),差异有统计学意义(P<0.001)。氧合指数、D-D水平联合炎症指标CRP、PCT评估老年肺炎患者预后的ROC曲线下面积为0.837,灵敏度为88.50,特异度为78.30。**结论** 盐酸氨溴索可提升老年肺炎患者的治疗效果,显著改善患者的氧合指数、D-D水平、炎症指标和预后生存率。氧合指数、D-D水平联合炎症指标CRP、PCT对患者预后有较高的预测价值,临床可进一步推广应用。

【关键词】 老年人;肺炎;盐酸氨溴索;氧合指数;D-二聚体;炎症反应;预后;预测效能

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Effect of ambroxol hydrochloride on oxygenation index, D-dimer and inflammation index in elderly patients with pneumonia and its predictive efficiency for patients' prognosis

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【Abstract】 Objective To explore the influence of ambroxol hydrochloride on oxygenation index, D-D and inflammatory indexes in elderly patients with pneumonia, and its predictive efficiency for prognosis of the patients. **Methods** A total of 226 elderly pneumonia patients admitted to the General Practice Department of Beijing Chaoyang Hospital Affiliated to Capital Medical University from January 2022 to January 2023 were enrolled and randomly divided into a control group and an ambroxol hydrochloride group, with 113 cases in each group. After exclusion and grouping modification, 110 patients were eventually included in each of the two groups.

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According to the severity of the disease, the control group was assigned into severe and mild subgroups (36 and 74 cases, respectively), and the ambroxol hydrochloride group also into severe and mild subgroups (38 and 72 cases, respectively). The control group was given routine treatments such as oxygen inhalation support, sedation, cough relieving and phlegm relieving, while the ambroxol hydrochloride group was given intravenous injection of ambroxol hydrochloride on the basis of routine treatments. The effective rate, as well as oxygenation index, and D-D, C-reactive protein (CRP) and procalcitonin (PCT) levels before and after treatment were observed in the two groups. Receiver operating characteristic (ROC) curve was plotted to analyze the predictive performance of each indicator. Kaplan-Meier curve was drawn to analyze the survival of these patients. **Results** The total effective rate was significantly higher in the ambroxol hydrochloride group than the control group [89.09% (98/110) vs 70.91% (78/110); $P < 0.05$]. When compared to the levels before treatment, the patients from the two mild subgroups of the control and ambroxol hydrochloride groups obtained significantly higher oxygenation index [(275.69±27.82) vs (153.26±11.89) mmHg, (297.19±23.53) vs (156.87±12.47) mmHg] and lower D-D level [(1.79±0.66) vs (2.43±0.91) mg/L, (1.34±0.47) vs (2.41±0.88) mg/L] after treatment; and those of the two severe subgroups had obviously increased oxygenation index [(257.58±25.19) vs (126.33±12.19) mmHg, (279.51±27.02) vs (127.83±13.53) mmHg] and decreased D-D level [(1.93±0.73) vs (2.56±0.78) mg/L, (1.77±0.59) vs (2.61±0.79) mg/L]. Ambroxol hydrochloride treatment resulted in statistically higher oxygenation index [(297.19±23.53) vs (275.69±27.82) mmHg, (279.51±27.02) vs (257.58±25.19) mmHg] and lower D-D level [(1.34±0.47) vs (1.79±0.66) mg/L, (1.77±0.59) vs (1.93±0.73) mg/L] in either mild or severe patients ($P < 0.05$). Both routine and ambroxol hydrochloride treatment decreased CRP [(54.35±9.27) vs (87.55±8.19) mg/L, (41.56±9.57) vs (88.49±9.17) mg/L] and PCT [(0.99±0.37) vs (1.89±0.52) µg/L, (0.53±0.21) vs (1.90±0.49) µg/L] levels in the two mild subgroups, and the ambroxol hydrochloride group obtained more lower CRP [(41.56±9.57) vs (54.35±9.27) mg/L, (55.12±7.58) vs (60.58±9.82) mg/L] and PCT [(0.53±0.21) vs (0.99±0.37) µg/L, (0.75±0.25) vs (1.12±0.55) µg/L] levels in both mild and severe patients than the control group (all $P < 0.05$). After the follow-up of 28 d, the cumulative survival rate was notably higher in the ambroxol hydrochloride group than the control group [89.09% (98/110) vs 69.09% (76/110), $P < 0.001$]. The area under the ROC curve of oxygenation index, D-D level, combined with inflammatory markers CRP and PCT for prognosis of elderly pneumonia patients was 0.837, with a sensitivity of 88.50 and a specificity of 78.30. **Conclusion** Ambroxol hydrochloride can promote the treatment effectiveness in elderly pneumonia patients, significantly improving their oxygenation index, D-D level, inflammatory indicators, and survival rate. The combination of oxygenation index and D-D, CRP and PCT levels has high predictive value for patient prognosis, and can be further promoted and applied in clinical practice.

[Key words] aged; pneumonia; ambroxol hydrochloride; oxygenation index; D-dimer; inflammatory response; prognosis; predictive efficiency

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肺炎在老年群体中较为常见,是机体的一种炎症反应,主要病因包括病毒、真菌和细菌感染,具有发病急和发展快的特点^[1]。随着我国老龄化进程的加快,老年肺炎的发病率呈现逐年上升趋势,对患者的生命安全造成严重威胁^[2]。肺炎的发生与炎症反应密切相关,因此临床对老年肺炎患者治疗的关键为缓解炎症^[3]。此外,部分患者在炎症反应介质及低氧环境的影响下,氧合指数明显降低,血管内皮细胞受到损害,激活机体凝血指标D-二聚体(D-dimer,D-D),导致患者出现凝血功能障碍,对生命安全造成严重影响^[4,5]。盐酸氨溴索是一种临床常用的呼吸道祛痰剂,有良好的抗炎效果,对患者肺脏起到保护作用^[6,7]。但目前关于盐酸氨溴索治疗老年肺炎的研究主要集中在其疗效和安全性,本研究探讨盐酸氨溴索治疗对老年肺炎患者氧合指数、D-D水平和炎症指标的影响,同时分析上述指标对患者预后的预测价值,以期为改善老年肺炎患者预后提供依据。

1 对象与方法

1.1 研究对象

选取2022年1月至2023年1月首都医科大学

附属北京朝阳医院全科医学科收治的226例老年肺炎患者为研究对象。纳入标准:(1)符合肺炎诊断标准^[8],存在发热、呼吸困难等症状;(2)经X线胸片检查、痰培养确诊为肺炎;(3)年龄≥60岁;(4)临床资料完整;(5)签署知情同意书。排除标准:(1)合并严重心肺功能疾病;(2)有盐酸氨溴索过敏史;(3)合并血液系统或免疫疾病;(4)入院48 h内死亡;(5)精神异常,无法正常沟通交流;(6)未行X线和痰培养等相关检查。采用随机数字表法将患者分为对照组和盐酸氨溴索组各113例。治疗过程中对照组2例因病情改善较差退组,1例因病情未得到有效改善进入盐酸氨溴索组治疗;盐酸氨溴索组中3例因个人原因转院。去除脱落及换组病例,两组最终各纳入患者110例。根据疾病严重程度,将对照组分为重症组36例及轻症组74例;盐酸氨溴索组分为重症组38例及轻症组72例。本研究经首都医科大学附属北京朝阳医院医学伦理委员会审核并批准(伦理审批号:20210378)。

1.2 方法

1.2.1 治疗方法 对照组给予常规治疗方式。首

先使患者呼吸道保持清洁状态。随后给予患者吸氧支持、镇静和止咳祛痰等治疗，并根据患者实际情况，针对性应用抗生素或抗病毒药物，必要时给予机械通气。盐酸氨溴索组在对照组基础上给予盐酸氨溴索(生产厂家：北京大洋药业，批准文号：国药准字H20010482)静脉滴注。剂量：轻症患者15 mg/次，2~3次/d；重症患者30 mg/次，3次/d。所有患者均进行14 d治疗。出院后，对所有患者行28 d随访，将28 d生存作为预后评估指标。

1.2.2 血清检测 (1)凝血象测定。取患者静脉血2 ml，放入枸橼酸钠抗凝采血管，并行离心处理(离心半径10 cm, 3 500转/min离心10 min)。抗凝分离血浆后低温保存待用，选用全自动凝血分析仪(厂家：武汉医盾医疗器械有限公司，型号：RAC-030)测定D-D水平。(2)炎症指标检测。抽取患者清晨空腹状态下肘静脉血5 ml(离心半径5 cm, 3 500 r/min离心10 min)，取血清待测。采用免疫比浊法酶联免疫吸附试验(enzyme linked immunosorbent assay, ELISA)试剂盒检测C反应蛋白(C-reactive protein, CRP)及降钙素原(procalcitonin, PCT)，操作步骤严格按照试剂盒说明书进行，试剂盒均购自上海西唐生物。(3)氧合指数。以呼吸监测仪(厂家：河南华南医电科技有限公司，型号：6-Y-6620)监测患者氧合指数。

1.3 疗效判定

参考Mahmoodpoor等^[9]学者制定的疗效标准。显效：测量体温正常，咳嗽和肺部喘鸣音消失，胸部X线检查示阴影面积缩小范围≥75%；有效：体温恢复正常，咳嗽和肺部喘鸣音症状仍存在但有明显好转，胸部X线检查示阴影面积缩小范围≥60%；无效：未达到上述标准。总有效率(%)=(显效+有效)例数/总例数×100%。

1.4 统计学处理

采用SPSS 26.0统计软件进行数据分析。对计量资料行正态和方差齐性检验，均符合正态分布，以均数±标准差($\bar{x}\pm s$)表示，组间比较采用独立样本t检验，组内比较采用配对样本t检验。计数资料以例数(百分率)表示，组间比较采用 χ^2 检验。采用受试者工作特征(receiver operating characteristic, ROC)曲线分析各指标的预测效能。绘制Kaplan-Meier曲线对比对照组及盐酸氨溴索组患者28 d累计生存率。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 两组患者基线资料比较

两组患者性别、年龄、体质量指数、合并症、疾病

严重程度以及肺炎类型比较，差异均无统计学意义(均 $P>0.05$ ；表1)。

表1 两组患者基线资料比较

Table 1 Comparison of baseline data between two groups
(n=110)

Item	Control group	Ambroxol hydrochloride group	t/ χ^2	P value
Gender[n(%)]			0.308	0.579
Male	70(63.64)	66(60.00)		
Female	40(36.36)	44(40.00)		
Age (years, $\bar{x}\pm s$)	72.26±8.15	73.59±8.73	-1.168	0.244
BMI(kg/m ² , $\bar{x}\pm s$)	22.69±3.17	22.85±3.24	-0.370	0.712
Complication[n(%)]			0.087	0.769
COPD	32(29.09)	34(30.91)		
Diabetes mellitus	46(41.82)	48(43.64)		
Hypertension	32(29.09)	28(25.45)		
Disease severity[n(%)]			0.081	0.775
Severe	36(32.73)	38(34.55)		
Mild	74(67.27)	72(65.45)		
Type of pneumonia[n(%)]			0.073	0.787
Bacterial pneumonia	58(52.73)	56(50.91)		
Viral pneumonia	52(47.27)	54(49.09)		

BMI：body mass index；COPD：chronic obstructive pulmonary disease.

2.2 两组患者治疗效果比较

盐酸氨溴索组治疗总有效率显著高于对照组，差异有统计学意义($\chi^2=11.364, P<0.05$ ；表2)。

表2 两组患者治疗效果比较

Table 2 Comparison of therapeutic efficacy between two groups
[n=110, n(%)]

Group	Remarkable	Effective	Invalid	Total efficiency
Control	34(30.91)	44(40.00)	32(29.09)	78(70.91)
Ambroxol hydrochloride	58(52.73)	40(36.36)	12(10.91)	98(89.09)

2.3 两组患者治疗前后氧合指数和D-D水平比较

与治疗前相比，治疗后对照组及盐酸氨溴索组的轻症患者和重症患者氧合指数均显著升高，D-D水平均显著降低。盐酸氨溴索组轻症和重症患者氧合指数分别显著高于对照组轻症和重症患者，D-D水平分别显著低于对照组轻症和重症患者，差异均有统计学意义(均 $P<0.05$ ；表3)。

2.4 两组患者治疗前后炎症指标比较

与治疗前相比，治疗后对照组及盐酸氨溴索组轻症患者CRP和PCT水平较治疗前均显著降低，且盐酸氨溴索组轻症和重症患者CRP及PCT水平分别显著低于对照组轻症和重症患者，差异均有统计学意义(均 $P<0.05$ ；表4)。

表3 两组患者治疗前后氧合指数和D-D水平对比

Table 3 Comparison of oxygenation index and D-D level between two groups before and after treatment ($\bar{x} \pm s$)

Group	n	Oxygenation index(mmHg)		D-D(mg/L)	
		Before treatment	After treatment	Before treatment	After treatment
Control					
Mild	74	153. 26±11. 89	275. 69±27. 82 *	2. 43±0. 91	1. 79±0. 66 *
Severe	36	126. 33±12. 19	257. 58±25. 19 *	2. 56±0. 78	1. 93±0. 73 *
Ambroxol hydrochloride					
Mild	72	156. 87±12. 47	297. 19±23. 53 *#	2. 41±0. 88	1. 34±0. 47 *#
Severe	38	127. 83±13. 53	279. 51±27. 02 *#	2. 61±0. 79	1. 77±0. 59 *#

D-D: D-dimer. 1 mmHg=0. 133 kPa. Compared with before treatment, * $P<0. 05$; compared with control group, # $P<0. 05$.

表4 2组患者治疗前后炎症指标比较

Table 4 Comparison of inflammatory indexes between two groups before and after treatment ($\bar{x} \pm s$)

Group	n	CRP(mg/L)		PCT($\mu\text{g}/\text{L}$)	
		Before treatment	After treatment	Before treatment	After treatment
Control					
Mild	74	87. 55±8. 19	54. 35±9. 27 *	1. 89±0. 52	0. 99±0. 37 *
Severe	36	91. 29±9. 37	60. 58±9. 82	2. 20±0. 47	1. 12±0. 55
Ambroxol hydrochloride					
Mild	72	88. 49±9. 17	41. 56±9. 57 *#	1. 90±0. 49	0. 53±0. 21 *#
Severe	38	90. 18±9. 68	55. 12±7. 58 #	2. 19±0. 43	0. 75±0. 25 #

CRP: C-reactive protein; PCT: procalcitonin. Compared with before treatment, * $P<0. 05$; compared with control group, # $P<0. 05$.

2.5 两组患者28d累计生存率的Kaplan-Meier曲线分析

盐酸氨溴索组患者28 d 累计生存率89. 09% (98/110) 显著高于对照组患者69. 09% (76/110), 差异有统计学意义($\chi^2 = 13. 303, P<0. 001$; 图1)。

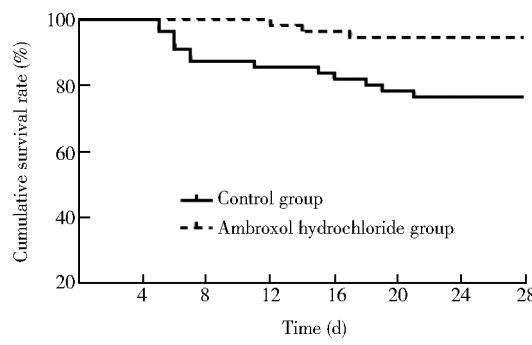


图1 两组患者28d累计生存率的Kaplan-Meier曲线

Figure 1 Kaplan-Meier curve of 28-day cumulative survival rate of two groups

2.6 氧合指数、D-D水平联合炎症指标对老年肺炎患者预后的预测价值

氧合指数、D-D水平联合炎症指标CRP、PCT评估老年肺炎患者预后的ROC曲线下面积为

0. 837, 灵敏度为88. 50, 特异度78. 30, 预测价值显著高于单一指标($P<0. 05$; 图2, 表5)。

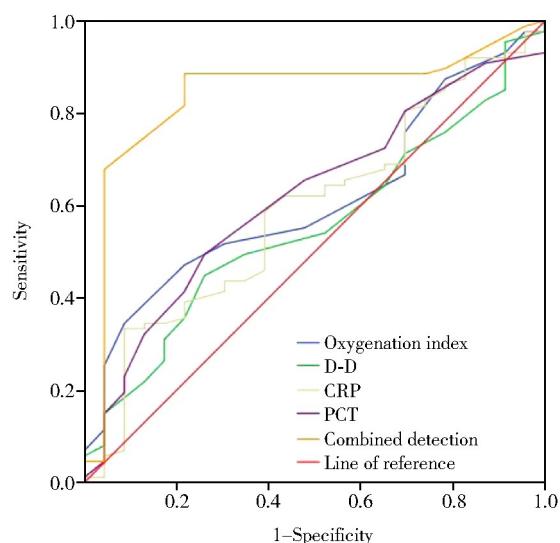


图2 氧合指数、D-D水平联合炎症指标预测老年肺炎患者预后的ROC曲线

Figure 2 ROC curve of oxygenation index, D-D level combined with inflammation index in predicting prognosis of elderly patients with pneumonia

ROC: receiver operating characteristic; D-D: D-dimer;

CRP: C-reactive protein; PCT: procalcitonin.

表5 氧合指数、D-D水平联合炎症指标对老年肺炎患者预后的预测价值

Table 5 Predictive value of oxygenation index, D-D level combined with inflammatory index on prognosis of elderly patients with pneumonia

Factor	Sensitivity	Specificity	Cut-off	AUC	95%CI
Oxygenation index	51.70	69.60	301.65 mmHg	0.611	0.495–0.727
D-D	44.80	73.90	2.21 mg/L	0.552	0.431–0.674
CRP	33.30	80.00	58.50 mg/L	0.590	0.464–0.716
PCT	49.40	73.90	0.73 μg/L	0.619	0.499–0.740
Combined detection	88.50	78.30	–	0.840	0.746–0.933

AUC: area under the curve; D-D: D-dimer; CRP: C-reactive protein; PCT: procalcitonin. 1 mmHg = 0.133 kPa. –: no datum.

3 讨 论

老年肺炎是呼吸内科较为常见的疾病,主要发病于终末气道、肺间质和肺泡。老年患者免疫力相对较低,肺部弹性明显较弱,会降低患者呼吸系统功能和抗病毒能力,导致肺炎的发生^[10]。此外,大部分老年患者常合并基础性疾病,对临床治疗效果及患者预后生存造成影响。因此,对于老年肺炎患者需尽快控制病情,改善肺部功能^[11]。本研究应用盐酸氨溴索对老年肺炎患者进行治疗,探讨盐酸氨溴索对氧合指数、D-D水平、炎症反应与预后的影响,旨在改善老年肺炎患者的临床治疗效果和预后。

本研究发现,经14 d治疗后,盐酸氨溴索组治疗总有效率显著高于对照组,且相较治疗前,治疗后对照组及盐酸氨溴索组轻症和重症患者氧合指数均显著升高,D-D水平均显著降低,盐酸氨溴索组轻症及重症患者氧合指数分别高于对照组轻症及重症患者,D-D水平分别低于对照组轻症及重症患者($P < 0.05$)。提示盐酸氨溴索可提高老年肺炎患者的临床疗效,改善氧合指数及D-D水平。盐酸氨溴索是一种痰液溶解剂,主要作用是保护肺泡组织。盐酸氨溴索联合抗生素使用,可有效提升气道内抗生素活性,强化局部抗菌效果,发挥协同抗菌作用。此外,盐酸氨溴索治疗可增强肺组织和呼吸道细胞活性。肺泡内Ⅱ型细胞受体可分泌大量活性物质,而盐酸氨溴索与其相结合,可降低肺泡张力,改善肺萎缩和肺不张症状,促进纤毛运动并将痰液排出体外,恢复通气和换气功能,改善患者的氧合指数,从而提升肺炎患者的临床治疗效果^[12]。D-D主要反映机体内纤维蛋白的溶解活性,当肺炎发生后,在炎性反应介质和低氧环境刺激下,使凝血系统发生亢奋,从而损伤血管内皮功能,影响纤溶系统运行。而盐酸氨溴索可促进体内纤维蛋白水解,纤维蛋白与D-D

之间存在协同作用,进而使凝血酶的活性增强,改善D-D水平^[13]。

炎症因子在肺炎发生过程中发挥重要作用,CRP和PCT是临床常见的评价肺部感染的炎症指标^[14]。已有研究证实,CRP和PCT对肺炎患者病情和预后具有一定评估价值^[15]。本研究发现,治疗后对照组及盐酸氨溴索组轻症患者CRP和PCT水平较治疗前均显著降低,且盐酸氨溴索组轻症和重症患者CRP及PCT水平分别显著低于对照组轻症和重症患者($P < 0.05$),提示对老年肺炎患者应用盐酸氨溴索治疗,可有效抑制CRP和PCT水平,降低体内炎症反应。分析原因为:虽然常规对症治疗可有效改善老年肺炎患者的临床症状(包括咳痰、发热和咳嗽等),但盐酸氨溴索可诱导肺表面活性物质分泌并提高其生物效能,从而增强老年肺炎患者的机体免疫,抑制机体炎症因子表达^[16]。此外,本研究对患者行28d随访,发现盐酸氨溴索组患者28d累计生存率89.09%(98/110)显著高于对照组患者69.09%(76/110)($P < 0.001$),分析原因为盐酸氨溴索通过刺激支气管腺体发挥吸附黏液作用,从而降低气道和黏液粘附力,使患者呼吸顺畅,降低预后病死率^[17]。在上述研究基础上,本研究还发现氧合指数、D-D水平联合炎症指标CRP、PCT对老年肺炎患者预后有较高的预测价值,可作为老年肺炎患者预后预测方案之一。

综上,盐酸氨溴索可显著改善老年肺炎患者的氧合指数、D-D水平、炎症指标和预后生存率。氧合指数、D-D水平联合炎症指标CRP、PCT对患者预后有较高的预测价值,临床可进一步推广应用。本研究仍存在一定的局限性:本研究纳入患者为单中心样本,代表性不足,结果可能存在一定的偏倚。今后将收集多中心样本,纳入不同类型的肺炎患者,进一步分析盐酸氨溴索治疗老年肺炎的效果及其临床应用价值。

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