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在线全文

白介素6、白介素12P70、血清淀粉样蛋白酶A和降钙素原对类风湿关节炎的诊断价值及与疾病活动度的关系*

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【摘要】 目的 观察血清炎症四项〔白介素6（interleukin 6, IL-6）、白介素12P70（interleukin 12P70, IL-12P70）、血清淀粉样蛋白酶A（serum amyloid A, SAA）和降钙素原（procalcitoninogen, PCT）〕对类风湿关节炎（rheumatoid arthritis, RA）的诊断价值，并分析其与疾病活动度的关系。**方法** 纳入2022年12月–2023年12月安徽省中医院风湿科住院的RA患者60例，以同期安徽省中医院体检中心的正常体检者30例为对照组。采用流式细胞术检测血清IL-6和IL-12P70，采用免疫比浊法测定SAA，采用化学发光法测定血清PCT。采用全自动生化分析仪检测血沉（erythrocyte sedimentation rate, ESR）、C反应蛋白（C-reactive protein, CRP）、类风湿因子（rheumatoid factor, RF）和抗环瓜氨酸肽（anticyclic citrullinated peptide, ACCP）。计算基于ESR的28个关节疾病活动评分（DAS28-ESR）。采用*t*检验、秩和检验和Kruskal Wallis *H*检验分析炎症四项在不同组间的表达差异，ROC曲线分析炎症四项对RA的诊断价值，Spearman相关性分析比较炎症四项与CRP、ESR、RF、ACCP和DAS28-ESR之间的相关性。**结果** ①RA组的SAA、IL-6和IL-12P70表达水平均比对照组表达水平高（$P<0.01$）。②ROC曲线结果显示，RA组与对照组相比PCT的ROC曲线下面积（area under the curve, AUC）为0.611〔95%置信区间（confidence interval, CI）：0.488～0.735，$P>0.05$〕；SAA的AUC为0.819（95%CI：0.733～0.906，$P<0.01$）；IL-6的AUC为0.875（95%CI：0.803～0.946，$P<0.01$）；IL-12P70的AUC为0.832（95%CI：0.746～0.917，$P<0.01$）；IL-6+IL-12P70+SAA+PCT联合指标的AUC为0.973（95%CI：0.942～1.000，$P<0.01$）。③PCT、SAA在RA高活动组、中活动组、低活动组3组中的表达水平不同（$P<0.01$）。④RA组患者中CRP与SAA（$r_s=0.75$，$P<0.01$）和IL-6呈正相关（$r_s=0.52$，$P<0.01$），ESR与SAA（$r_s=0.36$，$P<0.01$）呈正相关，DAS28-ESR与PCT（$r_s=0.34$，$P=0.01$）、SAA（$r_s=0.51$，$P<0.01$）和IL-6呈正相关（$r_s=0.33$，$P=0.01$）。**结论** 炎症四项（PCT、SAA、IL-6和IL-12P70）与RA疾病活动度关系密切，可作为协助诊断RA及评估RA疾病活动度的血清指标之一。

【关键词】 白介素6 白介素12P70 血清淀粉样蛋白酶A 降钙素原 类风湿关节炎 疾病活动度

Diagnostic Value of Interleukin 6, Interleukin 12P70, Serum Amyloid A, and Procalcitonin for Rheumatoid Arthritis and Their Relationship With the Disease Activity

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【Abstract】 Objective To observe the diagnostic value of four serum inflammatory biomarkers, including interleukin 6 (IL-6), interleukin 12P70 (IL-12P70), serum amyloid A (SAA), and procalcitonin (PCT), in rheumatoid arthritis (RA) and to analyze their relationship with the disease activity. **Methods** The study included 60 RA patients admitted to the Department of Rheumatology at Anhui Provincial Hospital of Traditional Chinese Medicine between December 2022 and December 2023. Thirty healthy individuals from the hospital's physical examination center served as the control group. Serum levels of IL-6 and IL-12P70 were detected using flow cytometry. SAA levels were determined by immunoturbidimetry, and PCT levels were assessed by chemiluminescence. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), and anticyclic citrullinated peptide (ACCP) were detected using an

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automated biochemical analyzer. The 28-joint disease activity scores (DAS28-ESR) based on ESR were observed. Statistical analysis included *t*-tests, rank-sum tests, and Kruskal-Wallis *H* tests to compare the expression differences of the biomarkers among different groups. The diagnostic value of these biomarkers for RA was analyzed by ROC curve analysis. Spearman correlation analysis was performed to assess the relationships between the four inflammatory biomarkers and CRP, ESR, RF, ACCP, and DAS28-ESR. **Results** 1) The expression levels of SAA, IL-6, and IL-12P70 in the RA group were significantly higher than those in the control group (P<0.01). 2) ROC curve analysis showed that the area under the curve (AUC) for PCT was 0.611 (95% confidence interval [CI]: 0.488-0.735, P>0.05), for SAA, it was 0.819 (95% CI: 0.733-0.906, P<0.01), for IL-6, it was 0.875 (95% CI: 0.803-0.946, P<0.01), and for IL-12P70, it was 0.832 (95% CI: 0.746-0.917, P<0.01). The combined index of IL-6, IL-12P70, SAA, and PCT had an AUC of 0.973 (95% CI: 0.942-1.000, P<0.01). This indicates that the four inflammatory biomarkers can assist in the diagnosis of rheumatoid arthritis. 3) The expression levels of PCT and SAA varied significantly among the high, moderate, and low activity RA groups (P<0.01). 4) In RA patients, CRP was positively correlated with SAA (r_s=0.75, P<0.01), and IL-6 (r_s=0.52, P<0.01). ESR was positively correlated with SAA (r_s=0.36, P<0.01). DAS28-ESR was positively correlated with PCT (r_s=0.34, P=0.01), SAA (r_s=0.51, P<0.01) and IL-6 (r_s=0.33, P=0.01). **Conclusion** The four inflammatory biomarkers (PCT, SAA, IL-6, and IL-12P70) are closely related to rheumatoid arthritis disease activity and can serve as serum indicators to assist in the diagnosis and assessment of RA.

【Key words】 Interleukin 6 Interleukin 12P70 Serum amyloid A Procalcitonin Rheumatoid arthritis Disease activity

类风湿关节炎(rheumatoid arthritis, RA)是风湿免疫科常见的慢性自身免疫性疾病之一,主要表现为慢性的滑膜炎症与关节软骨的破坏,其临床上多发生于小关节尤其是近端指间关节,多为对称分布,大多数患者会伴有晨僵、发热和关节肿痛,严重的患者会出现关节畸形和脱位,最后导致关节残疾及生活质量下降[1-3]。RA可能会对机体本身的组织及器官产生过度的免疫反应,导致脏器的损伤并引起相应器官功能紊乱或衰竭[4]。RA是由多种因素导致的疾病,随着免疫学的深入研究,发现大多数RA患者均伴有炎症指标的异常,如血沉(erythrocyte sedimentation rate, ESR)增快、C反应蛋白(C-reactive protein, CRP)增高等。RA可以累及肺脏、肾脏等多个器官及全身各个系统,其病情可伴随着病程的延长逐渐加重,甚至可以危及生命[5-6],故探索炎症指标与RA疾病活动度的关系尤为重要。炎症四项主要包括降钙素原(procalcitonin, PCT)、血清淀粉样蛋白酶A(serum amyloid A, SAA)、白介素6(interleukin 6, IL-6)、白介素12P70(interleukin 12P70, IL-12P70)[7-8]等。既往研究显示炎症四项中的IL-6与RA的炎症程度具有一定的相关性,PCT、SAA等炎症因子与其他类型炎性疾病如肺炎、强直性脊柱炎的疾病活动有一定关联[9-13]。但鲜有研究同时观察炎症四项与RA疾病活动度的关系。本文通过观察RA患者体内的炎症四项表达水平的变化,以及对不同疾病活动度之间炎症四项水平的比较,分析炎症四项对RA的诊断价值,并探索其与RA疾病活动度之间的关系,为寻找更为特异、敏感的临床指标对RA疾病活动度进行评估提供了新的思路与方法。

1 资料与方法

1.1 研究对象

收集2022年12月–2023年12月在安徽省中医院风湿科住院的60例RA患者〔其中男性15例,女性45例,平均年龄(56.08±7.79)岁〕;30例对照组来源于同期安徽省中医院体检中心的正常体检者,采用随机数字表法进行抽取〔其中男性8例,女性22例,平均年龄(59.50±8.70)岁〕。本研究经安徽中医药大学第一附属医院医学伦理委员会审批(伦理审查批件号2023AH-52)。

1.2 RA诊断标准

RA患者诊断依据参照2010年美国风湿病学会/欧洲风湿病防治联合会(ACR/EULAR)的分类标准[14]。

1.3 纳入标准

①RA组符合RA分类诊断标准,年龄30 ~ 65岁;②正常组无免疫系统及重大基础疾病,年龄35 ~ 65岁;③所有受试者均已签署知情同意书。

1.4 排除标准

①妊娠期或哺乳期女性;②患有神经、精神疾病而无法合作者;③合并有循环、呼吸、造血系统、肿瘤等严重疾病的患者;④合并有其他免疫系统疾病患者。

1.5 炎症四项测定

炎症四项包括SAA、PCT、IL-6和IL-12P70。采用免疫比浊法测定SAA,采用化学发光法测定血清PCT,采用流式细胞术检测血清IL-6和IL-12P70。操作过程严格按

照相应实验流程进行检测。

1.6　实验室指标测定

采用全自动生化分析仪检测ESR、CRP、类风湿因子(rheumatoid factor, RF)、抗环瓜氨酸肽(anticyclic citrullinated peptide, ACCP)等指标。

1.7　基于ESR的28个关节疾病活动评分（DAS28-ESR）疾病活动度评分

采用量表法收集RA患者关节压痛计数(tender joint count, TJC)、关节肿胀计数(swollen joint count, SJC)、患者总体评估(patient's global assessment of disease activity, PGA)和医生总体评估(physician's global assessment of disease activity, MDGA)。用软件计算DAS28-ESR; DAS28-ESR疾病活动度阈值: 高度> 5.1, 3.2< 中度≤5.1, 2.6< 低度≤3.2[15-16]。

1.8　统计学方法

采用GraPh Pad Prism8、SPSS26.0软件对所得数据进行统计分析。针对混杂因素进行了数据清洗, 删除明显异常数据; 对于Ⅰ型错误通过降低显著性水平控制。正态分布的资料用$\bar{x}\pm s$表示, 非正态分布数据用中位数(P_{25}, P_{75})表示。计量资料采用t检验或秩和检验, 计数资料采用χ^2检验。绘制ROC曲线, 计算曲线下面积(area under the curve, AUC)、截断值、灵敏度、特异度等。RA组内高、中、低3个不同疾病活动组之间的比较采用Kruskal Wallis H检验。RA组内炎症四项与RA疾病活动度指标的关联性采用Spearman相关性分析。$P\leqslant 0.01$为差异有统计学意义。

2　结果

2.1　一般资料

RA组与对照组的年龄、性别等差异无统计学意义。为消除性别因素对RA研究的影响, 以性别对RA患者分组统计分析后发现, 病程、DAS28-ESR、CRP、ESR、ACCP、RF、PCT、SAA、IL-6、IL-12P70等在不同性别间的差异无统计学意义, 具有基线可比性(表1)。

表 1　RA组不同性别间基线水平的比较〔中位数（P_{25}, P_{75}）〕

Table 1　Comparison of baseline levels between sexes in RA group (median [P_{25}, P_{75}])

Index	Male (n=15)	Female (n=45)	z	P
Course of disease/year	4.00 (3.00, 5.00)	3.00 (2.00, 4.00)	−1.91	0.06
CRP/(mg/L)	17.91 (2.05, 34.30)	14.64 (2.95, 26.11)	−0.27	0.79
ESR/(mm/1 h)	18.00 (7.00, 62.00)	16.00 (5.00, 30.00)	−0.90	0.37
ACCP/(mg/L)	72.20 (12.00, 695.00)	51.90 (9.51, 137.50)	−1.20	0.23
DAS28-ESR	4.51 (2.96, 6.48)	4.45 (2.75, 7.56)	−0.31	0.76
RF/(KIU/L)	80.90 (23.80, 244.00)	83.00 (34.15, 205.45)	−0.52	0.60
PCT/(ng/mL)	0.05 (0.03, 0.07)	0.05 (0.04, 0.07)	−0.18	0.86
SAA/(mg/L)	31.50 (2.38, 176.84)	32.40 (5.89, 80.39)	−0.30	0.77
IL-6/(pg/mL)	12.56 (6.60, 52.41)	17.15 (3.58, 24.14)	−0.67	0.50
IL-12P70/(pg/mL)	1.42 (0.50, 1.46)	1.40 (0.50, 1.53)	−0.10	0.92

2.2　炎症四项在RA组与对照组中的表达水平比较

结果显示, RA组的SAA、IL-6、IL-12P70表达水平均比正常组表达水平高(P< 0.01), RA组的PCT与对照组相比差异无统计学意义。见表2。

表 2　RA组与对照组炎症四项比较（$\bar{x}\pm s$）

Table 2　Comparison of four inflammation biomarkers between RA and control groups（$\bar{x}\pm s$）

Index	RA group (n=60)	Control group (n=30)	t	P
PCT/(ng/mL)	0.06±0.06	0.04±0.02	1.53	0.06
SAA/(mg/L)	72.49±88.69	6.18±7.19	5.75	<0.01
IL-6/(pg/mL)	24.19±35.43	2.14±1.35	4.81	<0.01
IL-12P70/(pg/mL)	1.25±0.81	0.50±0.26	6.53	<0.01

2.3　炎症四项预测RA的ROC曲线分析

ROC曲线结果显示, RA组与对照组相比, PCT的AUC为0.611〔95%置信区间(confidence interval, CI): 0.488 ~ 0.735, P> 0.05〕; SAA的AUC为0.819(95%CI: 0.733 ~ 0.906, P< 0.01); IL-6的AUC为0.875(95%CI: 0.803 ~ 0.946, P< 0.01); IL-12P70的AUC为0.832(95%CI: 0.746 ~ 0.917, P< 0.01); IL-6+IL-12P70+SAA+PCT联合指标的AUC为0.973(95%CI: 0.942 ~ 1.000, P< 0.01)。说明炎症四项可以作为协助诊断RA的分子标志物, 且联合指标的诊断效能更好。见表3和图1。

2.4　不同疾病活动度间炎症四项的水平差异

将RA组按照DAS28-ESR疾病活动度评分分为高度组、中度组和低度组, 每组各20例。结果显示, PCT、

表 3 炎症四项对RA诊断效能的相关参数

Table 3 Relevant parameters of diagnostic efficacy of four inflammatory markers for RA

Index	Cut-off point	Sensitivity/%	Specificity/%	AUC	95% CI	*P*
PCT	0.037 ng/mL	53.33	73.33	0.611	0.488-0.735	0.086
SAA	4.955 mg/L	76.67	83.33	0.819	0.733-0.906	<0.01
IL-6	3.855 pg/mL	93.55	75.00	0.875	0.803-0.946	<0.01
IL-12P70	1.150 pg/mL	96.67	61.67	0.832	0.746-0.917	<0.01
IL-6+IL-12P70+SAA+PCT	0.467	93.33	95.00	0.973	0.942-1.000	<0.01

AUC: area under the curve; CI: confidence interval.

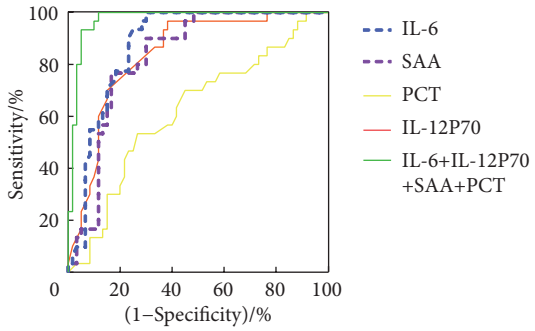

图 1 炎症四项诊断RA的ROC曲线分析

Fig 1 ROC curve analysis of four inflammatory biomarkers for diagnosing RA

SAA在高、中、低3组中的表达水平不同($P \leqslant 0.01$)，IL-6、IL-12P70在3组中的表达差异无统计学意义，见表4。

表 4 不同疾病活动度间炎症四项水平差异

Table 4 Differences in levels of four inflammation biomarkers among different disease activity groups

Index	High-group (n=20)	Middle-group (n=20)	Low-group (n=20)	*H*	*P*
PCT/(ng/mL)	0.08±0.09	0.06±0.04	0.04±0.17	8.49	0.01
SAA/(mg/L)	176.10±81.28	36.55±18.14	4.81±2.80	52.46	<0.01
IL-6/(pg/mL)	28.11±29.79	31.87±50.75	12.58±14.69	6.11	0.04
IL-12P70/(pg/mL)	1.31±0.84	1.31±1.00	1.13±0.54	0.03	0.98

2.5 炎症四项与反映RA疾病活动度指标的相关性分析

见表5。通过将RA组的炎症四项与RA活动性指标CRP、ESR、RF、ACCP、DAS28-ESR等指标进行相关性分析显示，RA组中CRP与SAA(r_s= 0.75, P< 0.01)和IL-6(r_s= 0.52, P< 0.01)呈正相关，ESR与SAA(r_s= 0.36, P< 0.01)，DAS28-ESR与PCT(r_s= 0.34, P= 0.01)、SAA(r_s= 0.51, P< 0.01)和IL-6(r_s= 0.33, P= 0.01)呈正相关。

表 5 炎症四项与反映RA疾病活动度指标的相关性分析

Table 5 Correlation analysis between four inflammatory biomarkers and indicators reflecting RA disease activity

Index	CRP		ESR		RF		ACCP		DAS28-ESR	
	r_s	*P*	r_s	*P*	r_s	*P*	r_s	*P*	r_s	*P*
PCT	0.32	<0.05	0.17	0.19	0.04	0.79	−0.11	0.40	0.34	0.01
SAA	0.75	<0.01	0.36	<0.01	−0.05	0.72	−0.09	0.52	0.51	<0.01
IL-6	0.52	<0.01	0.29	<0.05	0.01	0.45	0.17	0.19	0.33	0.01
IL-12P70	−0.07	0.61	−0.04	0.78	−0.01	0.45	0.07	0.62	−0.05	0.69

3 讨论

RA可以出现全身关节尤其是近端小关节的晨僵、肿痛、畸形、脱位[1-2]，还可以累及呼吸、循环、消化及神经系统等[4, 17]。通过对RA疾病活动度的评估既可以评估RA患者疾病进展，也可以指导RA临床用药，且对于RA患者临床症状改善效果评价同样具有深远的意义。既往对RA疾病活动度的诊断依靠患者晨僵时间，关节肿胀，血清ESR、CRP等，随着对RA的深入研究及现代检验技术的发展，寻找灵敏度和特异度更高的血清标志物来评估RA疾病活动度尤为重要。通过检测血清中炎症四项(PCT、SAA、IL-6和IL-12P70)表达水平可以为RA疾病活动度的评估提供新的方向。

本研究将RA组与对照组的炎症四项进行比较，发现RA组的SAA、IL-6、IL-12P70等炎症因子的表达水平明显比对照组高。SAA是一种由肝脏产生的急性时相蛋白，在RA急性活动期，机体受到炎症刺激时，产生一系列细胞因子如IL-1、IL-6、TNF-α等，其中IL-6和TNF-α协同刺激SAA表达水平增高，SAA在机体内发挥作用时又会促进炎症因子的释放，进一步加重RA患者的炎症反应。通过观察血清中SAA的表达水平，可以评估RA患者的炎症程度。ROC曲线分析结果显示PCT、SAA、IL-6、IL-12P70等炎症因子预测RA具有一定的灵敏度和特异度，且PCT+SAA+IL-6+IL-12P70联合指标对预测RA的AUC及特异度大于PCT、SAA、IL-6、IL-12P70单独指标，联合指标预测RA的灵敏度大于PCT和SAA，这说明PCT、SAA、IL-6和IL-12P70可以作为协助诊断RA的血清标志物，且联合运用对RA诊断效果更显著。PCT是一种来源于甲状腺C细胞的前体蛋白，在正常机体中几乎不表达，当机体发生较高的炎症反应时，血清PCT表达水平显著

升高。本研究将RA组患者按照DAS28-ESR疾病活动度评分进行分组并对不同组的血清PCT、SAA、IL-6、IL-12P70等指标进行分析，结果显示高度活动组、中度活动组和低度活动组血清PCT、SAA的组间差异有统计学意义（$P<0.01$），这说明血清PCT、SAA水平可能与RA疾病活动度有关。IL-6和IL-12P70是由免疫细胞分泌的细胞因子，IL-6多由单核巨噬细胞产生，一方面与IL-1共同作用可加重RA患者的炎症反应，另一方面IL-6升高，可促进巨噬细胞产生转化生长因子β（TGF-β）又可以导致RA免疫功能失调。IL-12P70主要由树突状细胞分泌，可以诱导辅助性T细胞分化进而参与到RA的免疫调节过程。通过将反映RA患者疾病活动度的指标（CRP、ESR、RF、ACCP、DAS28-ESR）与炎症四项指标进行相关性分析发现，CRP与SAA、IL-6呈正相关，ESR与SAA呈正相关，DAS28-ESR与PCT、SAA、IL-6呈正相关，这与既往文献[18-22]所报道发现的IL-6、SAA等指标与RA的疾病活动度呈正相关一致。这更进一步说明炎症四项在RA疾病活动与进展中有重要作用[23-24]。

综上，炎症四项与RA疾病活动度的关联密切，随着RA疾病活动度的升高，血清中炎症四项表达水平亦随之升高，炎症四项可以作为协助诊断RA及评估RA疾病活动度的血清指标之一。但本研究也存在一些不足，如样本量较少，研究对象存在一定地域局限性等，这些将在未来研究中继续予以完善。

*　　*　　*

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