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肺表面活性蛋白A在渗出性胸腔积液中的临床应用

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[摘要] 目的: 评估肺表面活性蛋白A(surfactant protein-A, SP-A)在诊断渗出性胸腔积液(exudate pleural effusions, EPE)中的临床应用价值。方法: 采用前瞻性研究, 选取215例胸腔积液患者, 分漏出性胸腔积液(transudate pleural effusions, TPE)和EPE两组, TPE组作为对照组。运用ELISA实验测定并比较胸腔积液中SP-A(pleural effusion SP-A, SP-A^{pl})和血清中SP-A(serum SP-A, SP-A^{se})浓度。运用受试者工作特征(receiver operator characteristic, ROC)曲线及多变量Cox回归研究SP-A在诊断胸腔积液中的临床价值。结果: EPE组SP-A^{pl}浓度明显高于TPE组[(189.8±43.4) ng/mL vs (22.3±5.1) ng/mL, P<0.01]; EPE组SP-A^{se}浓度明显高于TPE组[(78.9±11.3) ng/mL vs (25.8±12.4) ng/mL, P<0.05]; EPE组SP-A^{pl}浓度明显高于SP-A^{se}浓度(P<0.01)。EPE组中肺腺癌患者SP-A^{pl}浓度和SP-A^{se}浓度最高, 且SP-A^{pl}浓度明显高于SP-A^{se}浓度(P<0.01)。当SP-A^{pl}浓度≥484.5 ng/mL时, 诊断肺腺癌的敏感性为85.4%, 特异性为95.2%, 曲线下面积(area under the curve, AUC)为0.943(95% CI: 0.852~0.934, P<0.01); 当SP-A^{se}≥84.2 ng/mL时, 诊断肺腺癌的敏感性为76.4%, 特异性为94.3%, AUC为0.910(95% CI: 0.921~0.953, P<0.01)。结论: SP-A^{pl}浓度≥484.5 ng/mL和/或SP-A^{se}浓度≥84.2 ng/mL有助于诊断肺腺癌性胸腔积液。

[关键词] 肺表面活性蛋白A; 胸腔积液; 敏感性; 特异性; 受试者工作特征曲线

Clinical value of surfactant protein-A in exudate pleural effusion

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ABSTRACT

Objective: To evaluate the clinical value of surfactant protein-A (SP-A) in exudate pleural effusion (EPE).

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Methods: This clinical study was prospective, observational and cross-sectional. Two hundred and fifteen patients with pleural effusion were divided into the transudate pleural effusions (TPE) group and the EPE group. TPE patients served as the control group. The concentrations of pleural effusions SP-A (SP-A^{pl}) and serum SP-A (SP-A^{se}) were measured by ELISA, and receiver operator characteristic (ROC) curve and multivariate Cox analysis of SP-A was analysed for its clinical value.

Results: SP-A^{pl} concentrations in the EPE group were significantly higher than that in the TPE group [(189.8 ± 43.4) ng/mL vs (22.3 ± 5.1) ng/mL, $P < 0.01$]; SP-A^{se} concentrations in the EPE group were higher than that in the TPE group [(78.9 ± 11.3) ng/mL vs (25.8 ± 12.4) ng/mL, $P < 0.05$]; SP-A^{pl} concentrations were significantly higher than the concentrations of SP-A^{se} in the EPE group ($P < 0.01$). In EPE group, SP-A^{pl} and SP-A^{se} concentration in the patients with primary lung adenocarcinomas were the highest. The cut off value of SP-A^{pl} concentrations was more than 484.5 ng/mL, yielding a 85.4% sensitivity and 95.2% specificity for diagnosing primary lung adenocarcinomas, with an area under the curve (AUC) of 0.943 (95% CI 0.852 to 0.934, $P < 0.01$); when SP-A^{se} concentration was more than 84.2 ng/mL, it yielded a 76.4% sensitivity and 94.3% specificity for diagnosing primary lung adenocarcinomas, with an AUC of 0.910 (95% CI 0.921 to 0.953, $P < 0.01$).

Conclusion: While SP-A^{pl} concentration is more than 484.5 ng/mL and/or SP-A^{se} concentration is more than 84.2 ng/mL, it may be helpful for the diagnosis of primary lung adenocarcinomas with the usage of pleural effusion.

KEY WORDS

surfactant protein-A; pleural effusion; sensitivity; specificity; receiver operator characteristic curve

肺表面活性蛋白A(surfactant protein-A, SP-A)是一种主要由肺泡II型细胞和Clara细胞分泌的磷脂相关性糖蛋白, 分子量约35 kD^[1], 参与肺部各种炎症和肿瘤等疾病的发病过程, 是一种较新的生物学标志物。SP-A在肺炎、肺肿瘤、急性肺损伤和间质性肺病等患者的痰液、胸腔积液、血清和支气管肺泡灌洗液中均有一定程度的升高, 并与患者的临床症状、肺功能和影像学特点等有关^[2-3]。目前, 全球原发性肺癌发病率逐年升高, 而原发性肺癌常常累及胸膜导致恶性肿瘤性胸腔积液(malignant cancer pleural effusion, MCPE), 而临幊上要确诊肺或胸腔恶性病变必须行病理活检, 常常给患者带来的一定的痛苦^[4]。原发性肺腺癌是常见肺癌病理类型, SP-A可以作为诊断原发性肺腺癌和肺腺癌性胸腔积液的特征性生物标志物^[2-3]。本研究将评估SP-A在渗出性胸腔积液(exudate pleural effusion, EPE)中的临床诊断应用价值。

1 对象与方法

1.1 对象

采用前瞻性研究的方法, 选取2010年1月1日至2014年12月31日在湖南省人民医院呼吸内科住院治疗

的215例胸腔积液患者, 其中男124例, 女91例, 年龄50~70(69.4 ± 14.5)岁, 分漏出性胸腔积液(transudate pleural effusions, TPE)和EPE两组。其中TPE组为对照组, 共62例, 均为心功能不全性质胸腔积液; EPE组153例, 包括MCPE 85例、结核性胸腔积液(tuberculous pleural effusion, TBPE)46例和细菌性肺炎性胸腔积液(bacterial parapneumonic pleural effusion, BPPE)22例。MCPE 85例包括原发性肺癌72例(肺腺癌26例、鳞癌23例、小细胞肺癌10例、大细胞肺癌6例、肺泡癌7例)和转移性肺癌13例。

TPE诊断标准^[5-6]: 临床症状、病史、胸部X线片, 超声心动图测定左心室射血分数≤40%及应用利尿剂治疗。EPE诊断采用Light标准^[5-7]。MCPE诊断标准为胸水中找到癌细胞。

1.2 方法

1.2.1 血液生化指标检测

入院时血液常规检测腺苷脱氨酶(ADA)、乳酸脱氢酶(LDH)和C-反应蛋白(CRP)。

1.2.2 血清制备

入院时抽取静脉血3 mL, 在4 °C以3 000 g离心10 min后, 将血清分装到干净试管中, 并保存在-80 °C冰箱中, 待测血清SP-A(serum SP-A, SP-A^{se})和血清癌

胚抗原(serum CEA, CEA^{se})。

1.2.3 胸腔积液标本收集

于0.5%利多卡因局麻下行胸腔穿刺术或胸腔闭式引流术, 收集第1次胸腔积液标本, 并分装保存在-20℃冰箱中, 待测胸水SP-A(pleural effusion SP-A, SP-A^{pl})和胸水CEA(pleural effusion CEA, CEA^{pl})。

1.2.4 ELISA

采用ELISA试剂盒(武汉博士德生物工程有限公司), 按试剂盒说明书检测SP-A^{pl}, CEA^{pl}, SP-A^{se}, CEA^{se}浓度。

1.3 统计学处理

采用SPSS 13.0统计学软件分析数据, 数据采用

均数±标准差($\bar{x}\pm s$)表示。计量资料行Mann-Whitney检验和Pearson相关分析, 配对资料行Wilcoxon's检验, 采用秩和检验分析计数资料, 采用 χ^2 检验比较率, 采用受试者工作特征(receiver operator characteristic, ROC)曲线分析计量资料的敏感性和特异性, 采用多变量Cox回归分析影响MCPE患者生存的独立因素。 $P<0.05$ 为差异有统计学意义。

2 结 果

2.1 2组基础资料比较

入院时EPE组患者血LDH, CRP, CEA^{se}和CEA^{pl}明显高于TPE组($P<0.05$ 或 $P<0.01$, 表1)。

表1 TPE组与EPE组患者基础资料比较

Table 1 Comparison of basic data between the EPE and the TPE group

组别	n	男/女	年龄/岁	ADA/(U·mL ⁻¹)	LDH/(U·L ⁻¹)	CRP/(mg·L ⁻¹)	CEA ^{se} /(ng·mL ⁻¹)	CEA ^{pl} /(ng·mL ⁻¹)
TPE组	62	30/32	72.4±12.1	13.6±3.4	135.3±8.2	2.3±0.0	3.5±1.1	4.6±1.5
EPE组	153	85/68	68.6±16.3	17.6±4.1	270.7±8.3**	11.6±1.6*	45.5±7.1**	55.5±7.1**

与TPE组比较, * $P<0.05$, ** $P<0.01$

2.2 2组SP-A^{pl}和SP-A^{se}浓度比较

EPE组SP-A^{pl}浓度明显高于TPE组[(189.8±43.4) ng/mL vs (22.3±5.1) ng/mL, $P<0.01$; 图1A]; EPE组SP-A^{se}浓度明显高于TPE组[(78.9±11.3) ng/mL vs (25.8±12.4) ng/mL, $P<0.05$; 图1B]; EPE组SP-A^{pl}浓度明显高于SP-A^{se}浓度($P<0.01$, 图2)。

2.3 EPE组患者SP-A浓度与临床指标的相关性分析

SP-A^{pl}和SP-A^{se}浓度与年龄和性别比无相关关

系($P>0.05$); SP-A^{pl}和SP-A^{se}浓度与血ADA, LDH, CRP, CEA^{pl}和CES^{se}呈明显正相关($P<0.05$, 表2)。

2.4 EPE组中各类患者SP-A^{pl}和SP-A^{se}浓度比较

EPE组中肺腺癌患者SP-A^{pl}浓度[(512.0±140.0) ng/mL]和SP-A^{se}浓度最高[(63.5±6.2) ng/mL], 且SP-A^{pl}浓度明显高于SP-A^{se}浓度($P<0.01$, 图3)。

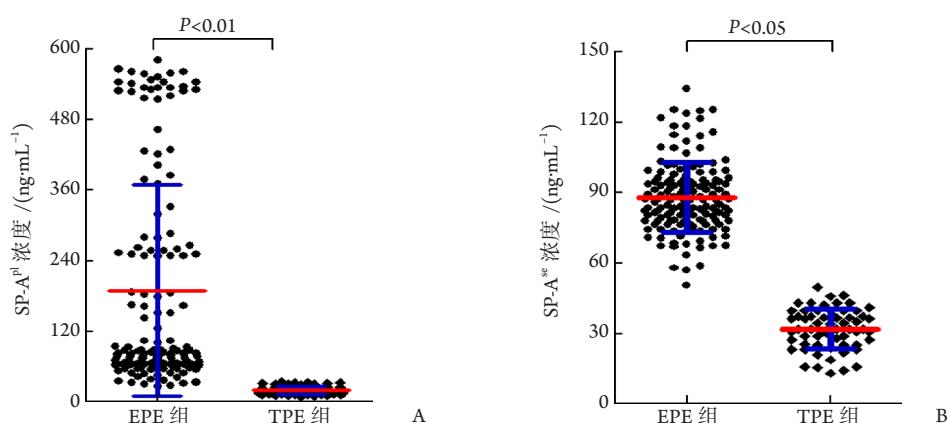


图1 EPE组与TPE组患者SP-A^{pl}浓度(A)和SP-A^{se}浓度(B)比较

Figure 1 Comparison of SP-A^{pl}(A) and SP-A^{se}(B) concentration between the EPE and TPE group

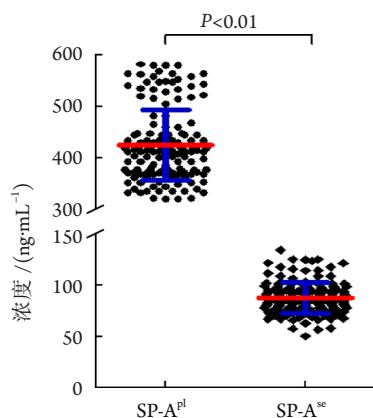
图 2 EPE 组患者 SP-A^{pl} 和 SP-A^{se} 浓度比较

Figure 2 Comparison of SP-A^{pl} and SP-A^{se} concentration of patients in the EPE group

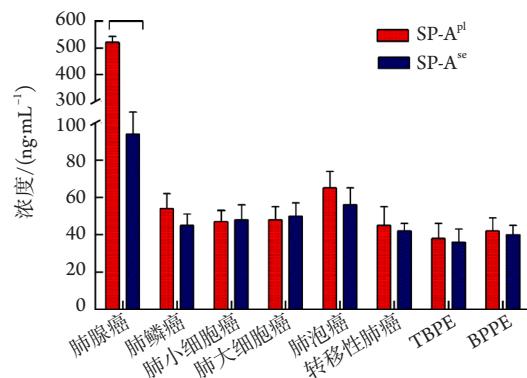
图 3 EPE 组中各类患者 SP-A^{pl} 和 SP-A^{se} 浓度比较

Figure 3 Comparison of SP-A^{pl} and SP-A^{se} concentration in all kinds of EPE patients

表2 EPE组患者SP-A浓度与各临床指标的相关性分析

Table 2 Correlative analysis of SP-A concentration with sex, age and blood biochemical indexes in EPE patients

临床指标	SP-A ^{pl}		SP-A ^{se}	
	r	P	r	P
男/女	0.165	1.854	0.234	1.286
年龄	0.265	1.643	0.231	0.086
ADA	0.721	0.022	0.437	0.025
LDH	0.903	0.002	0.775	0.023
CRP	0.824	0.017	0.573	0.032
CEA ^{pl}	0.919	0.001	0.882	0.026
CEA ^{se}	0.812	0.0002	0.853	0.003

2.5 SP-A 诊断 MCPE 的敏感性和特异性

以TPE组和EPE组中良性胸腔积液患者作为对照, 通过ROC曲线分析SP-A^{pl}和SP-A^{se}浓度诊断MCPE的敏感性和特异性, 并与CEA比较(图4)。当SP-A^{pl}浓度 $\geq 74.6 \text{ ng/mL}$ 时, 诊断MCPE的敏感性为81.4%, 特异性为85.5%, 曲线下面积(area under the curve, AUC)为0.913($P=0.002$, 95%CI: 0.822~0.914); 当SP-A^{se}浓度 $\geq 68.3 \text{ ng/mL}$ 时, 诊断MCPE的敏感性为72.3%, 特异性为90.3%, AUC为0.902($P<0.01$, 95% CI: 0.900~0.912)。SP-A^{pl}和SP-A^{se}浓度诊断MCPE的敏感性均较高, 与CEA^{pl}和CEA^{se}相似。

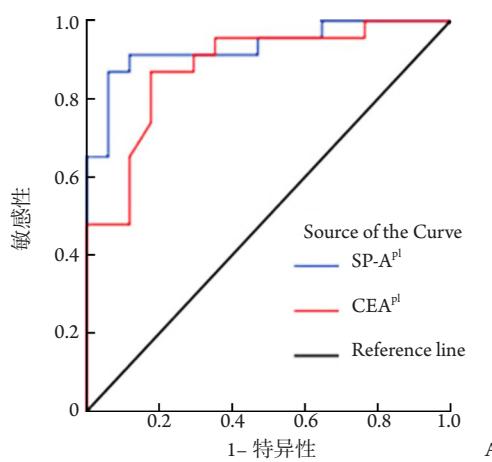
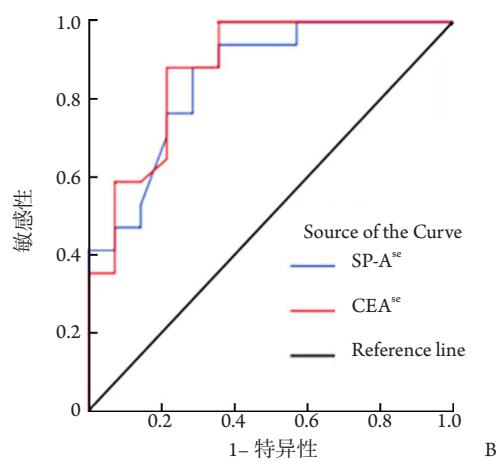
图 4 SP-A^{pl}(A) 和 SP-A^{se}(B) 诊断 MCPE 的敏感性和特异性

Figure 4 Sensitivity and specificity of SP-A^{pl} (A) and SP-A^{se} (B) in the diagnosis of MCPE



2.6 SP-A 诊断肺腺癌的敏感性和特异性

以TPE组和EPE组中非肺腺癌性胸腔积液患者作为对照, 通过ROC曲线分析SP-A^{p1}和SP-A^{s1}浓度诊断肺腺癌中的敏感性和特异性(图5)。当SP-A^{p1}浓度 $\geq 484.5 \text{ ng/mL}$ 时, 诊断肺腺癌的敏感性为85.4%, 特异性为95.2%, AUC为0.943($P<0.01$, 95% CI: 0.852~0.934); 当SP-A^{s1} $\geq 84.2 \text{ ng/mL}$ 时, 诊断肺腺癌的敏感性为76.4%, 特异性为94.3%, AUC为

0.910($P<0.01$, 95% CI: 0.921~0.953)。

2.7 多变量 Cox 回归分析

在85例恶性胸腔积液患者中, SP-A^{p1}浓度 $\geq 484.5 \text{ ng/mL}$ 组患者中位生存时间(24.3周)短于SP-A^{p1}浓度 $<484.5 \text{ ng/mL}$ 组(31.5周, $P=0.056$); SP-A^{s1} $\geq 84.2 \text{ ng/mL}$ 组患者中位生存时间(29.2周)短于SP-A^{s1} $<84.2 \text{ ng/mL}$ 组(42.6周; $P=0.020$, 图6)。

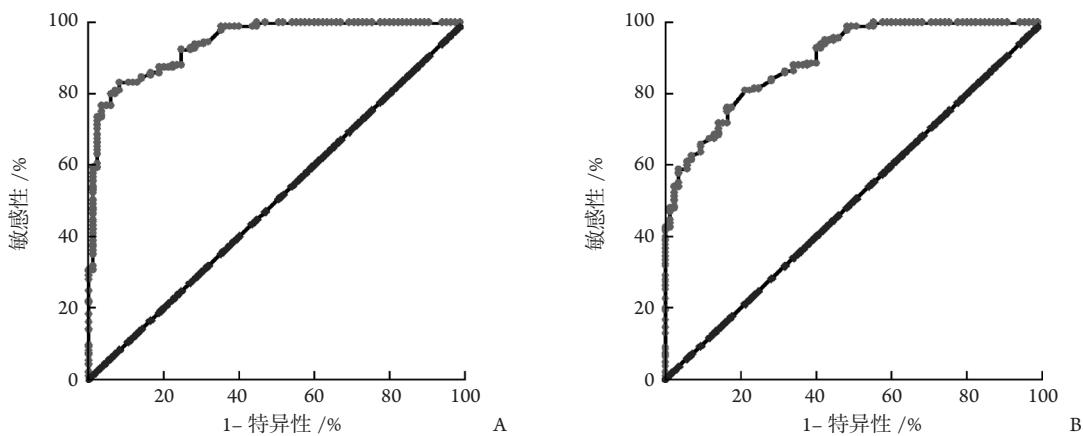


图 5 SP-A^{p1}(A) 和 SP-A^{s1}(B) 诊断肺腺癌的敏感性和特异性

Figure 5 Sensitivity and specificity of SP-A^{p1} (A) and SP-A^{s1} (B) in the diagnosis of lung adenocarcinoma

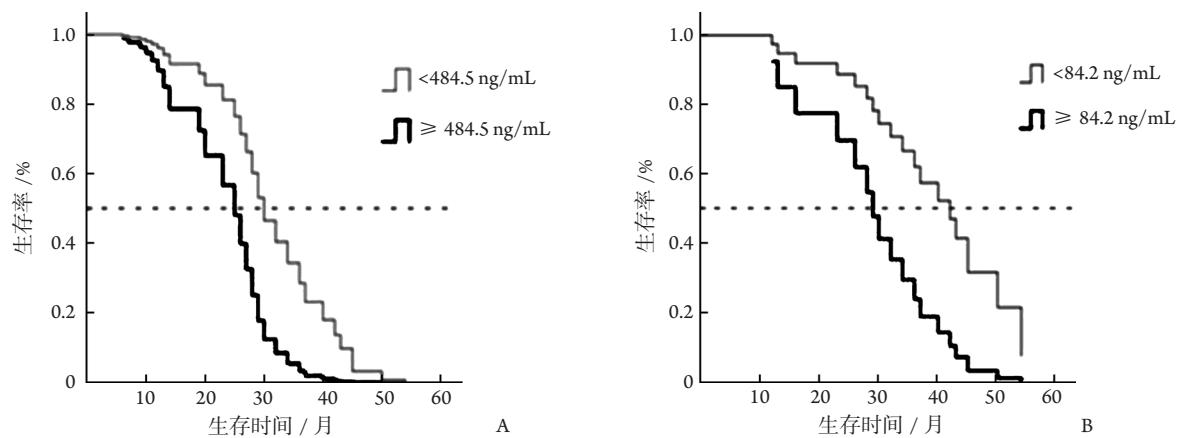


图 6 恶性胸腔积液患者中位生存时间

Figure 6 Median survival time in patients with malignant pleural effusion

A: SP-A^{p1} $<484.5 \text{ ng/mL}$ or $\geq 484.5 \text{ ng/mL}$; B: SP-A^{s1} $<84.2 \text{ ng/mL}$ or $\geq 84.2 \text{ ng/mL}$

3 讨 论

近年来有许多鉴别诊断胸腔积液的生物标志物的研究^[7-9]表明, CRP, IL-6, TNF和降钙素原等炎症

因子在EPE患者中明显增高。SP-A是一种活性糖蛋白, 参与多种炎症和肿瘤等的发病过程, SP-A在肺组织损伤、细胞增殖和细胞外基质重塑等病理过程中明显增加^[9-10], 并在一定程度上影响疾病的发展和转

归, 但其具体机制尚不明确。

渗出性胸腔积液患者肺泡II型细胞和Clara细胞分泌SP-A, SP-A大部分进入肺组织和胸水中, 同时血管通透性增加, 少部分SP-A可进入血液循环系统, 故SP-A^p浓度比SP-A^s浓度高^[9-10]。胸腔积液患者胸水中SP-A浓度明显增高, 且与血ADA, LDH, CRP和CEA呈明显正相关, 可能为肺部感染或恶性疾病伴随胸膜疾病所致^[10-13]。间质性肺疾病患者肺组织和血清SP-A浓度与患者肺功能指标变化、影像学改变和病情严重程度存在明显正相关, 并且血清SP-A浓度可以预测原发性肺纤维化患者的预后^[2, 11-13]。

本研究发现: 在胸腔积液定性诊断方面, SP-A^p和SP-A^s都具有很高的诊断敏感性和特异性; 与以往的研究结果^[9-13]相似。SP-A浓度在不同性质胸腔积液(包括结核性、肺炎性、肿瘤性和心源性胸腔积液)中不同, 原发性肺腺癌癌细胞侵袭胸膜后, 癌细胞能分泌大量SP-A, SP-A^p浓度是其他恶性肿瘤导致的胸腔积液的10倍以上。本研究中SP-A^p浓度≥484.5 ng/mL组患者生存时间短于SP-A^p浓度<484.5 ng/mL组, SP-A^s≥84.2 ng/mL组患者生存时间短于SP-A^s浓度<84.2 ng/mL组。运用SP-A可鉴别诊断肺腺癌性与其他性质的胸腔积液, 并可预测MCPE患者的生存时间^[2, 3, 14]。SP-A有助于诊断渗出性胸腔积液, 尤其是肺腺癌性胸腔积液。

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