

抗氨基甲酰化蛋白抗体在类风湿关节炎合并肺间质病变早期诊断中的价值

竺 红^{1△*}, 赵丽娟^{2*}, 周 艳¹, 陈 瑶²

(1. 宁夏医科大学总医院风湿免疫科, 宁夏银川 750004; 2. 宁夏医科大学临床医学院, 宁夏银川 750004)

[摘要] **目的:**探讨抗氨基甲酰化蛋白(carbamylated protein, CarP)抗体在类风湿关节炎(rheumatoid arthritis, RA)合并肺间质病变(interstitial lung disease, ILD)早期诊断中的价值。**方法:**选择2017年12月至2019年6月在宁夏医科大学总医院风湿免疫科住院确诊为RA的患者,收集病例资料及血清标本,依据胸部CT检查结果分为RA-ILD组及单纯RA组,采用酶联免疫吸附试验(enzyme linked immunosorbent assay, ELISA)法测定各组血清中抗CarP抗体水平,分析其与RA-ILD的发生及其他实验室指标的相关性。组间计量资料比较采用两独立样本 t 检验或Mann-Whitney U 检验;组间计数资料比较采用卡方检验;采用绘制受试者工作曲线(ROC曲线)确定抗CarP抗体对诊断RA-ILD最佳截断值并分析其诊断效能,相关性分析采用Spearman相关分析。**结果:**RA-ILD组抗CarP抗体水平为21.14(12.29, 29.75),明显高于单纯RA组的11.00(6.66, 19.05),差异有统计学意义($P < 0.05$)。RA-ILD组抗CarP抗体阳性率(53%)高于单纯RA组(16%),差异有统计学意义($P < 0.05$);两组间类风湿因子(rheumatoid factor, RF)及抗环瓜氨酸肽(cyclic citrullinated peptide, CCP)抗体水平差异无统计学意义($P > 0.05$)。RA-ILD组年龄及疾病活动指数(disease activity score 28, DAS28)显著高于单纯RA组,差异有统计学意义($P < 0.05$)。RA-ILD组男性和吸烟比例高于单纯RA组,但差异无统计学意义($P > 0.05$)。通过绘制ROC曲线显示抗CarP抗体对RA-ILD诊断的最佳截断值为20.56 U/mL,灵敏度为53.50%,特异度为84.20%,曲线下面积为0.76;Spearman相关性分析示RF、年龄与抗CarP抗体呈正相关($r = 0.172, P = 0.043; r = 0.200, P = 0.006$);抗CarP抗体水平与DAS28评分、红细胞沉降率(erythrocyte sedimentation rate, ESR)、C-反应蛋白(C-reactive protein, CRP)、抗CCP抗体、关节肿胀数和关节压痛数均无相关性($P > 0.05$)。**结论:**RA-ILD患者中血清抗CarP抗体浓度高于单纯RA患者,提示抗CarP抗体在RA-ILD发生发展中可能具有一定作用。

[关键词] 类风湿关节炎;抗氨基甲酰化蛋白抗体;肺间质病变

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Significance of anti-carbamylated protein antibodies in patients with rheumatoid arthritis-associated interstitial lung disease

ZHU Hong^{1△*}, ZHAO Li-juan^{2*}, ZHOU Yan¹, CHEN Yao²

(1. Department of Rheumatology, General Hospital of Ningxia Medical University, Yinchuan 750004, China; 2. Department of Clinical Medical College, Ningxia Medical University, Yinchuan, 750004, China)

ABSTRACT Objective: To evaluate the value of anti-carbamylated protein (CarP) antibody in the diagnosis of rheumatoid arthritis-associated interstitial lung diseases (RA-ILD). **Methods:** Clinical and laboratory data and serum samples of patients with RA between December 2017 and June 2019 in Department of Rheumatology, General Hospital of Ningxia Medical University were collected. The patients were subclassified as RA-ILD and RA-without ILD based on computed tomography scans of the chest, Enzyme linked immunosorbent assay (ELISA) was used to assess anti-CarP antibody in the serum of each group. The occurrence of ILD and other laboratory indexes were analyzed. Comparison of measurement data between the 2 groups was performed by two independent sample t -test or Mann-Whitney U nonparametric test, while the count data were compared by Chi square test; Receiver operating characteristic curve (ROC) was drawn to determine the cut-off value of anti-CarP antibody to RA-ILD diagnosis and to analyze its diagnostic efficacy. **Results:** The anti-CarP antibody level in the RA-ILD group was 21.14 (12.29, 29.75), which was significantly higher than that in the RA-without ILD group 11.6 (6.66, 19.05) ($P = 0.000$). The difference was statistically significant ($P < 0.05$). The positive rate of anti-CarP anti-

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△ A Corresponding author's e-mail, nxzhuh@126.com

* These authors contributed to the work equally

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body in RA-ILD group (53%) was significantly higher than that in RA-without ILD group (16%) ($P < 0.05$); There was no significant differences in the levels of rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP) between the two groups ($P > 0.05$). The age and disease activity score (DAS28) in the RA-ILD group were significantly higher than those in the RA-without ILD group ($P < 0.05$). The proportion of men and smoking in the RA-ILD group was higher than that in the RA-without ILD group, but the difference was not statistically significant. The ROC curve showed that the anti-CarP antibody had a cut off value of 20.56 U/mL, with the sensitivity of 53.50%, and specificity of 84.20%, the area under the ROC curve were 0.76. Spearman correlation analysis showed that rheumatoid factor (RF) and age were positively correlated with anti-CarP antibody ($r = 0.172$, $P = 0.043$; $r = 0.200$, $P = 0.006$). Anti-CarP antibody level was not associated with the DAS28 score, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), anti-CCP antibody, swollen joint count, and tender joint count ($P > 0.05$). **Conclusion:** The anti-CarP antibody level in RA-ILD patients is higher than that in RA-without ILD, suggesting that anti-CarP antibody may have a role in the development of RA-ILD.

KEY WORDS Rheumatoid arthritis; Anti-carbamylated protein antibody; Interstitial lung disease

类风湿关节炎(rheumatoid arthritis, RA)是一种以慢性破坏性关节炎为特征的全身性自身免疫病,肺间质病变(interstitial lung disease, ILD)是RA常见的关节外表现之一,最早关于类风湿关节炎合并肺间质病变(rheumatoid arthritis-associated interstitial lung disease, RA-ILD)的报道来自于1948年Ellman等^[1]的研究。RA-ILD发生率为4%~80%^[2-3], RA-ILD的发生、发展与遗传、环境以及免疫因素有关,因早期无明显临床症状及体征,极易漏诊,晚期预后极差,ILD正逐渐成为RA患者死亡的重要原因。除类风湿因子(rheumatoid factor, RF)和抗瓜氨酸蛋白抗体(anti-citrullinated protein antibodies, ACPA)外,1/3的患者有RA的典型临床表现时,其血清学抗体却是阴性^[4]。抗氨基甲酰化蛋白(carbamylated protein, CarP)抗体作为一种新型的自身抗体引起了人们的关注,研究发现,35%~69%的RA患者可以检测出抗CarP抗体^[5-7]。本课题组前期对RA组(病例组)126例和非RA组(对照组)121例测定血清抗CarP抗体浓度^[8],发现RA组抗CarP浓度明显高于非RA组,且差异有统计学意义,抗CarP抗体灵敏度为74.60%,特异度为71.07%。但关于抗CarP抗体与RA-ILD的关系的报道较少见,故本研究旨在分析RA-ILD与单纯RA患者血清中抗CarP抗体水平的差异,探讨抗CarP抗体在RA相关的肺间质改变中可能发挥的作用。

1 资料与方法

1.1 研究对象

选择2017年12月1日至2019年6月1日就诊于宁夏医科大学总医院风湿免疫科的RA住院患者,共186例。入选患者均符合2010年美国风湿病学会/欧洲抗风湿病联盟(ACR/EULAR)修订的RA诊断标准。排除合并其他自身免疫病(如系统性红

斑狼疮、干燥综合征、强直性脊柱炎、血管炎等)者,排除伴有严重感染、支气管扩张症、肺结核、矽肺、恶性肿瘤以及心、肝、肾等重要脏器病变的患者。根据肺CT检查结果判定有无肺间质病变,将患者分为RA-ILD组和单纯RA组,收集临床资料及实验室检验检查结果。RA-ILD组129例,其中男性29例,女性100例,年龄33~84岁,平均(60±10)岁;单纯RA组57例,其中男性7例,女性50例,年龄14~77岁,平均(48±13)岁。

本研究开始前获得宁夏医科大学总医院伦理委员会审查批准(2017-123),所有研究对象均签署知情同意书。

1.2 临床相关指标

记录的临床相关指标包括年龄、性别、是否吸烟、病程、红细胞沉降率(erythrocyte sedimentation rate, ESR)、C-反应蛋白(C-reactive protein, CRP)、疾病活动指数(disease activity score 28, DAS28)、抗环瓜氨酸肽(cyclic citrullinated peptide, CCP)抗体和RF。

1.3 胸部CT检查

186例RA患者均行胸部CT检查,CT扫描采用GE Lightspeed 16 pro机(HRCT扫描方式:层厚1.25 mm,层距6.2 mm,140 kV,100 MA,FOV 338 mm,窗宽1 000,窗位500),CT结果由固定两名放射科医师判读是否存在ILD,ILD表现包括肺结节、肺间质改变、肺间质纤维化、支气管扩张等,显示1种或1种以上影像学表现者则表示存在ILD改变。

1.4 主要试剂

应用ELISA方法测定人血清抗CarP抗体,抗CarP抗体试剂盒购自上海谷研实业有限公司,按试剂盒说明书进行操作。

1.5 抗体浓度的检测

1.5.1 血清的收集 抽取两组患者清晨空腹静脉血 5 mL,室温条件下静置 15 min 后,3 500 r/min,离心 15 min,离心半径为 4.6 cm,收集上清液,并存储于 $-80\text{ }^{\circ}\text{C}$ 冰箱中。

1.5.2 抗 CarP 抗体浓度的测定 按照试剂盒说明书进行测定,标准曲线的测定选择复孔加样,将加样完成的酶标包被板用酶标仪 (ELX808,购自美国 Bio-Tek 公司)进行光密度值 (D) 的测量,然后以标准物的浓度及其 D 值分别为纵、横坐标绘制出标准曲线并推算其线性回归方程式,将患者血清测量的 D 值代入方程式,计算出每一个受试者抗 CarP 抗体的实际浓度。

1.6 统计学分析

采用 SPSS 21.0 统计软件进行分析,符合正态分布的计量资料以 $\bar{x} \pm s$ 表示,组间比较采用两独立样本 t 检验;不符合正态分布时用中位数 (M) 和百分位数 (P_{25}, P_{75}) 表示,进行 Mann-Whitney U 检验;计数资料用率或构成比描述,组间率或构成比的比较采用卡方检验;通过绘制受试者工作曲线 (ROC 曲线),分析抗 CarP 抗体诊断 RA-ILD 的截断值,

用 ROC 曲线下面积 (A) 的大小来评估诊断的准确度。判断标准: $A \leq 0.5$ 完全无诊断价值, $0.5 < A < 0.7$ 诊断准确度较低, $0.7 \leq A < 0.9$ 诊断准确度较好, $A \geq 0.9$ 诊断准确性最高。双变量采用 Spearman 相关分析。 $P < 0.05$ 认为差异有统计学意义。

2 结果

2.1 RA-ILD 组与单纯 RA 组一般临床资料分析

共收集 186 例 RA 患者,诊断为 RA-ILD 组 129 例,单纯 RA 组 57 例,其中 RA-ILD 组较单纯 RA 组年龄偏大、病程较长、病情活动度更高,两组间年龄及 DAS28 差异具有统计学意义 ($P < 0.05$),病程差异无统计学意义 ($P > 0.05$)。RA-ILD 组男性和吸烟比例高于单纯 RA 组,但差异无统计学意义 ($P > 0.05$,表 1)。

2.2 RA-ILD 组与单纯 RA 组血清抗 CarP 抗体、RF 及抗 CCP 抗体水平比较

RA-ILD 组血清抗 CarP 抗体水平高于单纯 RA 组,差异有统计学意义 ($P < 0.05$),RF 及抗 CCP 抗体水平差异无统计学意义 ($P > 0.05$,表 2)。

表 1 两组患者一般资料比较

Table 1 Comparison of general data between the two groups of patients

Group	Total cases	Age/years, $\bar{x} \pm s$	Course of disease, $M(P_{25}, P_{75})$	DAS28, $\bar{x} \pm s$	Gender		Smoking	
					Male	%	Cases	%
RA-ILD	129	60 \pm 10	6 (2,12)	5.7 \pm 1.2	29	22	14	11
RA-without ILD	57	48 \pm 13	6 (2,10)	5.0 \pm 1.3	7	12	4	7
$t/U/\chi^2$		6.913	3 585	3.948	2.635		0.665	
P		0.000	0.786	0.000	0.105		0.415	

DAS28, disease activity score 28. $P < 0.05$ has statistical significance.

表 2 两组血清抗 CarP 抗体、RF 及抗 CCP 抗体水平比较 [$M(P_{25}, P_{75})$]

Table 2 Comparison of anti-CarP antibody, RF and anti-CCP antibody level in two groups [$M(P_{25}, P_{75})$]

Group	Cases	Anti-CarP/(U/mL)	RF/(U/mL)	Anti-CCP/(U/mL)
RA-ILD	129	21.14 (12.29, 29.75)	102.00 (12.50, 256.50)	71.35 (8.95, 200)
RA-without ILD	57	11.00 (6.66, 19.05)	70.70 (21.13, 223.75)	68.35 (7.00, 139.80)
U		1 803	3 668	3 273
P		0	0.98	0.346

Anti-CarP, carbamoylated protein; RF, rheumatoid factor; anti-CCP, anti-cyclic citrullinated peptid. $P < 0.05$ has statistical significance.

2.3 抗 CarP 抗体对于诊断 RA-ILD 价值分析

以抗 CarP 抗体作为检验变量绘制 ROC 曲线 (图 1),可以得到不同的截断值相对应的灵敏度和特异度。选取约登指数 (Youden index) 最大点对应

的截断值作为 RA-ILD 的诊断标准,分析发现最佳截断值为 20.56 U/mL,此时,灵敏度和特异度之和达到最大,灵敏度为 53.50%,特异度为 84.20%,约登指数为 0.377;曲线下面积为 0.76,95% CI 为

0.679 ~ 0.830, $P < 0.01$ 显示曲线下面积具有统计学意义,提示抗 CarP 抗体可能对 RA-ILD 发展具有一定的作用。

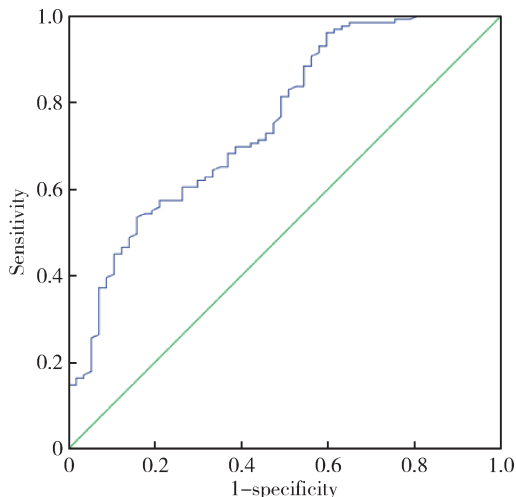


图 1 抗 CarP 抗体用于 RA-ILD 诊断的 ROC 曲线

Figure 1 ROC curve of anti-CarP antibody for identification of RA-ILD

2.4 抗 CarP 抗体与 RA 病情活动相关性分析

RA-ILD 组与单纯 RA 组行 Spearman 相关性分析,抗 CarP 抗体水平与 DAS28 评分、ESR、CRP、抗 CCP 抗体、关节肿胀数及关节压痛数均无相关性 ($P > 0.05$),RF、年龄与抗 CarP 抗体呈正相关(表 3)。

表 3 抗 CarP 抗体与 RA 病情活动相关性分析

Table 3 Correlation analysis between anti-CarP antibody and RA disease activity

Items	Anti-CarP	
	<i>r</i>	<i>P</i>
DAS28	0.029	0.691
ESR	0.05	0.941
CRP	0.35	0.632
RF	0.172	0.043
Anti-CCP	-0.039	0.598
Age	0.2	0.006
Swollen joint count	-0.084	0.254
Tender joint count	0.06	0.417

Anti-CarP, carbamylated protein; DAS28, disease activity score 28; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RF, rheumatoid factor; anti-CCP, anti-cyclic citrullinated peptid. $P < 0.05$ has statistical significance.

3 讨论

RA 是一种以滑膜炎为病理特征的慢性炎症性疾病,血清中自身抗体的检测提高了对 RA 的诊断。

目前,关于 RA-ILD 的报道日益增多,国内外研究发现^[9-10],ILD 在 RA 患者中的发生率约为 4% ~ 80%^[2-3],本研究 186 例患者中,RA-ILD 有 129 例(69%),与上述结果相符,RA-ILD 早期起病隐匿,常被忽略,晚期出现肺纤维化则预后差,多因呼吸衰竭而死亡。

目前 RA-ILD 的发病机制及危险因素仍不明确,有研究报道^[1,11-14],男性、吸烟、高龄、高滴度 RF、高滴度抗 CCP 抗体是 RA 合并 ILD 的危险因素。本研究显示,RA-ILD 组患者年龄高于单纯 RA 组患者,与上述文献报道一致。进一步分析 RA-ILD 组患者抗 CarP 抗体浓度高于单纯 RA 组,且年龄与抗 CarP 抗体呈正相关,提示高龄、血清高滴度抗 CarP 抗体 RA 患者更易合并 ILD。由于本研究样本量较小,抗 CarP 抗体在 RA-ILD 发生发展作用机制尚未明确,有待后续扩大样本量进一步研究。

大量临床报道^[15-16],RA 患者肺部病变与抗 CCP 抗体密切相关,2014 年英国一项多本研究报道发现^[17],抗 CCP 抗体在 RA 患者中与 ILD 相关,强调抗 CCP 抗体可视为 ILD 形成的独立危险因素之一。有学者提出环瓜氨酸蛋白存在 RA-ILD 患者肺内^[2],其可能作为抗原通过内源性或外源性刺激产生抗 CCP 抗体参与肺组织损伤进程。近年研究发现^[18],抗氨基甲酰化蛋白抗体作为一种新型的自身抗体引起人们的关注。氨基甲酰化是一种翻译后修饰,是赖氨酸在氰酸盐的作用下转化为高瓜氨酸的过程,2011 年 Shi 等^[19]首次报道了抗 CarP 抗体存在于 RA 血清中,有助于 RA 早期诊断,在 Li 等^[20]的荟萃分析中,纳入的 7 篇研究发现抗 CarP 抗体的敏感度是 42% [95% CI (38%, 45%)],特异度是 96% [95% CI (95%, 97%)]。本课题组既往对中国宁夏 247 例确诊 RA 患者分析显示,抗 CarP 抗体灵敏度为 74.60%,特异度为 71.07%^[8]。目前国内外多项研究发现^[21-23],抗 CarP 抗体对 RA 具有一定的诊断价值,然而关于抗 CarP 抗体对 RA-ILD 的诊断价值研究较少见。本研究 RA-ILD 组患者的抗 CarP 抗体水平及阳性率显著高于单纯 RA 患者,差异有统计学意义,15 例 RA-ILD 患者 RF、抗 CCP 抗体、AKA、ANA 均阴性,其中 6 例抗 CarP 抗体阳性,但单纯 RA 组血清学阴性者 4 例患者的抗 CarP 抗体均阴性。进一步绘制 ROC 曲线,发现最佳截断值为 20.56 U/mL,此时灵敏度为 53.50%,特异度为 84.20%,曲线下面积为 0.76,提示抗 CarP 抗体可能参与了肺间质病变的发生,95% CI 为 0.679 ~ 0.830, $P < 0.01$,可考虑与其他血清学指标联合检

测以提高诊断效能。此外,Restrepo 等^[24]研究表明,与单纯 RA 患者相比,RA-ILD 患者的关节疾病活动水平更高。本研究两组间也有差异,与之相符。在 2019 年一项前瞻性研究中发现^[25],DAS28 为高或中度疾病活动的患者与缓解或低疾病活动的患者相比,RA-ILD 的风险增加了 2 倍,这种关联独立于已知的 RA-ILD 危险因素(如性别、吸烟、RA 病程和 RA 血清学状态),提示炎症参与了 RA-ILD 的发病机制。本研究抗 CarP 抗体与 DAS28 无相关性,提示抗 CarP 抗体可能与全身炎症反应无关。

Othman 等^[26]对 105 例马来西亚 RA 患者的横断面研究显示,ACPA 与抗 CarP 水平无相关性($r = 0.065, P = 0.509$),而 RF 与抗 CarP 抗体有相关性($P = 0.019$),本研究 RF 与抗 CarP 抗体有相关性与之相符,提示 RF 可能参与了肺间质病变。

综上所述,RA 患者中年龄较大和高滴度抗 CarP 抗体者更易合并 ILD。抗 CarP 抗体在 RA-ILD 的发生、发展中可能具有一定的作用。现有的检测手段有放射性或者为有创检查,鉴于检测抗 CarP 抗体价廉、无创且标本易获得,故可用来监测 ILD 的发生、发展,但其诊断效能以及最佳截断值尚需更大样本的前瞻性研究进一步证实。

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